## Communications

#### Asymmetric Catalysis

# Enantioselective Organocatalyzed α Sulfenylation of Aldehydes\*\*

### Mauro Marigo, Tobias C. Wabnitz, Doris Fielenbach, and Karl Anker Jørgensen\*

Optically active  $\alpha$ -heterosubstituted aldehydes are versatile building blocks for the synthesis of chiral molecules that bear heteroatom functionalities. Recent advances in the synthesis of these molecules have been focused on the development of direct organocatalytic procedures<sup>[1]</sup> that avoid metal catalysts and reagents. Organocatalyzed additions of simple carbonyl compounds to diazocarboxylates and nitrosobenzene allow the incorporation of nitrogen-<sup>[2]</sup> and oxygen-containing<sup>[3]</sup>  $\alpha$  substituents into aldehydes and ketones with excellent levels of stereoselectivity. Very recently, organocatalyzed substitution reactions of *N*-halosuccinimides and related electrophiles have been developed for the  $\alpha$  halogenation of aldehydes and ketones.<sup>[4]</sup> In contrast, the analogous asymmetric introduction of sulfur-based substituents has not been reported, in spite of the synthetic potential of  $\alpha$ -sulfenylated

[\*] M. Marigo, Dr. T. C. Wabnitz, Dr. D. Fielenbach, Prof. Dr. K. A. Jørgensen The Danish National Research Foundation: Center for Catalysis Department of Chemistry, Aarhus University 8000 Aarhus C (Denmark) Fax: (+45) 8919-6199 E-mail: kaj@chem.au.dk
[\*\*] This work was made possible by a grant from The Danish National Research Foundation. M.M. and T.C.W. thank the EU (HMPT-CT-2001-00317) for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

aldehydes and the merits of organocatalytic processes, which circumvent the undesired association of sulfur reagents with metal catalysts. To date, all practical methods for the preparation of chiral  $\alpha$ -sulfenylated aldehydes have been multistep procedures that involve chiral auxiliaries.<sup>[5]</sup> According to our knowledge, no catalytic processes are available for the preparation of these useful optically active building blocks. Herein, we report the first direct organocatalyzed enantioselective  $\alpha$  sulfenylation of aldehydes [Eq. (1)].

$$\bigcap_{R}^{O} + Lg^{-S} \xrightarrow{Pg} RT RT R^{Catalyst} O = S Pg$$
(1)

In analogy to organocatalyzed halogenation reactions, sulfenylations are substitution reactions, which are inherently more difficult to perform enantioselectively than addition processes as a result of the more flexible nature of the transition state. Therefore, the design of a suitable leaving group (Lg) is crucial. Furthermore, a second substituent that can serve as a protecting group (Pg) needs to be chosen for sulfenylation reactions. To provide for facile product elaboration, S-benzyl-protected  $\alpha$ -sulfenylated aldehydes were chosen as synthetic targets, as there are well-established methods for the cleavage of this protecting group.<sup>[6]</sup> Similarly, the development of a practical sulfenylation process called for a leaving group that could be separated readily from the product after the reaction. Additionally, the protonated nucleofuge should be a neutral species that does not affect the equilibrium of enamine formation or deactivate the amine catalyst. In line with these considerations, initial experiments were carried out for the  $\alpha$  sulfenylation of isovaleraldehyde (1a) with the reagents shown in Scheme 1, all of which



**Scheme 1.** Sulfenylation reagents with different leaving groups tested in the organocatalyzed enantioselective  $\alpha$  sulfenylation of isovaleralde-hyde (1a).

contain weakly basic heterocyclic nitrogen-centered nucleofuges, in the presence of different pyrrolidine derivatives. Whereas the phthalimide and succinimide reagents 2a and 2bunderwent only sluggish conversion, and the imidazolederived electrophile 2c turned out to be unstable, the desired  $\alpha$ -sulfenylated product was obtained from isovaleraldehyde in good yield with the reagents 2d and 2e. Finally, the novel triazole derivative 1-benzylsulfanyl-1,2,4-triazole (2e) was

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chosen as the electrophilic sulfur source,<sup>[7]</sup> as it exhibited the highest level of reactivity.

Systematic studies of a model system comprising isovaleraldehyde (1a), the sulfur electrophile 2e, and  $10 \mod \%$  of a chiral secondary amine organocatalyst at ambient temperature are summarized in Table 1. With the L-proline-derived

**Table 1:** Organocatalyzed enantioselective  $\alpha$  sulfenylation of isovaleral-dehyde (**1** a).<sup>[a]</sup>



Entry <b>4</b>		Solvent	Yield [%] <sup>₪</sup>	ee [%] <sup>[c]</sup>
1	а	DMSO	_[d,e]	_
2	а	Et <sub>2</sub> O	5	18
3	а	$CH_2Cl_2$	7	22
4	а	toluene	30	25
5	Ь	toluene	16	0
6	с	toluene	56 <sup>[e]</sup>	52 <sup>[f]</sup>
7	d	toluene	_[d]	-
8	е	toluene	90	77
9	f	toluene	75 <sup>[e]</sup>	84
10	g	toluene	73 <sup>[e]</sup>	90
11	h	toluene	90	98
12 <sup>[g]</sup>	h	toluene	90	96
13 <sup>[h]</sup>	h	toluene	90	90

[a] Compound **2e** (0.27 mmol) was added to **1a** (0.25 mmol) and **4** (0.025 mmol) in the solvent (0.5 mL), and the mixture was stirred at room temperature. [b] Based on NMR spectroscopic analysis of the crude reaction mixture after 3 h. [c] The *ee* value was determined by GC on a chiral phase (chrompak CP-chiralsil dex CB column) and verified by HPLC (chiralpak AD column) after reduction of **3a** to the corresponding alcohol. [d] Compound **3a** was not formed. [e] The  $\alpha$ , $\alpha$ -disulfenylated aldehyde by-product was detected in the crude reaction mixture in >10% yield. [f] After 24 h at room temperature: 25% *ee*. [g] After 1 h in the presence of LiClO<sub>4</sub> (30 mol%). [h] After 1 h in the presence of *o*-nitrobenzoic acid (10 mol%). DMSO=dimethyl sulfoxide, Naph= naphthyl, TMS=trimethylsilyl.

amide **4a**, only traces of the product **3a**, but large amounts of the  $\alpha,\alpha$ -disulfenylated aldehyde, were observed in DMSO (Table 1, entry 1). In less polar solvents, such as toluene, the desired product **3a** was generated in low yield with low enantioselectivity in the presence of **4a** (Table 1, entries 2–4). Whereas L-proline (**4b**) was ineffective (Table 1, entry 5), the chiral pyrrolidine derivative **4c** increased the rate and enantioselectivity of the reaction (Table 1, entry 6), although it slowly racemized the product upon prolonged reaction times and led to  $\alpha,\alpha$  disulfenylation. To minimize such undesired interactions between the organocatalyst and the reaction product, we attempted the reaction in the presence of a catalyst with increased steric bulk. No reaction occurred with  $\alpha,\alpha$ -diphenyl-L-prolinol (**4d**; Table 1, entry 7), probably as a result of the reaction of **2e** with the hydroxy group<sup>[7]</sup> and/ or formation of an unreactive hemiaminal by reaction with the aldehyde. However, trimethylsilyl protection of the free hydroxy moiety of 4d restored reactivity and enhanced selectivity (Table 1, entry 8). Further improvements were made through variation of the aryl substituents in the catalyst structure. The silvlated L-prolinol derivatives 4f-h with sterically demanding aryl substituents furnished the product with high enantiomeric excess (Table 1, entries 9–11). The fluorinated derivative 4h was identified as the best of these catalysts, as it gave 3a in 90% yield and with 98% ee, with only traces of concomitant  $\alpha, \alpha$ -disulfenylation and no product racemization (Table 1, entry 11). However, the reaction rate was found to be strongly dependent on the purity of the reagent 2e, which slowly degraded upon storage. Nevertheless, in cases of slow conversion the turnover could be increased by adding salts such as LiClO<sub>4</sub> to the reaction mixture, with only a minor decrease in enantiomeric excess (Table 1, entry 12). Protic acids also accelerated the reaction, but led to a more pronounced loss of enantiomeric excess (Table 1, entry 13).<sup>[8]</sup>

Under the optimized conditions, a series of aldehydes 1ag underwent enantioselective  $\alpha$  sulfenylation in the presence of 2e as the S-benzyl-protected sulfur donor and 4h as the catalyst. To facilitate workup, the reaction products were isolated as the alcohols 5 after in situ reduction of the aldehyde moiety with NaBH<sub>4</sub>.<sup>[9]</sup> The reduction of the  $\alpha$ sulfenylated aldehyde 3a to the alcohol 5a showed that this process occurs without loss of enantiomeric excess. Simple aliphatic aldehydes 1a-c (Table 2, entries 1-3), as well as those containing a phenyl group or an additional double bond (Table 2, entries 4 and 5), underwent the desired reaction, and the optically active  $\alpha$ -sulfenylated alcohols **5a-e** were obtained in good yields and with excellent enantioselectivities. Similarly, the sterically encumbered aldehyde 1f was transformed smoothly into the corresponding chiral alcohol 5f with very high enantioselectivity (Table 2, entry 6). Furthermore, the method could be extended to the construction

**Table 2:** Organocatalyzed enantioselective  $\alpha$  sulfenylation of aldehydes.  $^{[a]}$ 

	4h (10 mol%), 2e toluene, RT			MaBH4 MeOH, RT	
1			3		5
Entry	1/5	R	R′	Yield of <b>5</b> [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	a	<i>i</i> Pr	н	81	98
2	Ь	Me	н	60	95
3	с	Et	н	85	96
4	d	Bn	Н	94	97
5	е	allyl	н	64	96
6	f	tBu	Н	83	95
7 <sup>[d]</sup>	g	Ph	Me	84	61

[a] Compound **2e** (0.33 mmol) was added to **1** (0.25 mmol) and **4h** (0.025 mmol) in toluene (0.5 mL), and the mixture was stirred at room temperature for 3 h. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC of the alcohols **5** on a chiral phase (see Supporting Information). [d] After 16 h with catalyst **4e** (10 mol%) and *o*-nitrobenzoic acid (10 mol%). Bn = benzyl.

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of quaternary stereocenters starting from  $\alpha,\alpha$ -disubstituted aldehydes, such as 2-phenyl propanal (**1g**). In this case, the optically active  $\alpha$ -sulfenylated alcohol **5g** was obtained in high yield and with good enantioselectivity when **4e** was used as the catalyst (Table 2, entry 7).

As well as reduction to the  $\alpha$ -sulfenylated alcohols **5**, the optically active  $\alpha$ -sulfenylated aldehydes **3** also undergo reductive amination with dibenzylamine and sodium triace-toxyborohydride. By using this procedure, the chiral  $\alpha$ -sulfenylated amine **6** was obtained directly from the aldehyde **3a** with only a minor loss of enantiomeric excess [Eq. (2)]. Moreover, after protection of the hydroxy group as a *tert*-butyldimethylsilyl (TBDMS) ether, the benzyl sulfide moiety could be cleaved reductively with Na/NH<sub>3</sub>(I). Thus, the free thiol **8** was formed from **7** in good yield [Eq. (3)]. These transformations underline the synthetic versatility of optically active  $\alpha$ -sulfenylated aldehydes in the preparation of chiral sulfur-containing compounds.



The absolute configuration of the optically active  $\alpha$ sulfenylated alcohols **5a** and **5b** was determined to be *S* by comparison of their optical rotation with values reported in the literature.<sup>[5f,10]</sup> This configuration is in agreement with *Si*face attack of the sulfur-centered electrophile on the *E*configured enamine intermediate. The *Re* face of the enamine is shielded effectively by the aryl and silyl substituents of the catalyst **4h**. A model for this mode of attack is depicted in Figure 1.



Figure 1. Postulated Si-face attack of the electrophile on the E enamine formed from isovaleraldehyde (1a) and catalyst 4h.

In summary, a novel class of organocatalysts in the form of sterically encumbered chiral pyrrolidine derivatives without additional free heteroatom functionalities has been developed. These compounds were found to be highly efficient organocatalysts for the direct enantioselective  $\alpha$  sulfenylation of aldehydes, which is one of the first examples of an asymmetric intermolecular substitution reaction mediated by a secondary amine. This procedure constitutes the first enantioselective catalytic preparation of α-sulfenylated aldehydes and, to the best of our knowledge, the first successful use of electrophilic sulfur sources in asymmetric catalysis. The optically active products were obtained in high yields with excellent enantioselectivities and underwent further facile modifications. Further exploration of the new class of chiral organocatalysts described are now in progress in our laboratory.

Received: September 24, 2004

Keywords: aldehydes  $\cdot$  asymmetric catalysis  $\cdot$  enantioselectivity  $\cdot$  organocatalysis  $\cdot$  sulfenylation

- For some recent reviews, see, for example: a) P. I. Dalko, L. Moisan, Angew. Chem. 2001, 113, 3840; Angew. Chem. Int. Ed. 2001, 40, 3726; b) B. List, Tetrahedron 2002, 58, 5573; c) R. O. Duthaler, Angew. Chem. 2003, 115, 1005; Angew. Chem. Int. Ed. 2003, 42, 975; d) P. Merino, T. Tejero, Angew. Chem. 2004, 116, 3055; Angew. Chem. Int. Ed. 2004, 43, 2995; e) B. List, Acc. Chem. Res. 2004, 37, 548; f) W. Notz, F. Tanaka, C. F. Barbas III, Acc. Chem. Res. 2004, 37, 580; g) P. I. Dalko, L. Moisan, Angew. Chem. 2004, 116, 5248; Angew. Chem. Int. Ed. 2004, 43, 5138.
- [2] a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, Angew. Chem. 2002, 114, 1868; Angew. Chem. Int. Ed. 2002, 41, 1790; b) B. List, J. Am. Chem. Soc. 2002, 124, 5656; c) H. Vogt, S. Vanderheiden, S. Bräse, Chem. Commun. 2003, 2448; d) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, J. Am. Chem. Soc. 2002, 124, 6254.
- [3] a) G. Zhong, Angew. Chem. 2003, 115, 4379; Angew. Chem. Int. Ed. 2003, 42, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, J. Am. Chem. Soc. 2003, 125, 10808; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, Tetrahedron Lett. 2003, 44, 8293; d) A. Córdova, M. Enqvist, I. Ibrahem, J. Casas, J. Am. Chem. Soc. 2004, 126, 8914; e) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, Proc. Natl. Acad. Sci. USA 2004, 101, 5374; f) W. Wang, J. Wang, H. Lia, L. Liao, Tetrahedron Lett. 2004, 45, 7235; g) A. Bøgevig, H. Sundéen, A. Córdova, Angew. Chem. 2004, 116, 1129; Angew. Chem. Int. Ed. 2004, 43, 1109; h) Y. Hayashi, J. Yamaguchi, T. Sumaiya, M. Shoji, Angew. Chem. 2004, 116, 1132; Angew. Chem. Int. Ed. 2004, 43, 1112; i) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, J. Org. Chem. 2004, 69, 5966; j) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, Chem. Eur. J. 2004, 10, 3673.
- [4] a) M. P. Brochu, S. P. Brown, D. W. C. MacMillan, J. Am. Chem. Soc. 2004, 126, 4108; b) N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, J. Am. Chem. Soc. 2004, 126, 4790; c) M. Marigo, S. Bachmann, N. Halland, A. Braunton, K. A. Jørgensen, Angew. Chem. 2004, 116, 5623; Angew. Chem. Int. Ed. 2004, 43, 5507.
- [5] See, for example: a) J.-H. Youn, R. Herrmann, I. Ugi, *Synthesis* 1987, 158; b) G. Poli, L. Belvisi, L. Manzoni, C. Scolastico, *J. Org. Chem.* 1993, 58, 3165; c) D. Enders, T. Schäfer, O. Piva, A. Zamponi, *Tetrahedron* 1994, 50, 3349; d) K. Chibale, S. Warren, *Tetrahedron Lett.* 1994, 35, 3991; e) D. Enders, T. Schäfer, W.

796 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Mies, *Tetrahedron* **1998**, *54*, 10239; f) D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, M. R. Gagné, *J. Am. Chem. Soc.* **2000**, *122*, 7905.

- [6] T. W. Greene, P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd ed., Wiley, New York, 1999, p. 458.
- [7] For a study of electrophilic sulfur reagents that contain nitrogen nucleofuges, see: D. N. Harpp, K. Steliou, T. H. Chan, J. Am. Chem. Soc. 1978, 100, 1222.
- [8] These additives accelerate enamine formation, but they can racemize tertiary  $\alpha$ -sulfenylated aldehydes.
- [9] The optically active  $\alpha$ -sulfenylated aldehyde **3a** slowly racemized during column chromatography on silica gel.
- [10] L. N. Owen, M. B. Rahman, J. Chem. Soc. C 1971, 2432.