Asymmetric conjugate addition of bromonitromethane to cyclic enones catalyzed by chiral monosulfonated diamines

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Abstract

A series of chiral monosulfonated diamines were prepared and used as the catalysts for asymmetric conjugate addition of bromonitromethane to α,β-unsaturated ketones. The reaction provided nitrocyclopropanes in the presence of appropriate acid and base additives. 1,3,5-Triisopropylbenzenesulfonated 1,2-diphenylethane-1,2-diamine was found to be the best catalyst. The reaction of cyclohex-2-enone and cyclohept-2-enone gave the nitrocyclopropanes in excellent enantioselectivities and yields. Moderate enantioselectivities were obtained for cyclopent-2-enone. The hydrogen-bonding interaction between N-H bonds of sulfonamides and bromonitromethane is suggested to be important for the catalytic activity and enantioselectivity.

Keywords: Asymmetric conjugate addition, organocatalysis, bromonitromethane, α,β-unsaturated ketone, nitrocyclopropane

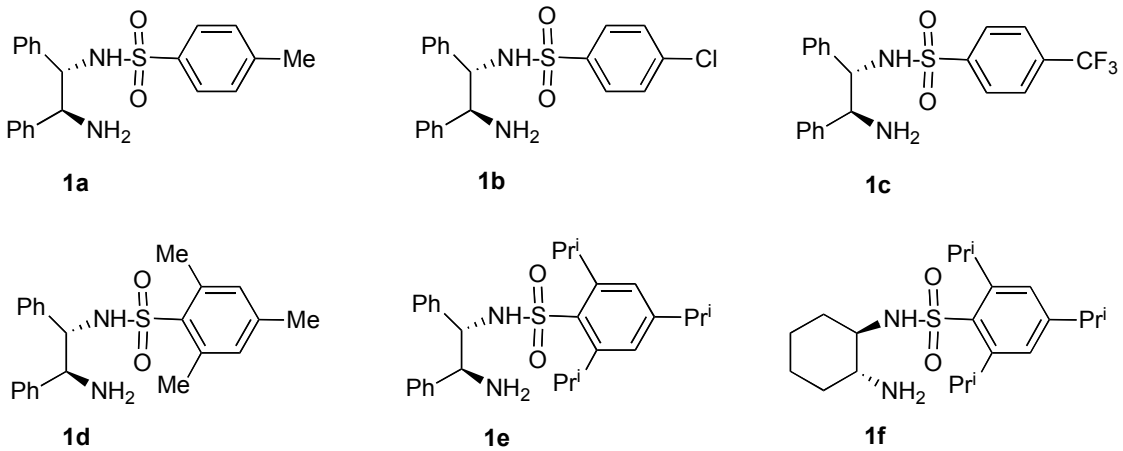
Introduction

In the past decade, significant progress has been achieved in asymmetric reactions catalyzed by chiral small organic molecules.[1] Among a large number of organocatalysts developed so far, chiral bifunctional catalysts combining hydrogen-bond donors and amines are extremely efficient for many asymmetric transformations.[2] Thioureas, ureas, guanidiums and trifluoromethanesulfonamides have been the most used hydrogen-bond donators. Recently we found that sulfamides are also efficient hydrogen-bond donors.[3] In a study of the effect of hydrogen-bond donors on the catalytic activity and enantioselectivity of bifunctional primary amine catalysts, we noticed that the catalytic activity is not proportional to the N-H acidity or generally related with the hydrogen-bonding interaction modes. Monosulfonated cyclohexane-1,2-diamine, which possesses a weakly acidic N-H bond, is able to provide efficient

hydrogen-bonding interaction for the conjugate addition of carbonyl compounds to nitroalkenes.[4] Chiral sulfonamides were also reported to be efficient catalysts for several other reactions.[5] Very recently, we found that thiourea-amines derived from 1,2-diphenylethanediamine are highly efficient catalysts for the conjugate addition of bromonitromethane to cyclic enones.[6,7] The reaction provided valuable nitrocyclopropanes in excellent yields and enantioselectivities. A bifunctional catalytic mechanism was suggested. As an interesting comparison, a series of monosulfonated 1,2-diphenylethanediamines was prepared and examined as the catalysts for this reaction.[8] The results are reported in this paper.

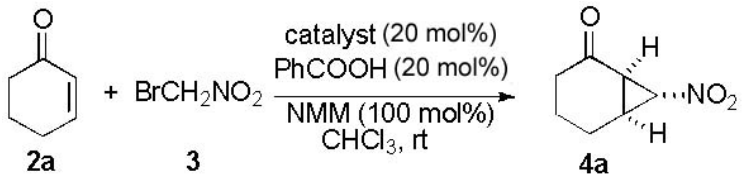
Results and Discussion

Chiral monosulfonated diamines **1a** - **1f** were prepared (Scheme 1) and examined as the catalysts for the reaction of cyclohex-2-enone **2a** and bromonitromethane **3**. The results are summarized in Table 1. The nitrocyclopropane **4a** was obtained in the presence of benzoic acid and *N*-methylmorpholine (NMM). *p*-Toluenesulfonated 1,2-diphenylethane-1,2-diamine **1a** provided **4a** in good yield and enantioselectivity (Table 1, entry 1). *p*-Chlorobenzenesulfonated 1,2-diphenylethane-1,2-diamine **1b** gave a similar yield and enantioselectivity (Table 1, entry 2). The introduction of a strongly electron-withdrawing trifluoromethyl group **1c** resulted in **a** better yield and enantioselectivity (Table 1, entry 3). The use of the sterically demanding 1,3,5-trimethylbenzenesulfonyl group **1d** also improved the enantioselectivity (Table 1, entry 4). Further increase of the volume of the sulfonyl group led to catalyst **1e**, which provided **4a** in excellent yield and enantioselectivity (Table 1, entry 5). For comparison, 1,3,5-triisopropylbenzenesulfonated cyclohexane-1,2-diamine (**1f**) was prepared and examined in the reaction. Only low enantioselectivity was obtained. The result implies that the structure of the 1,2-diamine influences the enantioselectivity significantly.



Scheme 1

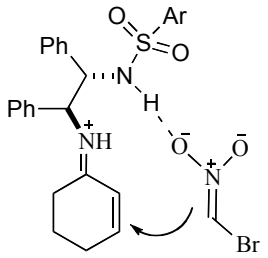
Table 1. The reaction of cyclohex-2-enone **2a** and bromonitromethane **3** catalyzed by **1a-1f**[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	Ee (%)[c,d]
1	**1a**	16	83	84
2	**1b**	16	85	84
3	**1c**	16	86	90
4	**1d**	16	85	90
5	**1e**	18	96	92
6	**1f**	28	80	-55

[a] Reaction conditions: **2a** (0.3 mmol), **3** (0.25 mmol), **1a-1f** (0.05 mmol), PhCOOH (0.05 mmol) and NMM (0.25 mmol) in $CHCl_3$ (0.5 mL); [b] Isolated yields; [c] Determined by chiral HPLC analysis ; [d] The absolute configuration of the product was determined to be (1*R*,6*S*,7*R*) for the catalysts **1a-1e**, and (1*S*, 6*R*,7*S*) for **1f** by comparing the optical rotations with the reported values.[7b,7c]

Although the exact catalytic mechanism is not clear at the present, the hydrogen-bonding interaction between weakly acidic N-H bonds of sulfonamides and 1-bromonitromethane is suggested to be important for the catalytic activity and enantioselectivity (Scheme 2).[6]

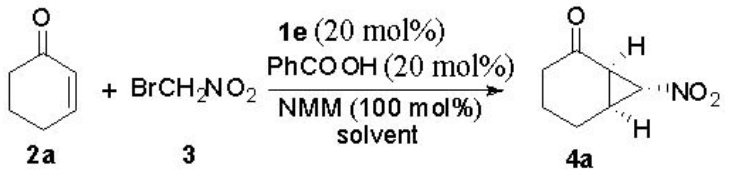


Scheme 2

A number of reaction solvents was screened using **1e** as the catalyst and the results are summarized in Table 2. Less polar solvents, such as CH_2Cl_2, toluene, Et_2O and THF provided **4a** in good yields and enantioselectivities (Table 2, entries 1-6). A mixed solvent, toluene/CH_2Cl_2 (*V*/*V* = 7/3), was identified as the best solvent in terms of enantioselectivity and yield (Table 2, entry 4). Wang and co-workers firstly used this solvent in the same reaction catalyzed by 9-amino-9-deoxyepiquinine and observed the enhanced effects.[7c] Polar solvents seemed to be detrimental to the reaction. Lower enantioselectivity and yield were observed in MeOH (Table 2,

entry 7). No reaction occurred in DMSO (Table 2, entry 8). The reaction in water gave almost racemic **4a** in low yield (Table 2, entry 9). The less efficient hydrogen-bonding interactions were expected in these polar solvents.

Table 2. The effect of reaction solvents[a]

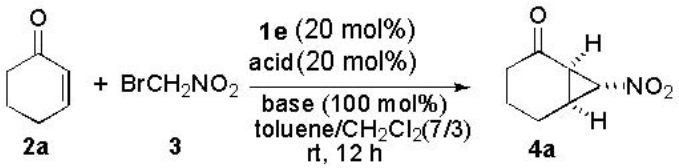


Entry	Solvent	Time (h)	Yield (%)	Ee (%)
1	$CHCl_3$	18	96	92
2	CH_2Cl_2	12	87	90
3	Toluene	16	85	95
4	Toluene/CH_2Cl_2 (V/V = 7/3)	12	90	95
5	THF	12	85	94
6	Et_2O	12	87	92
7	MeOH	16	70	66
8	DMSO	-	-	-
9	H_2O	12	34	4

[a] Reaction conditions: **2a** (0.3 mmol), **3** (0.25 mmol), **1e** (0.05 mmol), PhCOOH (0.05 mmol) and NMM (0.25 mmol) in solvent (0.5 mL) at room temperature.

The effect of acid and base additives on the reaction was studied and the results are summarized in Table 3. The product **4a** was obtained in low yield in the absence of acid additives (Table 3, entry 1). Acetic acid, trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (*p*-TSA) and benzoic acid accelerated the reaction (Table 3, entries 2-5). Benzoic acid was identified as the best acid additive in terms of both enantioselectivity and yield. On the other hand, base additives were also important for the reaction. No product was observed in the absence of base additive (Table 3, entry 6). Et_3N, DABCO, DMAP and morpholine gave **4a** in low yields (Table 3, entries 7-10). Imidazole and pyridine provided better yields (Table 3, entries 11-12). NMM was the most efficient base additive. Good yield and excellent enantioselectivity were achieved (Table 3, entry 5).

Table 3. The effect of the acid and base additives[a]

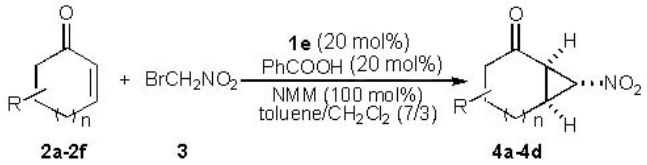


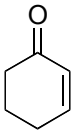
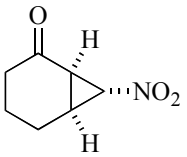
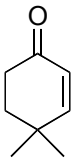
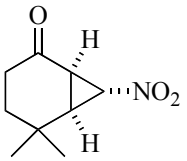
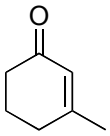
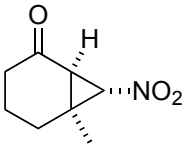
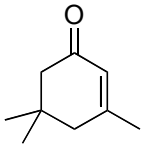
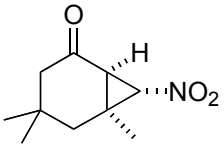
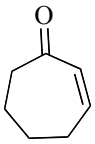
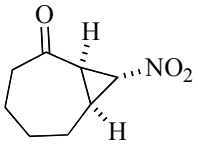
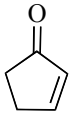
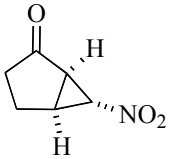
Entry	Acid	Base	Yield (%)	Ee (%)
1	-	NMM	60	90
2	AcOH	NMM	82	95
3	TFA	NMM	85	91
4	*p*-TSA	NMM	70	91
5	PhCOOH	NMM	90	95
6	PhCOOH	-	0	-
7	PhCOOH	Et_3N	39	59
8	PhCOOH	DABCO	28	92
9	PhCOOH	DMAP	39	84
10	PhCOOH	Morpholine	54	60
11	PhCOOH	Imidazole	70	93
12	PhCOOH	Pyridine	72	90

[a] Reaction conditions: **2a** (0.3 mmol), **3** (0.25 mmol), **1e** (0.05 mmol), acid additive (0.05 mmol) and base additive (0.25 mmol) in toluene/Et_2O (7/3) (0.5 mL) at room temperature for 12 h.

A number of cyclic enones were examined and the results are summarized in Table 4. Excellent enantioselectivities and yields were obtained for cyclohex-2-enone, 4,4-dimethyl-cyclohex-2-enone, and 3-methyl-cyclohex-2-enone (Table 4, entries 1-3). However 5,5,3-trimethyl-cyclohex-2-enone was unreactive, probably due to its substantial steric hindrance (Table 4, entry 4). Excellent enantioselectivity was also obtained for cyclohept-2-enone (Table 4, entry 5), however only moderate enantioselectivity was achieved for cyclopent-2-enone (Table 4, entry 6). Acyclic enones, such as chalcone and benzylideneacetone, did not react with 1-bromonitromethane under the present reaction conditions.

Table 4. Reaction of 1-bromonitromethane with cyclic enones catalyzed by **1e**[a]



Entry	Enone	Product	Time (h)	Yield (%)[b]	Ee (%)[c]
1	 **2a**	 **4a**	12	90	95
2	 **2b**	 **4b**	12	95	94
3	 **2c**	 **4c**	20	90	94
4	 **2d**	 **4d**	36	-	-
5	 **2e**	 **4e**	36	87	96
6	 **2f**	 **4f**	36	70	63

[a] Reaction conditions: **2a-2f** (0.3 mmol), **3** (0.25 mmol), **1e** (0.05 mmol), PhCOOH (0.05 mmol) and NMM (0.25 mmol) in toluene/CH_2Cl_2 (7/3) (0.5 mL) at room temperature; [b] Isolated yields; [c] Determined by chiral HPLC analysis.

Conclusions

In conclusion we have found that readily available monosulfonated diamines are efficient catalysts for the conjugate addition of bromonitromethane to cyclic enones. Excellent enantioselectivities and yields were achieved for cyclohex-2-enone and cyclohept-2-enone. Moderate enantioselectivities were obtained for cyclopent-2-enone. The results suggest that even weakly acidic N-H bonds of sulfonamides are also available for the bifunctional organocatalysis involving hydrogen-bonding interactions.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane (δ = 0). Chemical shifts of carbon are referenced to the carbon resonances of the solvent ($CHCl_3$: δ = 77.0). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Optical rotations were measured on a Perkin-Elmer digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The mass spectroscopic data were obtained at the Thermo DSQII mass spectrometer. Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AD-H, OD-H, column and eluting with a *n*-hexane/*i*-PrOH solution. Flash chromatography was performed over silica gel (230-400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Commercial reagents were used as received.

Typical procedure for the conjugate addition of bromonitromethane to cyclic enones
Catalyst **1e** (24 mg, 0.05 mmol), PhCOOH (6 mg, 0.05 mmol) and cyclohex-2-enone **2a** (29 mg, 0.3 mmol) were dissolved in toluene/CH_2Cl_2 (*V*/*V* = 7/3, 0.5 mL). The solution was stirred at room temperature for 15 minutes. Then NMM (25 mg, 0.25 mmol) and bromonitromethane **3** (35 mg, 0.25 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. The reaction solution was diluted with CH_2Cl_2 (5 mL) and washed with aqueous saturated $NaHCO_3$ (3 mL). The organic layer was separated and dried over anhydrous sodium sulfate. After the solvent was evaporated under vacuum, the residue was purified by flash column chromatography over silica gel (EtOAc/petroleum ether) to provide nitrocyclopropane **4a** as a white solid.

(1*R*,6*S*,7*R*)-7-Nitro-bicyclo[4.1.0]heptan-2-one (4a). White solid (90% yield), $[\alpha]_{20}^{589}$ = - 56.0 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67 (t, *J* = 2.8 Hz, 1H), 2.83 (dd, *J* = 9.6, 2.7 Hz,

1H), 2.70-2.65 (m, 1H), 2.38-2.31 (m, 1H), 2.21-2.12 (m, 2H), 2.04-1.95 (m, 1H), 1.91-1.83 (m, 1H), 1.60-1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 60.5, 37.2, 35.2, 26.8, 19.6, 18.2; MS (EI): 155 (M^+). The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 95/5, λ = 208 nm, 0.8 mL/min); t_R (major) = 22.7 min, t_R (minor) = 25.2 min, 95% ee.

(1*R*,6*S*,7*R*)-7-Nitro-5,5-dimethyl-bicyclo [4.1.0]heptan-2-one (4b). White solid (95% yield), $[\alpha]_{20}^{589}$ = -87.4 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.66 (t, *J* = 3.2 Hz, 1H), 2.85 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.44-2.40 (m, 1H), 2.30- 2.27 (m, 2H), 1.57-1.41 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 60.1, 38.2, 36.1, 33.3, 30.8, 29.1, 27.9, 26.2; MS (EI): 183 (M^+). The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 98/2, λ = 208 nm, 0.8 mL/min); t_R (minor) = 20.2 min, t_R (major) = 22.7 min, 94% ee.

(1*R*,6*S*,7*R*)-7-Nitro-6-methyl-bicyclo[4.1.0]heptan-2-one (4c). Colorless oil (90% yield), $[\alpha]_{20}^{589}$ = +44.0 (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (d, *J* = 3.2 Hz, 1H), 2.89 (d, *J* = 3.6 Hz, 1H), 2.40-2.34 (m, 1H), 2.25-2.19 (m, 1H), 2.13-2.04 (m, 1H), 1.91-1.80 (m, 2H), 1.60-1.50 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 65.4, 40.4, 36.4, 32.6, 28.4, 17.5, 17.4; MS (EI): 169 (M^+). The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 95/5, λ = 208 nm, 0.8 mL/min); t_R (major) = 14.2 min, t_R (minor) = 17.1 min, 94% ee.

(1*R*,7*S*,8*R*)-8-Nitro-bicyclo[5.1.0]octan-2-one (4e). Colorless oil (87% yield), $[\alpha]_{20}^{589}$ = -24.9 (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63 (t, *J* = 3.6 Hz, 1H), 3.12 (dd, *J* = 12.0, 3.6 Hz, 1H), 2.65-2.58 (m, 1H), 2.46-2.38 (m, 2H), 2.23-2.16 (m, 1H), 1.73-1.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 62.9, 43.1, 39.9, 27.3, 26.9, 25.6, 24.4; MS (EI): 169 (M^+). The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 98/2, λ = 208 nm, 0.8 mL/min); t_R (major) = 19.9 min, t_R (minor) = 21.2 min, 96% ee.

(1*R*,5*S*,6*R*)-6-Nitro-bicyclo[3.1.0]hexan-2-one (4f). Light yellow solid (70% yield), $[\alpha]_{20}^{589}$ = +11.2 (c 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (t, *J* = 2.0 Hz, 1H), 3.01-2.97 (m, 1H), 2.82 (d, *J* = 6.8 Hz, 1H), 2.41-2.20 (m, 3H), 2.02-1.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl3): δ 207.6, 61.8, 37.5, 32.4, 30.8, 22.0; MS (EI): 141 (M^+). The enantiomeric excess was determined by HPLC with an AD-H column (*n*-hexane/*i*-PrOH = 95/5, λ = 208 nm, 0.7 mL/min); t_R (major) = 29.8 min, t_R (minor) = 31.1 min, 63% ee.

Acknowledgments

We thank National Natural Science Foundation of China (No. 20772160, 20972195), Zhuhai Bureau of Science and Technology for the financial support of this study.

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