**SUPPORTING INFORMATION**

**Asymmetric Synthesis of Substituted Thiolanes through Domino Thia-Michael–Henry Dynamic Covalent Systemic Resolution using Lipase Catalysis**

Yan Zhang, Pornapee Vongvilai, Morakot Sakulsombat, Andreas Fischer, and Olof Ramström

---

**TABLE OF CONTENTS**

| Section                                                                 | Page |
|------------------------------------------------------------------------|------|
| General methods                                                       | S2   |
| Generation of dynamic systems and lipase-catalyzed asymmetric transformation | S2   |
| General procedure for synthesis of compounds 6, 9                      | S2   |
| General procedure for synthesis of racemic mixtures of compounds 13, 14 | S3   |
| Scheme S1. Evaluation of reversibility of domino thia-Michael–Henry reaction | S4   |
| Scheme S2. Thiolane stereoisomers from compounds 1 and 7                | S4   |
| Figure S1. 1H NMR spectra of the reaction mixture at different time intervals | S4   |
| HPLC analyses                                                         | S5   |
| NMR spectra of product 13A                                             | S6   |
| NMR spectra of product 13B                                             | S7   |
| NMR spectra of product 14A                                             | S8   |
| NMR spectra of product 14B                                             | S9   |
| Synthesis of MTPA esters of compound 10B_a                              | S10  |
| Thermal ellipsoid plot and XRD bonding pattern of compound 10A_a       | S11  |
General methods
Reagents were obtained from commercial suppliers and used as received. Lipases (EC 3.1.1.3) were from Amano Enzyme Inc. Or Sigma-Aldrich: *Burkholderia* (formerly *Pseudomonas* cepacia) lipase (BCL, Lipase PS “AMANO” IM), *Candida rugosa* lipase (Sigma L1754), lipase from *Pseudomonas fluorescens* (Aldrich 534730), and *Candida antarctica* lipase B (Sigma L4777). $^1$H and $^{13}$C NMR data were recorded on a Bruker Avance 400 (100) MHz or a Bruker Avance 500 (125) MHz spectrometer, respectively. Chemical shifts are reported as $\delta$-values (ppm) with CDCl$_3$ ($^1$H NMR $\delta$ 7.26, $^{13}$C NMR $\delta$ 77.0) as an internal standard. $J$-values are given in Hertz (Hz). Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on HP-Agilent 1110 Series controller, using a Daicel Chiralpak OJ column (4.6$\times$250 mm, 10 $\mu$m).

Solvents for HPLC use were of spectrometric grade. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV 254 silica plates (0.20mm, Macherey-Nagel), visualized with UV-detection. Flash column chromatography was performed on silica gel 60, 0.040-0.063 mm (SDS).

Generation of dynamic systems and lipase-catalyzed asymmetric transformation
The dynamic systems were generated by adding each nitropropene (1 equiv., 0.05 mmol), together with 2,5-dihydroxy-1,4-dithiane 7 (0.5 equiv., 0.025 mmol) and tetramethylguanidine (TMG, 0.025 mmol) in dry toluene (0.6 mL). After adding acylating reagent (3 equiv., 0.15 mmol), the solution was transferred to a 1.5 mL sealed-cap vial containing BCL (immobilized on diatomaceous earth, Amano Enzyme Inc., transesterification activity > 500 u/g, 150 mg), ZnI$_2$ (0.5 equiv., 0.025 mmol) and ground 4Å molecular sieves under argon atmosphere, pre-dried for 2 days before use. The reaction vials were subsequently kept at room temperature under continuous shaking (around 500 rpm).

General procedure for synthesis of compounds 6 and 9
A solution of aldehyde (1.05 mmol), nitroethane (2.5 mL), and ammonium acetate (0.675 mmol) was refluxed for 20 h. After evaporation of excess nitroethane, the resulting yellow solid was taken up in CH$_2$Cl$_2$ (3 mL), and washed with H$_2$O (3 $\times$ 3 mL). The organic phase was dried over MgSO$_4$, filtered and evaporated under vacuum. The crude product was purified by column chromatography using ethyl acetate and hexanes as eluent (1:4, v/v).

2,4-Dimethoxy-1-(2-nitroprop-1-enyl)benzene (6)
Yellow solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) $\delta$ 2.40 (s, 3H, CH$_3$), 3.86 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 6.49 (s, 1H, CH), 6.54 (d, $J$=8.5, 1H, CH), 7.28 (d, $J$=8.5, 1H, CH), 8.30 (s, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) $\delta$ 14.4, 55.7, 55.8, 98.5, 105.2, 114.5, 129.7, 131.2, 145.8, 160.0, 163.0.

3,4-Dimethoxy-1-(2-nitroprop-1-enyl)benzene (9)
Yellow solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) $\delta$ 2.49 (s, 3H, CH$_3$), 3.92 (s, 3H, OCH$_3$), 3.94 (s, 3H, OCH$_3$), 6.94-6.96 (m, 2H, CH), 7.09 (d, $J$=7.7, 1H, CH), 8.07 (s, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) $\delta$ 14.3, 56.1, 111.4, 113.3, 124.2, 125.2, 134.0, 146.1, 149.3, 151.0.
General procedure for synthesis of racemic mixtures of compounds 13, 14

Solutions of compounds 6 or 9 (0.5 mmol), 2,5-dihydroxy-1,4-dithiane (0.25 mmol), and TEA (0.25 mmol) in CH$_2$Cl$_2$ (3 mL) were heated to 40 °C under stirring for 3 h. The resulting mixtures were washed with 1 M HCl and brine, dried over MgSO$_4$, filtered and evaporated under vacuum. The crude products were purified by column chromatography using ethyl acetate and hexanes as eluent (1:6, v/v), yielding compounds 13 and 14, respectively. The compounds were dissolved in CH$_2$Cl$_2$ (3 mL), and subsequently acylated using acetyl chloride (6 equiv.) and pyridine (0.8 equiv.) at room temperature over 5 d. The resulting reaction mixtures were neutralized with 1 M HCl, washed with water and brine, dried over MgSO$_4$, and evaporated under vacuum. The crude products were purified by column chromatography with ethyl acetate and hexanes as eluent (1:4, v/v).

5-(2,4-Dimethoxyphenyl)-4-methyl-4-nitro-tetrahydrothiophen-3-yl acetate isomer A (13A)

White solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ 1.40 (s, 3H, CH$_3$), 2.05 (s, 3H, CH$_3$), 2.72 (t, J=9.8, 1H, CH$_2$), 3.47 (dd, J$_f$=9.8, J$_s$=8.7, CH$_2$), 3.65 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 5.56 (s, 1H, CH), 6.15 (t, J=8.7, 1H, CH), 6.37 (s, 1H, CH), 6.49 (d, J=8.6, 1H, CH), 7.58 (d, J=8.6, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ 13.1, 21.0, 29.4, 46.5, 55.5, 55.7, 79.2, 95.5, 98.4, 104.5, 114.6, 131.5, 159.2, 161.5, 169.7. HRMS: found 364.08240; calc. for C$_{15}$H$_{19}$NNaO$_6$S [M+Na$^+$] 364.08253.

5-(2,4-Dimethoxyphenyl)-4-methyl-4-nitro-tetrahydrothiophen-3-yl acetate isomer B (13B)

White solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ 1.25 (s, 3H, CH$_3$), 2.08 (s, 3H, CH$_3$), 3.23-3.26 (m, 1H, CH$_2$), 3.31 (t, J=8.4, 1H, CH$_2$), 3.73 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 5.24 (t, J=8.4, 1H, CH), 5.66 (s, 1H, CH), 5.64 (s, 1H, CH), 6.49 (d, J=8.4, 1H, CH), 7.41 (d, J=8.4, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ 20.0, 20.8, 31.7, 49.6, 55.3, 55.4, 80.1, 95.8, 98.3, 104.3, 117.0, 130.2, 158.2, 161.0, 169.8. HRMS: found 364.08241; calc. for C$_{15}$H$_{19}$NNaO$_6$S [M+Na$^+$] 364.08253.

5-(3,4-Dimethoxyphenyl)-4-methyl-4-nitro-tetrahydrothiophen-3-yl acetate isomer A (14A)

White solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ 1.47 ( s, 3H, CH$_3$), 2.07 (s, 3H, CH$_3$), 2.76 (t, J=9.9, 1H, CH$_2$), 3.29 (dd, J$_f$=9.9, J$_s$=8.7, 1H, CH$_2$), 3.86 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 5.20 (s, 1H, CH), 6.02 (t, J=8.7, 1H, CH), 6.79-6.82 (m, 2H, CH), 6.87 (d, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ 12.4, 21.0, 29.5, 50.4, 56.3, 56.3, 78.7, 96.9, 111.3, 112.2, 121.8, 125.5, 149.2, 150.0, 170.0. HRMS: found 364.08241; calc. for C$_{15}$H$_{19}$NNaO$_6$S [M+Na$^+$] 364.08253.

5-(3,4-Dimethoxyphenyl)-4-methyl-4-nitro-tetrahydrothiophen-3-yl acetate isomer B (14B)

White solid: $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) δ 1.58 (s, 3H, CH$_3$), 2.12 (s, 3H, CH$_3$), 3.02 (d, J=12.5, 1H, CH$_2$), 3.39 (dd, J$_f$=12.5, J$_s$=4.6, 1H, CH$_2$), 3.88 (s, 3H, OCH$_3$), 3.89 (s, 3H, OCH$_3$), 5.57-5.56 (m, 2H, CH, CH), 6.83 (d, J=8.3, 1H, CH), 7.12 (s, 1H, CH), 7.17 (d, J=8.3, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) δ 19.5, 21.2, 32.3, 52.3, 56.3, 56.3, 81.7, 97.0, 111.1, 113.8, 123.1, 126.1, 149.0, 150.0, 169.7. HRMS: found 364.08234; calc. for C$_{15}$H$_{19}$NNaO$_6$S [M+Na$^+$] 364.08253.
Evaluation of reversibility

Scheme S1. Evaluation of reversibility of domino thia-Michael–Henry reaction

Thiolane stereoisomers from compounds 1 and 7

Scheme S2. Reversible formation of thiolane stereoisomers from nitroprene 1 and dithiane 7

$^1$H NMR spectra of the reaction mixture at different time intervals:

**Fig. S1** a) Equilibrium signals (5-H) of intermediates; b) signals (5-H) of acylated products and remaining intermediates.
HPLC analyses

The dynamic transformation processes were analyzed using a two-column HPLC system based on a Zorbax normal phase column, coupled to an OD-H chiral separation column. Analyses were carried out at 298 K and 210 nm using mobile phase hexane:iPrOH=95:5 (v/v) for 40 min.

![Graphs of HPLC analyses](image-url)
$^1$H NMR-, $^{13}$C NMR-, and NOE-spectra of product 13A
$^1$H NMR-, $^{13}$C NMR-, and NOE-spectra of product 13B
$^1$H NMR-, $^{13}$C NMR-, and NOE-spectra of product 14A
$^1$H NMR-, $^{13}$C NMR-, and NOE-spectra of product 14B
Synthesis of MTPA esters of compound 10B_a

Purified product 10B_a from the kinetic resolution by PS-Im (ca. 2 mg, >99% ee) was treated by pyridine (0.5 mL) and (R)(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20 mg) or (S)(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (20 mg) at room temperature for 48 h without stirring. The resulting reaction mixture was acidified with 1 M HCl, extracted with EtOAc (3×1 mL), and washed with brine. The organic layer was dried over MgSO_4, providing the (S)-(−)-MTPA- or (R)(+)-MTPA esters of 10B_a (ca. 2 mg).

^1^H NMR of (S)-(−)-MTPA ester of 10B_a (400 MHz, CDCl₃, 25 °C): δ 1.60 (s, 3H, CH₃), 2.98 (d, J=12.9, 1H, CH₂), 3.42 (dd, J₁=12.9, J₂=4.3, 1H, CH₂), 3.85 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 5.36 (s, 1H, CH), 5.75 (s, 1H, CH), 6.79 (d, J=8.5, 1H, CH), 7.08 (s, 1H, CH), 7.15 (d, J=8.5, 1H, CH).

^1^H NMR of (R)(+)-MTPA ester of 10B_a (500 MHz, CDCl₃, 25 °C): δ 1.57 (s, 3H, CH₃), 3.10 (d, J=12.8, 1H, CH₂), 3.49 (dd, J₁=12.8, J₂=4.4, 1H, CH₂), 3.86 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 5.45 (s, 1H, CH), 5.76 (s, 1H, CH), 6.80 (d, J=8.4, 1H, CH), 7.10 (s, 1H, CH), 7.18 (d, J=8.4, 1H, CH).
Thermal ellipsoid plot and XRD bonding pattern of compound 10A_a