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Asymmetric Reduction of Lactam-Based β-Aminoacrylates. Synthesis of Heterocyclic β^2-Amino Acids

Hugo Rego Campello,[†] Jeremy Parker,[‡] Matthew Perry,[§] Per Ryberg,[∥,⊥] and Timothy Gallagher*[,†]

[†]School of Chemistry, University of Bristol, Bristol BS8 1TS U.K.

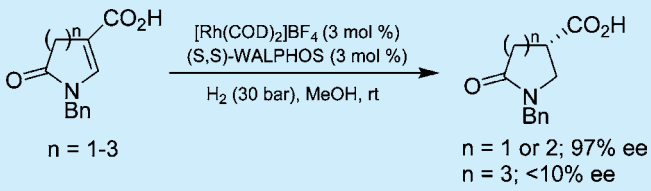
[‡]AstraZeneca, Pharmaceutical Development, Silk Road Business Park, Macclesfield SK10 2NA U.K.

[§]AstraZeneca, Innovative Medicines, R&I Chemistry, AstraZeneca R&D Mölndal, Peparedsleden, SE-431 83 Mölndal, Sweden

[∥]AstraZeneca, PR&D Södertälje, S-151 85 Södertälje, Sweden

Supporting Information

ABSTRACT: The ability to affect asymmetric reduction of heterocyclic β-aminoacrylates **1** (n = 1−3) has been assessed with pyrrolidine and piperidone variants generating the corresponding N-heterocyclic β^2-amino acids **3b** and **5b** with high enantioselectivity (≥97% ee) using a Rh/WALPHOS catalyst combination. The use of the carboxylic acid substrate was essential; the corresponding esters do undergo reduction but led to racemic products. The seven-ring azepanone variant (as the carboxylic acid **9b**) underwent reduction, but only a minimal level of asymmetric induction was observed.



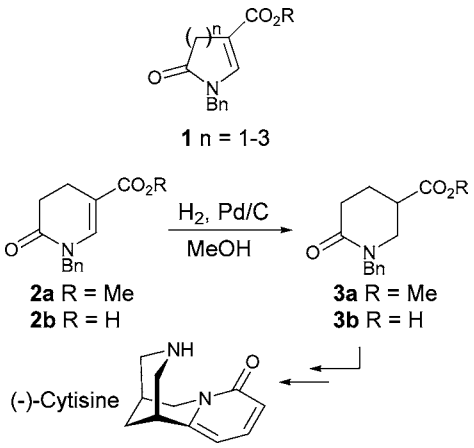
Functionalized and chiral N-heterocycles represent widely exploited and valuable synthetic units, where an ability to gain access to either enantiomer of the target heterocycle is often an important issue.[1] Asymmetric alkene reduction methods[2] are especially attractive in this area since other functional groups present in the alkene substrate, e.g., a carbonyl moiety often serves to direct the catalytic reduction step; such functionality can then also be of value in terms of the synthetic flexibility inherent within the reduction product.

In terms of general C═C reduction, high enantioselectivity has been reported for a range of functionalized alkenyl substrates, such as acrylates[3] and, relevant here, α- and β-amino/amidoacrylates.[4] Similarly, cyclic enamines are effective substrates for asymmetric reduction leading to substituted five-, six-, and seven-ring N-heterocycles.[5]

Our interest in this area has focused on reduction of an unusual class of β-amidoacrylates (i.e., lactams) of general structure **1** (n = 1−3). The potential of these systems is exemplified by lactam **2** (**1**, n = 2); reduction of the readily available ester **2a**[6] provides piperidone **3a** (a β^2-amino acid derivative) which has served as a key intermediate in the synthesis of cytisine as well as of a series of cytisine variants (Scheme 1).[7]

In previous work, we developed an asymmetric approach to cytisine by exploiting an ability to carry out a kinetic resolution of methyl ester **3a** using α-chymotrypsin (α-CHY).[8] This provided acid (*S*)-**3b** (>64% ee; 48% yield) and (unreacted) ester (*R*)-(+)-**3a** (>98% ee; 42% yield). While useful, such resolution processes are, however, inherently inefficient. Catalytic asymmetric reduction of **2a**/**b**, which is a more attractive option, had been explored using standard methods reported previously for acrylates. However, these efforts enjoyed limited success; we obtained low enantioselectivities and poor conversions.[9] One factor affecting the levels of asymmetric induction observed may link to the relative spatial disposition of the lactam carbonyl (as a potential ligand and directing group) with respect to either or both of the C═C or carboxylate functions.[10]

Scheme 1



Given these limitations, the value and attractiveness of enantiomerically pure piperidinone **3a**/**b** in other contexts,[11] and the opportunity to develop a methodology applicable to a wider range of substrates, we undertook a more extensive screening program to assess the potential for the asymmetric reduction of methyl ester **2a** and carboxylic acid **2b**. A wide range of metal catalysts, ligands, and reaction conditions were

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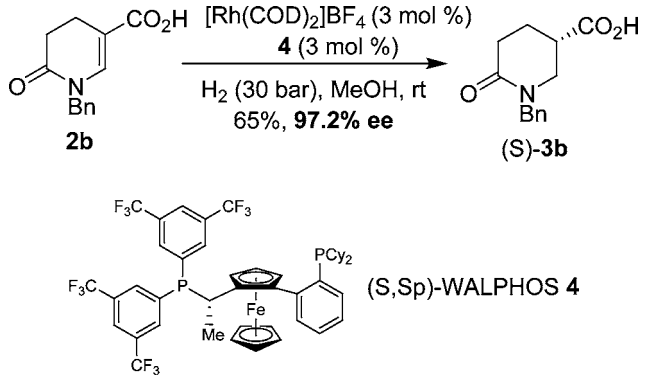
evaluated within AstraZeneca. Having screened a range of parameters, effective reaction conditions were identified, which are shown in Scheme 2, and asymmetric reduction of acid **2b** was achieved to product (*S*)-(−)-**3b** in over 97% ee with Rh catalysis in combination with (S,S_p)-WALPHOS **4** as ligand.[12]

Scheme 2. Asymmetric Reduction of 2b To Give (*S*)-3b

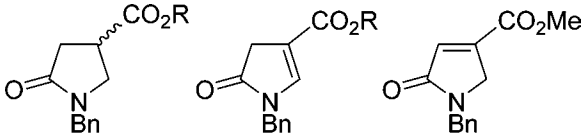


High selectivity was observed only with carboxylic acid **2b**; methyl ester **2a** did undergo reduction but with a negligible level of enantiomeric induction under all of the different conditions evaluated. Further, the isolated (after purification) yield (65%) of (*S*)-**3b** is likely a result of the high pressures involved necessary to achieve reasonable conversion under which N-debenzylation appeared to begin to compete.

The stereochemical outcome of this asymmetric reduction process (in terms of generating (*S*)-(−)-**3b**) was established by comparison to the piperidinone products obtained from enzymatic kinetic resolution. In this previous work, we had obtained as the unreacted enantiomer ester (*R*)-(+)-**3a** in high enantiomeric excess, which we had then converted to (unnatural) (+)-cytisine.

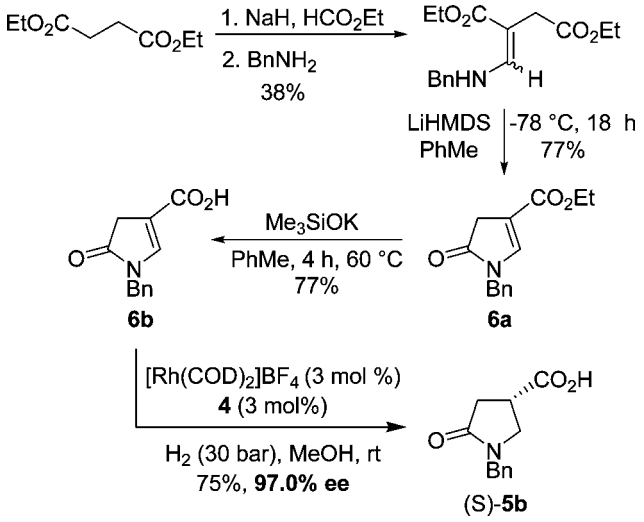
We have further explored the scope of this reduction methodology and examined the viability of the corresponding pyrrolidine and azepane-based lactams **1** (n = 0 and 2, respectively) given that, alongside piperidone **2**, these would provide a homologous series of enantiomerically enriched, functionalized, and synthetically versatile N-heterocyclic units.

In the case of the pyrrolidine variant, the enzymatic kinetic resolution of (±)-**5a** (to provide access to enriched ester (*R*)-(−)-**5a** and acid (*S*)-(+)-**5b**) has been reported.[13] This earlier work provided us with the basis for a later structural assignment, but two potential reduction substrates needed to be considered: the β-aminoacrylates **6a**/**b**[14] (the $\Delta^{4,5}$-lactam, analogous to **2a**/**b**) and the corresponding $\Delta^{3,4}$-isomer (incorporating a fumarate subunit), previously reported as the methyl ester **7**.[15]



The synthesis of β-aminoacrylate **6a**/**b** we have developed is shown in Scheme 3 and is based on formylation of diethyl succinate followed by enamine formation (using benzylamine),

Scheme 3. Synthesis of 6a and 6b: Asymmetric Reduction of 6b



cyclization of which was best carried out under strongly basic conditions. Given our experience in the piperidinone series, we focused attention on the use of the corresponding carboxylic acid **6b** as the reduction substrate, but the conversion of ester **6a** to acid **6b** proved to be surprisingly difficult; product degradation under standard conditions appeared to be facile.[16] Optimal conditions developed are shown in Scheme 3, and once isolated, acid **6b** is crystalline, stable, and easily handled.

Reduction of acid **6b** followed a very similar course to that of **2b**, and the (*S*)-(+)-carboxylic acid **5b** was isolated in 75% yield and in 97% ee. The configuration of **5b** was established by comparison with optical rotation data reported for this compound derived by enzymatic resolution,[13] and clearly, **2b** and **6b** undergo asymmetric reduction in the same sense as one another under these Rh/WALPHOS conditions.

We were interested in the behavior of the isomeric lactam **7** under reduction conditions, recognizing that C=C isomerization could be involved in the reduction of β-aminoacrylates such as **6b**. However, our attempts to reproduce the route reported to **7** failed to give the product claimed;[15] see the Supporting Information. In our hands, the only product obtained under these conditions was methyl ester **6c** (i.e., the $\Delta^{4,5}$-lactam isomer), which was isolated in 70% yield.

The azepane variant **9** was prepared using a nitrone-based Beckmann rearrangement (Scheme 4), which was based on the previous work of both Barton[17a] and Ward.[17b] To avoid a problematic separation of isomeric lactam products, it was critical to isolate the individual nitrone isomers **8** (isolated as a 3:1 mixture of *E*/*Z* isomers) prior to rearrangement. In this way azepene **9a** was obtained in 40% yield and converted efficiently to the corresponding acid **9b**.

Reduction of **9b**, under the conditions applied to **1b** and **5b**, provided the azepane **10** but in 10% ee, and the absolute configuration of the predominant product was not established. This was a surprising result given the relatively small structural modification involved, and further work will be needed to probe the mechanism by which this set of substrates interacts with the Rh/ligand complex.[18]

Given that both pyrrolidinone **5a** and piperidone **3a** are viable substrates for kinetic resolution using α-chymotrypsin (α-CHY), we have evaluated methyl ester **11** under these

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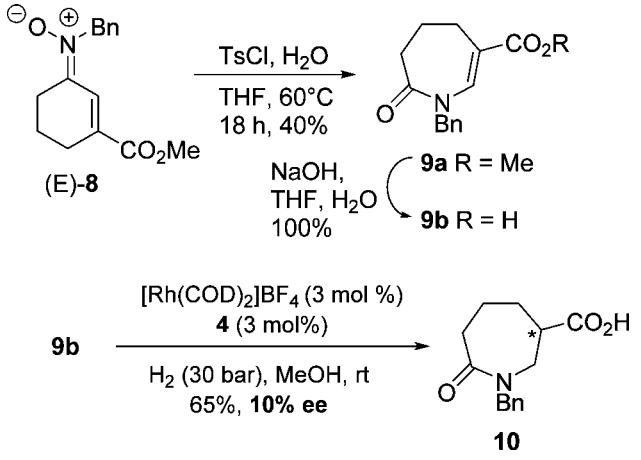
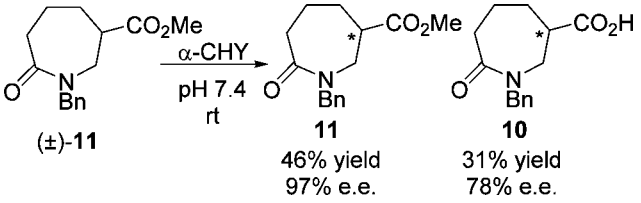
Scheme 4. Synthesis of 9a and 9b: Asymmetric Reduction of 9b



conditions (Scheme 5). Ester **11** was obtained in 85% yield by hydrogenation of **9a** (see the Supporting Information).

Scheme 5. Enzymatic Kinetic Resolution of (±)-11



At pH 7.4, racemic **11** underwent selective hydrolysis, and the corresponding acid **10** was isolated in 31% yield and 78% ee and the unreacted ester **11** was recovered in 46% yield and 97% ee (as assessed by chiral HPLC).[19] We have not assigned the absolute configurations of these products and this process has not been optimized further in terms of yields and enantiomeric purities.

In summary, we have shown that an unusual but synthetically useful class of heterocyclic β-aminoacrylates undergo efficient asymmetric reduction with a Rh-WALPHOS catalyst combination. This process works efficiently for the pyrrolidinone and piperidinone carboxylic acid substrates **6b** and **2b**, respectively, but the level of enantiomeric selectivity dramatically diminished in the case of the seven-ring azepine substrate **9b**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02074.

Experimental procedures and spectroscopic data for all new compounds and the X-ray crystallographic structure determination of (*S*)-**3b** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: t.gallagher@bristol.ac.uk.

Present Address

⊥Ferring Pharmaceuticals, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark.

Notes

The authors declare no competing financial interest.

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