ORGANIC
LETTERS

2005
Vol. 7, No. 18
4041−4043

Titanium(IV)-Catalyzed Enantioselective Sulfenylation of *β*-Ketoesters

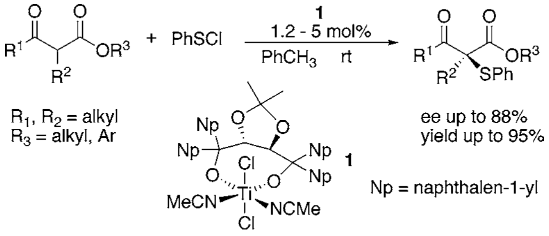
Marjan Jereb and Antonio Togni*

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH-Hönggerberg, CH-8093, Zürich, Switzerland

togni@inorg.chem.ethz.ch

Received July 5, 2005

ABSTRACT



A [Ti(TADDOLato)] complex (1) catalyzes the enantioselective sulfenylation of *β*-ketoesters using phenylsulfenyl chloride, giving ees of up to 88% and yields of up to 95%. The reaction does not require the presence of a base.

Chiral organic molecules containing a thioether moiety represent an important class of synthons in the synthesis of a wide variety of compounds. In addition, the sulfur atom can adopt several different oxidation states, thus enhancing the versatility of molecules containing sulfur functionalities. Optically active compounds containing such sulfur functionalities have been recognized as important auxiliaries, as well as ligands whose importance has been growing over the past decade.[1]

Thioether structural fragments also represent an important molecular tool as bioisosteric replacements in rational drug design.[2] Numerous sulfur-containing molecules exhibit diverse bioactive properties, e.g., antiinflammatory,[3] antiviral,[4] and inhibitory activity,[5] whereby the *β*-lactam and cephalosporin classes of antibiotics deserve special mention.

For this reason, selective and efficient methods for the direct generation of a stereogenic carbon center under concomitant formation of a new carbon−sulfur bond are of high importance. The vast majority of such methods that are available so far rely on the chiral auxiliary concept.[6] However, options such as the use of chiral sulfenylation reagents[7] and reaction under chiral PTC conditions[8] have

---

(1) See, for example: (a) Bayón, J. C.; Claver, C.; Masdeu-Bultó, A. M. *Coord. Chem. Rev.* **1999**, *193−195*, 73. (b) Skarżewski, J.; Gupta, A.; Wojaczyńska, E.; Siedlecka, R. *Synlett* **2003**, 1615.

(2) (a) Patani, G. A.;*Chem. Rev.* **1996**, *96*, 3147.

(3) (a) Procopiou, P. A.; Biggadike, K.; English, A. F.; Farrell, R. M.; Hagger, G. N.; Hancock, A. P.; Haase, M. V.; Irving, W. R.; Sareen, M.; Snowden, M. A.; Solanke, Y.; E.; Tralau-Stewart, C. J.; Walton, S. E.; Wood, J. A. *J. Med. Chem.* **2001**, *44*, 602. (b) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, 44.

(4) (a) Kucera, G. L.; Goff, C. L.; Iyer, N.; Morris-Natschke, S.; Ishaq, K. S.; Wyrick, S. D.; Fleming, R. A.; Kucera, L. S. *Antiviral Res.* **2001**, *50*, 129. (b) Nugent, R. A.; Schlachter, S. T.; Murphy, M. J.; Cleek, G. J.; Poel, T. J.; Wishka, D. G.; Graber, D. R.; Yagi, Y.; Keiser, B. J.; Olmsted, R. A.; Kopta, L. A.; Swaney, S. M.; Poppe, S. M.; Morris, J.; Tarpley, W. G.; Thomas, R. C. *J. Med. Chem.* **1998**, *41*, 3793.

(5) (a) Martin, L.; Cornille, F.; Turcaud, S.; Meudal, H.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **1999**, *42*, 515. (b) Gendron, F.-P.; Halbfinger, E.; Fischer, B.; Duval, M.; D'Orléans-Juste, P.; Beaudoin, A. R. *J. Med.* Chem. **2000**, *43*, 2239. (c) Buynak, J. D.; Chen, H.; Vogeti, L.; Gadhachanda, V. R.; Buchanan, C. A.; Palzkill, T.; Shaw, R. W.; Spencer, J.; Walsh, T. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1299.

(6) See, for example: (a) Yura, T.; Iwasawa, N.; Clark, R.; Mukaiyama, T. *Chem. Lett.* **1986**, *15*, 1809. (b) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159. (c) Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron Lett.* **1992**, *33*, 3797. (d) Poli, G. *J. Org. Chem.* **1993**, *58*, 3165. (e) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991. (f) Enders, D.; Schäfer, T.; Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349. (g) Kashima, C.; Takahashi, K.; Hosomi, A. *Heterocycles* **1996**, *42*, 241. (h) Enders, D.; Schäfer, T.; Mies, W. *Tetrahedron* **1998**, *54*, 10239. (i) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem.* Soc. **2000**, *122*, 7905.

(7) (a) Hiroi, K.; Nishida, M.; Nakayama, A.; Nakazawa, K.; Fujii, E.; Sato, S. *Chem. Lett.* **1979**, *8*, 969. (b) Tanaka, T.; Azuma, T.; Fang, X.; Uchida, S.; Iwata, C.; Ishida, T.; In, Y.; Maezaki, N. *Synlett* **2000**, 33.

(8) Wladislaw, B.; Marzorati, L.; Biaggio, F. C.; Vargas, R. R.; Bjorklund, M. B.; Zukerman-Schpector, J. *Tetrahedron* **1999**, *55*, 12023.

10.1021/ol051564g CCC: $30.25

been only scarcely studied. Indeed, the first report on catalytic asymmetric sulfenylation was published very recently.[9] Jørgensen reported that aldehydes could be transformed into their α-thioether analogues in high yields and excellent enantioselectivities using an organocatalytic methodology.[9b] However, the acid sensitivity of the pyrrolidine-derived catalyst and reaction intermediate requires the use of 1-benzylsulfanyl-1,2,4-triazole as the sulfenylation reagent, able to generate a neutral protonated leaving group.[9b]

Efficient catalytic properties of Ti(TADDOLato) complexes have been known for more that two decades.[10] A breakthrough in electrophilic atom-transfer reactions was achieved using [$TiCl_2$(*R*,*R*)-1-Np-TADDOLato)$(MeCN)_2$], **1** (1-Np = naphthalen-1-yl), for the first enantioselective catalytic fluorination reaction of β-ketoesters,[11] originally reported by our laboratory. The scope of this reaction was extended to bromination,[12] fluoro-chlorination,[13] chlorination,[12,14] and lately hydroxylation.[15] We therefore reasoned that the same system could be useful in view of developing a new catalytic and asymmetric carbon−sulfur bond-forming reaction. We report herein a highly effective catalytic asymmetric sulfenylation of β-ketoesters using complex **1** (Figure 1).

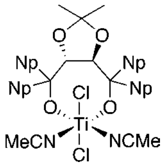
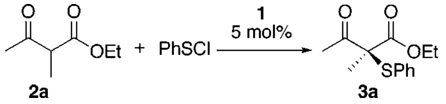


Figure 1. Ti[TADDOL(ato)] complex **1** (Np = 1-naphthyl)

Initially, ethyl 2-methylacetoacetate, **2a**, was reacted with 4-methylphenylsulfonyl chloride and 4-methylphenylsulfide in acetonitrile, respectively, in the presence of 5 mol % **1**, but after 20 h of stirring at room temperature, only starting material could be recovered. However, we assumed that phenylsulfenyl chloride would possess a sufficiently high electrophilic character to yield sulfenylated products and studied its reactivity on β-ketoester **2a** in different solvents. The results of this first screening are shown in Table 1.

Table 1. Role of Reaction Variables on the Sulfenylation of Ethyl-2-methylacetoacetate (**2a**)



entry	solvent	*T* (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	rt	12	94	40
2	Et_2O	rt	12	89	39
3	MeCN	rt	12	74	2
4	hexane	rt	14	92	50
5	$PhCH_3$	rt	12	94	53
6	$PhCH_3$	−58 to rt	15	92	44
7	$PhCH_3$	40	2.25	95	48
8	$PhCH_3$	50	1.5	90	49
9	$PhCH_3$	rt	12	82	38[c]

[a] Isolated yield. [b] Determined by chiral stationary phase HPLC. [c] Reaction in the presence of 2,6-di-*tert*-butylpyridine.

Reactions proceed smoothly at room temperature and reach complete conversions, as determined by NMR monitoring (Table 1, entries 1−8). In preparative experiments, the products are isolated in good yields from all selected solvents in nonracemic form. However, nonpolar solvents (entries 4 and 5) were found to be much more promising than polar ones (entry 3) in terms of enantioselectivity, toluene being the solvent of choice. It should be pointed out that hydrogen chloride, formed as a byproduct in stoichiometric amounts, does not hamper the transformation, despite the absence of a base in the reaction mixture. The observed acid tolerance of complex **1** and of its reaction intermediates formed during the catalytic reaction constitutes a significant advantage in terms of catalyst compatibility with different reaction systems and therefore enhances its versatility. Surprisingly, attempted neutralization of hydrogen chloride with 2,6-di-*tert*-butylpyridine in order to potentially increase enantiomeric excess had a deleterious effect on both yield and enantioselectivity (entry 9). The observed effect of temperature on enantioselectivity does not correspond to what one usually expects for asymmetric catalytic transformations. In fact, the highest values are obtained at room temperature, whereas low temperatures deteriorated the ee values more than elevated ones (entries 6−8).

As we reported before, the typical catalyst loading of **1** in halogenation and hydroxylation reactions is 5 mol %.[11−15] We were very pleased to find that for the new sulfenylation reaction, it is possible to go below this limit. Thus, model substrate **2a** was converted into **3a** in 92% yield and 52% ee using only 0.8 mol % **1**. Further decrease of the amount of **1** to 0.5 mol % had no influence on the conversion and yield (94%), but the ee decreased to 48%.

After a first optimization of the reaction conditions, we performed sulfenylations on a set of various substrates, **2b**−**f**, in toluene using 5 mol % catalyst **1** (see Table 2). Complete conversion for all substrates **2b**−**f** was established by NMR monitoring; the highest ee reached 88%, and the isolated yields were in the range 80−95%. The structure of the substrate plays a key role in influencing the enantioselectivity, the bulkiness of the ester group being crucial. Thus,

---

(9) (a) Wang, W.; Li, H.; Wang, J.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 8229 (first report on organocatalytic sulfenylation). (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.

(10) For a review, see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92.

(11) (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (b) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979.

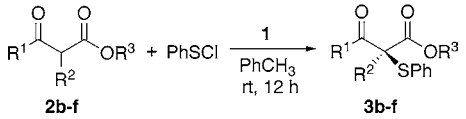
(12) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425.

(13) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709.

(14) Ibrahim, H.; Kleinbeck, F.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 605.

(15) Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810.

Table 2. Catalytic Asymmetric Sulfenylation of β-Ketoesters



entry	R_1	R_2	R_3	catalyst (mol %)	yield (%)[a]	ee (%)[b]
1	Me	Me	Am^t (**2b**)	1.2	80 (**3b**)	87
2	$(CH_2)_3$		Bu^t (**2c**)	1.2	84 (**3c**)	88
3	Me	Me	Bu^t (**2d**)	1.5	86 (**3d**)	88
4	Et	Me	Bu^t (**2e**)	5	80 (**3e**)	87
5	Et	Me	Ar^c (**2f**)	5	95 (**3f**)	86

[a] Isolated yield. [b] Enantiomeric excess determined by chiral stationary phase HPLC. [c] Ar is 2,4,6-triisopropylbenzyl.

replacement of the ethyl group in **2a** by *tert*-butyl, as in **2c**, brought about an ee increase of 35%. By further surveying the effect of catalyst loading on enantioselectivity for substrates **2b**−**f**, we found a threshold at around 1.2 mol % (Table 2, entries 1,2), though, unfortunately, this limit does not appear to be general. In fact, ees for other β-ketoesters (entries 3−5) eroded on average by 5−10% on going from a 5 mol % to a ca. 1 mol % catalyst loading. In the case of **2c** (entry 3), 1.5 mol % **1** was still sufficient to keep consistently high ees. β-Ketoesters derived from 2-methyl-3-oxopentanoic acid (entries 4 and 5) are sterically more demanding and seem to require 5 mol % **1** in order to prevent a decrease in enantioselectivity.

Although we did not yet determine the absolute configuration of any of the sulfenylated molecules obtained, the analogy to the related halogenation and hydroxylation reactions reported previously, for which the absolute stereochemistry of at least one product is known, allows us to make a well-founded prediction. We assume that the same intermediates containing a β-ketoester enolate coordinated to the Ti(IV) center in a chelating fashion is formed in all these reaction.[11b] By virtue of the shielding of the *re*-enantioface of the enolate by one of the two *face-on* naphthyl groups in the major diastereoisomeric intermediate containing the (*R*,*R*)-configured TADDOL, *si*-side attack by the electrophile leads to (*S*)-configured products (Figure 2).

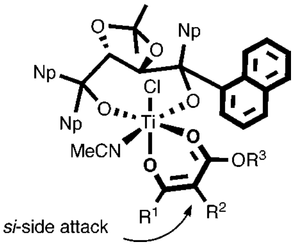


Figure 2. Proposed stereochemical model for the electrophilic attack of the sulfenylating agent.

In conclusion, we have developed a highly efficient, direct, enantioselective, catalytic sulfenylation of β-ketoesters using a chiral Ti(IV)(TADDOLato) catalyst that affords high yields and enantioselectivities of up to 88%. Reactions were carried out using phenylsulfenyl chloride, an easily accessible sulfenylation reagent, and without the need to add any base to neutralize the hydrogen chloride formed during the reaction. This catalyst compatibility towards the acidic byproduct under reaction conditions is a noticeable advantage with respect to alternative methods. This transformation opens a new entry to various classes of molecules containing a quaternary stereogenic carbon atom bearing a thioether functionality and should prove to be useful in the synthesis of optically active sulfur-containing molecules.

Acknowledgment. Financial support by ETH to M.J. is gratefully acknowledged.

Supporting Information Available: Experimental details, as well as spectroscopic and analytical characterization of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051564G