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Phthalimide-*N*-sulfenyl chloride in the Ti-catalyzed asymmetric sulfenylation of β-keto esters

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Abstract—The enantioselective sulfenylation of β-keto esters was carried out using phthalimide-*N*-sulfenyl chloride in the presence of a Ti(TADDOLato) catalyst affording up to 60% ee. X-ray crystal structures of product compounds **3a** and **9a** were determined.

1. Introduction

Optically active sulfur-containing compounds are important in the synthesis of a variety of versatile building blocks.[1] They play a relevant role in drug design as they exhibit bioactive properties such as anti-inflammatory,[2] antiviral,[3] and inhibitory activities.[4] Wang et al. described organocatalytic α-sulfenylations of aldehydes and ketones for the first time in the presence of chiral pyrrolidine trifluoromethane–sulfonamide.[5] Subsequently, Jørgensen reported the enantioselective transformation of aldehydes and 1,3-diketones into their α-thioether analogues using pyrrolidine-derived catalysts[6] and cinchona alkaloid derivatives.[7] Besides these recent approaches, chiral auxiliaries have been employed in the synthesis of compounds having a C–S bond at a stereogenic center.[8]

Chiral Ti(TADDOLato) complexes have been widely used in our group as catalysts in asymmetric electrophilic hydroxylation[9] and halogenation reactions (bromination,[10] chlorination,[10,11] and fluorination[12]) of β-keto esters. We recently extended the scope and utility of this type of catalysts to asymmetric sulfenylation reactions.[13] Excellent yields and high enantiomeric excesses were obtained when using PhSCl as a sulfenylating agent. However, a serious limitation of the α-phenylsulfenyl β-keto esters is the difficulty in converting the thioether group to, for example, the free thiol, thus reducing its versatility. Herein, we report that as an alternative to PhSCl, phthalimide-*N*-sulfenyl chloride **1**,[14] can also be applied in the electrophilic sulfenylation reactions of β-keto esters and show the cleavage of the product S–N bond in the presence of PhSH. We also describe the X-ray crystal structures of two sulfenylated products **3a** and **9a**.

2. Results and discussion

The sulfur-containing reagents *N*,*N*′-dithiobis(phthalimide),[15] a precursor to phthalimide-*N*-sulfenyl chloride, and S_2Cl_2 were initially reacted with ethyl 2-methylacetoacetate **3** at room temperature in toluene. Only starting material could be recovered when the reaction was carried out with *N*,*N*′-dithiobis(phthalimide). Compound **3a** could not be obtained either upon heating or in the presence of a catalyst. On the other hand, a mixture of two non-separable compounds **4** and **5** was recovered when ethyl 2-methylacetoacetate **3** was treated with S_2Cl_2 (Scheme 1).

The formation of compound **5** could not be avoided either in the presence of a catalyst or when the reaction was carried out at −78 °C.

Phthalimide-*N*-sulfenyl chloride **1** obtained by the cleavage of *N*,*N*′-dithiobis(phthalimide) displays a highly electrophilic character because of the presence of the phthalimide substituent. Prior to carrying out catalytic sulfenylations, we did some stoichiometric reactions between ethyl 2-methylacetoacetate **3** and phthalimide-*N*-sulfenyl chloride at room temperature in toluene. Complete conversion of the starting material was observed within a short time (45 min) and a yield of 97% was obtained, whereas the

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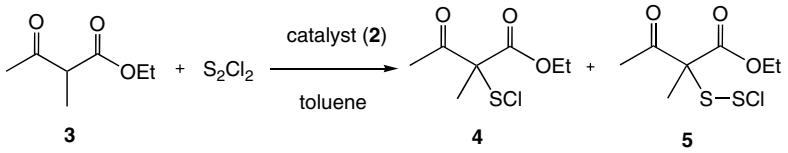


Scheme 1. Sulfenylation with S_2Cl_2.

starting material was recovered when PhSCl was used under the same conditions.[13] A single product **3a** was formed exclusively also when the reaction was carried out with a mixture of the two sulfenylating agents in toluene at room temperature. This simple competition experiment clearly shows the highly electrophilic nature of phthalimide-*N*-sulfenyl chloride. Despite the smooth uncatalyzed reaction of this reagent with β-keto ester **3**, a series of experiments were done in both polar as well as non-polar solvents (Table 1) using 2 mol % of the Ti(TADDOLato) catalyst **2**[16] (Scheme 2).

Although the reaction time was lowered to 30 min, excellent yields and promising enantiomeric excesses of up to 41% ee were obtained, whereby toluene turned out to be the solvent of choice. There was no increase in enantioselectivity when the reaction was carried out at low temperature (−78 °C). In the presence of a stoichiometric amount of NEt_3, used with the aim of neutralizing the HCl formed in the course of the reaction, surprisingly no reaction occurred. It is often observed that the enantioselectivity is directly related to the catalyst loading, but we observed an opposite trend whose reasons are unclear at present. The increase in the catalyst loading to 8 mol % had a negative effect on the enantioselectivity even though high yields were obtained (Table 2).

From the above experiments, we can say that the asymmetric sulfenylation reaction using phthalimide-*N*-sulfenyl chloride is successful in the absence of a base and when carried out at room temperature in the presence of 2 mol % catalyst. After optimizing the reaction conditions, asymmetric sulfenylation reactions were performed on different substrates at room temperature (Scheme 3, Table 3). The isolated yields were in the range of 94–98% with a maximum ee of 60% (for **8a**). All new compounds were characterized by ^1H and ^{13}C NMR spectroscopy, MS, and elemental analysis.

Replacement of the ethyl group in **3a** by a benzyl group, as in **6a**, did not result in an increase of enantioselectivity (42%). The replacement of the methyl ketone fragment in **3a** with a corresponding phenyl ketone in **7a** brought the enantioselectivity down to 35% ee. Ethyl cyclohexanone-2-carboxylate reacted smoothly with phthalimide-*N*-sulfenyl chloride to yield **8a** (yield 94%, ee 60%) whereas no product was observed starting from ethyl cyclopentanone-2-carboxylate at room temperature. Under reflux conditions, even for 1 day, only 10% conversion could be achieved. The enantiomeric excess for compounds **9a** and **10a** could not be determined by HPLC because no suitable conditions could be found using several different stationary phases.

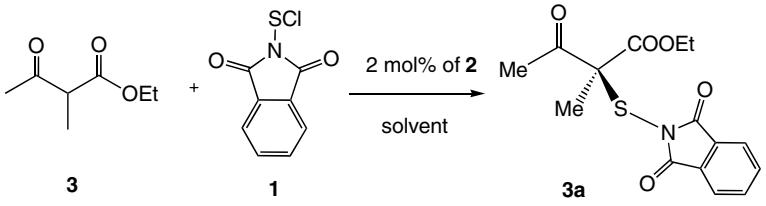
The reactivity of the S–N bond of the sulfenylated β-keto ester was studied in the presence of PhSH (Scheme 4). The stoichiomteric reaction between **3a** and PhSH in toluene at room temperature resulted in the generation of the disulfide **11** that was isolated in 84% yield. This reaction does not affect the enantioselectivity to any appreciable extent.

Table 1. Solvent effects on the asymmetric sulfenylation of ethyl 2-methylacetoacetate **3**

Solvent	Temperature	Time (min)	Yield (%)	ee (%)
CH_3CN	rt	30	94	2
THF	rt	30	86	6
CH_2Cl_2	rt	30	98	18
Et_2O	rt	30	98	29
Toluene	−78 °C to rt	4 h	95	40
Toluene	rt	30	97	41

3. Solid state structure of products

The absolute configuration of the products derived from β-keto esters was hitherto unknown, but it could be presumed that the use of the Ti(*R*,*R*-TADDOLato) catalyst would preferentially lead to products of (*S*)-configuration, as previously shown unambiguously for the analogous fluorination reaction.[17] Crystals of the solid products **3a** and **9a** suitable for X-ray structural analysis were obtained from dichloromethane solutions at room temperature.[18]

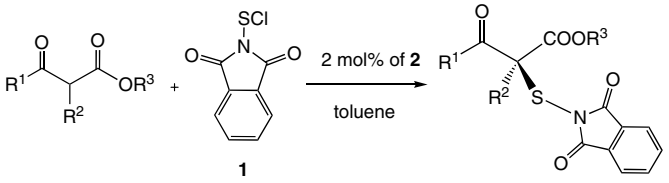


Scheme 2. Asymmetric sulfenylation of ethyl acetoacetate with phthalimide-*N*-sufenyl chloride **1**.

Table 2. Effect of catalyst loading on the sulfenylation of ethyl 2-methylacetoacetate **3**

Entry	Catalyst	mol %	Time (min)	Yield (%)[a]	ee[b] (%)
1	—	—	45	97	*rac*
2	$TiCl_4$	2	30	95	*rac*
3	Ti(TADDOLato)	1	30	96	36
4	Ti(TADDOLato)	2	30	97	41
5	Ti(TADDOLato)	4	30	93	31
6	Ti(TADDOLato)	6	30	95	29
7	Ti(TADDOLato)	8	30	95	30

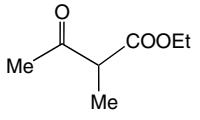
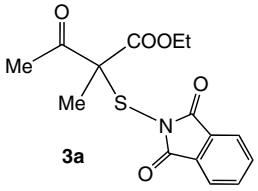
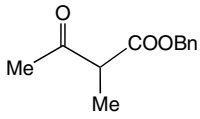
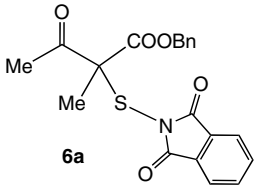
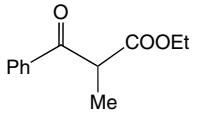
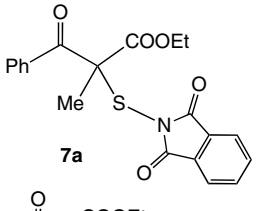
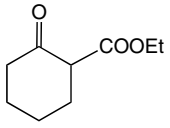
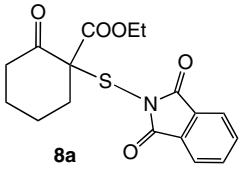
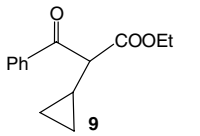
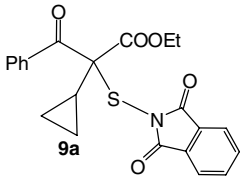
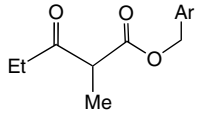
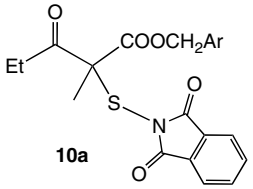
[a] Isolated yields.
[b] Determined by chiral HPLC.

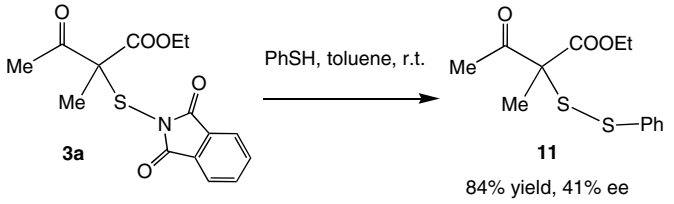


Scheme 3. Asymmetric sulfenylation of β-keto esters.

Compound **3a** crystallizes in the (chiral) monoclinic space group $C2$, while crystals of **9a** belong to the monoclinic centrosymmetric space group $P2_1/a$. ORTEP plots of these two compounds are shown in Figures 1 and 2, respectively. Whereas crystals of **9a** are racemic, crystals of **3a** are enantiomerically pure. In this case, when the structure is refined with the (*S*)-absolute configuration at C(1), the Flack parameter x[19] is −0.07(15), close enough to 0 for a correct absolute configuration [conversely, $x = 1.05(15)$ for the (*R*)-configuration]. Therefore, it is reasonable to assume that the enantiomer predominantly formed under catalytic

Table 3. Catalytic asymmetric sulfenylation of β-keto esters

Substrate	Product	Time (min)	Yield (%)	ee (%)	Mp (°C)
 **3**	 **3a**	30	97	41	134–135
 **6**	 **6a**	30	94	42	122–123
 **7**	 **7a**	30	97	35	145
 **8**	 **8a**	45	94	60	103
 **9**	 **9a**	30	96	nd	134–135
 **10** Ar=2,4,6-(*i*Pr)$_3$Ph	 **10a**	30	98	nd	95



Scheme 4. Cleavage of the S–N bond of **3a** in the presence of PhSH.

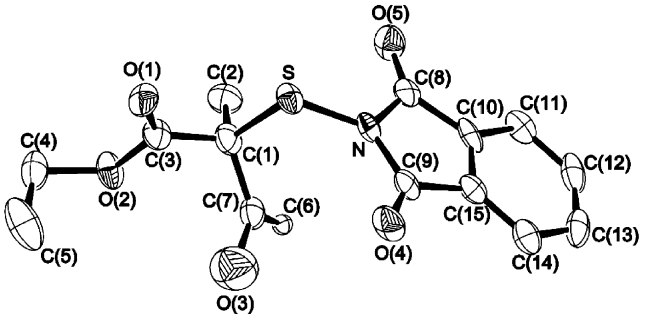


Figure 1. ORTEP view of compound **3a** in the crystal with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: C(1)–S 1.858(6); S–N 1.703(6); C(1)–C(2) 1.541(10); S–C(1)–C(3) 101.2(4).

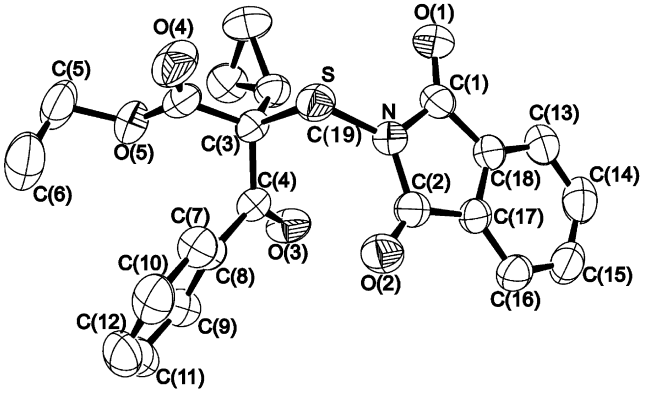


Figure 2. ORTEP view of compound **9a** in the crystal with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. The *S* enantiomer of the racemic compound is shown arbitrarily. Selected bond lengths [Å] and angles [°]: C(3)–S 1.860(16); S–N 1.690(15); S–C(3)–C(19) 102.12(11).

conditions using the Ti(*R*,*R*-TADDOLato) complex corresponds to the isolated crystalline compound having an (*S*)-configuration, as this is obtained from the enantiomerically enriched product mixture.

Both compounds display similar bonding parameters. The C–C bond (C(1)–C(3) (**3a**), and C(3)–C(19) (**9a**), respectively) and the S–N bond of thiophthalimide unit in both compounds are nearly anti periplanar to each other [dihedral angle: N–S–C(1)–C(3) 174.5° (**3a**), and N–S–C(3)–C(19) 175.6° (**9a**)]. The S–N bond distances are 1.703(6) (**3a**) and 1.690(15) Å (**9a**), respectively.

4. Conclusions

We have successfully used the reagent phthalimide-*N*-sulfenyl chloride **1** in the asymmetric sulfenylation of β-keto esters catalyzed by Ti(TADDOLato) complexes. The enantioselectivities obtained are lower than those of the corresponding reaction with PhSCl, probably due to a much higher contribution by the uncatalyzed reaction. Still, this reaction remains a rare example of transition-metal-catalyzed enantioselective carbon–sulfur bond-forming process. The presence of a base and a higher catalyst loading hinders the sulfenylation reaction. The (*S*)-configured product of β-keto ester **3a** was obtained in crystalline form and its X-ray crystal structures was studied. The cleavage of the S–N bond in the presence of PhSH shows the labile nature of S–N bond and the suitability of the phthalimido sulfenyl group as a masked thiol.

Acknowledgements

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References

1. (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363–382; (b) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453–461.
2. (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*, 602–612; (b) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, 41–44.
3. (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*, 129–137; (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*, 3793–3803.
4. (a) Martin, L.; Cornille, F.; Turcaud, S.; Meudal, H.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **1999**, *42*, 515–525; (b) Gendron, F.-P.; Halbfinger, E.; Fischer, B.; Duval, M.; D'Orléans-Juste, P.; Beaudoin, A. R. *J. Med. Chem.* **2000**, *43*, 2239–2247; (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*, 1299–1304.
5. Wang, W.; Li, H.; Wang, J.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 8229–8231.
6. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.
7. Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689–5694.
8. (a) Yura, T.; Iwasawa, N.; Clark, R.; Mukaiyama, T. *Chem. Lett.* **1986**, *15*, 1809–1812; (b) Youn, J.-H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159–161; (c) Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron Lett.* **1992**, *33*, 3797–3800; (d) Poli, G.

J. Org. Chem. **1993**, *58*, 3165–3168; (e) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991–3994; (f) Enders, D.; Schäfer, T.; Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349–3362; (g) Kashima, C.; Takahashi, K.; Hosomi, A. *Heterocycles* **1996**, *42*, 241–250; (h) Enders, D.; Schäfer, T.; Mies, W. *Tetrahedron* **1998**, *54*, 10239–10252; (i) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.

9. Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810–5814.
10. (a) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425–2435; (b) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709–1712.
11. Ibrahim, H.; Kleinbeck, F.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 605–610.
12. Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359–4362.
13. Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041–4043.
14. (a) Zibarev, A. V.; Miller, A. O.; Gatilov, Y. V.; Furin, G. G. *Heterocycl. Chem.* **1990**, *1*, 443–453; For applications, see: (b) Capozzi, G.; Delogu, G.; Fabbri, D.; Marini, M.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **2002**, *67*, 2019–2026; (c) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **1997**, *62*, 2611–2615; (d) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Raffaelli, B. *Chem. Eur. J.* **1999**, *5*, 1748–1754; (e) Capozzi, G.; Delogu, G.; Dettori, M. A.; Fabbri, D.; Menichetti, S.; Nativi, C.; Nuti, R. *Tetrahedron Lett.* **1999**, *40*, 4421–4424.
15. Hutchinson, S. A.; Baker, S. P.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem.* **2004**, *12*, 4877–4884.
16. Catalyst **2** is the bis(acetonitrile) adduct of dichloro[4*R*,5*R*-2,2-dimethyl-α,α,α′,α′-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanolato(2-)-*O*,*O*′]titanium.
17. (a) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979–982; (b) Perseghini, M.; Massaccesi, M.; Liu, Y.; Togni, A. *Tetrahedron* **2006**, *62*, 7180–7190.
18. CCDC 619939 and 619940 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].
19. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.