Tetrahedron xxx (2013) 1–6

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

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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ARTICLE INFO

Article history:
Received 25 June 2013
Received in revised form 14 August 2013
Accepted 16 August 2013
Available online xxx

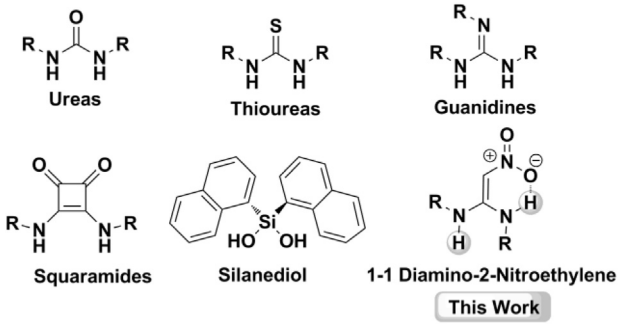
Keywords:
Organocatalysis
Hydrogen-bond donor
Michael addition
1,1-Diamino-2-nitroethylenes
β-Nitrostyrenes

ABSTRACT

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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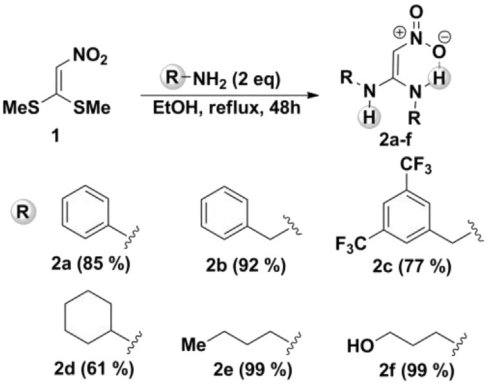
0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.08.040

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**.

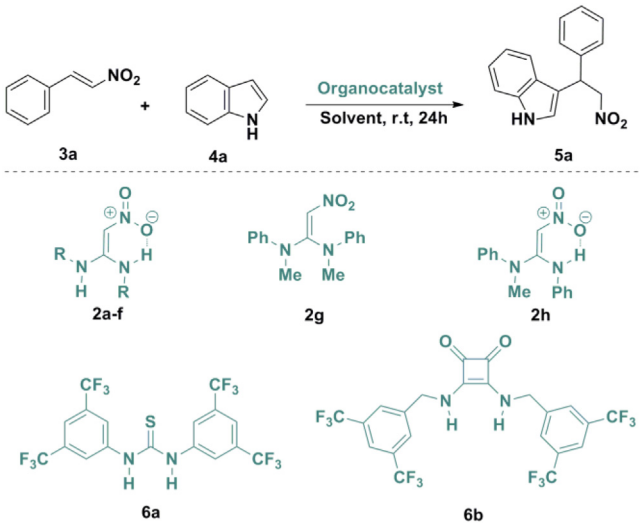
2. Results and discussion

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).

Please cite this article in press as: da Silva, R. C.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.08.040

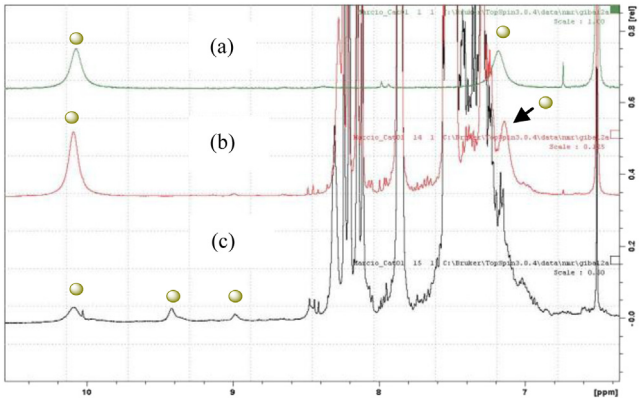


Fig. 1. Expanded region of sections of the ^{1}H NMR spectra in DMSO-d_6. (a) Free catalyst **2e**; (b) mixture of catalyst **2e** and nitroolefin **3a** (1:1); (c) mixture of catalyst **2e** and nitroolefin **3a** (1:2).

The ^{13}C NMR clearly indicates the complex formation in favor of a two hydrogen-bonding contributor, once both methylene carbon atoms next to the nitrogen showed a significant downfield shift over 3 ppm (Fig. 2). Therefore, based on the results obtained using catalysts **2g** and **2h** with the NMR studies our hypothesis is that there are two hydrogen-bonding contributors in the reaction equilibriums. Although, the single hydrogen-bonding interaction cannot be fully excluded, the dual hydrogen-bonding interactions with the substrate seem to be the most effective behavior for this catalytic system (Scheme 3).

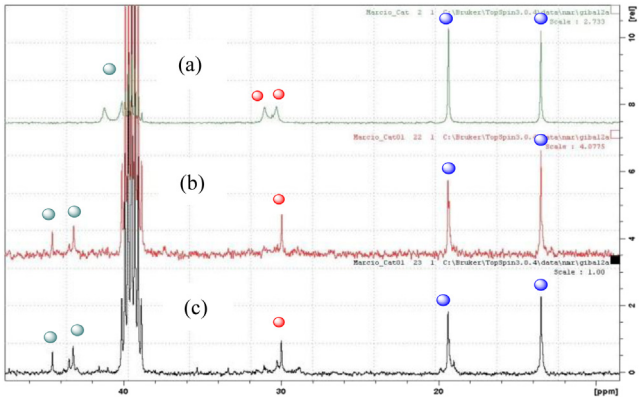
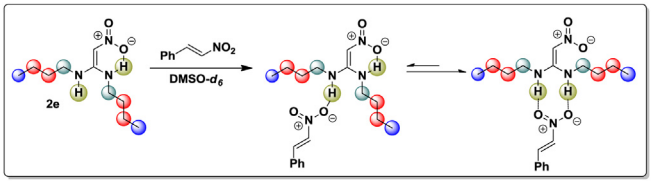


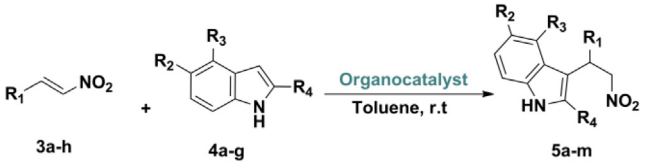
Fig. 2. Expanded region of sections of the ^{13}C NMR spectra in DMSO-d_6. (a) Free catalyst **2e**; (b) mixture of catalyst **2e** and nitroolefin **3a** (1:1); (c) mixture of catalyst **2e** and nitroolefin **3a** (1:2).



Scheme 3. The complex formation in favor of a two hydrogen-bonding contributor.

Having established the optimal conditions, the scope of the Michael addition was explored with a variety of nitroalkenes and indoles in the presence of organocatalyst **2c**. The results shown in Table 2 demonstrate the versatility of this novel class of hydrogen bond donor catalyst for this transformation. A number of nitroalkenes bearing either electron-donating or electron-withdrawing substituents at the aromatic ring were successfully applied in the nucleophilic addition (entries 2–8) with excellent results. However, when 4-bromo-β-nitrostyrene was employed, 48 h of reaction were required to achieve high yield (entry 3). In general, the electronic nature and steric properties of the substituents at the aromatic ring of the Michael acceptor have little effect on the reactivity of this catalytic system (entries 5–8). Taking into account that the indole skeleton is considered a privileged pharmacophore, widely applied in the pharmaceutical chemistry, we then turned our attention to the evaluation of a range of indoles in the presence of this catalytic system. Fortunately, we were able to demonstrate that the described Michael addition is unbiased toward substitution on the indole nucleophiles. Having an electron-donating substituent at the 5-position on the indole ring was well tolerated, furnishing the desired addition products **5h** and **5i** in 99% and 90% yield, respectively (Table 2, entries 9 and 10).

Table 2
Michael addition of indoles (**4a**–**g**) to nitroalkenes (**3a**–**h**) catalyzed by organocatalyst **2c**[a]



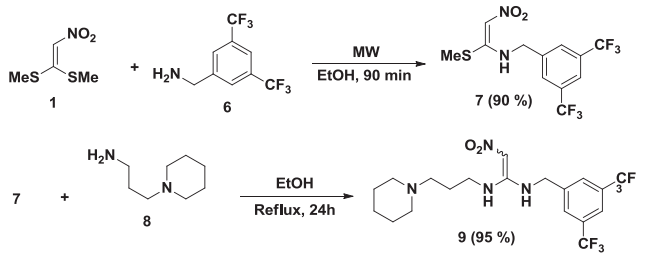
Entry	R_1	$R_2/R_3/R_4$	Product	Yield (%)[b]
1	Ph	H/H/H	**5a**	91
2	4-Br–C_6H_4	H/H/H	**5b**	70
3[c]	4-Br–C_6H_4	H/H/H	**5b**	85
4	4-Cl–C_6H_4	H/H/H	**5c**	91
5	2-Cl–C_6H_4	H/H/H	**5d**	85
6	4-MeO–C_6H_4	H/H/H	**5e**	80
7	3-MeO–C_6H_4	H/H/H	**5f**	73
8	2-MeO–C_6H_4	H/H/H	**5g**	65
9	Ph	OMe/H/H	**5h**	99
10	Ph	Me/H/H	**5i**	90
11	Ph	Br/H/H	**5j**	85
12	Ph	Cl/H/H	**5k**	70
13	Ph	H/H/Me	**5l**	99
14	Pent	OMe/H/H	**5m**	58
15	C_8H_9	H/H/H	**5n**	87

[a] Unless otherwise specified, reactions were conducted using *trans*-β-nitrostyrene **3a**–**h** (0.25 mmol), indole **4a**–**g** (0.375 mmol) in 0.2 mL of solvent.
[b] Yields of the isolated product.
[c] Reaction was conducted for 48 h.

Furthermore, electron-deficient nucleophiles in the context of a 5-halogen (Br and Cl) substituted indole could also be included as reaction partners; however, a slight variation in terms of yield was observed (entries 11 and 12). Such halogenated indole adducts proved to be valuable synthons, as they can be further elaborated using organometallic technologies. Incorporation of an alkyl substituent at the C(2)-indole position reveal that electronic and steric modification of the indole ring can be accomplished with a positive influence on the reaction performance, giving the corresponding addition product in 99% yield (entry 13).

To our delight, the reactions of *trans*-β-nitrostyrene bearing β-alkyl substituents (**5h** and **5i**) afforded the product in good to excellent chemical yield (Table 2, entry 14 and 15). Moreover, the applicability of this new type of hydrogen-bonding scaffold could be successfully extended utilizing a set of different carbon-based nucleophiles. Unfortunately, under the same protocol applied before, the addition of 2-hydroxy-1,4-naphthoquinone (**10a**) to *trans*-β-nitrostyrene (**3a**) completely failed. To circumvent this problem we explored the highly modular nature and easy synthesis of this new class of hydrogen-bond donor to fine-tuning the catalytic activity. Therefore, we

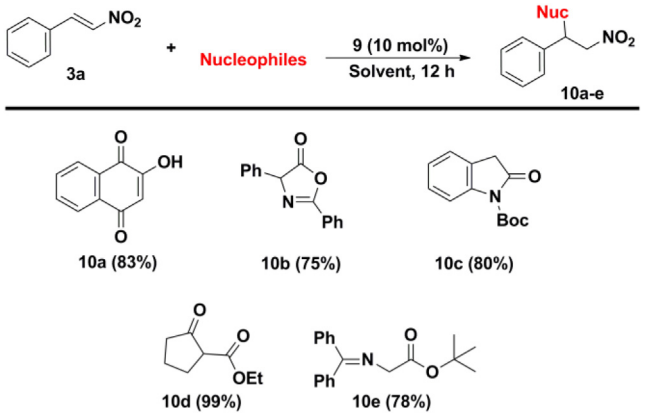
designed and synthesized a novel bifunctional organocatalyst **9** based on the 1,1-diamino-2-nitroethylene core (Scheme 4).[12]



Scheme 4. General synthesis of organocatalyst **9**.

We then applied the bifunctional organocatalyst (**9**) as a promoter in the Michael addition of 2-hydroxy-1,4-naphthoquinone (**10a**) to 1-phenyl-2-nitroethene (**3a**) in toluene as solvent. To our delight the desired product was afforded in excellent yield (83%).[13]

Encouraged by these results and the particular importance of non-natural amino acids,[14] the reactivity of oxazolone **10b** and glycine imine **10e** with hydrogen-bond donor system was also evaluated.[15] The α,α-disubstituted and α-monosubstituted amino acids were obtained in good yields and diastereoselectivities (**10b**: 75% yield, dr=62:38/**10e**: 78% yield, dr=75:25). Furthermore, 1,3-dicarbonyl compounds[16] reacted smoothly with β-nitrostyrene to afford the desired product in quantitative yield with a diastereomeric ratio of 88:22. Despite the usefulness and versatility of oxindoles as building blocks in a number of natural alkaloids and in many pharmaceuticals,[17] the focus was posed on the addition of this nucleophile. Notably, the oxindole **10c** underwent Michael addition in 80% yield and 85:15 dr (Scheme 5).

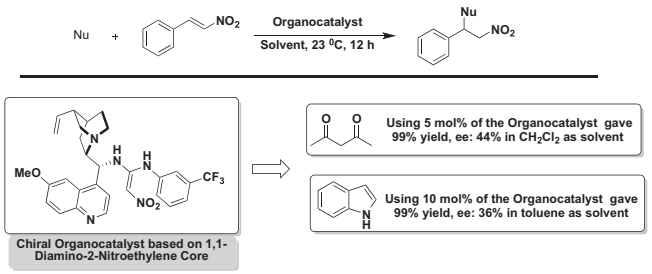


Scheme 5. Addition of a range of C-based nucleophiles to *trans*-β-nitrostyrene (**3a**). Reactions were conducted using *trans*-β-nitrostyrene **3a** (0.25 mmol), carbon-based nucleophile (0.375 mmol), organocatalyst **9** (10 mol %) in toluene (0.2 mL).

Moreover, we turned our attention to the chiral version of this new class of hydrogen bond donor organocatalyst, based on the 1,1-diamino-2-nitroethylene core. Preliminary studies have revealed that cinchona-derived organocatalyst **9b** effectively catalyzed the Michael addition of 2,4-pentanedione and indole (**4a**) to *trans*-β-nitrostyrene (**3a**), giving the desired products in excellent yields and promising enantioselectivities (44% and 36% ee), respectively (Scheme 6).

3. Conclusion

In summary, a novel class of hydrogen bond donor organocatalyst was designed, synthesized, and successfully applied to promoting the addition of several carbon-based nucleophiles to nitroalkenes, under mild reaction conditions. Remarkably, its modular nature and easy synthesis allows the preparation of a wide range of organocatalysts, especially with regard to the chiral environment. Ongoing efforts towards the fine-tuning of this chiral hydrogen bond donor organocatalyst are under evaluation and will be reported in due course.



Scheme 6. Preliminary applications of the chiral organocatalyst, based on the 1,1-diamino-2-nitroethylene core.

4. Experimental section

4.1. General remarks

Reactions were monitored by thin-layer chromatography using UV light to visualize the course of reaction. Purification of products was carried out by flash chromatography on silica gel. Mass spectra and high-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI). Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using deuterated solvents ($CDCl_3$ and DMSO-d_6) in a Bruker Avance III spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, h=heptet, m=multiplet, br=broad. Reagents were purchased from Aldrich Chemical Company and used as received.

*4.1.1. General procedure for the synthesis of organocatalysts **2a–f**.* To a solution of 1,1-bis(methylthio)-2-nitroethylene (1.5 mmol) in ethanol (5 mL) was added the respective amines (3 mmol). The reaction was refluxed for 48 h and then the solvent was removed to give a residue, which was purified by column chromatography on silica gel (60:40 hexane/EtOAc) to provide the organocatalysts **2a–f**. Spectral data of the products prepared are listed below.

*4.1.1.1. 2-Nitro-N,N′-diphenylethene-1,1-diamine (**2a**).* 85% yield; Yellow solid; mp 160–161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.31 (s, 1H); 7.19–7.38 (m, 10H); 10.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 100.5; 124.4; 126.1; 129.3; 136.4; 153.6; HRMS ($C_{14}H_{13}N_3O_2$) $[M+H]^+$: calcd: 256.1086; found: 256.1079.

*4.1.1.2. N,N′-Dibenzyl-2-nitroethene-1,1-diamine (**2b**).* 92% yield; Yellow solid; mp 203–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.35 (s, 2H); 4.62 (s, 2H); 6.40 (s, 1H); 7.20–7.44 (m, 10H); 8.01 (s, 1H); 10.4 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 44.1; 44.3; 97.8; 126.6 (br 2×); 127.3 (br 4×); 128.1; 128.6 (br 3×); 155.8; HRMS ($C_{16}H_{18}N_3O_2$) $[M+H]^+$: calcd: 284.1399; found: 284.1395.

*4.1.1.3. N,N′-Bis(3,5-bis(trifluoromethyl)benzyl)-2-nitroethene-1,1-diamine (**2c**).* 77% yield; Yellow solid; mp 97–99 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.52 (s, 2H); 4.79 (s, 2H); 6.56 (s, 1H); 7.75–8.09 (m, 7H); 10.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 43.0; 43.3; 97.7; 121.1; 121.8; 124.5; 129.8; 130.1; 130.4; 130.8;

141.3; 155.7; HRMS ($C_{20}H_{13}F_{12}N_3O_2$) $[M+H]^+$: calcd: 556.0894; found: 556.0882.

*4.1.1.4. N,N′-Dicyclohexyl-2-nitroethene-1,1-diamine (**2d**).* 61% yield; Yellow solid; mp 197–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06–1.78 (m, 22H); 6.56 (s, 1H); 6.67 (s, 1H); 10.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.6 (br); 24.4; 24.9; 31.9; 32.4; 97.2; 153.5; HRMS ($C_{14}H_{25}N_3O_2$) $[M+H]^+$: calcd: 268.2025; found: 268.2026.

*4.1.1.5. N,N′-Dibutyl-2-nitroethene-1,1-diamine (**2e**).* 99% yield; Yellow solid; mp 80–82 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, J=7.4 Hz, 6H); 1.31 (sext, J=7.4 Hz, 4H); 1.31–1.48 (m, 8H); 3.08–3.20 (m, 4H); 6.49 (s, 1H); 7.14 (s, 1H); 10.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.5; 19.3.7; 30.2; 31.0; 41.2; 96.9; 155.5; HRMS ($C_{10}H_{22}N_3O_2$) $[M+H]^+$: calcd: 216.1712; found: 216.1707.

*4.1.1.6. 5,5′-((2-Nitroethene-1,1-diyl)bis(azanediyl))bis(pentan-1-ol) (**2f**).* 99% yield; Brown liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31–1.50 (m, 16H); 3.07–3.19 (m, 2H); 6.49 (s, 1H); 7.15 (s, 1H); 10.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.7; 28.1; 28.8; 32.0; 40.4; 41.5; 97.0; 155.4; HRMS ($C_{12}H_{26}N_3O_4$) $[M+H]^+$: calcd: 276.1923; found: 276.1918.

*4.1.2. General procedure for the synthesis of compound **7**.* To a solution of 1,1-bis(methylthio)-2-nitroethylene (**1**) (1.5 mmol) in ethanol (3 mL) was added 3,5-bis(trifluoromethyl)benzylamine (**6**) (1.5 mmol) and irradiated during 90 min in a CEM Discovery® focused microwave oven at 110 °C and 70 W. Then the solvent was removed to give a residue, which was further purified using column chromatography on silica gel (75:25 hexane/EtOAc).[2]

*4.1.2.1. (E)-N-(3,5-Bis(trifluoromethyl)benzyl)-1-(methylthio)-2-nitroethenamine (**7**).* 91% yield; Yellow solid; Mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H); 4.78 (d, J=6.45 Hz, 2H); 6.62 (s, 1H); 7.77 (s, 2H); 7.86 (s, 1H); 10.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5; 47.1; 107.5; 121.6; 122.2; 122.3; 122.4; 124.3; 127.4; 131.9; 132.2; 132.6; 132.9; 138.6; 164.5; HRMS ($C_{12}H_{11}F_6N_2O_2$) $[M+H]^+$: calcd: 360.0367; found: 360.0398.

*4.1.3. General procedure for the synthesis of organocatalysts **9**.* A 25 mL round-bottomed flask was charged with EtOH (3 mL), and compounds **7** (1 mmol) and **8** (1 mmol, 0.159 mL) at reflux for 24 h. After this time, the solvent was removed to give a residue, which was further purified using column chromatography on silica gel (75:25 EtOAc/MeOH).

*4.1.3.1. (E)-N-(3,5-Bis(trifluoromethyl)benzyl)-2-nitro-N-(3 (piperidinyl)propyl)ethene-1,1-diamine (**9**).* 99% yield; Mp 51–52 °C; dr=8:2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 6H); 1.89 (m, 2H); 2.44 (m, 6H); 3.49 (m, 2H); 4.49 (s, 2H); 6.39 (s, 1H); 7.69 (m, 3H); 9.22 (s, 1H); 10.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4; 24.8; 25.0; 39.4 (br); 43.7 (br); 53.7; 55.1; 98.1; 119.1; 120.9; 121.0; 121.1; 121.8; 124.5; 127.1 (br); 127.2; 131.1; 131.4; 131.8; 132.1; 156.4; HRMS ($C_{19}H_{25}F_6N_4O_2$) $[M+H]^+$: calcd: 455.1882; found: 455.1881. The NMR data were described to major diastereomer.

*4.1.4. General procedure for the synthesis of compound **2g** and **2h**.* To a solution of compound **2a** (0.2 mmol) in acetone (3 mL) was added K_2CO_3 (1 mmol) and iodomethane (for synthesis of compound **2g** was used 1 mmol and for **2h** was used 0.2 mmol). After stirring for 12 h, the reaction mixture was concentrated, and the residue was purified using column chromatography on silica gel (85:15 hexane/EtOAc) to afford the product **2g** and **2h**.

*4.1.4.1. N,N′-Dimethyl-2-nitro-N,N′-diphenylethene-1,1-diamine (**2g**).* 44% yield; Yellow solid; mp 56–57 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.27 (s, 6H); 6.78 (s, 1H); 6.85–7.38 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 54.3; 100.9; 120.9; 124.9; 126.2; 128.8; 144.2; 147.0; 149.3; HRMS ($C_{16}H_{17}N_3O_2$) $[M+H]^+$: calcd: 284.1399; found: 284.1403.

*4.1.4.2. N-Methyl-2-nitro-N,N′-diphenylethene-1,1-diamine (**2h**).* 11% yield; Yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.80 (s, 3H); 6.83 (s, 2H); 6.87–7.02 (m, 6H); 7.25–7.75 (m, 5H); 9.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 54.5; 106.9; 119.3; 121.2; 122.5; 122.8; 128.6; 128.8; 139.8; 143.7; 148.8; HRMS ($C_{15}H_{15}N_3O_2$) $[M+H]^+$: calcd: 270.1164; found: 270.1184.

4.1.5. General procedure for diamino-2-nitroethylene catalyzed nucleophilic addition to nitrostyrene. To a vial containing a magnetic stir bar was added nitrostyrene (0.25 mmol), nucleophile (0.375 mmol), the catalyst (0.025 mmol), and the solvent (0.2 mL). After confirming the disappearance of starting material by TLC analysis, the reaction mixture was straight purified by flash chromatography on silica gel using hexane/ethyl acetate to afford the product. All spectral data match with those previously reported (see Supplementary data).

*4.1.5.1. General procedure for the synthesis of (E)-N-(1-(methylthio)-2-nitrovinyl)-3(trifluoromethyl)aniline was the same reported for the preparation of compound **7**.* 51% yield; Yellow solid; mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H); 6.71 (s, 1H); 7.60–7.63 (m, 4H); 11.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7; 108.6; 123.0; 124.7; 129.2; 130.1; 131.8; 132.2; 136.8; 162.6; HRMS ($C_{10}H_{10}F_3N_2O_2S$) $[M+H]^+$: calcd: 279.0415; found: 279.0428.

4.1.6. General procedure for the synthesis of chiral organocatalysts. To a solution of (*E*)-*N*-(1-(methylthio)-2-nitrovinyl)-3 (trifluoromethyl) aniline (0.36 mmol) in ethanol (8 mL) was added the respective 9-amino-9-deoxyquinine (0.36 mmol). The reaction was refluxed for 12 h and then the solvent was removed to give a residue, which was purified by column chromatography on silica gel (95:5 EtOAc/MeOH) to provide the organocatalysts in 75% yield; Yellow solid; mp 188–189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.99–0.81 (m, 1H); 1.27 (m, 4H); 1.65 (m, 3H); 2.38 (m, 2H); 2.85 (m, 1H); 3.90 (s, 3H); 5.15–4.88 (m, 2H); 5.92–5.72 (m, 1H); 6.12 (s, 1H); 7.77–7.08 (m, 9H); 7.99 (d, J=9.2 Hz, 1H); 8.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ 24.9; 26.1; 26.6; 38.2; 40.5; 54.0; 55.5; 77.1; 100.9; 102.0; 114.8; 121.6; 122.1; 126.3; 131.5; 140.9; 144.1; 147.5; 153.8; 157.5; HRMS ($C_{29}H_{31}F_3N_5O_3$) $[M+H]^+$: calcd: 554.2379; found: 554.2409.

Acknowledgements

The authors gratefully acknowledge FAPESP (09/07281-0) and CNPq (INCT-Catálise and INBEQMeDI) for financial support. R.C.S., and D.P.S. thanks FAPESP, while J.G.P.M. cordially acknowledge CNPq for their fellowships.

Supplementary data

Copies of ^{1}H NMR, ^{13}C NMR spectra of all unknown compounds are available as Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.040.

References and notes

1. (a) Lópes-Marques, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138; (b) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605; (c) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825.
2. For recent reviews on organocatalysis, see: (a) List, B. *Chem. Rev.* **2007**, *107*, 5413 (special issue on organocatalysis); (b) Dondoni, A.; Massi, A. *Angew. Chem., Int.*

Ed. **2008**, *47*, 4638; (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138; (e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167; (f) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243; (g) Albrecht, Ł.; Jiang, H.; Jųrgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.

3. (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; (b) Tsogoev, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (c) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058.
4. For selected examples on the organocatalytic conjugated addition to nitrostyrenes, see: (a) Herrera, R. P.; Sgarzani, V.; Bernadi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576; (b) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *131*, 16464; (c) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758; (d) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9*, 52; (e) Lin, J.; Tian, H.; Jiang, Y. J.; Huang, W. B.; Zheng, L. Y.; Zhang, S. Q. *Tetrahedron: Asymmetry* **2011**, *22*, 1434; (f) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.
5. Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, NY, 2001, p 392.
6. (a) Yamamoto, H.; Cheon, C. ,H. *Chem. Commun.* **2011**, 3043; (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890; (c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330; (d) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187; (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156; (f) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, 2209; (g) Rueping, D.; Nachtsheim, B. J.; Leawsuwan, W.; Iuliana Atodiresei, L. *Angew. Chem., Int. Ed.* **2008**, *50*, 6706.
7. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (b) Liu, Y. L.; Shi, T. D.; Zhou, F.; Zhao, X. L.; Wang, X.; Zhou, J. *Org. Lett.* **2011**, *13*, 3826; (c) Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J. H.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal.* **2011**, *353*, 3196; (d) Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 2976; (e) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620; (f) Kimmel, K. L.; Weaver, J. D.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 121.
8. (a) Isobe, T.; Fukuda, K.; Ishikawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1729; (b) Kitani, Y.; Kumamoto, T.; Isobe, T.; Fukuda, K.; Ishikawa, T. *Adv. Synth. Catal.* **2005**, *347*, 1653; (c) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1558; (d) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, *73*, 133; (e) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228; (f) Zhang, G.; Kumamoto, T.; Heima, T.; Ishikawa, T. *Tetrahedron Lett.* **2010**, *51*, 3927; (g) So, S. S.; Burkett, J. A.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 716; (h) Terada, M.; Ando, K. *Org. Lett.* **2011**, *13*, 2026; (i) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062; (j) So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444.
9. (a) Liu, M.; Tran, N. T.; Franz, A. K.; Lee, J. K. *J. Org. Chem.* **2011**, *76*, 7186; (b) Schafer, A. G.; Wieting, J. M.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 5228; (c) Tran, T. N.; Min, T.; Franz, A. K. *Chem.—Eur. J.* **2011**, *17*, 9897; (d) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Org. Lett.* **2012**, *14*, 186.
10. (a) Paixão, M. W.; Godoi, M.; Rhoden, C. R. B.; Westermann, B.; Wessjohann, L. A.; Lüdtke, D. S.; Braga, A. L. *J. Mol. Catal. A Chem.* **2007**, *261*, 120; (b) Schwab, R. S.; Galetto, F. Z.; Azeredo, J. B.; Braga, A.; Lüdtke, D. S.; Paixão, M. W. *Tetrahedron Lett.* **2008**, *49*, 5094; (c) Paixão, M. W.; Braga, A. L.; Lüdtke, D. S. *J. Braz. Chem. Soc.* **2008**, *19*, 813; (d) Godoi, M.; Paixão, M. W.; Braga, A. L. *Dalton Trans.* **2011**, *40*, 11347.
11. (a) He, H.; Liu, M.; Zheng, Z.; Liu, Y.; Xiao, J.; Su, R.; Hu, C.; Li, J.; Li, S. *Molecules* **2006**, *11*, 393; (b) Manley, P. W.; Quast, U. *J. Med. Chem.* **1992**, *35*, 2327.
12. For reviews on bifunctional catalysis, see: (a) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117; (b) Breslow, R. *J. Mol. Catal.* **1994**, *91*, 161; (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187; (d) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566; (e) Sangi, D. P.; Corrêa, A. G. *J. Braz. Chem. Soc.* **2010**, *21*, 795.
13. Yang, W.; Du, D. M. *Adv. Synth. Catal.* **2011**, *353*, 1241.
14. Martinek, T. A.; Fülöp, F. *Chem. Soc. Rev.* **2012**, *41*, 687.
15. For a selected examples on the application of these carbon base nucleophiles see: (a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031; (b) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 10958; (c) Alba, A. N. R.; Valero, G.; Calbet, T.; Bardía, M. F.; Moyano, A.; Rios, R. *Chem.—Eur. J.* **2010**, *16*, 9884; (d) Alba, A. N. R.; Rio, R. *Asian J. Chem.* **2011**, *6*, 720; (e) Kano, T.; Kumano, T.; Maruoka, K. *Org. Lett.* **2009**, *11*, 2023; (f) Wang, Y.-G.; Kumano, T.; Kano, T.; Maruoka, K. *Org. Lett.* **2009**, *11*, 2027.
16. Jiang, H.; Paixão, M. ,W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775.
17. (a) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2009**, *32*, 7846; (b) Liu, X.; Li, Y.-M.; Peng, F.-Z.; Wu, S.-T.; Li, Z.-O.; Sun, Z.-W.; Zang, H.-B.; Shao, Z.-H. *Org. Lett.* **2011**, *13*, 6160; (c) Tan, B.; Torres-Hernández, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354; (d) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473.

Please cite this article in press as: da Silva, R. C.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.08.040