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ASYMMETRIC HALOGENATION OF CHIRAL IMIDE ENOLATES. A GENERAL APPROACH TO THE SYNTHESIS OF ENANTIOMERICALLY PURE α-AMINO ACIDS.

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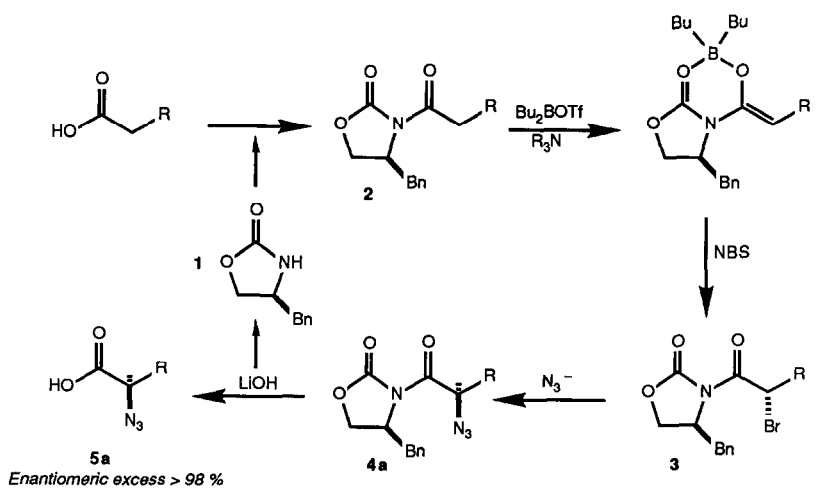
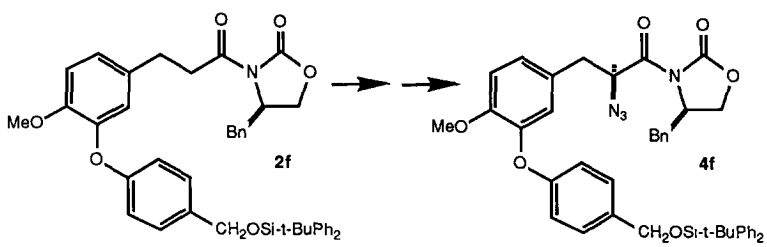
Abstract: The chiral N-acyl oxazolidones **2**, as the derived dibutyl boron enolates, have been demonstrated to undergo diastereoselective bromination and subsequent azide displacement to give the α-azido carboximides **4a** (5 cases). These adducts may be hydrolyzed under mild conditions to the enantiomerically pure α-azido carboxylic acids **5a**.

The development of efficient approaches to the asymmetric synthesis of nonproteinogenic amino acids remains a topic of considerable interest. Recent reports describing advances in the development of both nucleophilic[1] and electrophilic[2] chiral glycinate synthons have actively addressed this issue. As an alternative to the above approaches, we[3] and others[4] have been developing methods to effect the direct electrophilic amination of chiral enolates. The generality of this latter approach, which also provides access to both tert-butyl and arylglycines, is quite complementary to the cited strategies for α-amino acid synthesis. As an extension of our enolate amination studies, we wish to describe the asymmetric synthesis of α-azido carboxylic acids **5a** wherein the pivotal steps involve the diastereoselective bromination of N-acyl oxazolidones **2** and subsequent azide displacement (Scheme I).[5]

Scheme I



For practical considerations we have employed the (4S)-benzyl-2-oxazolidone chiral auxiliary **1** derived from (S)-phenylalanine;[6] however, the other chiral oxazolidones derived from either valine or (1S,2R)-norephedrine employed in earlier studies perform with equal facility.[7] Since both **1** and its enantiomer are now commercially available,[8] the present methodology provides ready access to a range of enantiomerically pure α-amino acid synthons. In direct analogy to our prior aldol studies,[9] the boron enolate derived from **2** was treated with N-bromosuccinimide (1.1 equiv, CH_2Cl_2, 75 min, -75 °C).[10] After an extractive workup of the reaction which afforded the α-bromo carboximide **3** as the principal adduct, azide displacement was effected with tetramethylguanidinium azide (3 equiv, CH_2Cl_2, 3 h, 0 °C) to give the (2R) azide **4a** as the principal product which was purified to high diastereomeric purity (>99:1) by flash chromatography on silica gel. Under the stated reaction conditions, negligible loss of stereochemistry accompanied azide displacement; however, other reaction conditions (NaN_3, DMF or DMSO, 0 °C) afforded 2-5% epimerization. The salient characteristics of this reaction sequence are summarized in Table I. In general (Entries A-D), the bromination step was found to be uniformly diastereoselective. The only exception that we have noted in this study was in the bromination of **2**, R=Ph (Entry E). In all cases, the sense of asymmetric induction is consistent with electrophilic bromination of the Si face of the illustrated (Z) boron enolate (Scheme I). It is of considerable interest that these boron enolates react with the electrophiles NBS and aldehydes from opposite diastereofaces! The above reaction sequence may be extended to more complex substrates as well (Eq 1). For example, **2f** may be transformed into the diastereomerically pure azido carboximide **4f** in an 83% overall yield. The combined diastereoselectivity for the two steps was 96:4.

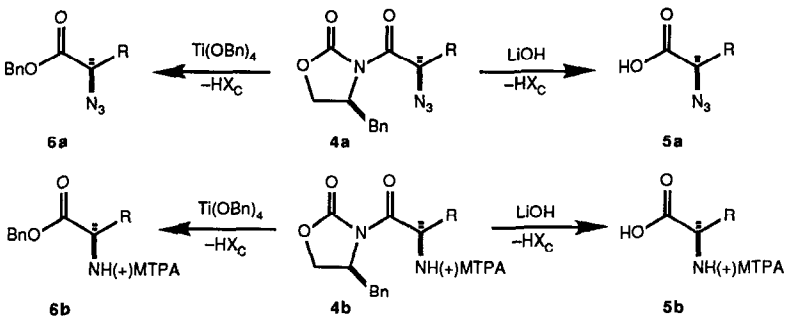


(1)

A representative procedure for the synthesis of α-azido carboximides **4a** follows: A 0.2-0.5 M solution of the di-n-butylboron enolate derived from **2** in CH_2Cl_2 at -78 °C[9] is cannulated into a slurry of N-bromosuccinimide (1.1 equiv) in CH_2Cl_2. The resulting purple slurry is stirred at -78 °C for 75 min and quenched with 0.5 N aqueous bisulfate solution. After the addition of ethyl acetate, the organic extract is washed with 0.5 N aqueous thiosulfate solution, dried and concentrated. The unpurified bromide **3** is then dissolved in CH_2Cl_2 to afford a 0.1-0.3 M solution and treated with tetramethylguanidinium azide (3.0 equiv, 3 h, 0 °C).[12] A conventional extractive isolation procedure affords the α-azido carboximide **4a** which may be freed of its epimeric azide contaminant by flash chromatography on silica gel.

Some of the important refunctionalization reactions which may be performed on the α-azido carboximides **4a** are summarized in Scheme II. The substrate **4a** (R=Bn) was chosen to represent a

Scheme II



"conventional" amino acid precursor while **4a** (R=Ph) was selected as a highly racemization-prone case. The latter example provides a critical probe for the propensity of a given refunctionalization reaction to effect racemization during the course of chiral auxiliary removal. The related carboximides **4b** (R=Bn, Ph) were also evaluated in the same reactions since azide reduction might be considered either before or after auxiliary removal. The reduction of both **4a** (R=Bn) and **4a** (R=Ph) was accomplished via hydrogenation (15 psi H_2, 10% Pd-C, MeOH-TFA, 10:1, 3 h, 25 °C) and subsequent acylation of the derived ammonium salt with (+)MTPA-chloride (1.8 equiv, Et_3N, 3 equiv, CH_2Cl_2, 1 h, 0 °C)[13] afforded **4b** (R=Bn) and **4b** (R=Ph) in > 96% overall yields for both cases.[14] The saponification of both sets of substrates with LiOH (2 equiv, 3:1, THF-H_2O, 30 min, 0 °C) afforded excellent yields (95-100%) of the four related acids **5a** and **5b** (R=Bn, Ph) as summarized in Table II (Entries A-D). While no detectable levels of racemization were noted for the conventional substrate pair **4a** and **4b** (R=Bn), 1% racemization was observed for the considerably more labile phenylglycine synthons **4a** and **4b** (R=Ph).[15]

TABLE I.
Synthesis of (2R)-Azidocarboximides (Scheme I).[11]

entry	carboximide 2	diastereoselection[a] (3S):(3R)	(4R):(4S)	yield,%[b,c] 4a
A	**R=$CH_2C_6H_5$**	95 : 5	94 : 6	83
B	**R=CH_2CHMe_2**	95 : 5	95 : 5	86
C	**R=$CHMe_2$**	96 : 4	94 : 6	80
D	**R=$CH_2CH=CH_2$**	94 : 6	94 : 6	82
E	**R=C_6H_5**	78 : 22	78 : 22	67

[a] Ratios of bromide and azide diastereomers were determined by HPLC analysis using a DuPont Zorbax column. [b]Values reported represent the overall yield of diastereomerically pure azide from imide 2.[c] Diastereomeric purity >99%.

TABLE II.
Hydrolysis and Transesterification of **4a & 4b** (Scheme II).[11]

entry	carboximide	reagent	yield,%	product	ratio (S):(R)[a]
A	**4a (R=Bn)**	LiOH	97	**5a (R=Bn)**	>99:1
B	**4b (R=Bn)**	LiOH	95	**5b (R=Bn)**	>99:1
C	**4a (R=Ph)**	LiOH	97	**5a (R=Ph)**	99:1
D	**4b (R=Ph)**[b]	LiOH	100	**5b (R=Ph)**	99:1
E	**4a (R=Bn)**	$Ti(OBn)_4$	93	**6a (R=Bn)**	>99:1
F	**4b (R=Bn)**	$Ti(OBn)_4$	89	**6b (R=Bn)**	>99.1
G	**4a (R=Ph)**	$Ti(OBn)_4$	94	**6a (R=Ph)**	82:18
H	**4b (R=Ph)**[b]	$Ti(OBn)_4$	81	**6b (R=Ph)**	98:2

[a] Enantiomer ratios (Entries A,C,E,G) determined by conversion to (+) MTPA methyl or benzyl esters and capillary GLC analysis. Diastereomer ratios (Entries B,D,F,H) determined directly by GLC. [b] Experiment performed by M.M. Morrissey.

Transesterification of **4a** and **4b** via titanium(IV)benzyloxide was also evaluated. After treatment of **4a,b** (R=Bn, Ph) with $Ti(OBn)_4$ (1.5-2.0 equiv) and benzyl alcohol (50 equiv) in accord with literature analogy (65-80 °C, 7 h),[16] the four benzyl esters were obtained in 81-94% yields (Table II, Entries E-H). The product racemization assay indicated little, if any, loss of stereochemistry accompanied the transesterification of both **4a** and **4b** (R=Bn), while only 2% racemization was noted for the more sensitive phenylglycine synthon **4b**. In contrast, significant loss of stereochemistry accompanied the transesterestification of azido carboximide **4a** (R=Ph). In conclusion, a judicious choice of refunctionalization reactions will provide the amino acid synthons **5a** and **6a** or their derived amides even for racemization-prone substrates.[17]

In summary, the versatile α-amino acid synthons **4a** (or their enantiomers) are readily available via a short sequence of reactions. These intermediates are easily derivatized under very mild conditions at either functional group with negligible loss of stereochemistry. This methodology is well suited to the asymmetric synthesis of multifunctional amino acids.

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5. For a related study see Oppolzer, W.; Pedrosa, R.; Moretti, R. Tetrahedron Lett. **1986**, 27, 831-834.
6. For the experimental details for the synthesis of **1** see: Evans, D.A.; Weber, A.E. J. Am. Chem. Soc. **1986**, 108, 6757-6761.
7. For a recent review see Evans, D.A. Aldrichimica Acta **1982**, 15, 23-32.
8. Both enantiomers of **1** are now commercially available from the Aldrich Chemical Co.
9. Evans, D.A.; Bartroli, J.; Shih, T.L. J. Am. Chem. Soc. **1981**, 103, 2117-2129.
10. An extensive list of other metal enolates and halogenating agents were evaluated with little success.
11. Satisfactory spectral data and elemental analyses were obtained on all compounds reported herein.
12. For more hindered substrates azide displacement was allowed to proceed for 10 h at 25 °C (Table I, Entry C).
13. Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. **1969**, 34, 2543-2549.
14. As a cautionary note, the immediate precursor to the MTPA amide **4b**, the α-amino carboximide, will undergo internal acylation of the oxazolidone carbonyl center in the absence of other acylating agents.
15. Since control experiments on the racemization levels accompanying the successive methyl esterification (2 equiv $SOCl_2$, MeOH, 2 h reflux) and acylation of (S)-phenylglycine with (+) and (-)-MTPA-chloride indicate ca 0.5% loss of stereochemistry, the values reported for the racemization assay (Table II) constitute lower limits.
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17. The proof of absolute stereochemistry for all of the α-azido carboxylic acids **5a** was accomplished via reduction and subsequent correlations with the known α-amino acids.

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