# Asymmetric Synthesis of β-Mercapto Carboxylic Acid Derivatives by Intramolecular Sulfur Transfer in *N*-Enoyl Oxazolidine-2-thiones Promoted by Lewis Acids

Claudio Palomo,*[,†] Mikel Oiarbide,[†] Flavia Dias,[†] Aurelio Ortiz,[†] and Anthony Linden[‡]

*Departamento de Química Orgánica I*
*Facultad de Química,Universidad del País Vasco*
*Apdo. 1072, 20080 San Sebastián, Spain*
*Organisch-chemisches Institut der Universität Zürich*
*Winterthurerstrasse 190, CH-8057, Zürich, Switzerland*

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β-Heterosubstituted carbonyl compounds are widespread in natural products, and their synthesis has attracted much interest. Unlike β-oxy and β-amino carbonyl compounds, which are accessible through many different approaches, β-thio carbonyl compounds can only be reached through a very narrow range of synthetic routes.[1] For instance, while the aldol and the Mannich methodologies have been profusely developed in the former cases, the aldol strategy involving thioaldehydes is of very limited use, because of the poor electrophilicity of thioaldehydes, among other reasons.[2] The general practice so far documented for the preparation of β-thio carbonyl compounds is the conjugate addition of thiols to α,β-unsaturated carbonyl systems. In recent years both diastereo- and enantioselective versions of this approach have been addressed with success. In the diastereoselective methods,[3] a chiral auxiliary is typically attached to the enoyl substrate prior to the intermolecular attack of a thiol,[4] while in the enantioselective cases,[5] both enoyl derivatives and enones have been reacted with thiols in the presence of chiral ligand−metal complexes. Common to both strategies is the use of arenethiols as the nucleophile.[6] In consequence, aryl sulfides are obtained, from which the dearylation process to yield the eventually desired free thiol is not always straightforward. We report herein on a conceptually new strategy for the asymmetric synthesis of β-mercapto carboxylic acids and alcohols that formally effects the conjugate addition of simple "SH$^-$" to enoyl imides in a highly stereocontrolled way. The new synthetic concept is outlined in Figure 1. This development is founded upon the effective asymmetric induction that could reasonably be expected in such an intramolecular process (**I** to give **II**), even if the stereogenic unit is remote from the bond-forming atoms.[7]

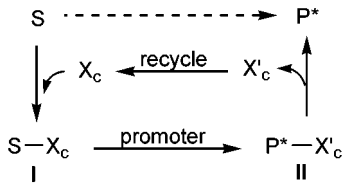


**Figure 1.** General principles of the new strategy: (1) attachment of a chiral auxiliary; (2) intramolecular reaction promoted by an additive, which also alters the auxiliary; (3) detachment of the product and of the modified auxiliary; and (4) regeneration of the original auxiliary.

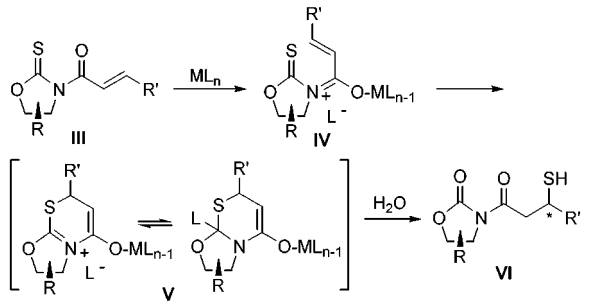


**Figure 2.** Possible course of the reaction from **III** to **VI**.

To put this idea into practice, we succeeded in carrying out the reaction of *N*-enoyl oxazolidine-2-thiones **III**, Figure 2, with some Lewis acids to yield, after hydrolysis, the corresponding β-mercapto carbonyl adducts **VI**. Our idea was inspired by the well-documented tendency for allyl thiocarbamates and thioureas to undergo electrocyclic intramolecular rearrangements.[8] Given the assumption that *N*-enoyl oxazolidine-2-thiones **III** upon complexation with a Lewis acid would render species **IV**, a subsequent electrocyclic cyclization followed by hydrolysis to **VI**, as described in Figure 2, is a plausible conjecture.

Accordingly, see Table 1, it was found that 0.01−0.05 M solutions of substrates **1**−**4** in methylene chloride react smoothly with $SnCl_4$ at −78 °C in a few hours to afford, after simple aqueous workup, adducts **5**−**8**. As the results in the table show, this unprecedented transformation is general for both aromatic and aliphatic R groups and successfully tolerates structurally different oxazolidine-2-thiones. Nevertheless, the presence of aromatic groups in the substrate has a significant influence on the reaction outcome. In fact, when R is an aromatic group, the initially formed solid in the reaction[9] did not evolve unless the reaction mixture was allowed to reach room temperature. The essentially perfect diastereocontrol exerted during the process for R = aliphatics (entries a−c, i−k, and n−o), regardless of the auxiliary employed, is, however, lowered for the aromatic cases (entries d−h, l, and m), presumably due to the higher reaction temperatures used.[10]

[†] Universidad del País Vasco.
[‡] Universität Zürich (X-ray analyses).

(1) Leading references, see: (a) Baird, C. P.; Rayner C. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1973. (b) Procter D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 641.

(2) See, for instance: (a) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99. (b) Usov, V. A.; Timokhina, L. V.; Voronkov, M. G. *Russ. Chem. Rev.* **1990**, *59* (4), 378. (c) Zhang, X.-M.; Malick, D.; Petersson, G. A. *J. Org. Chem.* **1998**, *63*, 5314. For a review on C−S bond formation, see: (d) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.

(3) For leading references, see: (a) Wu, M.-J.; Wu, C.-C.; Tseng, T.-C. *J. Org. Chem.* **1994**, *59*, 7188. (b) Tsai, W.-J.; Lin, Y.-T.; Uang, B.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1195. (c) Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1995**, *60*, 6188. (d) Taber, D. F.; Gorski, G. J.; Liable-Sands, L. M.; Rheingold, A. L. *Tetrahedron Lett.* **1997**, *38*, 6317. (e) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **1997**, *53*, 2421. (f) Lin, C.-H.; Yang, K.-S.; Pan, J.-P.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 6815.

(4) For a case of diastereoselective, reagent-controlled, addition of thiols to enones, see: Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927.

(5) (a) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2181. (b) Kobayashi, N.; Iwau, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071. (c) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (d) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363. (e) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974. (f) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (g) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett.* **1998**, *39*, 2141. (h) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675. (i) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589.

(6) Reactions with benzyl thiol as the nucleophile have been documented in ref 5f.

(7) For more information on this subject, see: Tokoroyama, T. *Chem. Eur. J.* **1998**, *4*, 2397.

(8) Selected examples: (a) Hayashi, T. *Tetrahedron Lett.* **1974**, 339. (b) Nakai, T.; Ari-Izumi A. *Tetrahedron Lett.* **1976**, 2335. (c) Soledade, M.; Pedras, C.; Okanga, F. I. *Chem. Commun.* **1998**, 67. For a recent paper dealing with a very similar cyclization of homoallylic systems, see: (d) Hari, A.; Miller, B. L. *Org. Lett.* **2000**, *2*, 3667.

(9) Upon the addition of the Lewis acid to a solution of the corresponding oxazolidine-2-thione in methylene chloride, a white solid slowly appears, which redissolves on stirring for 5−10 min at the same temperature (−78 °C) for R = aliphatics. This precipitate remains unaltered for R aromatics, unless the mixture is warmed close to room temperature.

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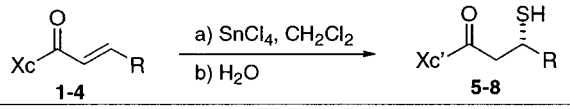
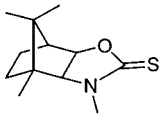
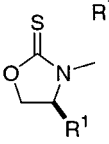
**Table 1.** $SnCl_4$ Promoted Rearrangement of *N*-Enoyl Chiral Imides **1**−**4** to *β*-Mercapto Carbonyl Derivatives[a]

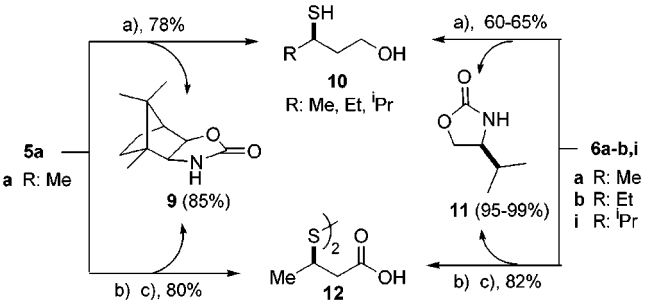



| | Xc | 1-4 | R | 5-8 | d.r.[b] | Yield[c] % |
|---|---|---|---|---|---|---|
| a |  | **1a** | Me | **5a** | ≥98:2 | 84 |
| b | | **1b** | Et | **5b** | ≥98:2 | 83 |
| c | | **1c** | $CH_3(CH_2)_6$ | **5c** | ≥98:2 | 85 |
| d | | **1d** | Ph | **5d** | 94:6 | 85 |
| e | | **1e** | 4-$CH_3$-Ph | **5e** | 70:30 | 98[d] |
| f | | **1f** | 4-$CH_3O$-Ph | **5f** | 65:35 | 95[d] |
| g | | **1g** | 4-Cl-Ph | **5g** | 93:7 | 76[d] |
| h | | **1h** | 4-Br-Ph | **5h** | 88:12 | 95[d] |
| i | $R^1$: $^i$Pr | **2a** | Me | **6a** | ≥98:2 | 72 |
| j |  | **2b** | Et | **6b** | ≥98:2 | 67 |
| k | | **2i** | $^i$Pr | **6i** | ≥98:2 | 70 |
| l | | **2d** | Ph | **6d** | 87:13 | 80[d] |
| m | | **2g** | 4-Cl-Ph | **6g** | 75:25 | 70[d] |
| n | $R^1$: Bn | **3a** | Me | **7a** | ≥98:2 | 56 |
| o | $R^1$: Ph | **4a** | Me | **8a** | ≥98:2 | 72 |

[a] Reactions conducted on a 1 mmol scale, at −78 °C, except for R aromatics, where the reaction mixture was warmed to room temperature after the addition of $SnCl_4$ at −78 °C. [b] Corroborated by HPLC in cases i−k. [c] Yields of isolated pure compounds after column chromatography. [d] Combined yield of the mixture of diastereomers after column chromatography.

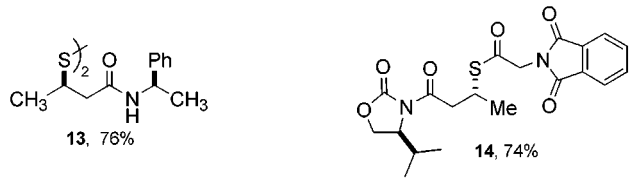
Diastereomeric ratios for the adducts were conveniently determined using $^{13}C$ NMR spectra from each crude reaction, and were corroborated by HPLC for selected cases. Apart from $SnCl_4$, among the other Lewis acids tested, i.e., $TiCl_4$, $Ti(^iPrO)_4$, $BF_3$:$Et_2O$, $ZnBr_2$, $Me_2AlCl$, $Cu(AcO)_2$, and $Cu(TfO)_2$, only $TiCl_4$ gave rise to comparable results. The reaction also occurred with $BF_3$:$Et_2O$ and $ZnBr_2$, although in lower chemical and stereochemical efficiency. On the other hand, although the best reaction conditions in terms of isolated yield of the adducts were obtained using 1.5 equiv of $SnCl_4$, the reaction also proceeded, more slowly, with substoichiometric amounts of the Lewis acid.[11] Detachment of the altered chiral auxiliary from the adducts, with simultaneous liberation of the corresponding *β*-mercapto alcohols or carboxylic acids, could be carried out as illustrated in Scheme 1. For instance, treatment of adducts **5a** and **6a**,**b**,**i** with sodium borohydride in a mixture of THF−$H_2O$[12] gave rise to oxazolidinones **9** and **11** in isolated yields of 85% and 95−99%, respectively, along with the respective mercapto alcohols **10** in 60−78% isolated yields. The enantiomeric purity of the mercapto alcohols was determined by HPLC analysis and comparison with racemic samples.[13] On the other hand, lithium peroxide assisted hydrolysis[14] of both **5a** and **6a**, after blocking of thiols as their symmetrical disulfides, afforded the dicarboxylic acid **12** as a glassy solid. Coupling of this compound with (*R*)-(+)-α-methylbenzylamine gave rise to the symmetrical diamide **13** as the only diastereomer detected, Chart 1. In addition, an X-ray structural analysis of crystalline compound **14**, obtained from acylation of **6a**, allowed us to confirm the assigned configuration of the newly created stereogenic center.

**Scheme 1.** Detachment of the Auxiliary[a]




[a] Conditions: (a) $NaBH_4$, $H_2O$−THF, room temperature, 2 h. (b) $I_2$, $CCl_4$, room temperature, 1 h. (c) LiOH, $H_2O_2$, THF−$H_2O$, 0 °C, 1 h.

**Chart 1**




Finally, regeneration of oxazolidine-2-thiones from the recovered oxazolidinones **9** and **11** was achieved by treatment with Lawesson's reagent.[15] In not fully optimized runs, we found that treatment of oxazolidinone **11** with Lawesson's reagent in dioxane at reflux for 7 h gave rise to a complete reaction conversion (56% conversion for **9**, after 3 days under same conditions), from which experiment the corresponding pure oxazolidine-2-thione could be isolated in 75% yield.

In conclusion, an unprecedented sulfur migration in *N*-enoyl oxazolidine-2-thiones promoted by Lewis acids has been found, which takes place with asymmetric inductions from perfect to high, to afford *β*-mercapto imides. The removal of the chiral auxiliary from these adducts provides *β*-disulfide carbonyl compounds and *β*-mercapto alcohols in very good yields. In this development, the chiral auxiliary plays a dual action as the chiral controller of the process and, at the same time, the reagent.

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**Supporting Information Available:** Complete experimental procedures for the preparation of new compounds, and for the determination of diastereo- and enantiomeric ratios (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In support of this assumption, when the reactions of the substrates bearing R aliphatic substituents were deliberately carried out at room temperature, a nearly equimolar mixture of the epimeric thiols was formed in each case. The isomeric mixtures thus obtained were valuable when determining the absence of the epimer in the reactions run at −78 °C (see Supporting Information).

(11) With loadings of $SnCl_4$ as low as 10 mol %, a reaction conversion of 85% was measured after 120 h; with 20 mol % of $SnCl_4$, the same conversion was measured after 24 h. In addition, no loss of diastereoselectivity was observed under these conditions.

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(13) For an efficient HPLC detection, adducts **10** as well as the corresponding racemic samples were derivatized to their dibenzoyl derivatives prior to analysis (for details, see Supporting Information).

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(15) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. O., Ed.; John Wiley: Chichester, 1995; Vol. 1, p 530.