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Synthesis of 3-sulfanylpropanols containing three consecutive stereocenters via tandem Michael–aldol reaction of enoylthioamides with acetals as key reaction

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Abstract—(2*S*,3*S*,1′*R*)-2-(α-Methoxybenzyl)-3-phenyl-3-sulfanylpropionamides were diastereoselectively prepared by the reactions of *N*-cinnamoyl-4*S*-isopropyl-5,5-dimethyloxazolidinethione with acetals in the presence of $SnCl_4$. The absolute configuration of the three newly created contiguous stereocenters was determined by the X-ray analysis of the disulfide. The amides were transformed into propanols by the reductive removal of the oxazolidinone moiety.

Efficiency and elegance are valued characteristics of tandem reactions. Even more appealing are those tandem processes which form carbon–carbon bonds and thereby generate new chiral centers stereoselectively. One of them is the Morita–Baylis–Hillman (tandem Michael–aldol–retro Michael) reaction,[1] which is an atom-economical, carbon–carbon bond-forming reaction involving the coupling of the α-position of activated alkenes with electrophiles (usually aldehydes) under the influence of Lewis bases such as DABCO,[1] Ph_3P,[1] chalcogen species,[2] and proazaphosphatrane sulfide.[3] This reaction is traditionally very slow, so we[4] and other groups[5] independently developed the $TiCl_4$–mediated tandem Michael–aldol reaction, to overcome this drawback. Recently, we succeeded in the simultaneous synthesis of four chiral centers by the tandem Michael–aldol reaction of *N*-cinnamoyl-4*S*-methyl-5*R*-phenyloxazolidinethione with aldehydes.[6] This reaction gave the chiral product with good to high diastereoselectivity, and we further investigated the chiral auxiliary, which induces the high diastereoselectivity and gives the stereochemically pure products easily. On the other hand, we have reported a simple procedure for the α-alkoxyalkylation of enones via the tandem Michael–aldol reaction of chalcogenide-enones with acetals using $BF_3{\cdot}Et_2O$.[2d] Herein, we describe the reaction of *N*-cinnamoyl-4*S*-isopropyl-5,5-dimethyloxazolidinethione (**1**) with acetals in the presence of a Lewis acid and transformation of the products into 2-(α-methoxybenzyl)-3-phenyl-3-sulfanylpropanols.

First, we used $BF_3{\cdot}Et_2O$ as a Lewis acid for the reactions of **1** with benzaldehyde dimethyl acetal (**2a**) and obtained a complex mixture.[2d] Then, $SnCl_4$ was used instead of $BF_3{\cdot}Et_2O$[6] because the chloride ion generated from $SnCl_4$ would react with the iminium intermediate to give a more stable chloroamine intermediate. The reaction of **1** with **2a** afforded the adduct **3a** in good chemical yield and with excellent diastereoselectivity.[7] Although no difference of the yields was observed between quenching the reaction mixture with water and with satd $NaHCO_3$, we worked up the reaction with saturated aqueous $NaHCO_3$ to avoid decomposition of the products with an acid (Table 1, entries 1 and 2). Reactions with 4-chloro **2b** and 4-methoxy derivative **2c** similarly gave **3b** and **3c** with excellent diastereoselectivity (entries 3 and 4). Reaction with 4-nitrobenzaldehyde dimethyl acetal (**2d**) formed **3d** with excellent diastereoselectivity but in a low chemical yield because of lability of the *p*-nitrobenzyl carbenium ion (entry 5).

Keywords: Tandem Michael–aldol reaction; Asymmetric synthesis; Oxazolidinethione; Acetal; Sulfanylpropanol.
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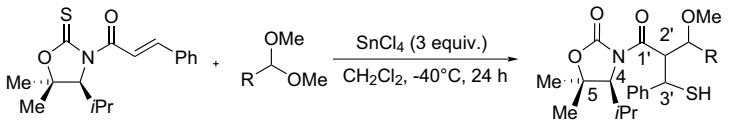
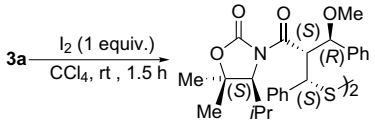
Table 1. Reaction of *N*-cinnamoylthioamide **1** with acetals **2a–d**



1 (1 equiv.) **2** (2 equiv.) **3**

Entry	Acetal **2**	Yield (%)[a]	de[b]
1	**2a** (R = Ph)	**3a** (79)	>95%
2[c]	**2a** (R = Ph)	**3a** (82)	>95%
3	**2b** (R = *p*-ClC_6H_4)	**3b** (87)	>95%
4	**2c** (R = *p*-$MeOC_6H_4$)	**3c** (66)	>95%
5	**2d** (R = *p*-$NO_2C_6H_4$)	**3d** (45)	>95%

[a] Isolated yield after the recycling HPLC.
[b] Determined by ^1H NMR.
[c] Quenched with water instead of aqueous saturated $NaHCO_3$.



4 (79%)

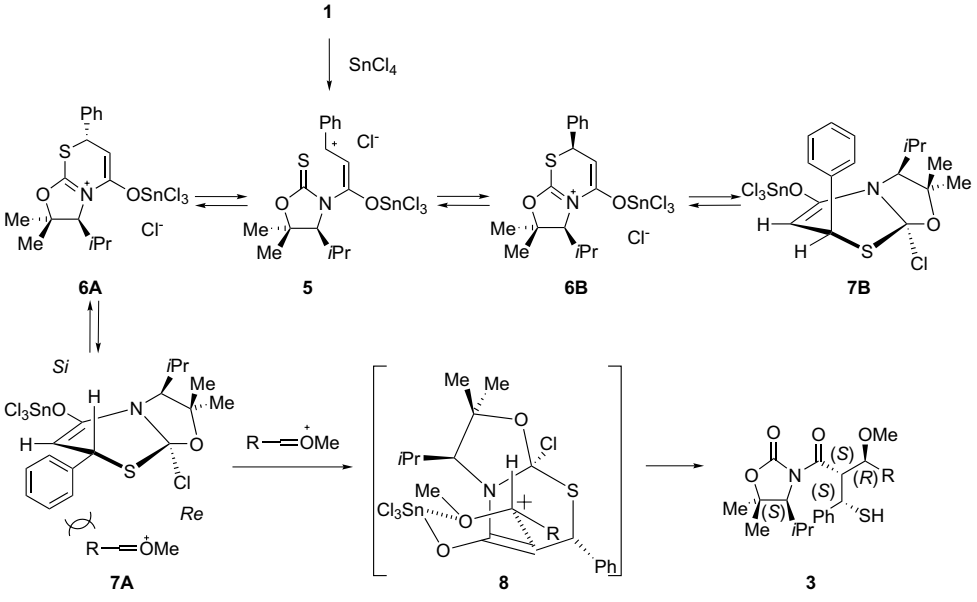
Scheme 1. Synthesis of dimer **4**.

Unfortunately, the expected reaction did not proceed in the case of aliphatic acetals.

An X-ray structural analysis of crystalline compound **4**, obtained by the oxidative dimerization of **3a**, allowed us to assign the configurations of the newly created stereogenic centers as shown in Scheme 1 (Fig. 1).[8]

Stereoselection would be effected in the steps of the Michael addition of the thiocarbonyl group to the enone moiety and the aldol reaction of the tin enolate with a methoxycarbenium ion. A plausible mechanism is shown in Scheme 2.

Intramolecular Michael addition of the thioamide group of **1** to the enone moiety activated by $SnCl_4$ forms cyclic chloroamine **7** rather than iminium chloride **6** via tin enolate **5**, because the absolute configuration of the benzylic position α to the sulfur atom of **3** is different from that of the product obtained from the reaction with aldehydes using $BF_3{\cdot}Et_2O$.[6] Since the *Si*-face is sterically more crowded than the *Re*-face and the $SnCl_3$ moiety occupies the opposite side of isopropyl, methyl, and phenyl groups, the chloride anion of **6** attacks the iminium carbon from the *Re*-face to form chloroamine **7**. Steric repulsion among the phenyl, methyl, and isopropyl groups of **7B** is quite strong on the *Si*-face. The chlorine atom interferes with the *Re*-face attack of the methoxycarbenium ion to the enolate ion. The other isomer **7A** has a pseudoequatorial phenyl group and this conformation relaxes the steric hindrance between the



Scheme 2. Reaction mechanism for the formation of **3**.

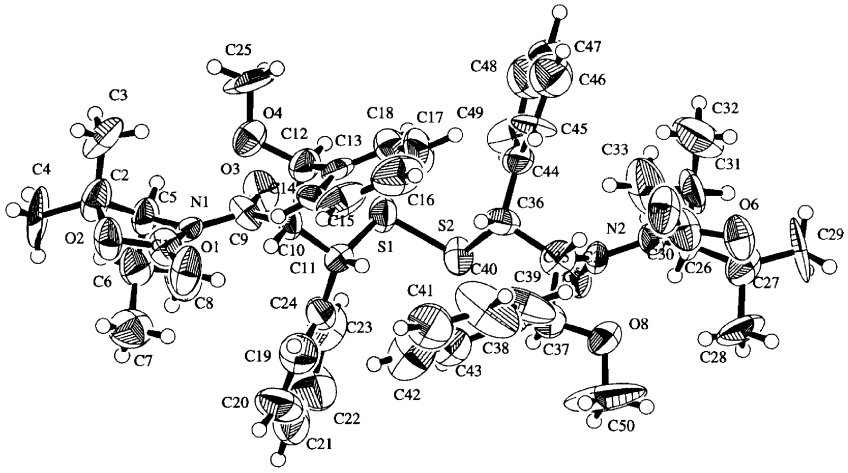
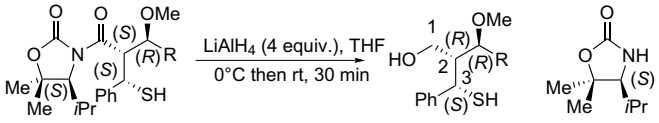


Figure 1. ORTEP drawing of **4**.

Table 2. Nondestructive cleavage of **3a–d**



3 **9** **10**

Entry	Sulfanylalcohol **3**	Yield (%)
1	**3a** (R = Ph)	**9a** (68), **10** (94)
2	**3b** (R = *p*-ClC_6H_4)	**9b** (60), **10** (98)
3	**3c** (R = *p*-$MeOC_6H_4$)	**9c** (59), **10** (98)
4	**3d** (R = *p*-$NO_2C_6H_4$)	**9d** (31), **10** (82)

phenyl group and the isopropyl or methyl group and is more stable than **7B**. The methoxy carbenium ions can attack from the *Si*-face to form the Michael–aldol product **3** via cyclic transition state **8**. The phenyl group and the chloro substituent block the *Re*-face approach of the carbenium ion.

Reductive removal of the chiral auxiliary from adduct **3a** with lithium aluminum hydride in THF gave rise to 2-(α-methoxybenzyl)-3-sulfanylpropanol **9a** in an isolated yield of 68% along with oxazolidinone **10** in an isolated yield of 94% (Table 2, entry 1).[9] Regeneration of oxazolidine-2-thione from the recovered oxazolidinone has been achieved by treatment with Lawesson's reagent.[10]

Other products **3b**,**c** were similarly transformed into 3-sulfanylpropanols **9b**,**c** in good yields. However, nitro derivative **3d** gave sulfanylpropanol **9d** in low yield probably due to the reduction of the nitro group by $LiAlH_4$.

In conclusion, we have developed an asymmetric tandem Michael–aldol reaction of *N*-cinnamoylthioamide **1** with acetals **2**. This reaction furnishes diastereomerically pure 2-(α-methoxybenzyl)-3-phenyl-3-sulfanylpropionamides **3**, which contain three contiguous chiral centers. The reductive removal of the chiral auxiliary from the adducts **3** provides 2-alkoxybenzyl-3-sulfanylpropanols **9** and chiral auxiliary **10** in good yields. Utilization of chiral products **3** and **9** is currently under investigation.

Acknowledgments

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7. Typical procedure for the synthesis of **3**: To a stirred solution of *N*-cinnamoyl-4*S*-isopropyl-5,5-dimethyloxazolidinethione (**1**) (152 mg, 0.5 mmol) and *p*-chlorobenzaldehyde dimethyl acetal (**2b**) (187 mg, 1.0 mmol) in dry CH_2Cl_2 (1.6 mL) was added dropwise a solution of $SnCl_4$ (176 μL, 1.5 mmol) at −40 °C. The mixture was stirred at the same temperature for 24 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL). The resulting solution was allowed to warm to room temperature and was stirred until the solution became clear. The aqueous layer was extracted with CH_2Cl_2 (5 mL × 2) and the combined organic layers were washed with brine. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by recycling preparative HPLC, eluting with chloroform to give **3b** as a white powder. Mp 47.5–50.0 °C; $[\alpha]_D^{23}$ +29.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$; TMS) $\delta = 0.85$ (d, $J = 6.8$ Hz, 3H; Me of $-CHMe_2$), 1.02 (d, $J = 6.8$ Hz, 3H; Me of $-CHMe_2$), 1.04 (s, 3H; 5-Me), 1.44 (s, 3H; 5-Me), 2.05–2.12 (m, 1H; $-CHMe_2$), 2.37 (d, $J = 9.6$ Hz, 1H; SH), 2.96 (s, 3H; OMe), 4.10 (d, $J = 2.0$ Hz, 1H; 4-H), 4.15 (d, $J = 7.5$ Hz, 1H; –C*H*OMe), 4.21 (t, $J = 9.6$ Hz, 1H; –C*H*SH), 5.37 (dd, $J = 7.5$ and 9.6 Hz, 1H; 2′-H), 7.14–7.31 (m, 9H; ArH); ^{13}C NMR (100 MHz; $CDCl_3$) $\delta = 16.5$ (q), 21.2 (q), 21.5 (q), 27.7 (q), 29.9 (d), 43.6 (d), 55.1 (d), 56.7 (d), 66.9 (d), 82.4 (s), 83.4 (d), 127.2 (d), 127.6 (d), 128.5 (d), 129.0 (d), 133.7 (s), 137.1 (s), 141.8 (s), 153.9 (s), 172.6 (s). A methyl carbon and four aromatic carbons are overlapped; IR (KBr): $\nu = 2976$ (SH), 1771 (C═O), 1693 cm^{-1} (C═O); MS (FAB; NBA) *m*/*z* (%): 476 (18) [M^++H], 154 (100); elemental analysis calcd (%) for $C_{25}H_{30}ClNO_4S$ (476.03): C, 63.08; H, 6.35; N, 2.94. Found: C, 62.87; H, 6.28; N, 2.89.
8. Crystal structure data for **8**: $C_{50}H_{60}N_2O_8S_2$, $M_r = 881.15$, orthorhombic, space group: $P2_12_12_1$, $a = 20.404(4)$, $b = 23.153(3)$, $c = 11.679(3)$ Å, $V = 5517(1)$ Å^3, $T = 296.2$ K, $Z = 4$, $D_{calcd} = 1.061$ g/cm^3, μ(MoKα) = 1.43 cm^{-1}, $R = 0.243$, $R_w = 0.288$. CCDC-229571 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge via www.ccdc.cam.au.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.au.uk).
9. Typical procedure for the transformation of **3** into **9** and **10**: To a stirred solution of 2-(α-methoxybenzyl)-3-sulfanylamide (**3a**) (178 mg, 0.4 mmol) in dry THF (3.2 mL) was added $LiAlH_4$ (16 mg, 0.4 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min and then quenched by the addition of aqueous NH_4Cl. The aqueous layer was extracted with AcOEt (5 mL × 3). The extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by PTLC (hexane/AcOEt/*i*-PrOH = 30:10:1, v/v) to give **9a** as a colorless oil and **10** as a yellow solid. Compound **9a**: Colorless oil; $[\alpha]_D^{24}$ −117.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$; TMS) $\delta = 2.02$–2.04 (m, 1H; 2-H), 2.11 (d, $J = 5.9$ Hz, 1H; SH), 3.05–3.07 (m, 1H; OH), 3.10 (s, 3H; OMe), 3.83–3.86 (m, 1H; CH_2), 3.94–3.99 (m, 1H; CH_2), 4.16 (d, $J = 3.4$ Hz, 1H; –C*H*OMe), 4.49 (dd, $J = 5.9$ and 9.8 Hz, 1H; –C*H*SH), 7.15 (d, $J = 6.8$ Hz, 2H; ArH), 7.25–7.40 (m, 8H; ArH); ^{13}C NMR (100 MHz; $CDCl_3$) $\delta = 42.4$ (d), 54.1 (d), 57.7 (q), 59.6 (t), 84.8 (d), 126.0 (d), 127.4 (d), 127.5 (d), 127.6 (d), 128.5 (d), 128.9 (d), 136.7 (s), 143.3 (s). Four aromatic carbons are overlapped; IR (NaCl) $\nu = 3524$ (OH), 2560 cm^{-1} (SH); MS (FAB; Gly) *m*/*z* (%): 289 (3) [M^++H], 121 (100); HRMS (FAB, Gly); calcd for $C_{17}H_{20}O_2S$ [M^++H]: 289.1184; found: 289.1252.
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