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Factors Influencing Asymmetric Induction in the Addition of Thioacids to 2-Cyclohexenone

Short Communication

Małgorzata Brzostowska and **Jacek Gawroński***

Department of Chemistry, Adam Mickiewicz University,
PL-60780 Poznań, Poland

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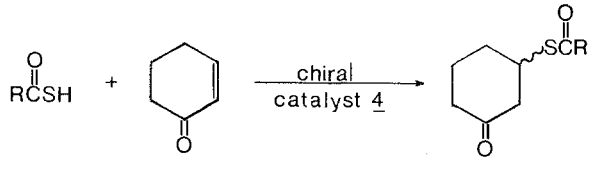
The enantiomeric excess of the product of conjugate addition of a thioacid to 2-cyclohexenone can be increased by proper choice of the thioacid structure, concentration and modification of the structure of the chiral catalyst.

(Keywords: Asymmetric catalysis; Optically active β-hydroxy amines; Cinchona Alkaloids; Enantiomeric excess)

Die asymmetrische Induktion beeinflussende Faktoren bei der Addition von Thiocarbonsäuren an 2-Cyclohexen (Kurze Mitteilung)

Es konnte der enantiomere Überschuß in den Produkten aus der Addition von Thiocarbonsäuren an 2-Cyclohexen durch die Auswahl geeigneter Thiocarbonsäuren, deren Konzentration und durch Modifikation am chiralen Katalysator gesteigert werden.

Conjugate addition of thioacetic-*S*-acid (**1 a**) to 2-cyclohexenone (**2**)[1] or α,β-unsaturated esters[2] is known to produce optically active adducts (exemplified by **3 a**) with enantiomeric excess (e.e.) up to 54%, if catalyzed by cinchona alkaloids as chiral bases. A detailed mechanistic study on the related addition of aromatic thiols to conjugated cycloalkenones has shown that a high e.e. of the product can only be achieved with optically



1 2 3

active β-hydroxy amines as catalysts and by the use of nonpolar solvents and dilute solutions. Although *erythro*-cinchona alkaloids were found to give the highest asymmetric induction, the authors suggested that an even higher e.e. could be obtained by modification of the structure of the catalyst[3]. Indeed, it has been recently demonstrated that modification of cinchona alkaloids at the remote C-3-vinylic group by copolymerization with acrylonitrile[4] or chemical derivatization[5] has some effect on the asymmetric induction in the addition of thiols to activated olefins.

Table 1. *Results of the asymmetric addition of* **1a** *to* **2** *using chiral β-hydroxy amines* **4**

	Catalyst	Adduct **3a** $[\alpha]_{578}$ (CCl_4) (°)	e.e. (%)	Absolute config.
4a	Cinchonine	− 54.0	53	*S*
4b	11-Thiobenzylcinchonine[a, b]	− 62.4	61	*S*
4c	Quinidine	− 54.0	53	*S*
4d	11-Thiobenzylquinidine[a, c]	− 60.8	59.5	*S*
4e	Cinchonidine	+ 58.4	57	*R*
4f	11-Thiobenzylcinchonidine[a, d]	+ 54.4	53.5	*R*
4g	Quinine	+ 45.6	45	*R*
4h	11-Thiobenzylquinine[a]	+ 45.8	45	*R*
4i	(—)-*N*-Methylephedrine	+ 39.2	38.5	*R*

[a] Prepared according to procedure of Ref.[5]
[b] M.p. 224–226°, $[\alpha]_D$ + 147.0 ($CHCl_3$).
[c] M.p. 60–64°, 150–153°, $[\alpha]_D$ + 153.3 ($CHCl_3$).
[d] M.p. 163–165°, $[\alpha]_D$ − 61.0 ($CHCl_3$).

We present our resent results on the addition of thioacids **1** to **2** under the chiral catalysis of β-hydroxy amines **4**. The results demonstrate that certain additional factors have an effect on the e.e. of the product **3**.

We extended the systematic study over the range of optically active β-hydroxy amine catalysts, some of them (**4b**, **4d**, **4f**, and **4h**, Table 1) being cinchona alkaloids, modified by free-radical addition of benzyl mercaptane to the vinyl group of the alkaloid. The standard reaction conditions (1 mol% catalyst, ambient temperature, solvent benzene) were essentially the same as in our previous report[1]. In a β-hydroxy amine catalyst the nitrogen atom serves as a basic center for ionization of the thioacid, while the hydroxy group enhances the rate of the reaction as well as the e.e. of the product through hydrogen bonding with the carbonyl group of the acceptor. It can be seen from Table 1 that the modified alkaloids where the additional thiobenzyl substituent at C-11 is *cis* to the

Table 2. *Effect of catalyst concentration* (**4a**) *on the e.e. of* **3a**

mol-% **4a**	0.1	0.5	1.0	2.0	5.0	10.0
e.e. **3a** (%)	50	51	53	58	61	45

Table 3. *Results of the asymmetric addition of thioacids* **1** *to* **2** *with* **4a** *as catalyst*

	R in **1**	Adduct **3** $[\alpha]_{578}$ (CCl_4) (°)	e.e. (%)[a]
a	CH_3	− 54.0	53
b	$(CH_3)_3C$	− 53.6	64
c	cyclo-C_6H_{11}	− 52.8	68[b]
d	C_6H_5	− 33.0	53[c]
e	*p*-$O_2NC_6H_4$	− 7.2	13

[a] Determined by ^{13}C-NMR—cf. Ref. [1]. All adducts **3** have (*S*)-configuration.
[b] Two crystallizations from *n*-hexane give a product with m.p. 58–59.5°, $[\alpha]_{578}$ − 75.6 (CCl_4); e.e. 98%.
[c] Crystallization from *n*-hexane affords a product, m.p. 81–84°, with no change of e.e.

hydroxy group (**4b**, **4d**) give a higher e.e. of the product compared to the parent compounds (**4a**, **4c**). The opposite effect is observed for the pair of alkaloids **4e**–**4f** and no effect for **4g**–**4h**. Apparently in **4b** and **4d** the thiobenzyl substituent exerts an additional steric hindrance to the acceptor **2**, bound to the catalyst by hydrogen bonding. This is in line with the transition state model proposed recently[3]. It should be noted that while cinchona and ephedra alkaloids give the best results as asymmetric catalysts, numerous other optically active β-hydroxy amines not mentioned in Table 1 [e.g. *L*-norepinephrine, *L*-phenylalaninol, *D*-phenylglycinol, (*R*)-1-amino-2-propanol], as well as other alkaloids (reserpine, α-isoparteine) give a product **3a** with low e.e.

We have also observed that the extent of asymmetric induction under otherwise standard conditions depends on the catalyst concentration (Table 2). With **4a** as catalyst the highest e.e. (61%) of **3a** was obtained at a concentration of 5 mol-%.

Since the structural demand of the thioacid nucleophile **1** is expected to affect the e.e. of the adduct **3**, we have used several thioacids **1a**–**1e** in a standard reaction with **2** (Table 3). It was gratifying to find a substantial increase of the e.e. of the product in the case of cyclohexanethiocarboxylic acid (**1c**). While no detailed explanation can be offered, we note that **1c** is of lowest symmetry and of higher conformational flexibility among the

thioacids **1a**–**1e**. On the other hand, the polar nitro-group in **1e** apparently cleaves the transition state formed by hydrogen bonding between the alkaloid and **2** molecules, thus lowering the e.e. of the product.

In summary, we have shown that an improved e.e. (up to 68%) of the addition product of a thioacid to 2-cyclohexenone can be obtained under chiral catalysis conditions with a proper choice of reactants and reaction conditions. Our efforts are aimed at a further development of these results.

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