Highly Diastereoselective Desymmetrisation of Cyclic *meso*-Anhydrides and Derivatisation to Mono-Protected 1,4-Diols

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Abstract: A new and efficient desymmetrisation of bi- and tricyclic *meso*-anhydrides is described, providing good yields and diastereoselectivities in all cases (routinely >95% de). Derivatisation of the chiral compounds synthesised is then demonstrated by their conversion into mono-protected 1,4-diols.

Key words: chiral auxiliary, diastereoselectivity, desymmetrisation, stereoselective synthesis, anhydride

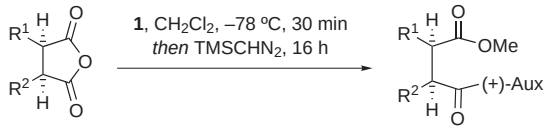
The desymmetrisation of prochiral cyclic anhydrides is a very useful synthetic process that generates optically-enriched chiral hemiesters, containing one or more stereogenic centres and two chemically differentiated carbonyl functionalities.[1] These chiral hemiesters, and derivatives thereof, have proven to be versatile building blocks in asymmetric synthesis.[2]

However, existing methods for the desymmetrisation of *meso*-anhydrides can suffer from one or more problems: extended reaction times, low enantio- or diastereoselectivities and limited scope of anhydride substrates.[1,2] We report herein a new, auxiliary-mediated method for anhydride desymmetrisation that combines reduced reaction times with good to excellent diastereoselectivities and broad reaction scope.

1 (+)-auxiliary: "(+)-Aux" **2** (–)-auxiliary: "(–)-Aux"

Figure 1 Chiral amine auxiliaries **1** and **2** used for *meso*-anhydride desymmetrisation.

Work published by Abiko et al. describes the synthesis and use of a new chiral isoxazolidine auxiliary **1** (Figure 1).[3] Synthesis of the auxiliary is straightforward and scalable, and isolation of both highly crystalline (+)- and (–)-enantiomers (**1** and **2**, respectively) from the racemic reaction mixture is possible via kinetic resolution using (+)-CSA.



Scheme 1 General depiction of desymmetrisation of *meso*-anhydride to hemiester using **1**.

Abiko et al. report the effective use of **1** as a chiral auxiliary for asymmetric alkylation and also demonstrate its Weinreb amide-like cleavage to yield alcohols, aldehydes, ketones and carboxylic acids.[3] However, the use of **1** as a desymmetrisation agent has not been further investigated; we thus hoped to use **1** as a new reagent for the asymmetric desymmetrisation of cyclic *meso*-anhydrides. Due to the literature precedent,[3] auxiliary cleavage was not envisioned to present difficulties. Additionally, given the highly crystalline nature of **1** and **2**, it was anticipated that the diastereoselectivity observed within the desymmetrisation reaction could be further enhanced by standard recrystallisation methods.

Initial investigations of the desymmetrisation reaction of *cis*-1,2,3,6-tetrahydrophthalic anhydride (Scheme 1, Entry 1) with (+)-auxiliary **1** ['(+)-Aux'] at –78 °C in dichloromethane proved to be problematic, due to the apparent instability of the amide-acid product. However, when the desymmetrisation reaction was carried out with subsequent trapping of the resulting carboxylic acid with TMS-diazomethane, only one diastereomeric amide-ester product **3** was isolated, as confirmed by both ^{1}H NMR and chiral HPLC. Investigation of the scope of **1** as a desymmetrising reagent proved to be encouraging: the one-pot desymmetrisation and consequent ester formation proceeds with high yields and diastereoselectivities on a broad range of substrates, as shown in Table 1. Both bi- and tricyclic succinic anhydrides are desymmetrised with high yields and diastereomeric ratios. All desymmetrised products are crystalline, as demonstrated by the crystal structure of the desymmetrized anhydride product **6** (Figure 2); thus recrystallisation could potentially, where necessary, be used to give diastereomerically pure products.

In order to prove the synthetic utility of our desymmetrisation process, it was necessary to demonstrate that the two carbonyl functionalities can indeed be chemically differentiated, and that further derivatisation of the desymmetrisation products is possible. Conditions were

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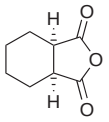
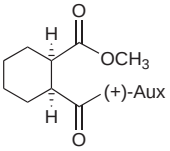
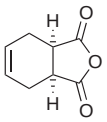
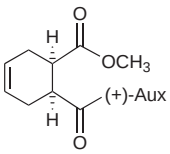
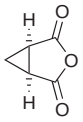
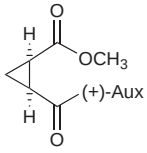
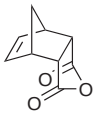
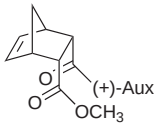
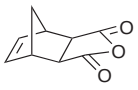
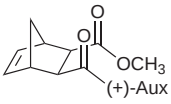
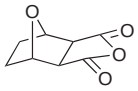
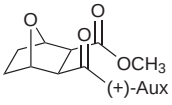
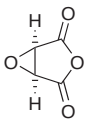
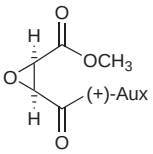
Table 1 Scope of (+)-Aux **1**[a] as a Desymmetrising Chiral Auxiliary

Entry	Anhydride	Product	Yield (%)	de (%)[b]
1		 **3**	96	>95
2		 **4**	90	>95
3		 **5**	74	92
4		 **6**	99	>95
5		 **7**	90	>95
6		 **8**	98	>95
7		 **9**	98	>95

[a] (–)-Aux **2** has been demonstrated to be equally diastereoselective.
[b] The de (%) was confirmed by ^{1}H NMR and chiral HPLC.

obtained, after some investigation, whereby 1,4-mono-protected diols could be formed in good yield and with retention of the initial chirality induced in the desymmetrisation process (Scheme 2).

Chemoselective reduction is achieved using Schwartz reagent, which selectively reduces the methyl ester moiety to the alcohol at room temperature in 30 minutes, leaving the amide portion of the molecule intact.[4] Protection of the alcohol and Weinreb amide-like reductive cleavage of the auxiliary to the 1,4-mono-protected diol proceeds in good

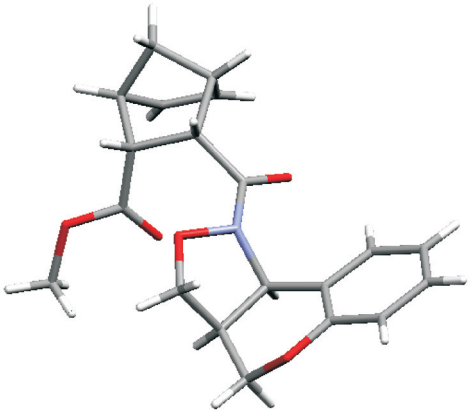
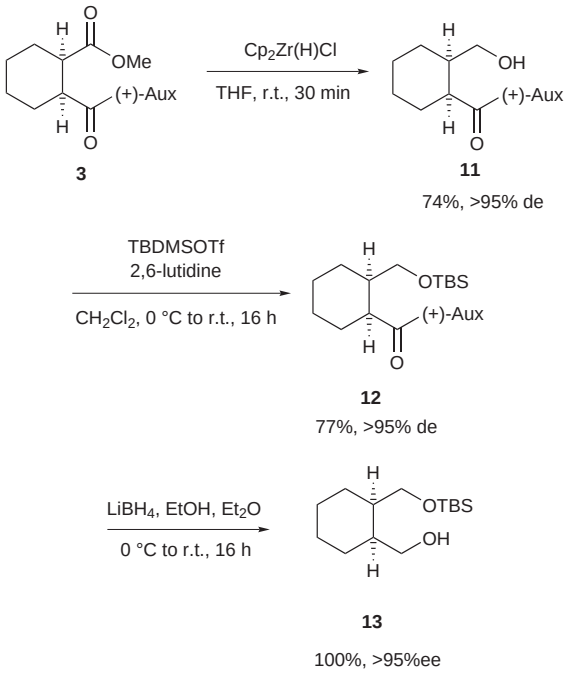


Figure 2 X-ray diffraction analysis of desymmetrised anhydride product **6**.

overall yields. The diastereoselectivity of the original desymmetrisation step is maintained throughout the derivatisation process, as monitored by ^{1}H NMR. Indeed, the diastereoselectivity of the original anhydride desymmetrisation ultimately translates into excellent enantioselectivity upon auxiliary cleavage, as proven by derivatisation via Mosher's ester formation and subsequent ^{1}H NMR analysis.



Scheme 2 Derivatisation of chiral products to 1,4-mono-protected diols; ee (%) of **13** proven by Mosher's ester formation.

Further work is ongoing to provide alternative derivatisation pathways for the desymmetrisation products using Weinreb amide cleavage conditions. The desymmetrisation of monocyclic and glutaric anhydrides is also currently being investigated.

General Experimental Protocol

A solution of cyclic *meso*-anhydride (0.55 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) was cooled to –78 °C. A solution of (+)-auxiliary **1** (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added dropwise, and the resulting solution was stirred at –78 °C for 30 min. TMS-diazomethane (1.25 mmol, 2.5 equiv, 2.0 M in hexanes) was then added dropwise. After 16 h at –78 °C, the reaction was quenched with MeOH (4 mL) and allowed to warm to r.t. Following solvent removal and column chromatography (silica gel, 1% MeOH in CH_2Cl_2), the pure desymmetrised anhydrides were isolated in yields up to 99%.

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