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1,1-Diamino-2-nitroethylenes as excellent hydrogen bond donor organocatalysts in the Michael addition of carbon-based nucleophiles to β-nitrostyrenes

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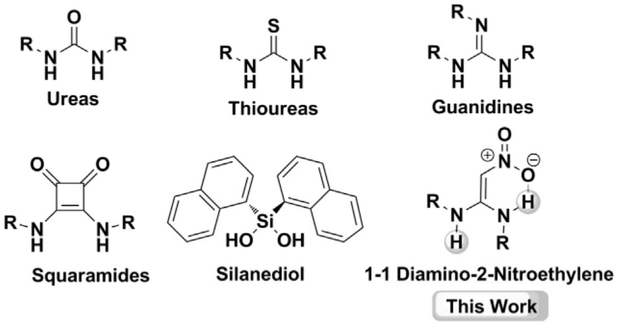
A new class of hydrogen bond donor catalysts based on the 1,1-diamino-2-nitroethylene scaffold has been introduced for the activation of *trans*-β-nitrostyrenes toward reactions with a range of carbon-based nucleophiles, affording the corresponding adducts in excellent yields. Importantly, this new set of organocatalysts is easily prepared from commercially available starting materials in mild reaction conditions.

1. Introduction

Over the past few years, organocatalysis has been widely studied, developed, and employed for the synthesis of novel organic molecules in the fine chemicals industry.[1] This new concept has rapidly become a complementary method to classical strategies employed in synthetic organic chemistry for the construction of carbon–carbon and carbon–heteroatom bonds.[2] Among the range of reactions promoted by organocatalysts, the conjugate addition of carbon-based nucleophiles to electron-deficient alkenes is recognized as one of the most powerful and atom-economical synthetic tools for the construction of densely functionalized compounds from simple precursors.[3] In this context, various electrophilic species have been examined, and recent efforts have been devoted to the application of nitroalkenes as suitable Michael acceptors.[4] This can be rationalized by the strong electron-withdrawing property of the nitro group, which also represents a highly useful reactive handle for further synthetic manipulations into a variety of building blocks, such as amines, acids, oximes, and others.[5] Small molecules capable of activating α,β-unsaturated carbonyls or related compounds through double hydrogen-bonding interactions have emerged as a powerful alternative to metal catalysis. Among the series of molecular architectures that have proven to be effective as hydrogen-bond donors are urea, thiourea, guanidines, and squaramide-derived catalysts.[6] Hence, many useful transformations and elegant reaction sequences have been developed employing these frameworks.[7,8] Very recently, Franz and Mattson independently introduced a new class of catalyst, namely silanediols, which also operates through hydrogen bonding[9] (Scheme 1).



Scheme 1. Hydrogen-bonding catalysts.

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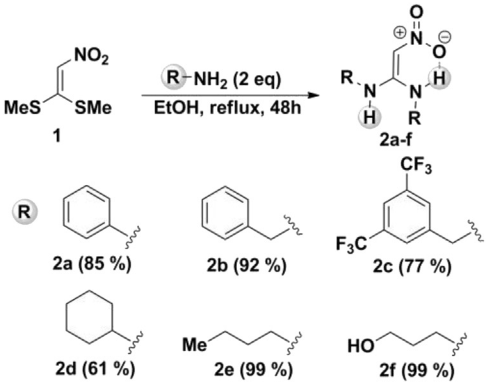
Owing to the success of hydrogen-bonding catalysis, the pursuit of new and efficient catalytic systems, providing excellent yields at low catalyst loading and under mild reaction conditions, still stands as a significant challenge. As part of our ongoing research program toward the development of practical catalytic synthetic methods,[10] herein we disclose the synthesis of a new class of hydrogen-bonding organocatalysts and their catalytic performance in Michael additions of C-based nucleophiles to nitroalkenes. Initially, a series of 1,1-diamino-2-nitroethylene catalysts **2a**–**f** was readily prepared from L,L-bis(methylthio)-2-nitroethene (**1**) and different amines, which are commercially available, inexpensive starting materials, without the need of inert or dry conditions (Scheme 2),[11] hence greatly enhancing the applicability of this new type of organocatalysts.



Scheme 2. General synthesis of organocatalysts **2a**–**f**.

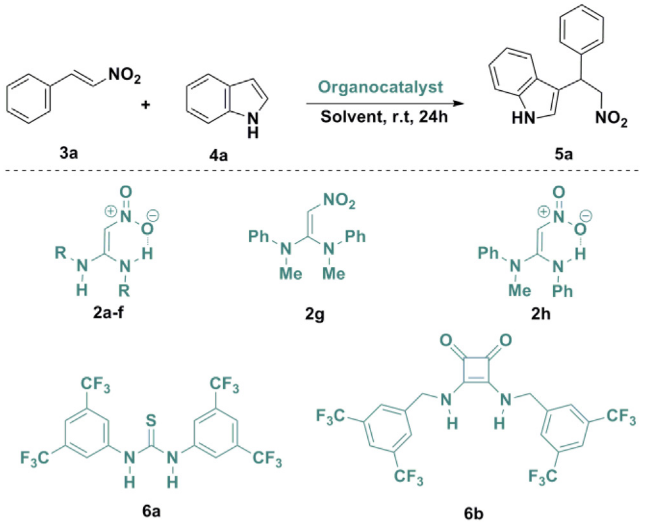
2. Results and discussion

With these novel hydrogen-bond donors in hand, screening studies were initiated to find a proof of concept for their application in hydrogen-bonding catalysis. The addition of indole (**4a**) to *trans*-β-nitrostyrene (**3a**) was chosen as a model reaction for catalyst screening in CH_2Cl_2 at room temperature for 24 h and 10 mol % of catalyst loading. After screening a variety of hydrogen-bond donor catalysts based on the 1,1-diamino-2-nitroethylene core, it was discovered that organocatalyst **2c** showed the best activity, leading to the addition product in 86% yield (entry 3, Table 1). This result clearly indicates that the CF_3 substituent on the aromatic ring is important for the efficient conversion. Unfortunately, a slight erosion in the chemical yield was observed when decreasing the catalyst loading to 5 mol % (entry 7). By comparing our catalytic system with conventional thiourea and squaramide catalysts (**6a**–**b**), the superiority of 1,1-diamino-2-nitroethylene **2c** was manifested, providing higher yield of the desired product, after 24 h using CH_2Cl_2 and toluene, respectively (86% vs 58% and 66%, entries 3 vs 8 and 15).[9d]

For further optimization of the reaction conditions, we turned to address the solvent effect in the catalyst efficacy. From the nonpolar solvents investigated, which are all generally suitable for hydrogen-bonding catalysis, it was found that ethereal solvents like THF had a negative influence on the activity of organocatalyst **2c**, whereas the use of toluene led to an improvement in the reaction yield (entries 9–12).

Finally, the effect of the reaction stoichiometry was examined. When equimolar amounts of indole and nitroalkene were used, the isolated yield dropped from 91% to 81% (entry 12 vs 13). The use of an excess of Michael acceptor (1.5 equiv) had a negative influence on the reaction course, furnishing the desired product in 45% yield (entry 14).

Table 1
Catalytic Michael addition reaction of indole **4a** with *trans*-β-nitrostyrene **3a** in the presence of organocatalysts **2a**–**f** under different reaction conditions[a]



Entry	Catalyst (10 mol %)	Solvent	Yield (%)[b]
1	**2a**	CH_2Cl_2	82
2	**2b**	CH_2Cl_2	79
3	**2c**	CH_2Cl_2	86
4	**2d**	CH_2Cl_2	72
5	**2e**	CH_2Cl_2	79
6	**2f**	CH_2Cl_2	76
7[c]	**2c**	CH_2Cl_2	71
8[d]	**6a**	CH_2Cl_2	58
9	**2c**	Hexane	73
10	**2c**	THF	26
11	**2c**	$CHCl_3$	85
12	**2c**	Toluene	91
13[e]	**2c**	Toluene	81
14[f]	**2c**	Toluene	45
15	**6b**	Toluene	66
16	—	Toluene	11
17	**2g**	Toluene	13
18	**2f**	Toluene	36

[a] Unless otherwise specified, reactions were conducted using: *trans*-β-nitrostyrene **3a** (0.25 mmol), indole **4a** (0.375 mmol) in 0.2 mL of solvent.

[b] Yields of the isolated product.

[c] Reaction was performed using 5 mol % of the catalyst **2c**.

[d] See Ref. 9d.

[e] Reaction was performed using *trans*-β-nitrostyrene **3a** (0.25 mmol), indole **4a** (0.25 mmol) in 0.2 mL of solvent.

[f] Reaction was performed using *trans*-β-nitrostyrene **3a** (0.375 mmol), indole **4a** (0.25 mmol) in 0.2 mL of solvent.

In order to investigate the mode of action with this new class of organocatalyst, the activity of catalysts **2g** and **2h** was examined. As expected, when the di-methylated organocatalyst **2g** was evaluated, no hydrogen-bonding catalysis can take place, as the chemical yield matches the background rate (entries 16 vs 17). On the other hand, organocatalyst **2h**, having a single hydrogen bonding capability, which can also engage in an intramolecular hydrogen bonding,[11b] exhibits catalytic activity, albeit with lower reactivity (entry 18). In order to better investigate the mode of action with nitroethenediamine, we performed an NMR binding study. ^1H and ^{13}C NMR spectra of organocatalyst **2e** and mixtures (1:1 and 1:2) of **2e** with nitroolefin were recorded at ambient temperature in DMSO-d_6 on a 400-MHz liquid NMR spectrometer. We found that the corresponding ^1H NMR spectra of **2e** from a 2:1 mixture of **2e** and nitroolefin showed the appearance of two new peaks with large changes in the chemical shifts for the NH protons. Furthermore, several other signals of the **2e** side chain were split due to its complexation with the nitroolefin (Fig. 1).