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Chiral sulfamide-catalyzed asymmetric Michael addition of protected 3-hydroxypropanal to β-nitrostyrenes

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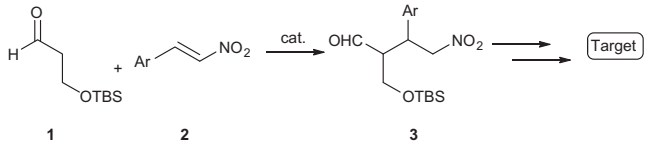
ABSTRACT

Organocatalytic asymmetric Michael addition of 3-(OTBS)-propanal to β-nitrostyrenes catalyzed by chiral sulfamides was investigated. Good d.r. (up to 80:20) and excellent enantioselectivities (up to >99% ee) were achieved. Both the *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-*N*′-(phenylmethyl)sulfamide **7b** and the novel chiral *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-*N*′-[3,5-bis(trifluoromethyl)phenyl]sulfamide **7a** were identified as efficient primary amine organocatalysts.

Carbon–Carbon bond formation through Michael reaction is one of the most powerful and versatile tools available in organic synthesis. By means of asymmetric catalysis, the formation of stereogenic centers can be controlled and predicted, affording, selectively, products with a stereo-defined architecture.[1] The enamine organo-catalysis in the addition to aldehydes and ketones meets the criteria of an elegant and efficient asymmetric process under simple and environmentally friendly conditions.[2] L-proline, and some of its analogues, were the first catalysts of this type found to be effective in such a transformation[3a] leading to the rapid growth of the asymmetric organocatalysis. Recent publications highlighted the beneficial effect of a chiral H-bond donor for electrophile activation as a way of mimicking the mode of action of many enzymes in a biological matrix.[3b] Therefore, new types of bifunctional organocatalysts were designed: ureas, thioureas, guanidinium, and amidinium were found to be effective H-bond donors and chiral primary amine-thiourea organocatalysts were used to develop several enantioselective conjugate additions of carbonyl compounds to enones and nitroolefins.[2,4]

One of the applications we became interested in was the organocatalyzed asymmetric Michael addition of the aldehyde **1** to *trans*-β-nitrostyrenes **2** as the key step to access highly functionalized adducts of type **3**, with a wide opportunity of functional groups manipulation. Adducts **3** were further progressed to the targets of biological relevance, of which we cannot disclose the nature at the present time (Scheme 1).



Scheme 1. Michael addition of aldehyde **1** into β-nitrostyrenes **2**.

Primary amine organocatalysis with un-substituted aldehydes such as **1** is a relatively unexplored field due to the risk of side reactions.[2] In particular, the use of aldehyde **1** as nucleophile, to the best of our knowledge, has never been reported.[5] To address the issue of the stereoselectivity, we took into consideration several types of primary and secondary amine organocatalysts which proved to be successful in similar reactions (Fig. 1). Some commercially available L-proline derivatives **4a–c**[6] were selected, as well as Jacobsen's L-*t*-leucine thiourea derived catalyst **5**.[4d] Simple thiourea catalyst **6a** was recently used by Barbas and co-workers in a very elegant *anti*-selective asymmetric addition of (TBS)acetaldehyde to nitroolefins[2] and the structural related thiourea catalyst **6b** was also selected.[4c] Sulfamides are structurally similar to thioureas with an increased H-bond donor ability due to the effect of the strong electron-withdrawing sulfonyl group which results in higher acidity of N–H bonds compared to the

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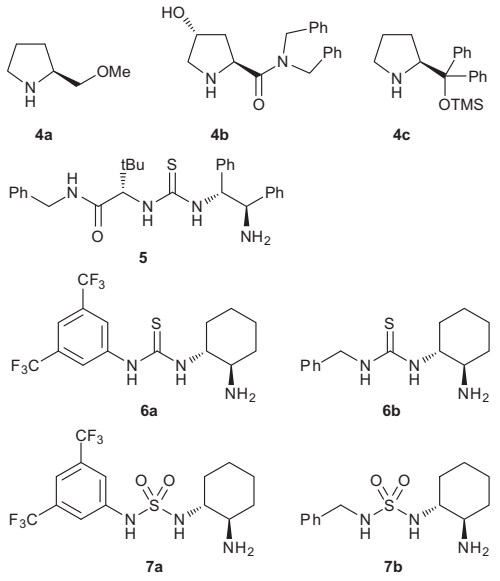


Figure 1. Selected organocatalysts.

thioureas.[7] Surprisingly, the use of simple chiral bifunctional sulfamides as organocatalysts has been very limited, despite their potential as double H-bond donors. Only recently, sulfamide **7b** was used by Yan and co-workers in the enantioselective conjugate addition of isobutyraldehyde to trans-β-nitrostyrenes.[7b]

In order to explore the promising potential of sulfamides organocatalysts, we decided to use **7b** as a model and to prepare and test the new sulfamide **7a** due to the similarity with the thiourea **6a**[8]. In this Letter, we report preliminary results on the asymmetric addition of 3-(*tert*-butyldimethylsilyloxy)propanal (**1**) to β-nitrostyrenes **2**. These studies identified the new sulfamide **7a** and sulfamide **7b** as efficient primary amine organocatalysts. The preparation of **7a** is also described.

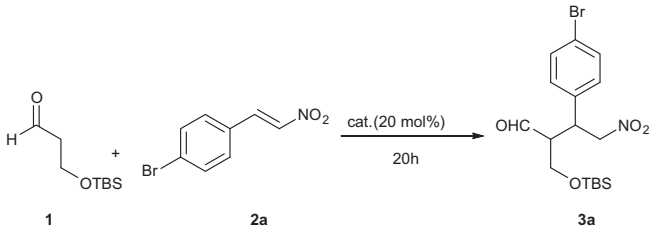
We began the screening of the catalysts using *trans*-(4-bromo)-β-nitrostyrene **2a** as Michael acceptor. The results are reported in Table 1.

The different conditions applied for each catalyst were designed combining both the solvent screening experiments and the examples already reported in the literature.[2,4d,6,7] The proline class gave high to full conversion after 20 h and in particular, L-diphenyl prolinol trimethylsilylether **4c** was the more promising catalyst, giving a good 80:20 d.r. with 90% ee for the major diastereomer in a respectable yield (entry 3).

The thioureas derivatives gave disappointing results with the Jacobsen's catalyst **5** achieving a modest 12% conversion (entry 4). The simple thioureas **6a** and **6b** instead gave high to full conversion raising the d.r. up to an interesting level (80:20 and 75:25, respectively) alongside with high ee for the major diastereomers (93% and 98%, respectively).[9]

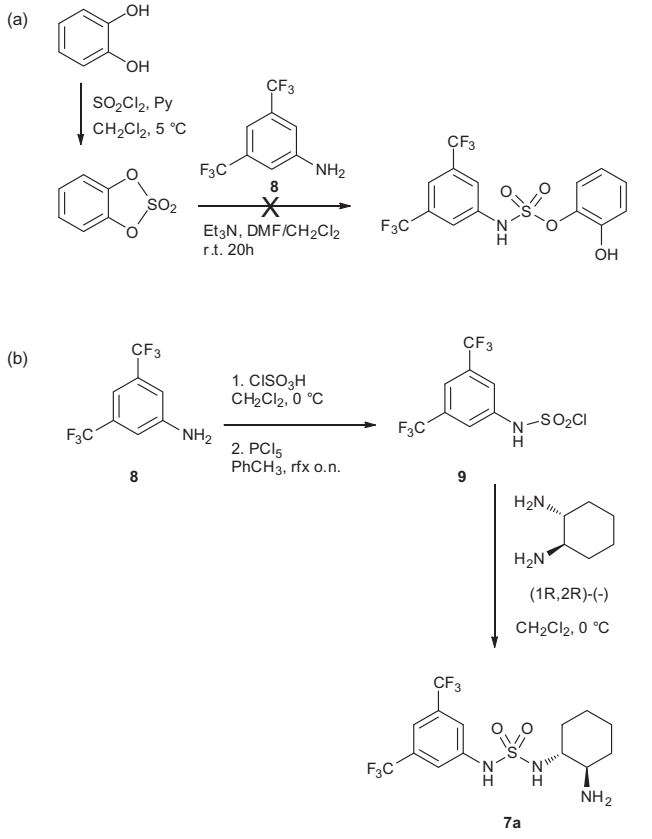
We were thus pointed toward the study of the effect of bifunctional sulfamides as catalysts. Compound **7b** was easily prepared according to the literature,[7b] while the preparation of sulfamide **7a** in a standard stepwise route via cathecol sulfate failed due to the reduced nucleophilic ability of 3,5-bis(trifluoromethyl)aniline (**8**) (Scheme 2a). A new synthetic approach for **7a** was devised and it is shown in Scheme 2b. Treatment of aniline **8** with chlorosulfonic acid gave the corresponding sulfamate salt, converted with PCl_5 into the sulfamyl chloride **9** that reacted with (−)-(1*R*,2*R*)-1,2-diaminocyclohexane to give (+)-*N*-[(1*R*,2*R*)-2-aminocyclohexyl]-*N*'-[3,5-bis(trifluoromethyl)phenyl]sulfuric diamide (**7a**) with an overall yield of 17% molar over 3 steps (see Supplementary data).

Table 1
Preliminary catalysts/conditions screening



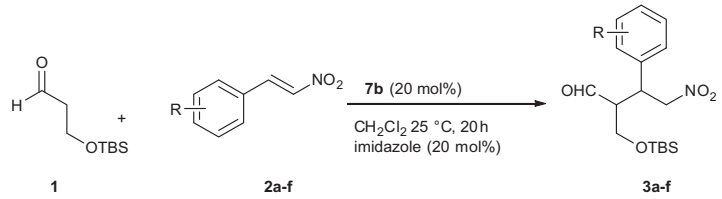
Entry	Cat.	d.r.[e]	ee_M[f]	ee_m[f]	C[g] (%)	Y[h] (%)
1	**4a**[a]	62:38	69	57	>99	42
2	**4b**[a]	65:35	71	45	>99	52
3	**4c**[a]	80:20	90	29	94	60
4	**5**[b]	—	—	—	12	—
5	**6a**[b]	80:20	93	75	95	63
6	**6b**[b]	75:25	98	82	>99	41
7	**7a**[c]	65:35	>99	78	89	47
8	**7b**[c]	75:25	98	92	>99	66
9	**7b**[d]	76:24	>99	96	91	69

[a] Conditions: MeCN/H_2O, 5 °C.
[b] Conditions: CH_2Cl_2, 25 °C and a catalytic amount of water (Ref. 4d).
[c] Conditions: CH_2Cl_2/Imidazole (0.2 equiv), 25 °C.
[d] Conditions: CH_2Cl_2/Imidazole (0.2 equiv), 0 °C, 48 h.
[e] Diastereomeric ratios were measured with chiral HPLC (See Supplementary data) and ^1H NMR analyses; the sense of diastereomeric induction was the same in all cases.
[f] ee were measured with chiral HPLC analysis; the sense of enantiomeric induction was the same (See Supplementary data).
[g] Reaction conversions were measured by LC/MS.
[h] Yields of isolated products after column chromatography (adducts **3a** was found to partially decompose over silica; no retro-Michael products observed); the results are the average of at least two runs.



Scheme 2. Synthesis of sulfamide **7a**.

Table 2
Asymmetric Michael addition of 3-(OTBS)-propanal to β-nitrostyrenes catalyzed by **7b**[a]



1 **2a-f** **3a-f**

Entry	R	d.r.[b]	ee_M[c]	ee_m[c]	Y[d] (%)
1	4-Br (**2a**)	75:25	98	92	66
2	H (**2b**)	76:24	92	78	62
3	4-Me (**2c**)	68:32	99	98	46
4	4-OMe (**2d**)	70:30	98	99	65
5	2,4-diCl (**2e**)	60:40	98	97	42
6	4-CF_3 (**2f**)	74:26	99	99	48

[a] Representative procedure (see Supplemenatry data): nitrostyrene **2a**–**f** (0.88 mmol), 3-[(*tert*-butyldimethylsilyl)oxy]propanal **1** (1.76 mmol, 2.0 equiv), imidazole (0.2 equiv), and the catalyst **7b** (0.2 equiv) were dissolved in dichloromethane (2 ml). The resulting mixture was stirred at room temperature for 20 h before quenching with 2 ml of HCl 0.5 M.
[b] Diastereomeric ratios were measured with chiral HPLC (See Supplementary data) and ^{1}H NMR analyses on the isolated material.
[c] ee were measured with chiral HPLC analysis (See Supplementary data) on the isolated material.
[d] Yields of isolated products after column chromatography; the results are the average of at least two runs.

The two catalysts **7a** and **7b** were tested in the model reaction using imidazole as the additive as reported in the literature.[7b] The reaction with sulfamide **7a** provided an 89% conversion after 20 h with a significant >99% ee for the major diastereomer, while the d.r. was moderate (entry 7). Catalyst **7b** showed to be more active, giving full conversion, an increased d.r. (75:25), and more importantly, the reaction was highly enantioselective, especially for the major diastereomer (entry 8). Lowering the temperature did not significantly improve the selectivity (entry 9).

Having identified sulfamide **7b** as the best catalyst for the asymmetric conjugate addition of 3-(OTBS)-propanal **1** to *trans*-(4-bromo)-β-nitrostyrene (**2a**), we decided to extend the reaction to a series of *trans*-β-nitrostyrenes **2b**–**f** (Table 2). Sulfamide **7b** proved to be an efficient catalyst for all the substrates examined, providing a level of diastereoselectivity up to 76:24 (entry 2), the lowest being β-nitrostyrene **2e** with a modest 60:40 (entry 5), with yields ranging from 42 to 66% molar. By using sulfamide **7b**, we observed an unprecedented high level of enantioselectivity, especially for the major enantiomer (92–99% ee) for the entire series. Moreover, the selectivity observed seemed to be independent of the presence of electron-withdrawing or electron-donating groups on the phenyl ring of styrenes.

From the mechanistic point of view, when using bifunctional organocatalysts **6a**–**b**, **7a**–**b** a double activation effect could be conceived as depicted on Figure 2a.[7] As already described in a detailed study,[7a] there is no general correlation between the acidity of N–H bond with the catalytic activity and enantioselectivity of the catalyst. When looking at the pK_a values (Fig. 2b), sulfamides **7a**–**b** are relatively more acidic than the corresponding thioureas **6a**–**b**.[10] No relevant differences in reactivity could be found between catalysts **6b** and **7b** however, sulfamide **7a** showed to be slightly less active than the corresponding thiourea **6a**. Similarly, the increase in enantioselectivity observed using sulfamide **7b** cannot be only justified with the acidity of the N–H bonds of the sulfamide, but it might advocate a substrate specific effect.

In summary, the examined chiral bifunctional sulfamides were found to be effective organocatalysts for the enantioselective Michael addition of unbranched aldehyde **1** to various *trans*-β-nitrostyrenes **2**. The chiral (1*R*,2*R*)-*trans*-1,2-diaminocylohexyl moiety seemed to play a fundamental role for the asymmetric induction of most of the studied catalysts. This privileged structure,[11] in combination with the sulfamide moiety, pointed us toward the identification of organocatalysts with an improved efficacy. The recent results on chiral bifunctional sulfamides indicate a new class of promising organocatalysts for which scope and application are mostly to be unveiled.

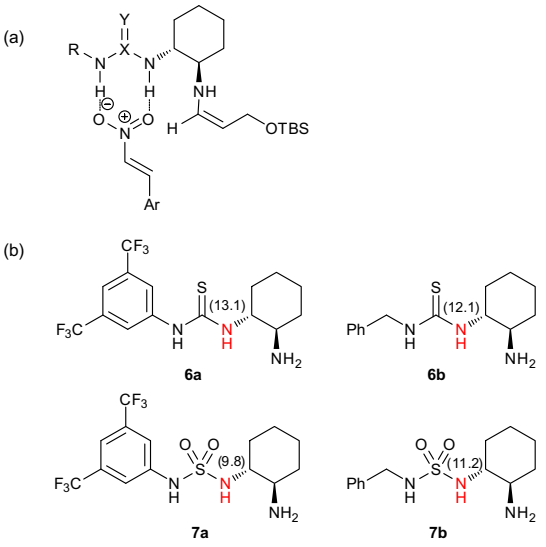


Figure 2. (a) Plausible transition state; (b) pK_a's of sulfamides versus thioureas.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.072.

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