Highly enantioselective conjugate addition of aldehydes to nitroolefins catalyzed by chiral bifunctional sulfamides†

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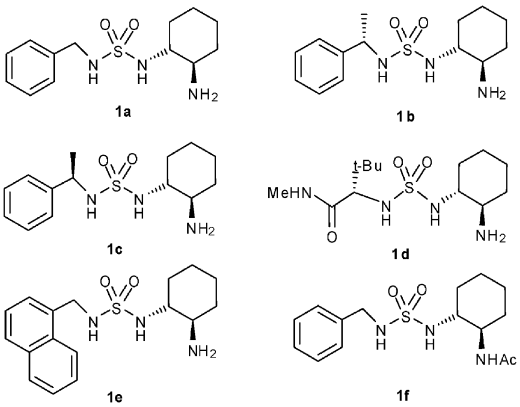
Chiral bifunctional sulfamides were found to be highly efficient organocatalysts for the conjugate addition of aldehydes to nitroolefins in the presence of base additives.

Recently electrophile activation by chiral hydrogen-bond donors has emerged as an important tool for enantioselective synthesis.[1] Ureas, thioureas, guanidiniums and amidinium ions, which are capable of simultaneously donating two hydrogen bonds, are proved to be the privileged catalaphores. In addition, the compatibility of these hydrogen-bond donators with a range of Brønsted bases or Lewis bases allows the development of bifunctional systems, which provide new opportunities for simultaneous activation of both the electrophile and the nucleophile.[1–3] In general, the hydrogen-bond donating ability of (thio)urea catalysts is proportional to the acidity of N–H bonds.[1] For the most successful (thio)urea catalysts, strongly electron-withdrawing groups, such as 3,5-ditrifluoromethylaryl and trifluoromethanesulfonyl, are preferred to enhance the acidity of N–H bonds. The sulfamides are structural relatives of (thio)ureas and can provide two hydrogen bonds to electrophiles (double hydrogen-bonding interactions). The higher electron-withdrawing ability of the sulfonyl group results in the stronger acidity of N–H bonds than the corresponding (thio)ureas.[4] The self-assembly of sulfamides through hydrogen-bonding has been reported.[5] However, to the best of our knowledge, application of sulfamides as double hydrogen-bonding donators in organocatalysis has not been explored. Herein we report the synthesis of chiral sulfamide–primary amine bifunctional catalysts and their application in asymmetric conjugate addition of aldehydes to nitroolefins.

Sulfamides **1a–1e** were prepared *via* stepwise reaction of the corresponding amines and (1*R*,2*R*)-cyclohexane-1,2-diamine with catechol sulfate (Scheme 1).[6,7] For a comparative study of the function of the primary amino group in the catalytic reaction, **1f** was also prepared.

The asymmetric conjugate addition of ketones or aldehydes to nitroolefins is a highly useful reaction to prepare chiral γ-amino acids and related derivatives. A variety of chiral secondary amines and bifunctional thio(urea)–primary amines were used as the catalysts in the transformation.[8,9] Chiral sulfamides **1a–1f** were examined in the conjugate addition of

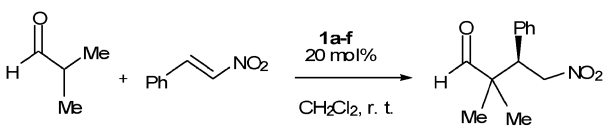


Scheme 1 Chiral sulfamides **1a–1f**.

isobutyraldehyde to *trans*-β-nitrostyrene and the results are summarized in Table 1.

Excellent enantioselectivities and moderate yields were achieved with **1a–1d** as the catalyst (Table 1, entries 1–4). The reactions were very slow and complete conversions of *trans*-β-nitrostyrene were not achieved even after 160 h. The enantioselective induction seems to be controlled by the chiral cyclohexanediamine unit. The additional chiral centers in **1b**, **1c** and **1d** did not exert beneficial effects on the enantioselectivity. In contrast, chemical yields were decreased. It is interesting to note that the additional chiral centers were necessary for excellent enantioselectivities when structurally analogous Jacobsen's catalysts were used.[9k,l] Inferior enantioselectivity and chemical yield were observed with **1e**, which has

Table 1 Addition of isobutyraldehyde to *trans*-β-nitrostyrene catalyzed by sulfamides **1a–1f**



2a **3a** **4a**

Entry	Catalyst	*t*/h	Yield (%)[a]	ee (%)[b,c]
1	**1a**	160	74	94
2	**1b**	160	52	94
3	**1c**	160	50	94
4	**1d**	160	62	93
5	**1e**	160	38	77
6	**1f**	240	—[d]	n.d.[e]

[a] Isolated yield after column chromatography. [b] ee values were determined *via* HPLC with a Daicel Chiralpak-AD column. [c] The absolute configuration of the product was determined as *R* by comparing the optical rotation with reported data. [d] No reaction. [e] Not determined.

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a bigger naphthalenylmethyl substituent. The results suggest that the catalytic activities of sulfamides are quite sensitive to their steric hindrance. The primary amino group of sulfamide catalysts is necessary for the catalytic activity, since **1f** did not show any catalytic activity.

A range of solvents were screened for the conjugate addition of isobutyraldehyde to *trans*-β-nitrostyrene catalyzed by **1a**. Excellent enantioselectivities were obtained in CH_2Cl_2, $CHCl_3$, ^iPrOH, THF, Et_2O, hexane and toluene.[10] $CHCl_3$ provided the best enantioselectivity and an acceptable yield (61% yield, 98% ee). To improve the reaction rate, a series of acid and base additives were examined and the results are listed in Table 2. In previous studies Brønsted acids were found to be efficient promoters for the reactions with (thio)urea–primary amine catalysts and many proline derivative catalysts.[9g,h,k,l,m] However, in our case benzoic acid and AcOH showed detrimental effects on reaction rate and enantioselectivity (Table 2, entries 1–2). Unexpectedly, base additive DIPEA significantly accelerated the reaction without erosion of the enantioselectivity. Thus various base additives were examined in detail. A number of bases, such as TEA, DABCO, DMAP, quinine, imidazole and 2,2,6,6-tetramethylpiperidine, were also highly efficient (entries 4–9). DMAP was identified as the best additive considering the excellent enantioselectivity, good chemical yield and short reaction time (entry 6). When secondary amines such as piperidine and pyrrolidine were used, the enantioselectivities were decreased significantly. The competitive process catalyzed by the secondary amines was supposed to provide achiral products and to result in low enantioselectivities (entries 11 and 12). In the cases of DBU and sparteine (entries 13 and 14) a large amount of white deposit was formed, which was insoluble in all tested solvents. The deposit is proposed to be a polymerized product of nitrostyrene based on IR and elemental analysis.[11] A similar polymer was also observed in previous reactions of nitroolefins.[9i,12]

A variety of β-aryl-nitroethenes and aldehydes were examined and the results are listed in Table 3. Excellent enantioselectivities and good yields were achieved for the conjugate addition of isobutyraldehyde to β-aryl-nitroethenes. Substitutions of the benzene ring are tolerated well (Table 3, entries 1–4). *trans*-β-Styryl-nitroethene gave 1,4-addition product with excellent enantioselectivity (entry 5). Both 2-furanyl-nitroethene and 2-thiophenyl-nitroethene afforded excellent yields and enantioselectivities (entries 6–7). Cyclopentanecarbaldehyde also gave good enantioselectivity, however the yield was low (entry 8). The addition of propionaldehyde, butyraldehyde and 2-phenylacetaldehyde provided two diastereoisomers (d.r. = 2/1 to 4/1) with good yields and enantioselectivities (entries 9–11). Imidazole was found to provide a better yield than DMAP for the reactions of cyclopentanecarbaldehyde, propionaldehyde, butyraldehyde and 2-phenylacetaldehyde. The match of aldehydes with base additives seems to be important for the chemical yield. The base additives exerted small effects on the diastereoselectivity of the reaction. For the addition of propionaldehyde to *trans*-β-nitrostyrene, the diastereoselectivities were 1.6/1, 1.5/1 and 2/1 respectively with no base additive, DMAP and imidazole.

A catalytic mechanism for chiral sulfamides is proposed in Scheme 2.[9h] An imine intermediate **A** is generated from the catalyst **1a** and isobutyraldehyde. The tautomerization of **A** is promoted by the base additive and provides the enamine **B**. Two hydrogen bonds are formed between the nitro group of nitrostyrene with the sulfamide (intermediate **C**), thus the nitrostyrene becomes more electrophilic and is also sufficiently close to the reactive enamine. The resulting nucleophilic attack of enamine occurs from the *si* face of the double bond and provides intermediate **D**. The consequent proton transfer and hydrolysis give the product and regenerate the catalyst **1a**. The base additive may also accelerate the proton transfer step by removing proton from the imine cation.

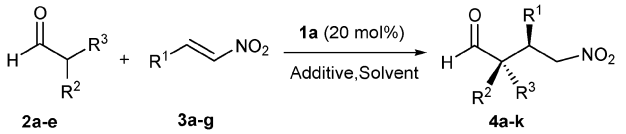
In summary, chiral bifunctional sulfamides are prepared and found to be efficient catalysts for the conjugate addition of

Table 2 Effect of additives[a]

Entry	Additive[b]	*t*/h	Yield (%)	ee (%)
1	PhCOOH	204	<10	37
2	AcOH	240	~0	n.d.
3	DIPEA	9	65	96
4	TEA	6	39	81
5	imidazole	76	64	97
6	DMAP	3	83	99
7	DABCO	4	71	99
8	quinine	27	73	97
9	2,2,6,6-tetramethylpiperidine	18	81	98
10	2,6-dimethylpyridine	216	20	96
11	piperidine	4.5	64	84
12	pyrrolidine	5.5	61	46
13	(−)-sparteine	240	20[c]	99
14	DBU	1	—[c]	n.d.

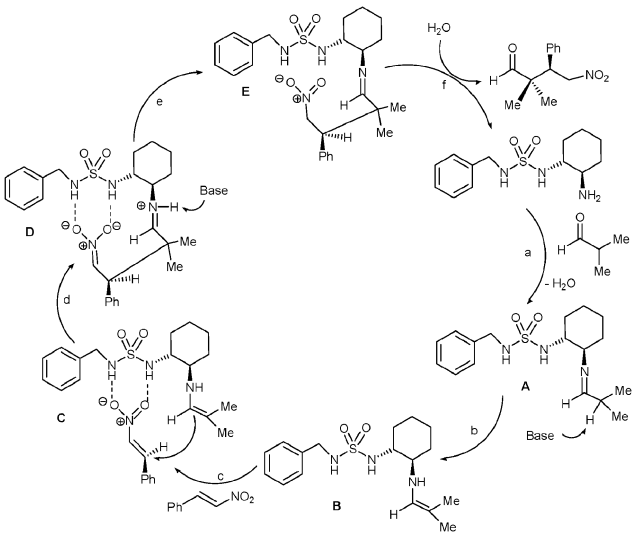
[a] The reactions were carried out with **1a** (0.06 mmol), **2a** (1.1 mmol) and **3a** (0.3 mmol) in $CHCl_3$ (0.4 mL) at room temperature. [b] The amount of additive was 0.06 mmol. [c] A large amount of deposit was formed.

Table 3 Conjugate addition of aldehydes to β-aryl-nitroethenes catalyzed by **1a**[a]



Entry	R^1	R^2	R^3	*t*/h	**4**	Yield (%)[b]	ee (%)[c]
1	Ph	CH_3	CH_3	3	**4a**	83	99
2	4-MeO-Ph	CH_3	CH_3	2	**4b**	79	99
3	4-Cl-Ph	CH_3	CH_3	3	**4c**	79	98
4	4-NO_2-Ph	CH_3	CH_3	3	**4d**	74	99
5	PhCH=CH	CH_3	CH_3	24	**4e**	53	98
6	2-furanyl	CH_3	CH_3	6	**4f**	94	98
7	2-thiophenyl	CH_3	CH_3	24	**4g**	99	99
8	Ph	$CH_2(CH_2)_2CH_2$		23	**4h**	41	91
9	Ph	H	CH_3	23	**4i**	96 (2/1)[d]	78/70
10	Ph	H	CH_3CH_2	24	**4j**	72 (2/1)[d]	91/93
11	Ph	H	Ph	21	**4k**	90 (4/1)[d]	82/80

[a] The reactions were carried out at room temperature using 20 mol% **1a** as the catalyst. The additive and solvent were DMAP/$CHCl_3$ for entries 1–7, and imidazole/CH_2Cl_2 for entries 8–11, respectively. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The diastereoisomer ratios in parentheses were determined by HPLC.



Scheme 2 Proposed catalytic mechanism.

aldehydes to nitroolefins. Base additives greatly accelerate the reaction. The results suggest that the sulfamide is another useful catalaphore for double hydrogen-bonding activation in organocatalysis.

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