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

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**Abstract:** Dynamic systems based on consecutive thia-Michael and Henry reactions were generated and transformed using lipase-catalyzed asymmetric transformation. Substituted thiolane structures with three contiguous stereocenters were resolved in the process in high yields and high enantiomeric excesses.

**Keywords:** adaptive features; biotransformations; chiral resolution; domino reactions; dynamic chemistry; enzymes; lipase; stereochemistry

Dynamic chemistry at the constitutional level enables generation of complex molecular systems possessing adaptive features.[1,2] The dynamic nature can be employed in resolution protocols, for example, leading to identification of ligands and receptors. In addition to thermodynamically controlled selection of the systems, kinetic resolution can be applied. This amounts to dynamic systemic resolution (DSR), or dynamic systemic asymmetric transformation (DYSAT), processes that allow for system adaptivity through rate-limiting pathways.[3] With this concept, the dynamic systems are coupled to a kinetically controlled secondary process, such as enzyme-catalyzed asymmetric transformation. Through constant re-equilibration of the systems, the fittest constituents can be selectively transformed through kinetically favored processes, leading to amplification of optimal species. Previous attempts of chemoenzymatic DSR have focused on resolutions of compounds containing single stereogenic centers. These include for example dynamic nitroaldol,[4] α-aminonitrile,[5] cyanohydrin,[6] and hemithioacetal systems,[7] where DSR has yielded both high substrate-specific and stereospecific amplifications. However, the concept is general and may in principle be applied to more complex systems. This has been addressed in the present study, where expanded diversity and complexity of the systems have been applied to the selective enzymatic resolution of products possessing multi-stereogenic centers. Double covalent thia-Michael–Henry type reaction schemes were developed and coupled to lipase-catalyzed transesterification, leading to selective asymmetric transformation of substituted thiolanes from a pool of isomeric constituents (Figure 1).

Multiple dynamic covalent reactions operating concertedly or in sequence present a significant challenge in the generation and resolution of dynamic systems. Although a multitude of reversible reactions has been developed, double covalent reactions are still rarely applied. This is generally a consequence of the difficulty arising from two or more chemistries being compatible with each other under the same reaction conditions, while efficient reversibility is maintained for the whole system. Recently, domino Michael–Henry-type reaction schemes have emerged as a strategy in

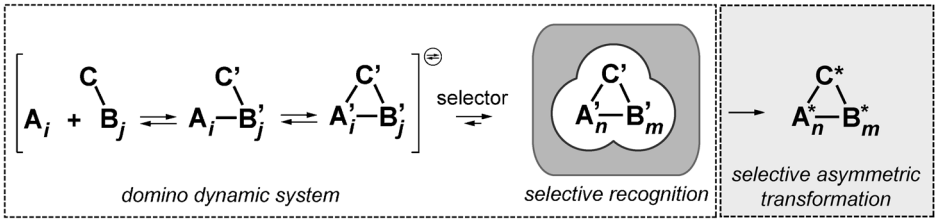
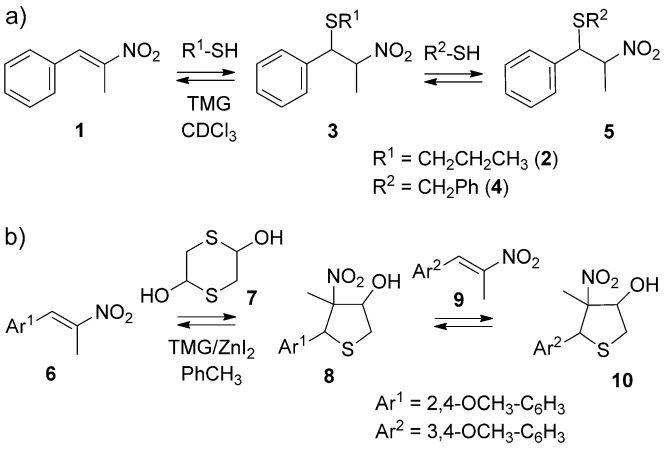



**Figure 1.** Domino dynamic systemic asymmetric resolution.

the syntheses of a variety of cyclic structures.[8] A significant advantage of these routes is that multisubstituted products can be synthesized in one-pot processes, potentially useful for high-throughput chemistry formats. Furthermore, the reversible nature of both Michael- and Henry-type reactions has been demonstrated under basic conditions.[4,9] However, generation of dynamic systems based on Michael-type reactions has mainly been reported in aqueous media,[9b] and conditions for efficient reversibility in an organic phase was thus first addressed, and subsequently coupled to, and further developed with, the Henry reaction. The conditions were furthermore optimized for compatibility with the enzymatic resolution process.

In order to generate dynamic Michael-type systems in organic solvents, different organic bases were initially screened. Triethylamine (TEA), having proven suitable for the Henry reaction resolution schemes, was first selected to initiate the reaction between (*E*)-1-phenyl-2-nitropropene **1** and propane-1-thiol **2** in $CDCl_3$ (Scheme 1, a), monitored by $^1$H NMR spectroscopy. Following consumption of the nitropropene, phenylmethanethiol **4** was then added to the reaction mixture, however, not resulting in any new product. This may ascribed to the low basicity of TEA, and several stronger bases were subsequently tested, including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,1,3,3-tetramethylguanidine (TMG) and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD). Reversibility of the reactions was recorded in all cases, but only TMG provided the final equilibrium products in a sufficiently rapid way while avoiding any side reactions.

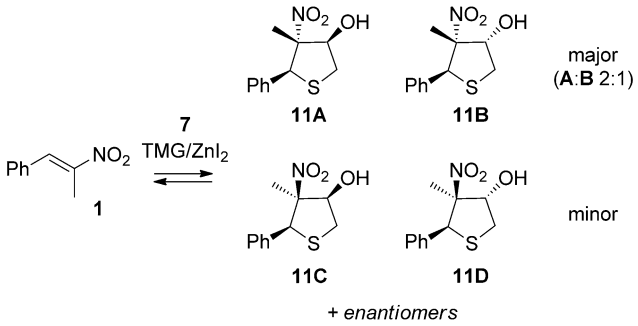



**Scheme 1.** Evaluation of reversibility of a) thia-Michael reaction; b) domino thia-Michael–Henry reaction.

The generation of the domino thia-Michael–Henry dynamic systems was subsequently evaluated in toluene, using (*E*)-1-(2,4-dimethoxyphenyl)-2-nitropropene **6** and 1,4-dithiane-2,5-diol **7** as a combined thiol and aldehyde source (Scheme 1, b). In this case, (*E*)-1-(3,4-dimethoxyphenyl)-2-nitropropene **9** was added to monitor the reversibility after consumption of the thiol. Nitropropenes of similar structures were chosen in this case, in order to avoid an unbalanced distribution of intermediates when the dynamic system reached equilibrium. Unfortunately, TMG did not prove sufficiently efficient for fast reversibility, and only small amounts of products could be detected by $^1$H NMR after several days. To address this effect, various Lewis acids were evaluated to function together with TMG in order to accelerate the process, primarily AgOTf, $HgBr_2$, $ZnBr_2$, $ZnI_2$, and $Zn(OTf)_2$. Among these, $ZnI_2$ proved superior, resulting in equilibrium formation within one day.

As an advantage of the domino thia-Michael–Henry reaction, multi-chiral centers can be generated within the products, but a good method for enantioselective resolution of the intermediates is needed. This effect has been addressed in the synthesis of thiochromanes using cupreine derivatives, resulting in fair enantiomeric purities.[10] However, enzymes, as a most efficient way to resolve racemic compounds have not been applied to this domino reaction. Lipase-mediated (trans)esterification can also be used in organic solvents, resulting in high regio- and enantioselectivities.[11] Moreover, lipases are commercially available, environmentally friendly, and easily recoverable; features that make them widely used in organic synthesis. In the present study, lipases were chosen to effectuate the resolution process through selective esterification of compounds from the dynamic system. The selectivity of lipases would thus perturb the dynamic system through constant re-equilibration, selecting the fittest



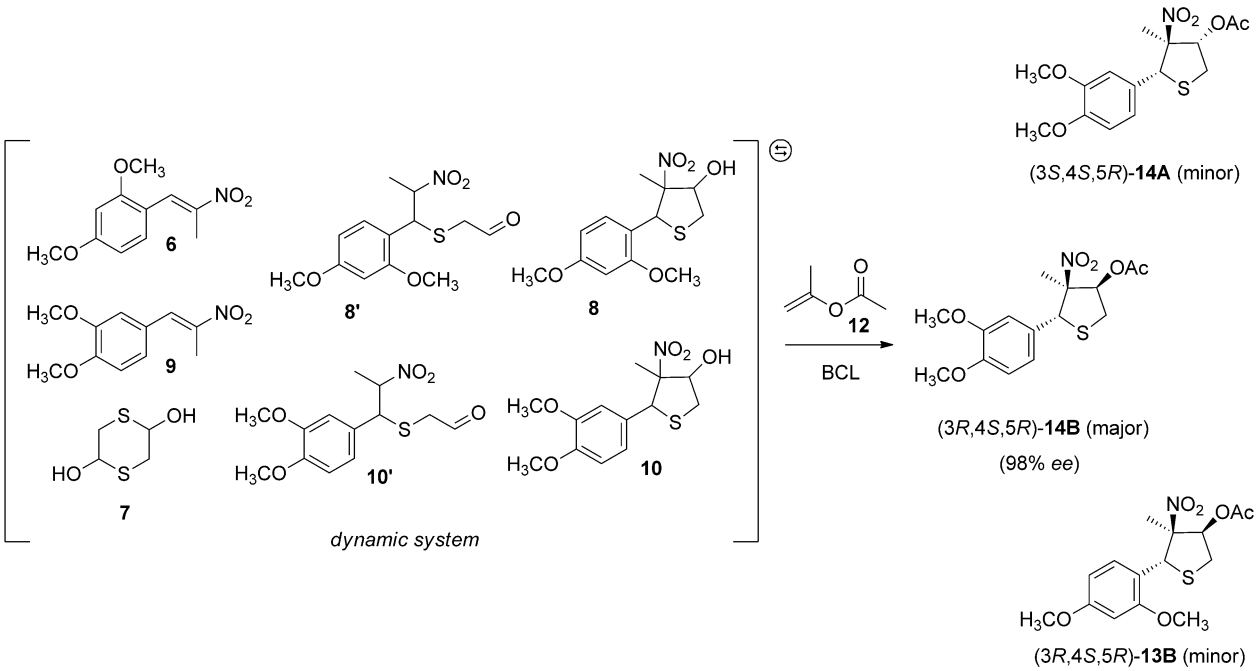

**Scheme 2.** Reversible formation of thiolane stereoisomers from nitropropene **1** and dithiane **7**.

constituent in a kinetically controlled secondary process.

In order to optimize the conditions suitable for the biocatalytic transformation, compound **11** was first synthesized from nitropropene **1** and dithiane **7**, giving rise to cyclic thiolane structures possessing three contiguous stereocenters (Scheme 2). All stereoisomers were formed, four of which in a combined yield of 95%. NOESY analysis confirmed these to be of *trans,trans* (**11A** enantiomers) and *cis,trans* (**11B** enantiomers) configuration, respectively, thus indicating a preferred *trans*-relationship between the phenyl and nitro groups. Moreover, the ratio between the major stereoisomers **A** and **B** was almost 2:1, indicating a preference for a *trans*-hydroxy/nitro relationship.

Different lipases and acyl donors were next evaluated to find the best conditions for the resolution process. Four enzymes were thus tested: *Burkholderia* (formerly *Pseudomonas*) *cepacia* lipase (BCL), *Candida rugosa* lipase, lipase from *Pseudomonas fluorescens*, and *Candida antarctica* lipase B. Of these, BCL provided the best diastereoselectivity, giving one major product of compound **11B**. Considering the enzyme promiscuity of lipases, individual Henry and Michael reactions can also be catalyzed under certain conditions.[12] However, in the present system, catalytic effects besides transesterification could not be discerned. From the probed acyl donors: ethyl acetate, isopropenyl acetate, isopropyl acetate, and phenyl acetate, isopropenyl acetate (**12**) was selected because it resulted in moderate acylation rates without formation of any side reactions.

Having optimized the conditions for the lipase-catalyzed kinetic resolution, dynamic asymmetric transformation and resolution of the entire system was next evaluated (Scheme 3). The domino dynamic system was initiated by adding 0.5 equivalents of TMG/$ZnI_2$ to equimolar amounts of nitropropenes **6** and **9**, and dithiane **7** in toluene at ambient temperature. This resulted in equilibrium formation within one day, generating intermediates **8A**–**8′B**, **8A**–**8D**, **10A**–**10′B** and **10A**–**10D**. Acyl donor **12** was subsequently added, and the resulting solution added to the enzyme preparation and the process followed by $^1$H NMR (Figure 2). In analogy to the single reaction of compound **11**, a biased distribution of the intermediates before enzyme resolution was observed. Compounds




**Scheme 3.** Dynamic asymmetric resolution of domino thia-Michael–Henry system.

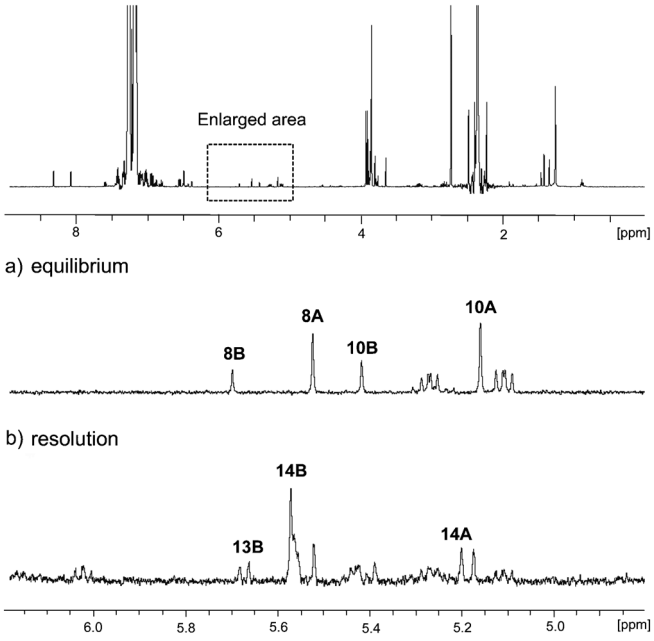



**Figure 2.** $^1$H NMR spectra of the reaction mixture at different time intervals: a) equilibrium signals (4-H) of intermediates; b) signals (4-H) of acylated products and remaining intermediates.

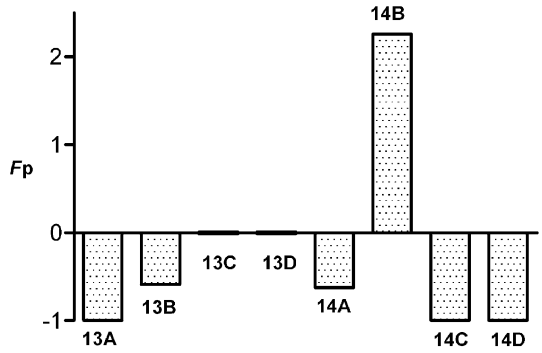



**Figure 3.** Substrate preference factors[6] of domino thia-Michael–Henry system. $Fp = [C_r(\text{product}) - C_r(\text{intermediate})]/C_r(\text{intermediate})$, where $C_r$(intermediate) and $C_r$(product) represent the relative concentrations of the intermediate and the product, respectively.

exhibiting *trans*-relationships between the aryl and nitro groups were thus preferred, and formed in a combined ratio of more than 24:1. However, this thermodynamically controlled distribution was dramatically altered upon connecting the dynamic system to the kinetic enzymatic esterification process, resulting in a different pattern of acetylated products. As can be seen in Figure 2, the major product from this dynamic system was compound **14B**, while the concentration of its related intermediate **10B** was comparatively low. The product from intermediate **10A** was also produced to some extent, indicating that the 3,4-substituted aromatic structures provide a better fit with BCL than the corresponding 2,4-substituted derivatives.

That low amounts of compound **13B**, produced from intermediate **8B**, were also produced, even though the structure was not preferred by BCL, implies a strong preference for the **B**-stereoisomers by the enzyme in comparison with the thermodynamically more stable **A**-stereoisomers.

Figure 3 shows the enzymatic selectivity between the different isomers in terms of preference factors ($F_p$),[6] representing the difference of the relative ratios between the intermediates in the dynamic system and the final products. Positive values of $F_p$ indicate selected intermediates, whereas compounds showing negative values are deselected by the enzyme. As can be seen, only stereoisomers **14B** displayed a positive $F_p$ value, and intermediate **10B** in the dynamic system was thus clearly preferred by the enzyme.

To explore the enantioselectivity of lipases toward this dynamic system, chiral chromatography, supported by Mosher analysis and XRD (see the Supporting Information), was employed to monitor the enantiomeric purities of the ester products selected by the enzyme. High enantioselectivities were observed for both compound **14B** and compound **14A**, formed in 98% *ee* and 95% *ee*, respectively, at a total conversion of 68%. Thus, not only high chemoselectivity and high diastereoselectivity between the different substrates, but also high enantioselectivity was successfully achieved through the chemoenzymatic systemic resolution process.

In conclusion, a dynamic systemic asymmetric transformation process based on a domino thia-Michael–Henry reaction has been developed. Using the double reversible covalent process, dynamic systems of compounds possessing multi-stereogenic centers were efficiently generated using a combination of Lewis acid and base activation. The dynamic systems were further coupled, directly *in situ,* to a secondary kinetically controlled enzymatic resolution step, resulting in the selection of a major product in high enantiomeric purity. This demonstrates the high preference of the *Burkholderia cepacia* lipase toward similar, multi-stereogenic thiolane substrates, including different diastereomers and enantiomers, from a complex dynamic system in a one-pot process.

## Experimental Section

### General Remarks

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 δ 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 a chiral stationary phase was performed on HP-Agilent 1110 Series controller, using a Daicel Chiralpak OJ column (4.6× 250 mm, 10 μm). Solvents for HPLC use were of spectrometric grade. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV 254 silica plates (0.20 mm, Macherey–Nagel), visualized with UV detection. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm (SDS).

### General Procedure for Dynamic Systemic Resolution

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 4 Å molecular sieves under an argon atmosphere, pre-dried for 2 days before use. The reaction vials were subsequently kept at room temperature under continuous shaking (around 500 rpm).

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