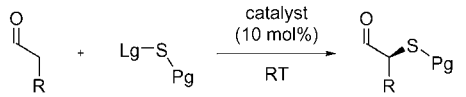
Asymmetric Catalysis

Enantioselective Organocatalyzed α Sulfenylation of Aldehydes**

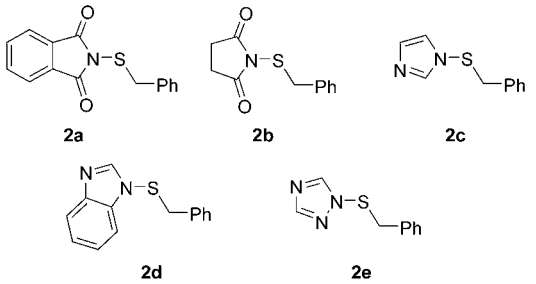
*Mauro Marigo, Tobias C. Wabnitz, Doris Fielenbach, and Karl Anker Jørgensen**

Optically active α-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[1] that avoid metal catalysts and reagents. Organocatalyzed additions of simple carbonyl compounds to diazocarboxylates and nitrosobenzene allow the incorporation of nitrogen-[2] and oxygen-containing[3] α 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 α halogenation of aldehydes and ketones.[4] In contrast, the analogous asymmetric introduction of sulfur-based substituents has not been reported, in spite of the synthetic potential of α-sulfenylated 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 α-sulfenylated aldehydes have been multistep procedures that involve chiral auxiliaries.[5] 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 α sulfenylation of aldehydes [Eq. (1)].



(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 α-sulfenylated aldehydes were chosen as synthetic targets, as there are well-established methods for the cleavage of this protecting group.[6] 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 α 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 α sulfenylation of isovaleraldehyde (**1a**).

contain weakly basic heterocyclic nitrogen-centered nucleofuges, in the presence of different pyrrolidine derivatives. Whereas the phthalimide and succinimide reagents **2a** and **2b** underwent only sluggish conversion, and the imidazole-derived electrophile **2c** turned out to be unstable, the desired α-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

[*] 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.

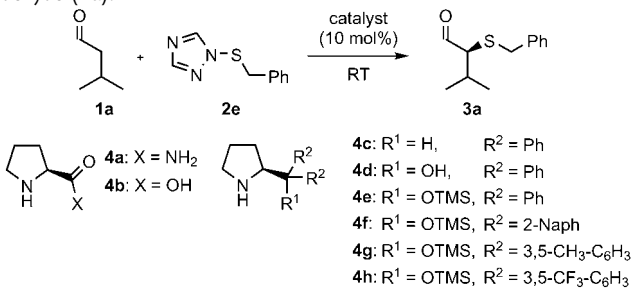
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200462101

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

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

Table 1: Organocatalyzed enantioselective α sulfenylation of isovaleraldehyde (**1a**).[a]



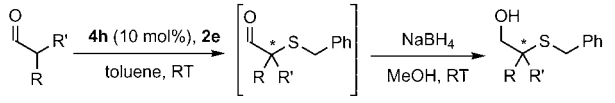
Entry	4	Solvent	Yield [%][b]	*ee* [%][c]
1	**a**	DMSO	–[d,e]	–
2	**a**	Et_2O	5	18
3	**a**	CH_2Cl_2	7	22
4	**a**	toluene	30	25
5	**b**	toluene	16	0
6	**c**	toluene	56[e]	52[f]
7	**d**	toluene	–[d]	–
8	**e**	toluene	90	77
9	**f**	toluene	75[e]	84
10	**g**	toluene	73[e]	90
11	**h**	toluene	90	98
12[g]	**h**	toluene	90	96
13[h]	**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 α,α-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 $LiClO_4$ (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 α,α-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 α,α 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 α,α-diphenyl-L-prolinol (**4d**; Table 1, entry 7), probably as a result of the reaction of **2e** with the hydroxy group[7] 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 silylated 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 α,α-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 $LiClO_4$ 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).[8]

Under the optimized conditions, a series of aldehydes **1a–g** underwent enantioselective α 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 $NaBH_4$.[9] The reduction of the α-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 α-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 α sulfenylation of aldehydes.[a]

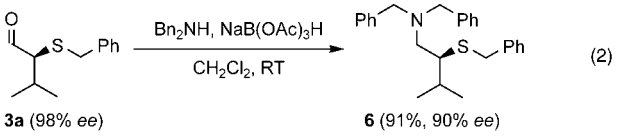


Entry	1/5	R	R′	Yield of 5 [%][b]	*ee* [%][c]
1	**a**	*i*Pr	H	81	98
2	**b**	Me	H	60	95
3	**c**	Et	H	85	96
4	**d**	Bn	H	94	97
5	**e**	allyl	H	64	96
6	**f**	*t*Bu	H	83	95
7[d]	**g**	Ph	Me	84	61

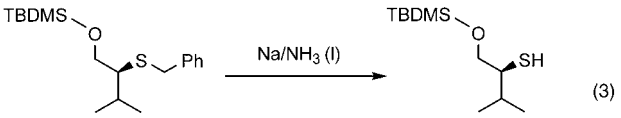
[a] Compound **2e** (0.33 mmol) was added to **1** (0.25 mmol) and **4h** (0.025 mmol) in toluene (0.5 mL), and the mixture was stirred at room temperature for 3 h. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC of the alcohols **5** on a chiral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

of quaternary stereocenters starting from α,α-disubstituted aldehydes, such as 2-phenyl propanal (**1g**). In this case, the optically active α-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 α-sulfenylated alcohols **5**, the optically active α-sulfenylated aldehydes **3** also undergo reductive amination with dibenzylamine and sodium triacetoxyborohydride. By using this procedure, the chiral α-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 $Na/NH_3(l)$. Thus, the free thiol **8** was formed from **7** in good yield [Eq. (3)]. These transformations underline the synthetic versatility of optically active α-sulfenylated aldehydes in the preparation of chiral sulfur-containing compounds.



3a (98% *ee*) **6** (91%, 90% *ee*) (2)



7 **8** (65%) (3)

The absolute configuration of the optically active α-sulfenylated alcohols **5a** and **5b** was determined to be *S* by comparison of their optical rotation with values reported in the literature.[5f,10] 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.

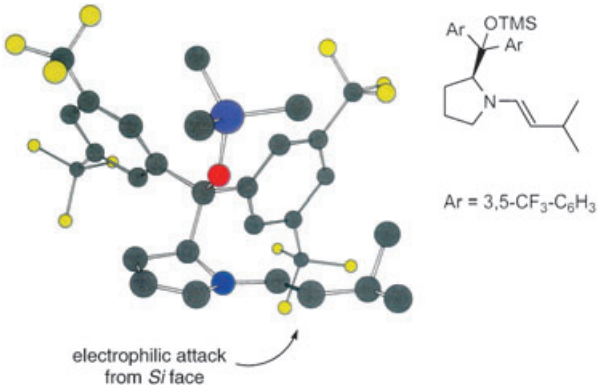


Figure 1. Postulated *Si*-face attack of the electrophile on the *E* enamine formed from isovaleraldehyde (**1a**) and catalyst **4h**.

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 α 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 · asymmetric catalysis · enantioselectivity · organocatalysis · sulfenylation

[1] 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.

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 α-sulfenylated aldehydes.
[9] The optically active α-sulfenylated aldehyde **3a** slowly racemized during column chromatography on silica gel.
[10] L. N. Owen, M. B. Rahman, *J. Chem. Soc. C* **1971**, 2432.

