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Enantioselective Catalytic Desymmetrization of Maleimides by Temporary Removal of an Internal Mirror Plane and Stereoablative Over-reduction: Synthesis of (*R*)-Pyrrolam A

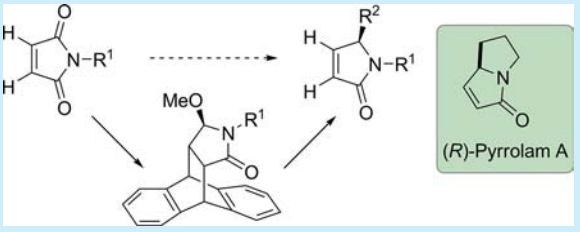
Barrie J. Marsh,[†] Harry Adams,[†] Mike D. Barker,[‡] Ibrahim U. Kutama,[†] and Simon Jones*[,†]

[†]Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield S3 7HF, United Kingdom

[‡]Medicines Research Centre, GlaxoSmithKline Research and Development Ltd., Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, United Kingdom

Supporting Information

ABSTRACT: A highly enantioselective (>95% ee) strategy to affect the desymmetrization of a maleimide has been performed by temporary attachment to an anthracene template followed by asymmetric reduction with an oxazaborolidine catalyst. A stereoablative over-reduction process was partially responsible for the high levels of enantioselectivity. Exemplification of the strategy by stereoselective functionalization and retro-Diels–Alder reaction provided the natural product pyrrolam A.

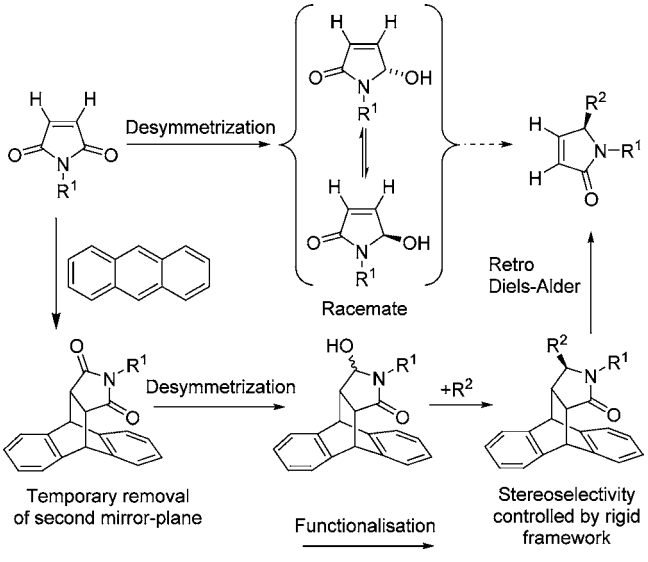


Desymmetrization of a *meso*-compound using a chiral reagent or catalyst provides a powerful and versatile strategy in asymmetric synthesis as a single stereodifferentiating step can facilitate the formation of multiple stereogenic centers.[1] Cyclic *meso*-imides represent a useful class of such compounds as stereoselective reduction of one of the carbonyl groups leads to a product with three contiguous stereogenic centers. Various strategies have been reported for the desymmetrization of *meso*-imides to achieve chiral compounds with high enantioselectivity,[2] including reduction using oxazaborolidine catalysts.[3] Work from this laboratory has shown that an alternative catalyst derived from *cis*-1-aminoindan-2-ol is much more effective for this desymmetrization process and that the protecting group on the nitrogen atom of the imide plays an important role in moderating the yield and selectivity of the transformations.[4]

Although reductive enantioselective desymmetrization of *meso*-imides is a very effective strategy, it is limited to 3,4-disubstituted saturated imides. Direct desymmerization of maleimides and succinimides by reduction cannot be performed due to the C_s symmetry from the second mirror plane in the molecule, coupled with the propensity of the newly installed hydroxylactam stereogenic center to undergo inversion, leading to racemization. A way to circumvent this is to temporarily change the symmetry to C_{2v} by a transformation that removes the second mirror plane, for example, through a Diels–Alder reaction with anthracene. Desymmetrization followed by functionalization of the intermediate hydroxylactam and removal by a retro-Diels–Alder reaction would reveal the chiral α,β-unsaturated lactam (Scheme 1).

A secondary advantage of this method is that the stereoselectivity of any subsequent functionalization step should be enhanced due to the rigid bicyclic nature of the intermediate before the final retro-Diels–Alder reaction.[5]

Scheme 1. Use of Anthracene Template for Desymmerization of N-Substituted Maleimides



Previous work from this group demonstrated that desymmetrization of N-functionalized *meso*-imides derived from *cis*-cyclohexane-1,2-dicarboxylic acid gives essentially one enantiomer of product when *N*-phenyl groups are used.[4b] However, only moderate yields were obtained with this protecting group, in addition to it being problematic to remove. For the substrates in this work, it was not clear which protecting group would provide the better results since it could

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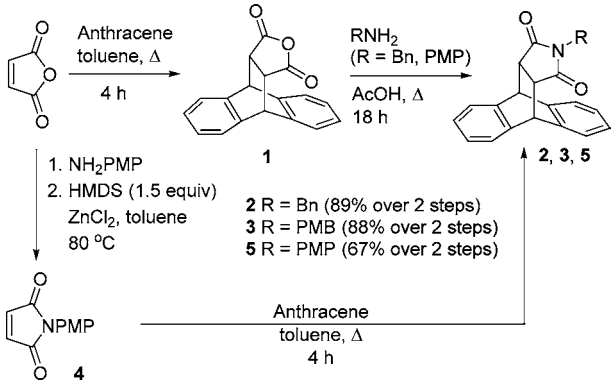
be envisioned that the presence of the anthracene framework would allow the use of the more useful *N*-benzyl protecting group, as the conformation of this substrate would be effectively restricted compared to the those previously investigated. Thus, the synthesis of *N*-benzyl imide cycloadduct **2** was achieved by a Diels–Alder reaction between maleic anhydride and anthracene to furnish the anhydride cycloadduct **1**, which was condensed with benzylamine to give the desired *N*-benzyl imide cycloadduct **2** in 89% yield over two steps (Scheme 2).

Scheme 2. Preparation of *N*-Bn, *N*-PMB, and *N*-PMP Cycloadducts



The *p*-(methoxybenzyl) derivative was synthesized using the same methodology employed for the *N*-benzyl derivative giving the *N*-PMB imide **3** in 88% yield. In the case of the *p*-(methoxyphenyl) derivative **5**, an alternative route was adopted first involving formation of maleimide **4** in 67% yield, followed by cycloaddition that proceeded in quantitative yield.

In previous work, BH_3·THF was determined to be the optimal borane source for the desymmetrization process as there was no competing background reaction, with the optimal catalyst loading being 10 mol %.[4] The *N*-PMP cycloadduct **5** also showed only 2% conversion to the corresponding hydroxylactam when treated with BH_3·THF stirred at room temperature for 18 h. With this information in hand, various oxazaborolidine catalysts were tested using the *N*-PMP derivative **5** as a benchmark substrate, using 10 mol % loading and BH_3·THF as the reducing agent. In every case, the hydroxylactam formed was converted into the more stable corresponding methoxyaminal by treatment with acid in methanol (Scheme 3). The initial results showed the *cis*-1-aminoindan-2-ol-based catalysts to be superior to the diphenyl prolinol catalyst both in terms of yield and enantiomeric excess (compare entries 1–3 with entry 4, Table 1), all giving excellent enantiocontrol and a consistent yield of around 55% over the two steps (Table 1). As observed in previous studies, there was evidence from the ^{1}H NMR spectra that the low yield obtained is due to over-reduction of the pyrrolidine.[4b]

Upon further investigation, we found that this over-reduction process is critical for obtaining products of high enantiomeric excess. Scalemic hydroxylactam **13** (34% ee) was subjected to both enantiomers of catalyst **10** under standard reaction conditions (Scheme 4), leading to a stereoablative process that upgraded the enantiomeric purity through selective over-reduction of only one enantiomer of hydroxylactam.[6] This appears to be the first example of such a transformation being used in an oxazaborolidine-catalyzed reduction.

Scheme 3. Evaluation of Catalyst and Nitrogen Protecting Group

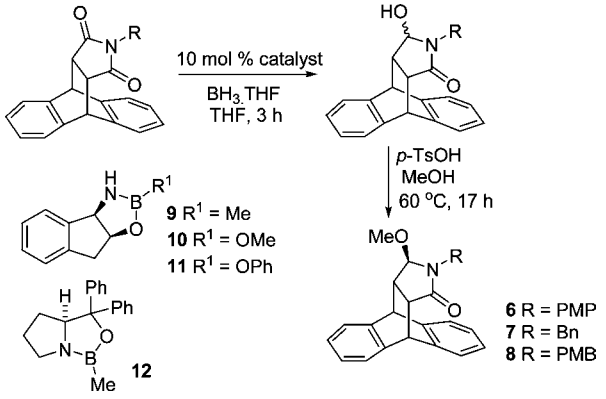
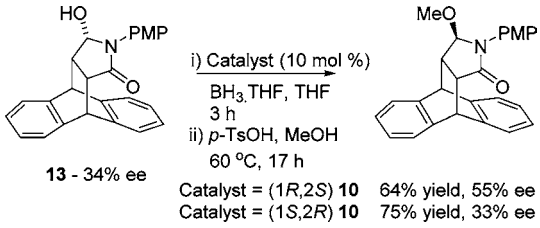


Table 1. Evaluation of Catalyst and Nitrogen Protecting Group[a]

entry	catalyst	substrate/product	yield (%)[b]	ee (%)[c]
1	**9**	**5**/**6** (R = PMP)	55	96
2	**10**	**5**/**6** (R = PMP)	61	99
3	**11**	**5**/**6** (R = PMP)	50	99
4	**12**	**5**/**6** (R = PMP)	15	4
5	**10**	**2**/**7** (R = Bn)	85	95
6	**10**	**3**/**8** (R = PMB)	21	97

[a]Reactions performed by addition of catalyst **9**–**11** (0.25 mmol) in THF (1 mL) to a stirred solution of imide **2**, **3**, or **5** (2.5 mmol) in THF (20 mL), followed by addition of BH_3·THF (2.5 mL, 2.5 mmol) at rt. Standard workup and conversion to the methoxylactam is described in the Supporting Information. [b]Refers to isolated product. [c]Enantiomeric excess determined by chiral stationary phase HPLC.

Scheme 4. Stereoablative Upgrade of Enantioselectivity



As all the three aminoindanol-based oxazaborolidines demonstrated near identical yields and enantioselectivity, only the B-OMe catalyst **10** was used in subsequent tests with the other nitrogen protecting groups. With the *N*-benzyl derivative **2**, the yield of the methoxylactam **7** was increased to 85%; however, the enantioselectivity dropped slightly to 95% (Table 1, entry 5), following the previously reported trend with *meso*-imides.[4b] With *N*-PMB derivative **3**, the enantioselectivity of the reaction was similar at 97%; however, the yield dropped to a disappointing 21% (Table 1, entry 6). In this case, the low yield is due to poor conversion (53% of starting material) in the asymmetric reduction. In all cases, the relative stereochemistry of the resulting products was confirmed from the crystal structures for methoxyaminals **6** and **7**, clearly indicating that the methanol had approached from the top face of the intermediate *N*-acyl iminium ion. Correlation of the coupling constants of these compounds with that of methoxyaminal **8** indicated that this was also likely to possess the same relative

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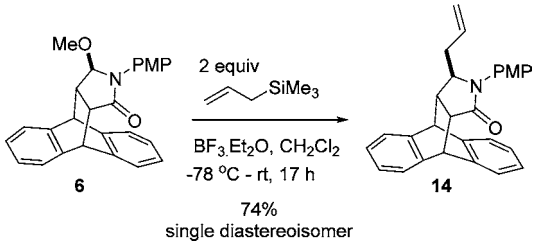
configuration. The absolute configuration was confirmed by subsequent synthetic studies.

Functionalization of these products was demonstrated by Lewis-acid-mediated displacement of the methoxy group of aminal **6** and reaction of the *N*-acyl iminium ion formed with allyltrimethyl silane.[3a] Thus, *N*-PMP *O*-methyl aminal **6** was treated with allyl trimethylsilane in the presence of boron trifluoride at −78 °C, providing the *C*-allyl lactam **14** in good yield (74%) as a single diastereoisomer (Scheme 5). Correlation of the coupling constants again provided evidence that addition had occurred at the top of the intermediate *N*-acyl iminium ion.

Scheme 5. Allyl Trimethylsilane Addition to Aminal 6



To illustrate the synthetic applicability, lactam **14** was used as a substrate to prepare pyrrolam A. This natural product was first isolated by Grote et al. in 1990 from the bacterial strain *Streptomyces olivaceus* (strain Tü 3082) along with three other related compounds, pyrrolams B−D.[7] Pyrrolam A was shown to have only modest biological activity, with low herbicidal activity and was inactive against both Gram-positive and Gram-negative bacteria, fungi, molds, viruses, worms, protozoa, and tumor cell lines. Since its isolation, there have been a number of reported syntheses, many of which employ a chiral pool approach.[8]

Deprotection of PMP-lactam **13** using CAN gave the lactam **15** in 84% yield (Scheme 6). Hydroboration of this by treatment with BH_3·THF followed by $NaOH/H_2O_2$ yielded the alcohol **16**. Although the ^1H NMR spectrum of the crude reaction material showed 100% conversion of the lactam **15**, all efforts to purify compound **16** by both flash chromatography and recrystallization failed. Hence, the alcohol **16** was treated with methanesulfonyl chloride and triethylamine to give the mesylate **17** with complete conversion of starting material. Again, the compound was not purified and immediately cyclized by heating at reflux in methanol with DBU to give amide **18** in 20% yield over three steps. Conditions were tested for flash vacuum pyrolysis of this material. The inlet temperature was kept at 226 °C (the melting point of the cycloadduct), and the pressure set at 1×10^{-2} mbar. The initial temperature of the furnace was set at 560 °C, which initiated the retro-Diels−Alder reaction but led to decomposition. A similar observation was made when the temperature was lowered to 520 °C (Table 2, entries 1 and 2). At a temperature

Table 2. Flash Vacuum Pyrolysis of Bicycle 18[a]

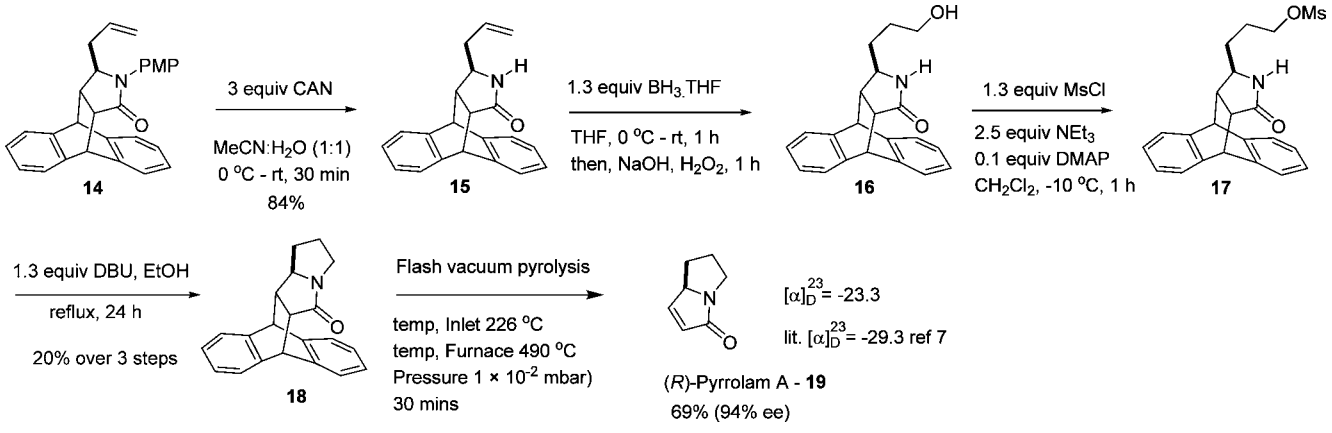
		product distribution (%)[b]		
entry	furnace temp (°C)	**18**	anthracene	pyrrolam **19**
1	560	0	73	0
2	520	0	50	0
3	510	50	11	0
4	490	30	69	68
5	470	87	0	0

[a]Inlet temperature of 226 °C at a pressure of 1×10^{-2} mbar. Reactions performed over a period of 20−40 min until no further sublimation of the starting material was observed. [b]Refers to yield of isolated material.

of 510 °C, a mixture of anthracene and starting material was obtained alongside some decomposed material in the u-tube collection vessel. Although some peaks of pyrrolam A were observed in the crude ^1H NMR spectrum, pure material was not successfully isolated (Table 2, entry 3). The best result was obtained when the furnace temperature was set at 490 °C (Table 2, entry 4), which led to the isolation of pure desired product **19** in 68% yield with no decomposition being observed. The slight drop in the ee of product compared to starting material (94 vs 99%) is probably due to the stability of the product, as has been noted in previous isolation and synthetic studies on this target.[7,8a] When the temperature was further lowered to 470 °C, a retro-Diels−Alder failed to occur, returning only the starting material, indicating the narrow window of operation for conducting the FVP process.

A model for the stereoselectivity of this reaction can be proposed using the same basis as previously noted.[4b] Thus, preferential coordination of the Lewis acidic boron center of the oxazaborolidine occurs to minimize steric interactions of the B-Me group with the nitrogen substituent (the "large" group using the traditional CBS model). This leads to two possible intermediates, where only in one case can reduction

Scheme 6. Synthesis of Pyrrolam A



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then occur from the more sterically accessible face of the imide (Figure 1).

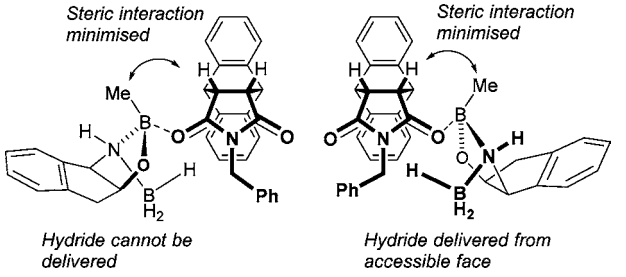

Figure 1. Model for the stereoselectivity observed in the reduction of imide **2**.

In conclusion, an efficient strategy has been developed to effect the highly enantioselective desymmetrization of maleimide, with the discovery of an in situ stereoablative process that serves to upgrade the observed enantioselectivity. Here we have exemplified the strategy in the synthesis of pyrrolam A, paving the way for further functionalization of the intermediate hydroxyaminals to provide access to more complex pyrrolidine building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Copies of experimental procedures, data, spectra, and crystallographic data for compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: simon.jones@sheffield.ac.uk.

Notes

The authors declare no competing financial interest.

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