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Amino Acid Homologation by the Blaise Reaction: A New Entry into Nitrogen Heterocycles

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A general strategy for the amino acid homologation via Blaise reaction and subsequent reduction is presented. This strategy involves the preparation of protected α-amino nitriles from the corresponding amino acids, followed by the zinc-mediated condensation of *tert*-butyl bromoacetate, to give the imidazolidones after iminozincate cyclization. Reduction gave the saturated imidazolidinones with *cis* or *trans* stereochemistry, depending on the reduction conditions. This strategy was applied to nonfunctionalized amino acids and to functionalized amino acids such as serine and aspartic acid. Additionally, acidic hydrolysis of *cis* or *trans* imidazolidinones to the corresponding chiral 4-aminopyrrolidones is described.

Introduction

The design and synthesis of new amino acid derivatives is a continuous challenge in organic and bioorganic chemistry. Within the ever-growing families of nonproteinogenic amino acids, β-amino acids[2] and γ-amino acids[3] have emerged as powerful tools in peptide science, as their corresponding peptides possess interesting conformational properties. More recently, a new class of functionalized amino acids, the β,γ-diamino acids (of *syn* or *anti* configuration), has been the subject of closer scrutiny. These compounds, which possess the 1,2-diamine structural motif, may be found in several natural products such as pseudotheonamide A_1[4] or aminocarnitine,[5] and are valuable and flexible building blocks, as they can be precursors for both β- or γ-peptides[6] or various families of heterocyclic compounds (Figure 1). Moreover, 1,2-diamines are often used as ligands for transition metals or as organic catalysts.[7]

β,γ-Diamino acids are structurally related to statines (γ-amino β-hydroxy acids), which can be found in several biologically relevant natural products. Early work by Schostarez and coworkers showed that the replacement of the hydroxyl group in statine **1**, a component of the antihypertensive peptide pepstatin, by an amino group resulted in an enhancement of biological activity (Figure 2).[8] This set the stage for the interest in the synthesis of various β,γ-diamino acids.

Several other approaches to the stereoselective synthesis of β,γ-diamino acids have been reported, including intramolecular conjugate addition of amines onto α,β-unsaturated esters,[9] enolate condensation onto aminoacetals,[10] or stereoselective imine reduction.[11] As we were interested in β,γ-diamino acids,

(1) Erasmus student from Åarhus University, Denmark.

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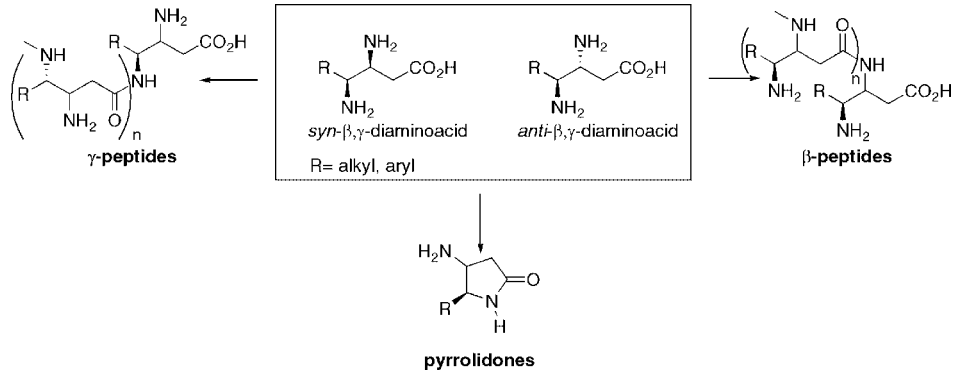

FIGURE 1. β,γ-Diamino acids and their synthetic derivatives.

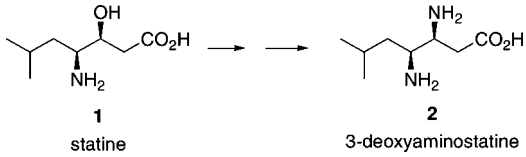

FIGURE 2. Statine **1** and its deoxyamino analogue.

we planned to prepare these compounds in a practical and selective fashion by homologation of α-amino acids by the Blaise reaction.

The Blaise reaction, first reported in 1901,[12] involves the condensation of the zinc enolate of a haloester (generally an α-bromoester) onto a nitrile, giving a β-ketoester after acidic hydrolysis (Figure 3).[13] Despite being close to the Reformatsky reaction with carbonyl compounds, the Blaise reaction has received less attention because of low yields and side reactions, especially self-condensation of the starting haloester. Several improvements have been made in order to improve the yields and to minimize side reactions: slow addition of the bromoester and use of *tert*-butyl esters in place of methyl or ethyl esters resulted in an increase in yields and purities. The activation of zinc metal was also found to be beneficial. Typical experimental procedures describe zinc dust preactivation by washing with acid or *in situ* sonochemical or chemical activation with strong Bronsted acids.[14] These methods allow the obtention of β-ketoesters in good and reproducible yields. More recently, a practical and highly efficient method for organozinc reagent formation by decarboxylation of a malonate monoester in the presence of zinc salts and subsequent condensation (the "decarboxylative Blaise reaction") has been disclosed, making the Blaise reaction an efficient synthetic tool.[15]

The synthetic versatility of the Blaise reaction was further improved when Kishi and co-workers discovered that hydrolysis of the reaction mixture with a basic solution (50% potassium carbonate) resulted in the fomation of an enamino ester instead of the classical β-ketoester.[16] This made the Blaise reaction a convenient method for the synthesis of nitrogen-containing compounds from nitriles.[17]

It appeared that the Blaise reaction could also be used as an entry into β-amino acids by reduction of the subsequent enamino ester. This strategy was applied to the synthesis of β-amino-γ-hydroxyesters from cyanohydrins,[18] β-lactams,[19] and methylphenidate analogs[20] and to the preparation of carbohydrate-derived β-amino acids.[21] In all cases, the enamino ester was reduced by sodium cyanoborohydride under acidic conditions.[22] As organozinc reagents are known to be tolerant of many functional groups and of adjacent stereogenic centers, we thought it would be possible to apply the Blaise reaction−enamino ester reduction synthetic sequence to chiral α-amino nitriles obtained from α-amino acids for the synthesis of stereochemically defined β,γ-diamino acids and derivatives thereof, according to the sequence in Figure 4.

We have recently demonstrated the viability of this synthetic route by the synthesis of chiral 4-aminopyrrolidones[23] and its application to the synthesis of the antipsychotic compound nemonapride.[24] In this article, we would like to present a full account of our studies, including the transformation of functionalized α-amino acids.

Results and Discussion

As depicted in Figure 4, the synthesis of β,γ-diamino acids according to our strategy started with the synthesis of conveniently protected α-amino nitriles from α-amino acids. L-Valine **3** was chosen as model for early studies. Protection of L-valine as its Cbz carbamate or as its *N*-phthalimide, followed by

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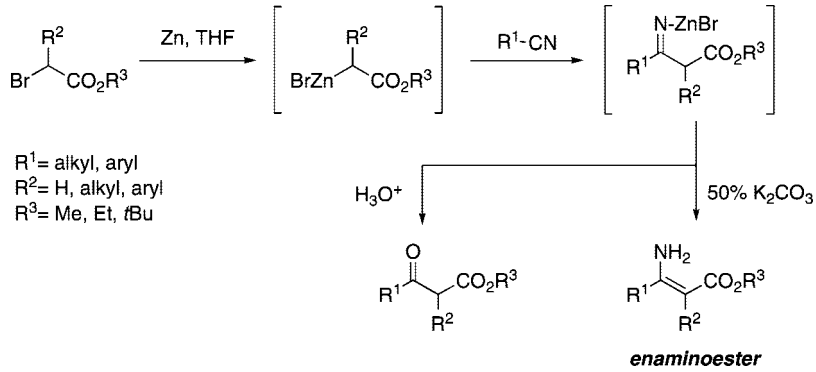


FIGURE 3. Blaise reaction and its outcome.

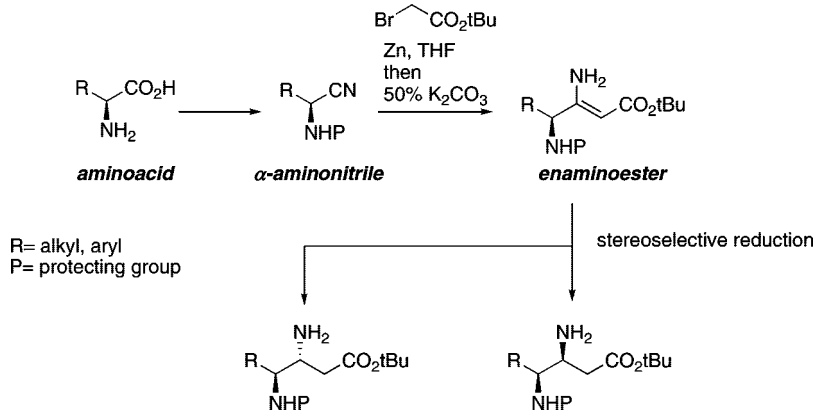
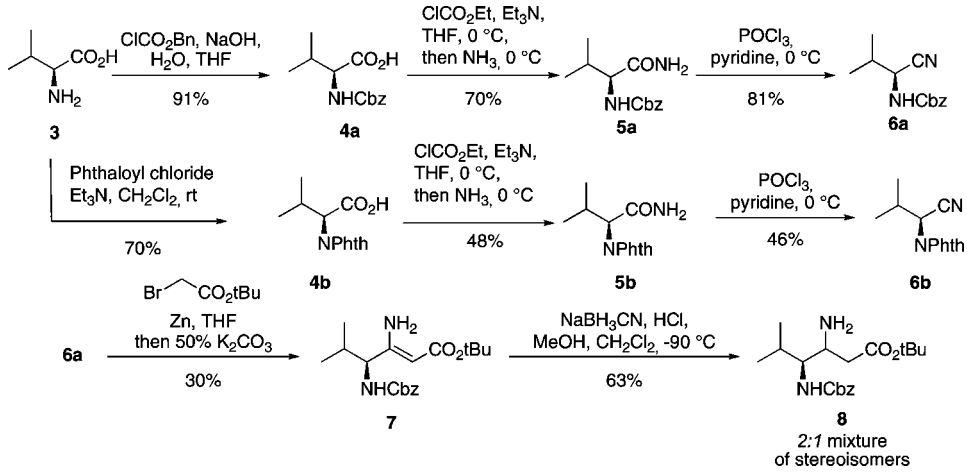


FIGURE 4. Strategy for the synthesis of β,γ-diamino acids from α-amino acids by the Blaise reaction.

SCHEME 1. Initial Attempts for the Blaise Reaction with α-Amino Nitriles



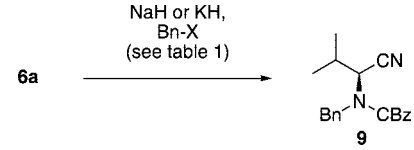
primary amide formation and phosphorus oxychloride-mediated dehydration, gave nitriles **6a,b** in good yields and without racemization. These nitriles were used for the Blaise reaction (Scheme 1): slow addition of methyl bromoacetate to a suspension of zinc dust (preactivated by washing with acid, followed by water and ethanol, then drying under vacuum) in refluxing THF containing nitrile **6a** resulted in the formation of enamino ester **7**, albeit in low yield. None of the in situ zinc activation methods allowed better yields. Replacement of methyl bromoacetate for *tert*-butyl bromoacetate gave only a slightly better yield (30%).

These experiments suggested that α-amino nitriles having a free N−H group were not suitable substrates for the Blaise reaction. Unfortunately, the *N*-phthalimido α-amino nitrile **6b** was not stable under the Blaise reaction conditions, the organozinc reagent reacting with the imide function rather than the nitrile function.

Enaminoester **7** was then submitted to reduction according to the previously described conditions.[22] The corresponding β,γ-diamino ester **8** was obtained as a 2:1 mixture of diastereomers, which were separated but not assigned.

Although this synthetic route gave rise to the expected β,γ-diamino acid **8** (in its protected form) in a short synthetic sequence, it suffered from low yields in the condensation reaction and low stereoselectivity in the reduction step. Since we thought that these problems arose from the presence of an N−H group in the substrate, we decided to add a second stable protecting group on the amine nitrogen before undertaking the

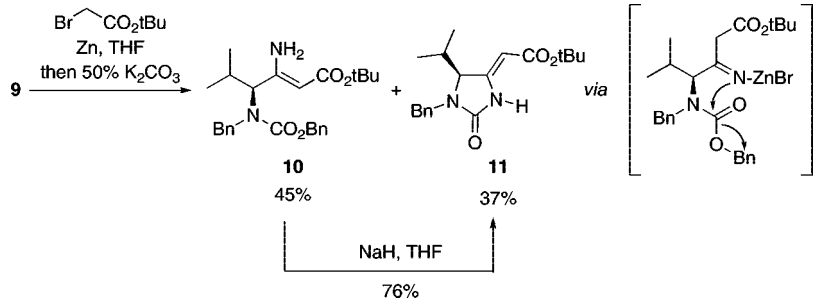
TABLE 1. Benzylation of α-Amino Nitrile 6a



entry	base (equiv)	X (equiv)	solvent	conditions[a]	time	yield (%)	ee (%)[b]	sm (%)	ee (%)[b]
1	NaH (3)	Br (3)	THF	A	12 h	86	9		
2	NaH (1)	Br (3)	THF	A	12 h	74	21		
3	NaH (0.8)	I (3)	THF	A	1 h 30 min	67	62	17	99
4	NaH (1)	I (10)	THF	B	1 h 30 min	94	78		
5	KH (1)	I (10)	THF	B	10 min	94	87		
6	NaH (1)	I (10)	DMF	B	10 min	84	99		

[a] A: addition of benzylating reagent onto the anion; B: addition of the anion onto the benzylating reagent. [b] Determined by HPLC on chiral column.

SCHEME 2. Blaise Reaction on Diprotected Amino Nitrile 9



Blaise reaction. Therefore, *N*-Cbz amino nitrile **6a** was benzylated (NaH, benzyl bromide, THF) to give the amino nitrile **9** in high yield (Table 1).[25] However, determination of enantiomeric excess by HPLC on a chiral column indicated that extensive racemization occurred, the diprotected amino nitrile being obtained with only 9% ee (Table 1, entry 1). Reducing the amount of base led to an incomplete reaction, and the benzylated product was obtained in 21% ee (entry 2). Switching to the more reactive benzyl iodide gave **9** with increased ee, together with enantiomerically pure remaining starting material (entry 3). Therefore, we concluded that racemization occurred on product **9**, probably due to the presence of the unreacted amide anion. It was then important to perform a fast alkylation reaction: using a large excess of benzyl iodide and performing inverse addition of the anion onto the benzylating reagent dramatically improved the ee's (entries 4 and 5). Finally, using DMF as solvent at room temperature gave the enantiomerically pure benzylated amino nitrile in a good yield (entry 6).

With the enantiomerically pure α-amino nitrile **9** in hand, the Blaise reaction was attempted using *tert*-butyl bromoacetate. Optimization studies showed that the best method for activation of zinc dust was with 1,2-dibromoethane. Addition of a few drops of *tert*-butyl bromoacetate just after zinc activation ensured that the reaction had started by the appearance of a green color.[16] Satisfactory yields were obtained this time, thus demonstrating the need for a double nitrogen protection. However, two products were obtained, which could be separated by chromatography: the enamino ester **10** and the imidazolidinone **11**, the latter arising from a cyclization of the intermediate iminozincate onto the carbamate protecting group (Scheme 2). It is remarkable that the sole iminozinc reagent reacts on the carbamate and not the organozinc reagent. Treating the crude product with sodium hydride in THF led to complete conversion into the imidazolidinone, which was then isolated in 76% yield.[26]

HPLC analysis of both products showed complete conservation of stereochemical integrity, thus demonstrating that neither the Blaise reaction nor the cyclization induced racemization.

The Blaise reaction was then performed with α-amino nitriles derived from other α-amino acids: L-alanine, L-phenylalanine, L-leucine, L-proline, and L-serine (Scheme 3). Amino nitriles **15**−**17** were prepared according to the described procedure,[23] and compounds **18** and **19** according to known procedures.[27,28] Blaise reaction followed by cyclization gave cleanly the imidazolidinones **20**−**24** in good yields and in enantiomerically pure form. In some cases, complete cyclization to the imidazolidinone occurred, without adding sodium hydride to the crude mixture. All imidazolidinones were obtained as *Z* isomers, as determined by ^{1}H NMR NOE experiments, except for proline-derived compound **23**, which was obtained as a mixture of *Z* and *E* isomers. With L-serine-derived α-amino nitrile **19**, it was possible to isolate in good yield the noncyclized enamino ester **25** by omitting the sodium hydride mediated reaction.

Another interesting substrate would be the α-amino nitrile **29** derived from L-aspartic acid, in which a second electrophilic group is present. Indeed, the intermediate iminozincate could cyclize in a *5-exo-trig* fashion, either on the carbamate protecting group or on the ester carboxyl group. Accordingly, the known[29] α-amino nitrile **29** was prepared in four steps from L-aspartic acid methyl ester **26** (Scheme 4). As we faced difficulties in introducing a benzyl group on the amine nitrogen, the Blaise

(25) All compounds described from now on were synthesized in both racemic and enantiomerically pure form. The enantiomeric purity of each intermediate was checked by HPLC on chiral column.

(26) Control experiments showed that cyclization occurred before potassium carbonate workup. Adding sodium hydride before this workup did not improve the yields.

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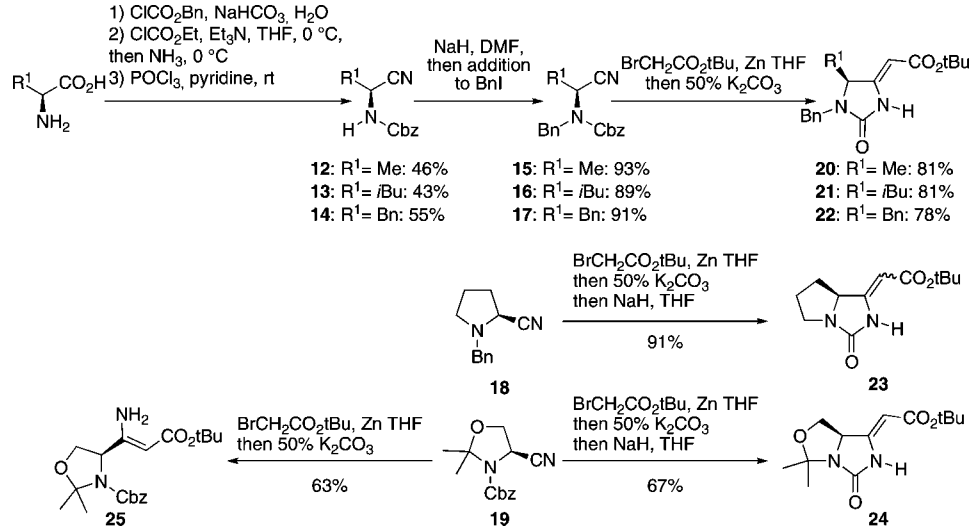
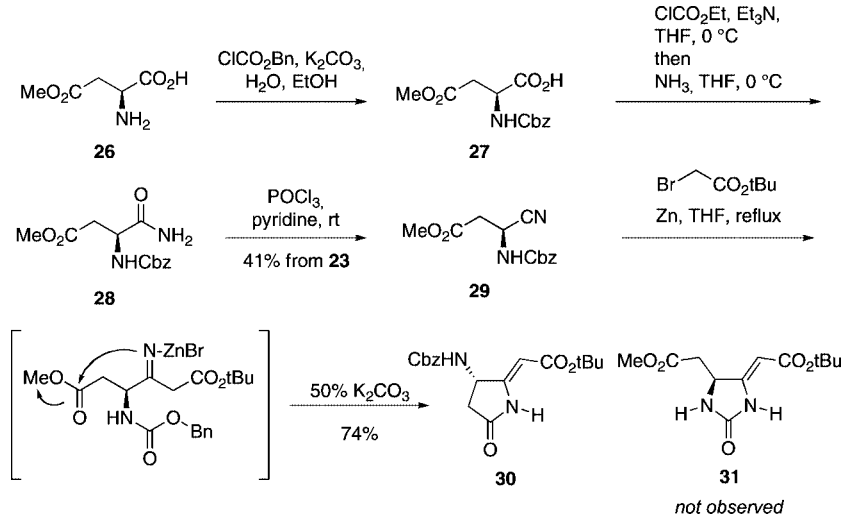
SCHEME 3. Blaise Reaction with Amino Acid Derived Amino Nitriles



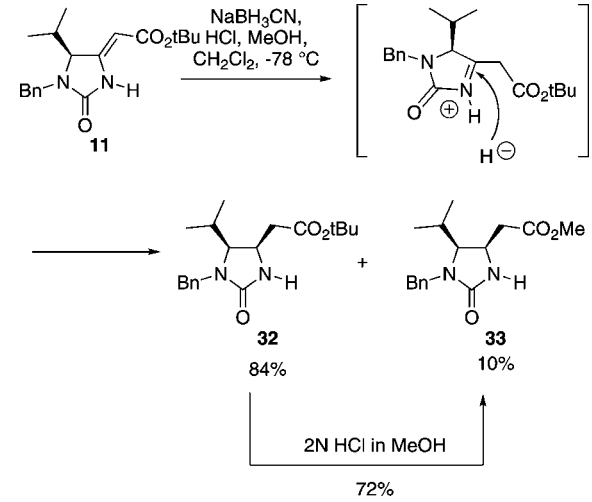
SCHEME 4. Blaise Reaction with L-Aspartic Acid Derived α-Amino Nitrile



reaction was attempted on the monoprotected substrate. Fortunately, the reaction proceeded cleanly to give exclusively the lactam **30** resulting from cyclization of the iminozincate onto the ester, no cyclization onto the carbamate to give **31** being observed.[30] Compound **30**, which was obtained as a single *Z* isomer and in enantiomerically pure form, is actually (as its enantiomer) a fragment of the macrocyclic peptide microsclerodermin E,[31] which possesses interesting cytotoxic properties.

In view of the rigid, cyclic structure of imidazolidinones, their reduction might provide better stereoinduction than that of acyclic enamino esters, as observed in the early studies. Indeed, reduction of imidazolidinone **11** with sodium cyanoborohydride at −78 °C and under acidic conditions gave the imidazolidinone **32**, together with a small amount of transesterified methyl ester **33** (Scheme 5). Both compounds were obtained as single isomers. Treatment of *tert*-butyl ester **32** with acidic methanol gave the methyl ester, identical to compound **33**, thus proving

SCHEME 5. Stereoselective Reduction of Imidazolidinone 11 with Sodium Cyanoborohydride

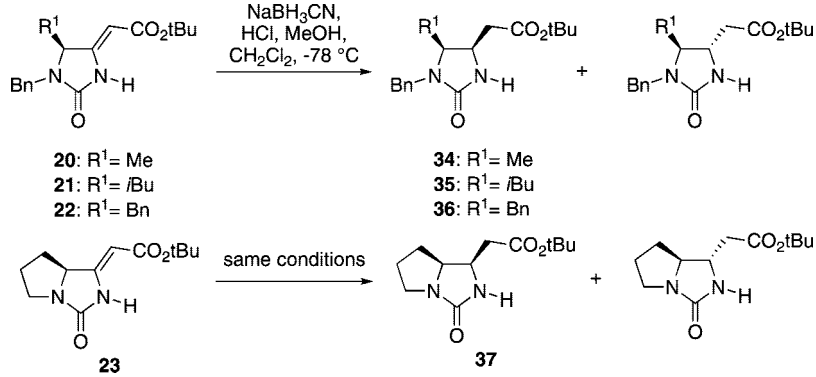


that both products have the same configuration. The *cis* relationship between the two ring substituents was determined

(30) In contrast, Blaise reaction with the L-glutamic acid derived amino nitrile led to a mixture of products arizing from both possible cyclizations. Zulauf, A.; Alezra, V.; Kouklovsky, C. Unpublished results.

(31) (a) Isolation: Schmidt, E. W.; Faulkner, D. J. *Tetrahedron* **1998**, *54*, 3043. (b) Total synthesis: Zhu, J.; Ma, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5348.

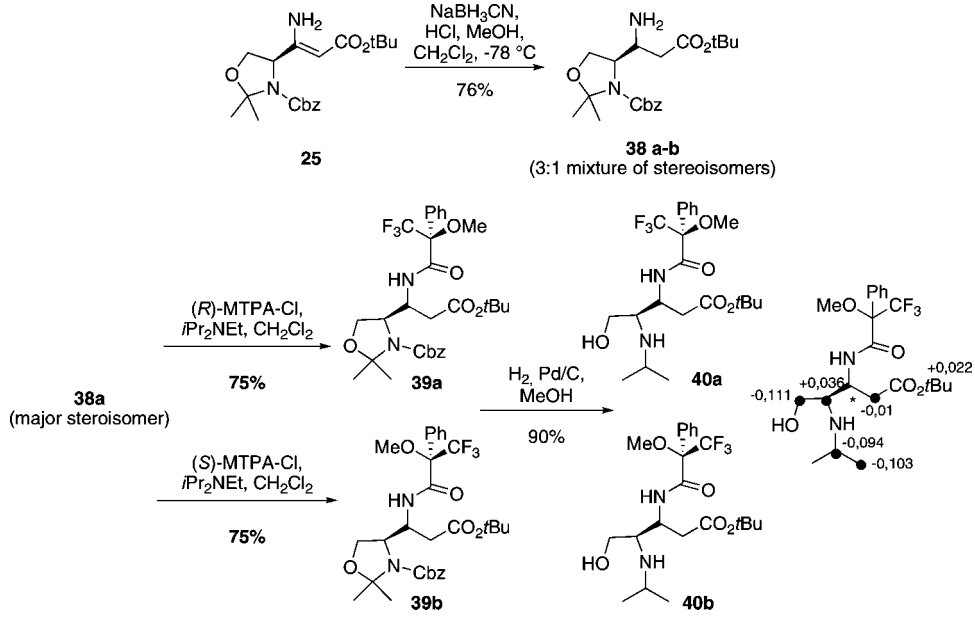
TABLE 2. Sodium Cyanoborohydride Reduction of Imidazolidinones 20−23



entry	substrate	R^1	yield (%)	*cis*:*trans*[a]
1	**20**	Me	74	1.6:1
2	**21**	*i*Bu	55	1:2
3	**22**	Bn	55	1:1.5
4	**23**	-$(CH_2)_3$-	67	1:2

[a] Ratio determined by ^{1}H NMR.

SCHEME 6. Determination of Absolute Configuration of Enaminoester 38



on the basis of NOE experiments in ^{1}H NMR and later confirmed by X-ray analysis.[23]

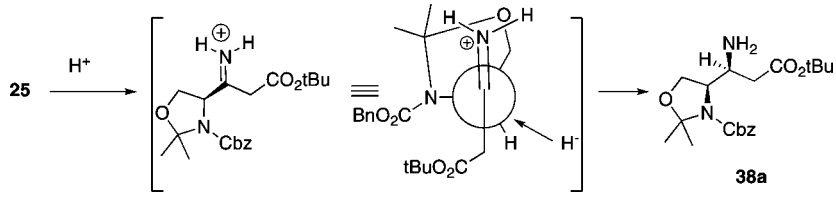
Although reduction of L-valine-derived imidazolidinone occurred with complete stereoselectivity, other substrates gave disappointing results, with very low selectivity (Table 2). Furthermore, the *cis*/*trans* selectivity was inverted for L-leucine, L-phenylalanine, and L-proline derived substrates (entries 2−4; for a method for stereomer assignement, vide infra). Attempts to improve selectivity using other reducing reagents such as sodium triacetoxyborohydride, zinc borohydride, DIBAL-H, or L-Selectride were unsuccessful, no reaction occurring. Reduction of lactam **30** with sodium cyanoborohydride led to low conversion and stereoselectivity.

Reduction of bicyclic enamino ester **24** derived from L-serine was thwarted by concomitant reduction of the oxazolidine ring. Alternatively, reduction of the acyclic enamino ester **25** gave a separable 3:1 mixture of diastereomers under the same conditions. Determination of the absolute configuration of the new stereogenic center was accomplished with the Mosher protocol (Scheme 6): [32,33] the major diasteromer **38a** was acylated with both enantiomers of MTPA-Cl. Since analysis of the resulting diastereomeric amides **39a,b** was hampered by the presence of rotamers, the carbamate protecting group was removed by hydrogenation. This reaction was accompanied by the opening of the oxazolidine ring, to give *N*-isopropylamines **40a,b**. ^{1}H NMR analysis showed differences in chemical shifts of +0.022 for the ester group and of −0.111 for the primary hydroxyl group, thus indicating the *S* configuration for the new stereogenic center.

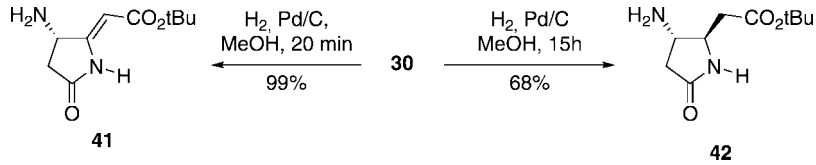
The stereoselectivity of this reduction could be explained using a Felkin−Anh model, in which the intermediate imminium ion adopts a conformation with the iminium C=N bond perpendicular to the polar and bulky *N*-Cbz group. Attack of

(32) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(33) The enantiomeric purity of each of stereoisomers of **38** was determined by HPLC after trifluoroacetylation (see Supporting Information).

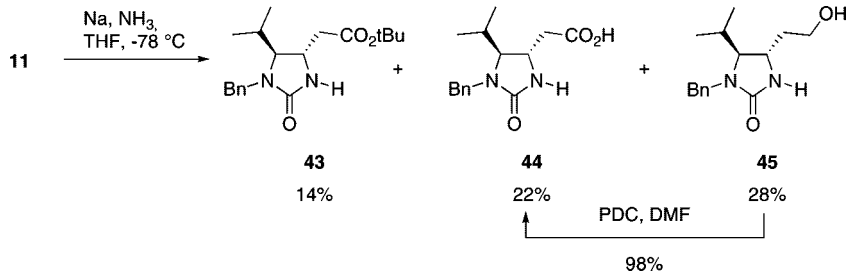
SCHEME 7. Model for Stereoinduction in the Reduction of Enaminoester 25



SCHEME 8. Hydrogenation of Lactam 30



SCHEME 9. Birch Reduction of Imidazolidinone 11



the hydride *anti* to this group, results in the formation of the (*R*,*S*) product **38a** as the major diastereomer (Scheme 7).[34]

As reduction with hydride reagents gave unsufficient stereoselectivity, other reduction conditions were tested. Hydrogenation[35−38] of imidazolidinone over palladium or platinum catalysts resulted only in migration of the alkene into the imidazolidinone ring, thus removing the stereogenic center in the imidazolone substrate. Hydrogenation of compound **25** led to extensive degradation including reductive opening of the oxazolidine ring. However, lactam **30**, obtained from L-aspartic acid, proved to be a good substrate for hydrogenation (Scheme 8). Although a short (20 min) hydrogenation over palladium catalyst removed selectively the carbamate protecting group, overnight reaction gave the saturated lactam **42** as a single diastereomer.[39] The *trans* configuration was determined after extensive NMR studies and can be explained by the coordination of the free amine group (after in situ hydrogenolysis of the benzyl carabamate) to the catalyst, thus directing hydrogen attack on the *si* face. This exceptionally high selectivity for reduction allows the stereoselective preparation of a new type of γ-amino acid, which could be used as building block for γ-peptide synthesis or as chiral organic catalyst.

1,4-Reduction of α,β-unsaturated carbonyl or carboxylic derivatives under dissolving metal conditions (the Birch reduction) is a popular method for stereoselective reduction or enolate formation and has been widely used in synthesis.[40] However, the Birch reduction of enamino esters has received little attention: to the best of our knowledge, only a single experiment was reported, in which a cyclic enamino ester was reduced with lithium in liquid ammonia (stereochemistry not determined).[41] As we were looking for accurate conditions for imidazolidinone reduction, we attempted Birch reduction (Scheme 9). Treatment of imidazolidinone **11** with excess sodium in THF/NH_3 gave a mixture of three products after analysis of the crude product by ^{1}H NMR: the reduced ester **43**, the corresponding carboxylic acid **44**, and the reduced alcohol **45**. In each product, the double bond has been cleanly reduced. The presence of carboxylic acid is due to partial saponification of the *tert*-butyl ester. As drying of the ammonia prior reaction improved the ratio of products, we assume that the presence of the primary alcohol is due to traces of moisture in the reaction mixture. For the sake of isolation, the crude mixture was saponified (2.5 N NaOH, THF, reflux) to give the carboxylic acid **44** and the alcohol **45** in good overall yield. Moreover, each compound was obtained as a single diastereomer and was enantiomerically pure. Oxidation of the alcohol **45** (PDC, DMF) returned the acid **44**, thus proving that both compounds have the same configuration. The Birch reduction of imidazolidinone is therefore totally stereoselective.

(34) For a discussion about the stereoselectivity of the reduction of related ketones, see: Liang, X.; Andersch, J.; Bols, M. *J. Chem Soc., Perkin Trans. 1* **2001**, 2136, and references therein.

(35) Heterogeneous hydrogenation of enamino esters: (a) Hashiguschi, S.; Natsugari, H.; Ochiai, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2345. (b) Hiyama, T.; Nishide, K.; Kobayashi, K. *Chem. Lett.* **1984**, 361.

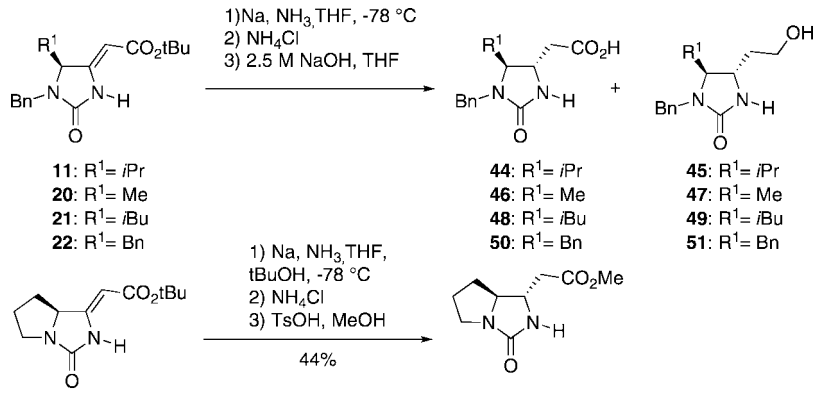
(36) Rhodium-catalyzed hydrogenation of (Z)-enamino esters: (a) Yan, Y.; Zhang, X. *Tetrahedron Lett.* **2006**, *47*, 1567. (b) Kubryk, M.; Hansen, K. B. *Tetrahedron: Asymmetry* **2006**, *17*, 205. (c) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343. (d) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419. (e) Wu, H.-P.; Hoge, G. *Org. Lett.* **2004**, *6*, 3645. (f) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918. (g) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; B̈; orner, A. *J. Org. Chem.* **2003**, *68*, 1701. (h) Pena, D.; Minaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (i) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159. (j) Lee, S.-G.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429.

(37) Rhodium-catalyzed hydrogenation of (*E*)-enamino esters: (a) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509. (b) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (c) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907. (d) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

(38) Ruthenium-catalyzed hydrogenation of enamino esters: Wu, J.; Chen, X.; Guo, R.; Yueng, C.-H.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 2490.

(39) The enantiomeric purity of lactam **42** was determined after conversion into its Fmoc carbamate (see Supporting Information).

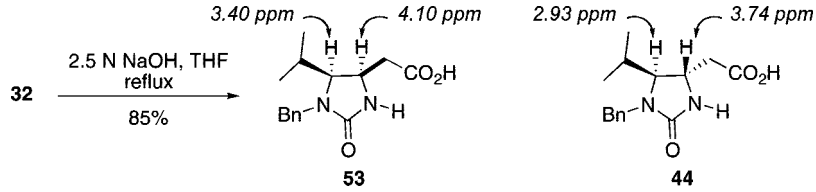
TABLE 3. Birch Reduction of Imidazolidinones 11, 20−23



entry	substrate	acid (yield %)	alcohol (yield %)	de[a] (%)
1	**11**	**44** (52)	**45** (27)	>99
2	**20**	**46** (66)	**47** (14)	>99
3	**21**	**48** (47)	**49** (15)	>99
4	**22**	**50** (50)	**51** (18)	>99

[a] Ratio determined by ^{1}H NMR.

SCHEME 10. Chemical Shits in ^{1}H NMR for Both Isomers of Valine-Derived Imidazolidinones



The same behavior was observed with Birch reduction of other imidazolidinones (Table 3), except for substrate **24**, for which hydrolysis of the oxazolidine ring was observed. A mixture of carboxylic acid and alcohol, both obtained as single diastereomers, was obtained with all substrates except for proline-derived imidazolidinone, which gave only the carboxylic acid. However, the latter compound proved to be very difficult to extract from the reaction mixture and had to be converted to the methyl ester to be isolated.

Although this reduction was found to be general for all imidazolidinones mentioned above, attempts for the reduction of lactam **30** under the same conditions only led to degradation.

Determination of the relative configuration was made on the basis of ^{1}H NMR analysis with comparison with cyanoborohydride reduction products. Thus, the *tert*-butyl ester of the *cis*-disubstituted valine-derived imidazolidinone **32** (for which configuration was secured by X-ray analysis) was removed by saponification to give the free acid **53** (Scheme 10). Comparison of ^{1}H NMR spectra with acid **44** (obtained after Birch reduction) showed differences in the chemical shifts for the protons next to the nitrogen atoms, thus indicating that **53** and **44** were diastereomers. Therefore, the *trans* relative configuration was assigned to the Birch reduction products.

This difference in chemical shifts was found to be consistent for all products:[42] H_a has a chemical shift of 3.4−3.7 ppm for the *cis* isomers and 2.9−3.3 ppm for the *trans* isomers, whereas chemical shifts for H_b are 4.0−4.1 ppm for the *cis* isomers and 3.6−3.7 for the *trans* isomer. For proline derivatives, the chemical shifts were sensibly higher due to the conformation of the bicyclic molecule. This consistency in the chemical shift allows easy diastereomer assignement.

The origin of the *trans* selectivity for the Birch reduction could be explained according to the generally admitted mechanism:[40b] first electron transfer gives rise to a sp^3 dianionic radical in which the R substituent and the enolate are in an *anti* configuration due to steric repulsion and to stabilization of the SOMO orbital with the parallel neigbouring C−C bond (Scheme 11). The second electron transfer affords a trianionic species that is reprotonated with retention of configuration to give the *trans* isomer. Deprotonation of the nitrogen atom prevents β-elimination of the enolate. Therefore, we assume that the Birch reduction proceeds under kinetic control, the preferred configuration of the carbon atom bearing the anion being the source of the stereoinduction.

In conclusion, we have demonstrated that enamino esters can be reduced under dissolving metal conditions in good yields and with a high degree of stereoselectivity. This reaction proved to be general and useful for the synthesis of β,γ-diamino acids.

Hydrolysis of the substituted imidazolidinones was accomplished under strongly acidic conditions:[43,44] *cis*-disubstituted imidazolidinone **32** was hydrolyzed in 3 N HCl at 90 °C

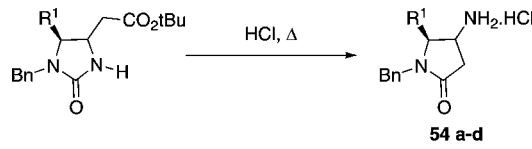
(40) Reviews: (a) Venturello, P.; Barbero, M. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2005; *8b*, p 881. (b) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351. (c) Caine, D. *Org. React. (New York)* **1976**, *23*, 1.

(41) Adams, A. D.; Schlessinger, R. H.; Tata, J. R.; Venit, J. J. *J. Org. Chem.* **1986**, *51*, 3070.

(42) For a table of chemical shifts, see Supporting Information.

(43) Acidic hydrolysis of cyclic ureas: (a) Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett.* **1995**, *36*, 8607. (b) Misiti, D.; Santaniello, M.; Zappia, G. *Synth. Commun.* **1992**, *22*, 883. (c) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017.

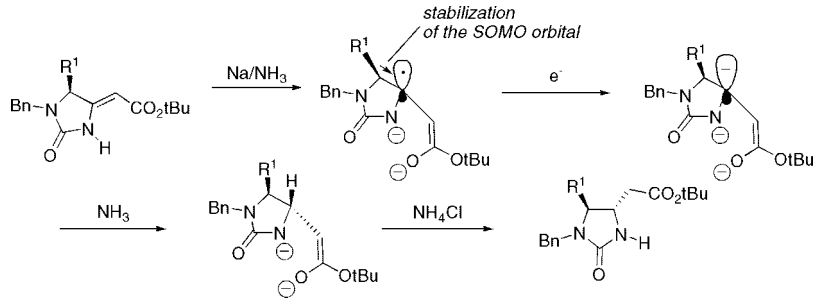
TABLE 4. Hydrolysis of *trans*-Imidazolidinones



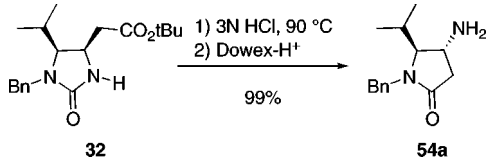
entry	substrate	R^1	substrate relative configuration	conditions	product	yield (%)
1	**32**	iPr	*cis*	3 N HCl, 90 °C, 12 h	**54a**	99[a]
2	**46**	Me	*trans*	3 N HCl, 140 °C, 120 h	**54b**	99
3	**48**	*i*Bu	*trans*	3 N HCl, 140 °C, 120 h	**54c**	99
4	**52**	$-(CH_2)_3-$	*trans*	3 N HCl, 90 °C, 12 h	**54d**	99
5	**37**	$-(CH_2)_3-$	*cis*/*trans* (2:1)	3 N HCl, 90 °C, 12 h	**54d**	99

[a] Isolated as the free base after purification on Dowex-H^+ column.

SCHEME 11. Hypothesis for the Stereoselectivity of the Birch Reduction



SCHEME 12. Hydrolysis of *cis*-Imidazolidinone 32



for 12 h (Scheme 12). However, instead of the expected β,γ-diamino acid, the 4-aminopyrrolidone **54a** was obtained, resulting fom lactamization. This compound was obtained neutral after purification on an ion-exchange resin (Dowex H^+). Although this lactam was very resistant toward acidic or basic hydrolysis, it could be easily reduced to the corresponding 3-aminopyrrolidine.[24]

Hydrolysis of the *trans*-disubstituted imidazolidinones (resulting from Birch reduction) was carried out under similar conditions (Table 4), except for the alanine- and leucine-derived compounds, which proved to be more resistant (entries 2 and 3). In this case, it was necessary to use harsher conditions (140 °C, 5 days) to ensure complete conversion. Nevertheless, high yields of the corresponding pyrrolidones were obtained. In all cases the hydrolysis reaction proceeded without racemization or epimerization. For instance, hydrolysis of a *cis*/*trans* mixture of proline-derived imidazolidinone gave the same stereochemical ratio of pyrrolidones (entry 5). Ring opening of these lactams to β,γ-diamino acids is still under investigation. Since it is known that *N*-Boc lactams are very prone to basic hydrolysis,[45] a change in nitrogen protecting group could provide a solution.

In conclusion, we have demonstrated that the Blaise reaction−stereoselective reduction sequence is a valuable tool for the synthesis of new, amino acid derived heterocyclic structures. We have shown that the Blaise reaction is compatible with chiral, functionalized amino nitriles obtained from amino acid, and we have introduced the Birch reduction for the stereoselective reduction of the corresponding cyclic enamino ester. Deprotection to β,γ-diamino acids as well as their use in peptide synthesis is currently under investigation in our laboratory.

(44) Basic hydrolysis of cyclic ureas: (a) Jones, R. C. F.; Schofield, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 375. (b) Hoffmann, K.; Melville, D. B.; du Vigneaud, V. *J. Biol. Chem.* **1941**, *137*, 207.

(45) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

Experimental Section

General Methods. See Supporting Information.

General Procedure for the Synthesis of Monoprotected α-Amino Nitriles. A solution of *N*-Cbz L-amino acid (prepared from 50 mmol of L-amino acid according to standard procedure) in dry THF (100 mL) was cooled to 0 °C, and Et_3N (7 mL, 49.8 mmol) was added. After 15 min at 0 °C, ethyl chloroformate (4.8 mL, 50.2 mmol) was added dropwise, and the clear solution stirred for 30 min, before addition of 30% aqueous ammonia solution (15 mL). After 30 min at 0 °C, the mixture was diluted with H_2O (60 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The solid residue was used in the next step without any further purification.

A solution of the crude amide in pyridine (100 mL) was cooled to 0 °C, and phosphorus oxychloride (4.42 mL, 47.3 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for additional 4 h. The reaction mixture was quenched with a 2 M aqueous HCl solution (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with saturated $CuSO_4$ aqueous solution, water, and brine, then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the pure α-amino nitrile.

(*S*)-*N*-Benzyloxycarbonyl-2-amino-isopentanenitrile (6a). Obtained in 45% overall yield from L-valine (5.22 g, 22.5 mmol); yellowish solid; mp 53 °C; ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) 1.06 (d, $J = 7.0$ Hz, 3H), 1.09 (d, $J = 7.0$ Hz, 3H), 2.04 (t, $J = 8.8$

Hz, 1H), 4.46−4.56 (m, 1H), 5.15 (s, 2H), 5.64 (d, J = 8.8 Hz 1H), 7.30−7.44 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 17.8, 18.3, 31.5, 48.8, 67.4, 117.6, 128.0, 128.2, 128.4, 135.5, 155.3; HRMS (electrospray) (M + Na) calculated for $C_{13}H_{16}N_2O_2Na$: 255.1104, found 255.1103; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3322.5, 2244.8, 1702.3; $[\alpha]^{20}_D$ = −55 (c 1.13, CH_2Cl_2).

General Procedure for the Synthesis of *N*,*N*-Diprotected α-Amino Nitriles. Preparation of Benzyl Iodide. Benzyl bromide (7.2 mL, 60 mmol) was added to a solution of sodium iodide (18 g, 120 mmol) in acetone (80 mL). The mixture was stirred for 24 h in the dark at room temperature, then quenched with water (50 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the pure product as yellow oil. Yield: quantitative (7.5 mL, 60 mmol).

Sodium hydride (152 mg, 6.3 mmol) was washed three times with *n*-pentane, and then DMF (10 mL) was added. The suspension was cooled to 0 °C, and the amino nitrile (6.0 mmol) dissolved in dry DMF (8 mL) was added. The mixture was stirred for 30 min and then transferred by cannula into a flask containing benzyl iodide (7.5 mL, 60 mmol) in dry DMF (15 mL). The mixture was stirred for additional 10 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/Et_2O 8/2) to give the diprotected amino nitrile.

(*S*)-*N*-Benzyl-*N*-Benzyloxycarbonyl-2-amino-isopentanenitrile (9). Yield: 84% (1.61 g, 5 mmol); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 330 K) δ (ppm) 0.80 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 5.9, 3H), 2.07−2.16 (m, 1H), 4.40 (d, J = 15.7, 1H), 4.54 (d, J = 9.8, 1H), 4.71 (d, J = 15.7, 1H), 5.17 (s, 2H), 7.22−7.28 (m, 10H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 18.3, 19.2, 30.7, 49.7, 55.3, 68.0, 117.1, 127.5, 127.8, 128.0, 128.3, 135.4, 136.6, 155.5; HRMS (electrospray) (M + Na) calculated 345.1573, found 345.1584; IR (CH_2Cl_2) ν (cm^{-1}) 2241.3, 1705.7. Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.24; H, 6.83; N, 8.52; $[\alpha]^{20}_D$ = −48 (c 1.15, CH_2Cl_2); HPLC analysis: ee = 99%; (*S*,*S*) Whelk-01 column (hexane/ethanol 99:1, 1 mL/min, 254 nm); retention times of racemic mixture: 15.7 min (*S*) and 17.5 min (*R*).

General Procedure for the Blaise Reaction of α-Amino Nitriles. Procedure A. To a stirred suspension of Zn dust (503 mg, 7.7 mmol) in refluxing THF (10 mL) were added 1,2-dibromoethane (0.3 mL, 3.5 mmol) and few drops of *tert*-butyl bromoacetate. To the resulting greenish suspension was then rapidly added a solution of amino nitrile (1.1 mmol) in THF (3 mL). A solution of *tert*-butyl bromoacetate (0.61 mL, 4.2 mmol) in dry THF (3 mL) was added dropwise in 10 min, and the mixture was stirred for additional 1 h at reflux. After cooling to room temperature, the reaction was quenched with 50% K_2CO_3 aqueous solution (10 mL). After stirring for 15 min, the resulting mixture was filtered through Celite, and the precipitate was washed with Et_2O. The aqueous layer was extracted with Et_2O (2 × 20 mL), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude material was dissolved in dry THF (10 mL) and cooled to 0 °C before addition of sodium hydride (32 mg, 1.3 mmol). The mixture was warmed up to room temperature and stirred for additional 2 h. The reaction was quenched by introduction of saturated NH_4Cl aqueous solution, and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (heptane/ethyl acetate 8:2) to give pure 2-imidazolidinone.

Procedure B. This procedure is identical to the previous one, except that the crude material is not treated with sodium hydride but directly purified by flash chromatography (pentane/Et_2O 7:3).

(*S*)-1-Benzyl-4-(*Z*)-*tert*-butyloxycarbonylidene-5-(1-methylethyl)-imidazolidine-2-one (11). Prepared according to procedure A. Yield: 72% (261 mg, 0.8 mmol); white solid; mp 105 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.87 (d, J = 7.0, 3H), 0.95 (d, J = 7.0, 3H), 1.45 (s, 9H), 2.00−2.15 (m, 1H), 3.92−3.97 (m, 1H), 3.97 (d, J = 15.2, 1H), 4.75 (s, 1H), 5.02 (d, J = 15.2, 1H), 7.17−7.35 (m, 5H), 9.34 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 16.1, 17.1, 28.2, 30.1, 44.5, 63.5, 79.9, 88.6, 127.7, 127.9, 128.7, 136.0, 153.4, 156.9, 167.8; HRMS (electrospray) (M + Na) calculated 353.1836, found 353.1868; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3377.9, 1740.3, 1677.4, 1633.8. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93, N, 8.48. Found: C, 68.82; H, 7.95; N, 8.33; $[\alpha]^{20}_D$ = −81 (c 0.81, CH_2Cl_2); HPLC analysis: ee > 99%; Chiralpak AD column (hexane/ethanol 85:15, 1 mL/min, 254 nm); retention times of racemic mixture: 6.8 min (*R*) and 8.7 min (*S*).

(*S*,*Z*)-*tert*-Butyl 2-(3-(benzyloxycarbonylamino)-5-oxopyrrolidin-2-ylidene)-acetate (30). Prepared according to procedure B. Yield: 74% (281 mg, 0.81 mmol); yellowish solid; mp 126 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.20 (s, 9H), 2.38 (dd, J = 10.4 Hz, J = 17.4 Hz, 1H), 2.85 (dd, J = 4.9 Hz, J = 17.4 Hz, 1H), 4.95 (m, 1H), 5.12 (s, 3H), 5.60 (m, 1H), 7.20−7.40 (m, 5H), 9.75 (br s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 28.1, 35.8, 48.9, 67.3, 80.6, 92.6, 128.1, 128.3, 128.5, 135.7, 151.1, 155.7, 167.3, 173.8; HRMS (electrospray) (M + Na) calculated for $C_{18}H_{22}N_2O_5Na$: 369.1426, found 369.1421; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3424, 3214, 1719, 1701, 1265, 1154; $[\alpha]^{20}_D$ = −72.4 (c 0.99, CH_2Cl_2).

General Procedure for the Reduction of Enaminoesters with Sodium Cyanoborohydride. Preparation of dry HCl 2 N (2 mL). Acetyl chloride (0.3 mL, 4.7 mmol) was added dropwise to MeOH (2 mL) at 0 °C, and the solution was stirred for15 min at 0 °C.

Enaminoester (0.50 mmol) was dissolved in CH_2Cl_2/MeOH (9 mL, 2/1 mixture), and a small amount of bromocresol green was added. The mixture was cooled to −78 °C, and dry HCl (1.6 mL) solution was added. To the resulting yellow solution was added sodium cyanoborohydride (47 mg, 0.75 mmol). After 15 min at −78 °C, the mixture was warmed to room temperature and stirred for additional 1 h 30. The reaction was quenched with 2.5 M NaOH aqueous solution to give a deep blue solution and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were washed with saturated brine, then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography.

(4*R*,5*S*)-5-(1-Methylethyl)-1-phenylmethyl-imidazolidine-2-one-4-acetic Acid *tert*-Butyl Ester (32). A single diastereomer was observed by ^{1}H NMR of the crude material. Purification by flash chromatography (heptane/AcOEt 1:1) gave **32** (*cis* relative configuration). Yield: 84% (139 mg, 0.42 mmol); white solid; mp 90 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) 0.97 (d, J = 7.0, 6H), 1.41 (s, 9H), 1.82−1.94 (m, 1H), 2.49−2.55 (m, 2H), 3.38 (dd, J = 3.5, 7.9, 1H), 3.92−4.02 (m, 1H), 3.95 (d, J = 15.8, 1H), 4.99 (d, J = 15.8, 1H), 5.18 (s, 1H), 7.18−7.31 (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 17.5, 20.5, 27.8, 28.0, 36.0, 46.0, 51.1, 60.9, 81.3, 127.0, 127.5, 128.3, 137.1, 162.4, 170.6; HRMS (electrospray) (M + H) calculated for $C_{19}H_{29}N_2O_3$: 333.2173, found 333.2181; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3234.9, 2973.6, 1699.4. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43; O, 14.44. Found: C, 68.62; H, 8.48; N, 8.28; O, 14.59; $[\alpha]^{20}_D$ = +14 (c 1.08, CH_2Cl_2); HPLC analysis: ee > 99%; (*S*,*S*) Whelk-01 column (hexane/ethanol 100:3, 1 mL/min, 225 nm); retention times of racemic mixture: 33.4 min (4*S*, 5*R*) and 39.0 min (4*R*, 5*S*).

(*S*,*Z*)-*tert*-Butyl 2-(3-aimno-5-oxopyrrolidin-2-ylidene) Acetate (41). A solution of enamino ester **30** (0.44 mmol) in dry methanol (2 mL) was hydrogenated at 1 bar for 25 min in the presence of 10% Pd/C (85.5 mg, 0.79 mmol). Filtration of the catalyst through a Celite pad and concentration under reduced pressure gave pure compound **41** as a colorless oil. Yield: quantitative (93 mg, 0.44 mmol); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.23 (s, 9H), 1.7 (br s, 2H), 2.21 (dd, J = 5.5 Hz, J = 17.7 Hz, 1H), 2.79 (dd, J = 8.9 Hz, J = 17.7 Hz, 1H), 4.10 (dd, J = 5.5 Hz, J = 8.9 Hz, 1H), 5.10 (s, 1H), 9.70 (br s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 28.1, 38.6, 50.2, 80.4, 91.7, 160.6, 167.6, 174.5; HRMS (electrospray) (M + H) calculated for $C_{10}H_{17}N_2O_3$: 213.1236; found 213.1234;

IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3347, 1748, 1682, 1265; $[\alpha]^{20}_D = -34.7$ (c 1.02, CH_2Cl_2).

((2*R*,3*S*)-3-Amino-5-oxopyrrolidin-2-yl)-2-acetic Acid *tert*-Butyl Ester (42). A solution of enamino ester **30** (0.25 mmol) in dry methanol (3 mL) was hydrogenated at 1 bar for 15 h in the presence of 10% Pd/C (53 mg, 0.5 mmol). Filtration of the catalyst through a Celite pad and concentration under reduced pressure gave pure compound **42** as a yellowish solid. Yield: 68% (36 mg, 0.17 mmol); mp 67 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.44 (s, 9H), 1.96 (br s, 2H), 2.10 (dd, J = 6.1 Hz, J = 17.1 Hz, 1H), 2.35 (dd, J = 9.2 Hz, J = 16.5 Hz, 1H), 2.62 (dd, J = 4.9 Hz, J = 16.5 Hz, 1H), 2.65 (dd, J = 7.9 Hz, J = 17.1 Hz, 1H), 3.32 (m, 1H), 3.57 (dt, J = 4.3 Hz, J = 9.2 Hz, 1H), 6.51 (br.s, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 27.9, 39.5, 40.0, 53.1, 59.5, 81.4, 170.3, 175.3; HRMS (electrospray) (M + Na) calculated for $C_{10}H_{19}N_2O_3Na$: 237.1186; found 237.1210; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3423, 3054, 2984, 1700, 1265, 1154; $[\alpha]^{20}_D = +57.2$ (c 1.02, CH_2Cl_2).

General Procedure for the Birch Reduction of Enaminoesters. NH_3 gas (25 mL) was passed through a tube containing NaOH pellets and condensed into a cooled (−40 °C) glass tube containing some pieces of sodium metal, giving a deep blue solution. The cooling bath was removed, and dried ammonia gas was transferred into a cooled (−40 °C) trinecked flask containing a solution of enamino ester (0.5 mmol) in dry THF (5 mL). Sodium pieces (69 mg, 3 mmol) were added, and the deep blue solution was stirred for an additional 30 min at −40 °C. The reaction was quenched by addition of solid NH_4Cl (268 mg, 5 mmol) and warmed to room temperature to remove NH_3 gas. Aqueous 10% NaOH solution (25 mL) was added, and the mixture stirred at 80 °C for 12 h. After cooling to room temperature, the solution was acidified to pH 1 with 2 M HCl solution and extracted with AcOEt (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt/AcOH 99:1) to give two products, the carboxylic acid (less polar product) and the primary alcohol (more polar compound).

(4*S*,5*S*)-5-(1-Methylethyl)-1-phenylmethyl-imidazolidine-2-one-4-acetic Acid (44). Yield: 52% (84 mg, 0.3 mmol); yellow solid; mp 130−131 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 0.76 (d, J = 7.0, 3H), 0.78 (d, J = 7.0, 3H), 1.85−2.02 (m, 1H), 2.32 (d, J = 6.3, 2H), 2.93 (t, J = 3.5, 1H), 3.69−3.77 (m, 1H), 3.83 (d, J = 15.5, 1H), 4.80 (d, J = 15.5, 1H), 6.76 (s, 1H), 7.14−7.30 (m, 5H), 10.32 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 14.8, 17.4, 27.8, 41.9, 44.5, 46.7, 64.0, 127.5, 127.8, 128.7, 136.5, 161.9, 174.8; HRMS (electrospray) (M + Na) calculated for $C_{15}H_{20}N_2O_3Na$: 299.1366, found 299.1370; IR (thin film, CH_2Cl_2) ν (cm^{-1}) 3333.3, 1704.2, 1651.9; $[\alpha]^{20}_D = -65$ (c 0.45, CH_2Cl_2).

General Procedure for the Cleavage of the Imidazolidines-2-ones. A solution of the imidazolidinone in 3 M HCl solution (60 mL for 1 mmol of substrate) was heated in an open flask at the appropriate temperature (see Table 4). After cooling to room temperature, the mixture was concentrated under reduced pressure.

(4*R*,5*S*)-4-amino-5-(1-methylethyl)-1-phenylmethyl-pyrrolidin-2-one (54a). Obtained after purification on Dowex 50X4 resin (10 g, 200−400 mesh), Yield: 99% (96 mg, 0.41 mmol); yellow oil; ^{1}H NMR (250 MHz, D_2O) δ (ppm) 0.59 (d, J = 7.0, 3H), 0.82 (d, J = 7.0, 3H), 1.99−2.12 (m, 1H), 2.40 (dd, J = 1.9, 19.0, 1H), 2.95 (dd, J = 8.8, 19.0, 1H), 3.43 (dd, J = 1.3, 3.2, 1H), 3.77 (dd, J = 1.9, 8.8, 1H), 4.16 (d, J = 15.8, 1H), 4.66 (d, J = 15.8, 1H), 7.21−7.36 (m, 5H); ^{13}C NMR (62.5 MHz, D_2O) δ (ppm) 13.7, 17.1, 27.3, 36.6, 44.0, 44.8, 68.6, 128.1, 128.5, 128.9, 135.2, 173.7; HRMS (electrospray) (M + Na) calculated for $C_{13}H_{20}N_2ONa$: 255.1468, found 255.1468; IR (MeOH) ν (cm^{-1}) 3414.6, 1671.1; $[\alpha]^{20}_D = -26$ (c 1.0, D_2O).

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Supporting Information Available: Full characterization data for compounds **12**−**14**, **15**−**17**, **20**−**25**, **29**, **34**−**40**, **45**−**53**, **54b**−**d**. Table of NMR data for imidazolidinones **29**, **31**, **33**, **41**, **43**, **45**, **47**, **49**, **50**; copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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