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Desymmetrisation of (4*R*,5*S*)-4,5-diphenylimidazolidine-2-thione using pentafluorophenyl active esters

Anna Andreou [a], Jason Eames [a,*], Majid Motevalli [b], Timothy J. Prior [a], Michael Watkinson [b]

[a] Department of Chemistry, University of Hull, Cottingham Road, Kingston upon Hull HU6 7RX, UK
[b] School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London E1 4NS, UK

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ABSTRACT

(4*R*,5*S*)-4,5-Diphenylimidazolidine-2-thione is efficiently desymmetrised by stereorandom deprotonation with NaHMDS, followed by kinetic resolution of the resulting racemic intermediate with an enantiomerically pure pentafluorophenyl active ester. The levels of diastereocontrol were found to be excellent (86–92% de at ~30% conversion). This desymmetrisation reaction is an example of a masked resolution.

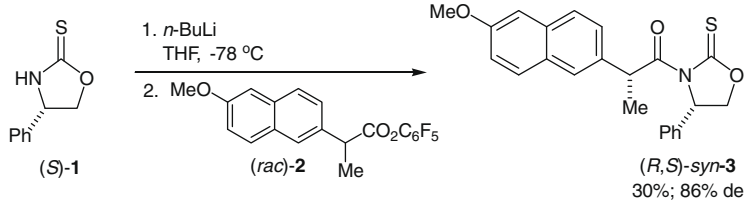
Since 2000, we have been interested in the kinetic, mutual and parallel kinetic resolutions of pentafluorophenyl active esters, such as (*rac*)-**2**, using 4-phenyl-oxazolidin-2-(thi)ones, such as (*S*)-**1** (Scheme 1).[1–3] Treatment of 4-phenyl-oxazolidin-2-thione (*S*)-**1** in THF with *n*-BuLi at −78 °C followed by the addition of pentafluorophenyl 2-(6-methoxynaphthalen-2-yl)propanoate (*rac*)-**2** gave after 2 h the corresponding oxazolidin-2-thione adduct (*R*,*S*)-*syn*-**3** in 30% yield with high levels of diastereoisomeric control (Scheme 1).[3] The resolved active ester, (*S*)-**2**, was recovered in 50% yield with 44% ee.[3]

We now report a novel application of this methodology for the desymmetrisation of *meso*-thioureas using enantiomerically pure pentafluorophenyl active esters. We first chose to investigate the desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4**[4,5] due to its structural resemblance to 4-phenyl-oxazolidin-2-thione (*S*)-**1** (Schemes 1 and 2). Treatment of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** in THF with NaHMDS at −78 °C followed by the addition of pentafluorophenyl 2-(6-methoxynaphthalen-2-yl)propanoate (*S*)-**2** gave after 2 h the substituted thiourea (*S*,*R*,*S*)-*syn*,*syn*-**5** {$[\alpha]_D^{20}$ +173.2 (*c* 3.2, $CHCl_3$)} in 32% yield with excellent levels of diastereocontrol (92% de) (measured by 400 MHz ^{1}H NMR spectroscopy)[6] (Scheme 2).

The stereochemical outcome of this process was identical to that of our previous kinetic, mutual and parallel kinetic resolution studies;[1] the level of molecular recognition between the (*S*)-enantiomer of active ester **2** and the C(4)–carbon atom of the thiourea **4** bearing the (*R*)-stereocentre/phenyl group was excellent (92% de). The stereochemistry of the major diastereoisomeric 4,5-diphenylimidazolidine-2-thione (*S*,*R*,*S*)-*syn*,*syn*-**5** was confirmed by X-ray crystallography (Fig. 1).[7]

With this information at hand, we next investigated the desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** using three structurally related pentafluorophenyl active esters (*S*)-**6**, (*R*)-**7** and (*R*)-**8** (Fig. 2).

These active esters behaved similarly to active ester (*S*)-**2** giving the corresponding substituted thioureas (*S*,*R*,*S*)-*syn*,*syn*-**9** {$[\alpha]_D^{20}$ +64.7 (*c* 3.4, $CHCl_3$)}, (*R*,*S*,*R*)-*syn*,*syn*-**10** {$[\alpha]_D^{20}$ −24.5 (*c* 2.2, $CHCl_3$)} and (*R*,*S*,*R*)-*syn*,*syn*-**11** {$[\alpha]_D^{20}$ −32.4 (*c* 1.8, $CHCl_3$)} in 30–35% yields with good levels of diastereocontrol (84–92% de) (Scheme 3). The levels of diastereocontrol were higher for the more sterically



Scheme 1. Resolution of active ester (*rac*)-**2** using 4-phenyl-oxazolidin-2-thione (*S*)-**1**.

* Corresponding author. Tel.: +44 1482 466401; fax: +44 1482 466410.
E-mail address: j.eames@hull.ac.uk (J. Eames).

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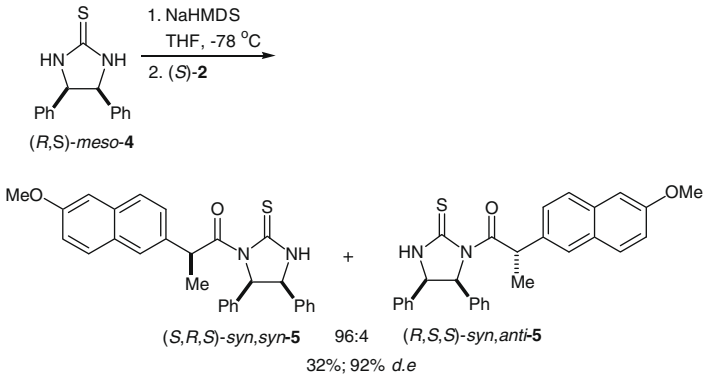


Scheme 2. Desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** using active ester (*S*)-**2**.

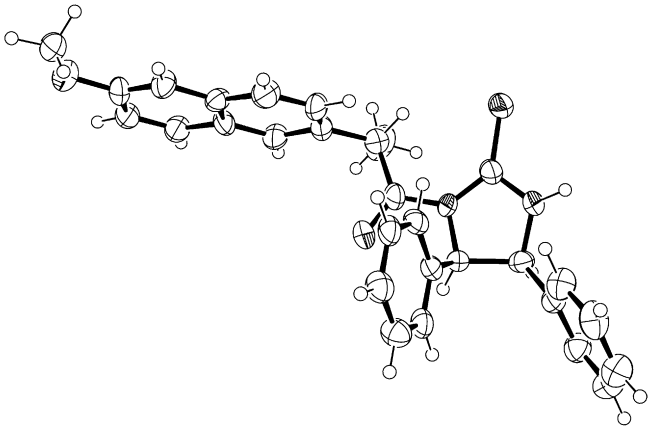


Figure 1. ORTEP diagram of 3-[2-(6-methoxynaphthalen-2-yl)propionyl]-4,5-diphenyl-imidazolidine-2-thione (*S*,*R*,*S*)-*syn*,*syn*-**5**. Displacement ellipsoids are drawn at 50% probability level.

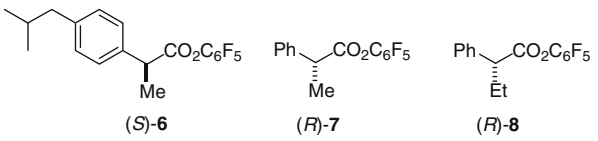


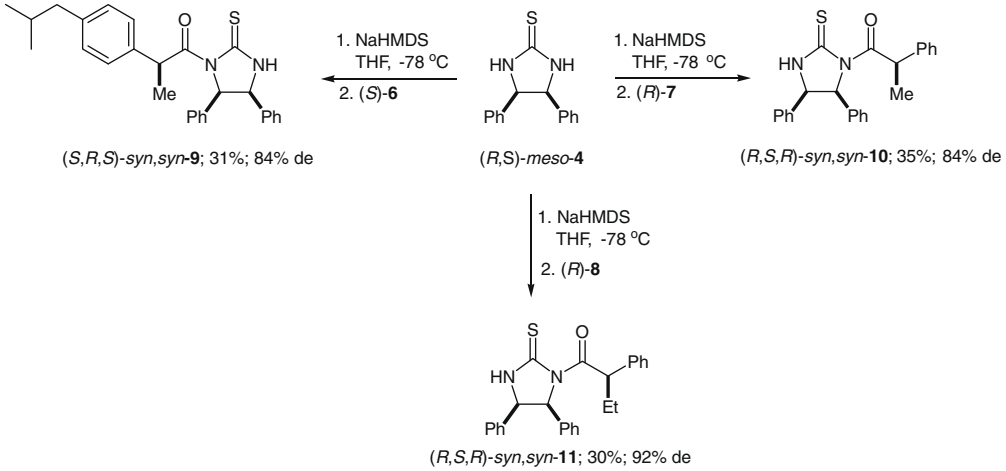
Figure 2. Pentafluorophenyl active esters (*S*)-**6**, (*R*)-**7** and (*R*)-**8**.

demanding pentafluorophenyl 2-phenylbutanoate (*R*)-**8**. It is worthy of note that the use of active esters (*R*)-**7** and (*R*)-**8** allows the access to two similar *quasi*-enantiomeric 4,5-diphenylimidazolidine-2-thiones (*R*,*S*,*R*)-*syn*,*syn*-**10** and (*R*,*S*,*R*)-*syn*,*syn*-**11**; in addition their specific rotations have the expected opposite sign of rotation [compared to (*S*,*R*,*S*)-*syn*,*syn*-**9**].

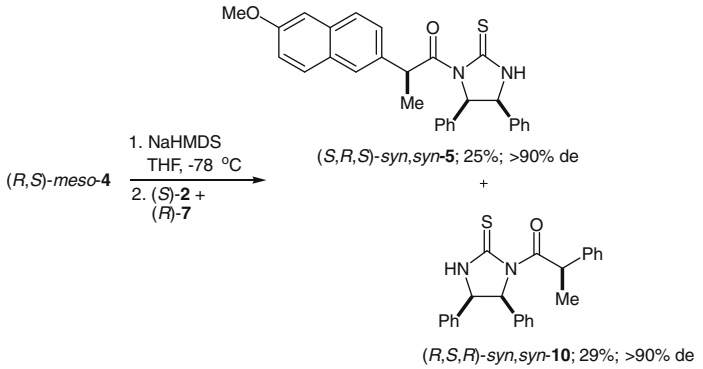
We next turned our attention towards a parallel desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** using a pair of *quasi*-enantiomeric active esters (*S*)-**2** and (*R*)-**7** (Scheme 4). Deprotonation of (*R*,*S*)-*meso*-**4** using NaHMDS in THF at −78 °C followed by the addition of a solution of *quasi*-enantiomeric active esters (*S*)-**2** and (*R*)-**7** in THF gave after 2 h a mixture of two diastereoisomeric thioureas (*S*,*R*,*S*)-*syn*,*syn*-**5** (in 25% yield) and (*R*,*S*,*R*)-*syn*,*syn*-**10** (in 29% yield) with >90% de. These adducts **5** and **10** were easily separable by column chromatography due to the more polar 6-methoxynaphthalen-2-yl group in **5** {ΔR_f [light petroleum ether/diethyl ether (1:1)] = ∼0.10}.

This overall desymmetrisation procedure is an example of a masked resolution as stereorandom deprotonation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** with NaHMDS leads to a racemic[8] sodiated thiourea **4**-**Na** (Scheme 5). Parallel resolution[9] of this sodiated thiourea (*rac*)-**4**-**Na** using an equimolar amount of active esters (*S*)-**2** and (*R*)-**7** gives complementary 4,5-diphenylimidazolidine-2-thiones (*S*,*R*,*S*)-*syn*,*syn*-**5** and (*R*,*S*,*R*)-*syn*,*syn*-**10**, respectively, in a near equal amount.

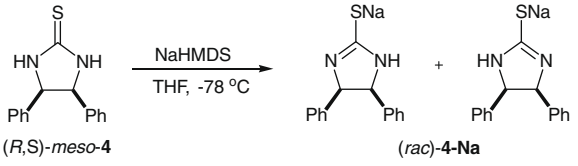
In conclusion, we have shown that a series of structurally related pentafluorophenyl active esters (*S*)-**2**, (*S*)-**6**, (*R*)-**7** and (*R*)-**8** can be used to efficiently desymmetrise 4,5-diphenylimidazolidine-2-



Scheme 3. Desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** using active esters (*S*)-**6**, (*R*)-7 and (*R*)-**8**.



Scheme 4. Parallel desymmetrisation of 4,5-diphenylimidazolidine-2-thione (*R*,*S*)-*meso*-**4** using two active esters (*S*)-**2** and (*R*)-**7**.



(*R*,S)-*meso*-**4** (*rac*)-**4-Na**

Scheme 5. Formation of racemic sodiated 4,5-diphenylimidazolidine-2-thione (*rac*)-**4-Na**.

thione (*R*,*S*)-*meso*-**4** in good yields.[10] The levels of diastereocontrol were found to be excellent (84–92%) favouring the formation of the corresponding (*R**,*S**,*R**)-*syn*,*syn*-thiourea adducts **5**, **9**, **10** and **11**. This desymmetrisation process is a masked kinetic resolution as it proceeds via the formation and resolution of an intermediate racemic sodiated thiourea (*rac*)-**4-Na**. Enantioselective desymmetrisation of *meso*-compounds[11] such as alkenes,[12] amines,[13] anhydrides,[14] diols[15] and epoxides[16] is very well documented. The nearest analogy to our study is Fu's desymmetrisation of *meso*-1,5-diols using an enantiomerically pure acyl transfer reagent.[17]

Acknowledgement

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6. For 4,5-diphenylimidazolidine-2-thione (*S*,*R*,*S*)-*syn*,*syn*-**5**, the PhCHNC=O doublet appeared at 5.92 ppm (1 H, d, *J* = 9.2). In comparison, for 4,5-diphenylimidazolidine-2-thione (*R*,*S*,*R*)-*anti*,*syn*-**5**, the PhCHNC=O doublet appeared at 5.69 ppm (1 H, d, *J* = 9.1).
7. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (reference number: CCDC 756360).
8. This comprises of an equimolar mixture of (*R*,*S*)-**4-Na** and (*S*,*R*)-**4-Na**.
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