Enantioselective Synthesis of α-Amino Acids and Monosubstituted 1,2-Diamines by Conjugate Addition of 4-Phenyl-2-oxazolidinone to Nitroalkenes

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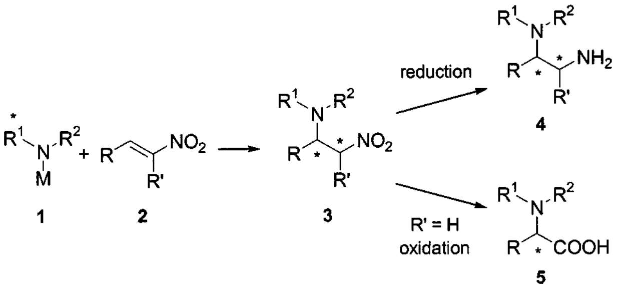
The addition of the potassium salt of (*R*)- or (*S*)-4-phenyl-2-oxazolidinone to monosubstituted nitroalkenes proceeded with very good diastereoselectivity. Several of the addition products were converted into α-amino acids and monosubstituted 1,2-diamines of high enantiomeric purity.

Introduction

Studying the conjugate addition of a chiral nitrogen nucleophile **1** to a nitroalkene **2** (Scheme 1) interested us as part of a programme directed towards the synthesis of biologically active, diastereomerically pure 1,2-diamines. This reaction would lead to adduct **3**, which could be converted into the corresponding 1,2-diamine precursor **4** by reduction of the nitro function. In addition, if **3** is unsubstituted at the α-nitro position (R′ = H), an amino acid precursor could be produced by oxidizing the nitromethyl moiety to a carboxylic acid.



Scheme 1. Strategy for the synthesis of 1,2-diamines and α-amino acids

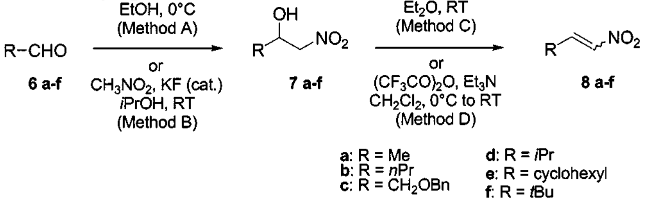
There is a steady interest in the design of efficient methods for the enantioselective synthesis of α-amino acids[1][2] and 1,2-diamines.[3] Many rare, naturally occurring nonprotein α-amino acids or peptides containing such α-amino acids are biologically active. Peptides that contain α-amino acids that are not naturally occurring can also be used in biological studies, either to provide information on the active conformation of related peptides, or as enzyme inhibitors. Chiral, enantiomerically pure 1,2-diamines and their derivatives are increasingly used in stereoselective organic synthesis as chiral auxiliaries or as metal ligands in catalytic asymmetric synthesis. Various platinum 1,2-diamino complexes are being evaluated as antitumor agents.

In this paper we describe our results in designing a highly diastereoselective conjugate addition of a nitrogen nucleophile, as well as finding an enantioselective access to representative α-amino acids and monosubstituted 1,2-diamines.[4]

Results and Discussion

Preparation of the Nitroalkenes

The monosubstituted nitroalkenes, which were not commercially available, were prepared by the Henry condensation of the corresponding aldehydes and nitromethane[5], catalysed by sodium hydroxide (Method A) or potassium fluoride (Method B) (Scheme 2). One of two possible methods was used for the conversion of the nitro alcohol to the nitroalkene: dehydration with either dicyclohexylcarbodiimide (DCC) and CuCl[6] (Method C), or with trifluoroacetic acid anhydride and triethylamine[7] (Method D). The results are summarized in Table 1. The nitroalkenes were generally obtained as the *E*-isomer, although in some cases (**8d**, **8e**), more of the *Z*-isomer was present in the purified product, as shown by the ^{1}H NMR spectra.



Scheme 2. Preparation of nitroalkenes **8a−f**

The α,β-disubstituted nitroalkene **10** was prepared from butyraldehyde and nitroethane, according to a one-pot procedure developed by Ballini et al.[8] In our case, however,

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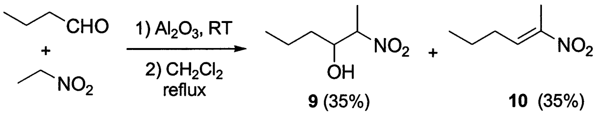
Table 1. Preparation of monosubstituted nitroalkenes

R	Method for aldol reaction with nitro	Yield of **7** (%)	Dehydration method	Yield of **8** (%)	*E*/*Z* ratio in **8**[a]
Me	A	95	D	52	> 99/1[b]
*n*Pr	A	100	C	81	> 99/1[b]
$BnOCH_2$	B	100	D	82	> 99/1[b]
*i*Pr	A	78	C	47	90/10
cyclohexyl	A	82	C	40	83/17
*t*Bu	A	83	C	53	> 99/1[b]

[a] Determined by ^1H NMR spectroscopy. – [b] *Z*-isomer not detected in the purified product.

after heating in the presence of alumina, some nitro alcohol remained, which was dehydrated in the usual manner (Scheme 3).

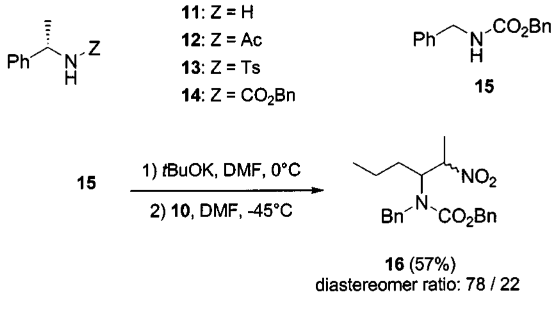


Scheme 3. Preparation of nitroalkene **10**

Choice of the Nucleophile

The most important problem was finding a suitable chiral nucleophile which would add with good stereoselectivity to the nitroalkenes and lead to stable products. The products resulting from the addition of amines to nitroalkenes are reportedly unstable, probably due to retro-addition which is possible because these molecules contain both a basic moiety and one or two acidic protons in the α-nitro position.[9] There are several solutions to this problem,[10] in particular that of using a moderately basic nitrogen nucleophile.

Nucleophiles derived from α-methylbenzylamine **11**, an amine which is commercially available as both enantiomers, were tested first, and we therefore prepared *N*-acetyl, *N*-tosyl, and *N*-carboxybenzyl derivatives of (*S*)-**11**. However, the potassium or lithium salts of these compounds did not add, or added very sluggishly to the nitroalkenes. Comparing the reactivities of the potassium anions generated, under similar conditions, either from benzyl *N*-benzylcarbamate (**15**) or from the more sterically crowded **14**, towards nitroalkene **10** proved very instructive (Scheme 4). Whereas **16** was obtained, as a mixture of diastereomers and in 57% yield, from **15**, only a small amount (5%) of the corresponding adduct was observed in the crude product of the reaction of **14**.

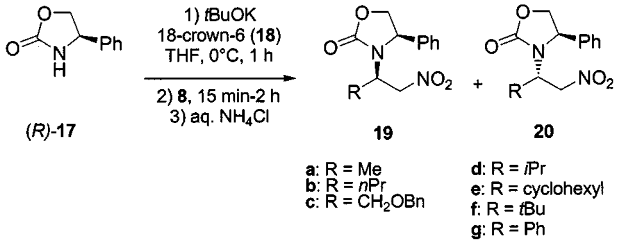


Scheme 4. Nitrogen nucleophiles evaluated in the conjugate addition to nitroalkenes

Since it was obvious that an efficient nucleophile should be less bulky than the derivatives of α-methylbenzylamine, we utilized 4-phenyl-2-oxazolidinone (**17**) for this purpose. Both enantiomers of this compound are commercially available, or may be readily prepared from (*R*)- or (*S*)-phenylglycine.[11] Moreover, it is known that the 4-phenyl-substituted oxazolidinone ring can be easily cleaved to generate an amino group.[11][12]

Conjugate Addition of 4-Phenyl-2-oxazolidinone

Several conjugate additions of **17** were carried out in DMF, with potassium *tert*-butoxide as the base. This tended to be inconvenient, because it became difficult to stir the reaction mixtures after addition of the electrophile and because the temperature could not be decreased below −45 °C. THF was then rather used as the solvent, so that the reaction could be performed at −78 °C. At first, one equiv of the crown ether 18-crown-6 was also added, to dissolve the oxazolidinone salt well. The results of the conjugate addition of either (*R*)- or (*S*)-4-phenyl-2-oxazolidinone (**17**) to monosubstituted nitroalkenes (Scheme 5) are summarized in Table 2.



Scheme 5. Reaction of the potassium salt of (*R*)-**17** with nitroalkenes

The potassium salt of **17** was usually generated from the oxazolidinone in THF at 0 °C, and in the presence of one equiv of 18-crown-6. The temperature was reduced to −78 °C, and the nitroalkene was added, to afford the corresponding adduct after rapid reaction. Under these conditions, all the nitroalkenes led to a single diastereomer **19** (or *ent*-**19**), according to the ^1H- and ^{13}C NMR spectra of the crude products. After investigating several parameters, we found that: (a) The crown ether does not play a role in the observed facial selectivity, it just permits the reaction to proceed more rapidly; without 18-crown-6, the reaction was finished after 2 h (entries 2, 10); with 0.1 equiv, only 30 min

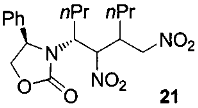
Table 2. Conjugate addition of the potassium salt of (*R*)- or (*S*)-4-phenyl-2-oxazolidinone **17** to monosubstituted nitroalkenes **8**

Entry	(*R*)- or (*S*)-**17**	R	Reaction temperature	**18** (equiv)	Yield (%)	**19**/**20** or *ent*-**19**/*ent*-**20** ratio
1	(*R*)-**17**	Me	−78 °C	0.1	68	> 99/1[a]
2	(*R*)-**17**	Me	−78 °C	0	63	> 99/1[a]
3	(*R*)-**17**	*n*Pr	−78 °C	1	59	> 99/1[a]
4	(*R*)-**17**	*n*Pr	−78 °C	0.1	58	> 99/1[a]
5	(*R*)-**17**	BnOCH2	−78 °C	0.1	60	> 99/1[a]
6	(*R*)-**17**	*i*Pr	−78 °C	1	87	> 99/1[a]
7	(*R*)-**17**	*i*Pr	−78 °C	0.1	79	> 99/1[a]
8	(*R*)-**17**	cyclohexyl	−78 °C	1	78	> 99/1[a]
9	(*R*)-**17**	*t*Bu	−78 °C	1	87	> 99/1[a]
10	(*R*)-**17**	*t*Bu	−78 °C	0	71	> 99/1[a]
11	(*R*)-**17**	Ph	−78 °C	1	43c	> 99/1[a]
12	(*S*)-**17**	*t*Bu	−78 °C	1	89	> 99/1[a]
13	(*S*)-**17**	Ph	−78 °C	1	54[c]	> 99/1[a]
14	(*S*)-**17**	cyclohexyl	0 °C	1	72	96/4[b]
15	(*S*)-**17**	cyclohexyl	25 °C	1.1	91	90/10[b]
16	(*S*)-**17**	cyclohexyl	−78 °C	0.1	85	> 99/1[a]

[a] Evaluated by ^{13}C NMR spectroscopy; only one diastereomer was seen in the ^{1}H NMR and ^{13}C NMR spectra of the crude product. – [b] Determined by ^{1}H NMR spectroscopy. [c] Five equiv of nitroalkene was used.

were needed (entries 1, 4, 5, 7, 16); (b) The use of higher reaction temperatures resulted in a lower diastereomeric excess, although it was still 80% at room temperature (entries 14, 15).

By-products were obtained in some instances. For example, the reaction of nitroalkene **8b** led to adduct **19b** (59% yield) as well as compound **21** which was isolated in 21% yield as a mixture of diastereomers. This by-product results from the addition of the intermediate nitronate to another molecule of nitroalkene **8b**. Oligomerization products formed in the reaction of the very reactive *β*-nitrostyrene (**8g**), therefore a large excess of this nitroalkene had to be used to isolate compound **19d**, albeit in moderate yield. It is worth noting that no addition product was obtained when a 2,2-disubstituted nitroalkene, α-methyl-β-nitrostyrene, was used as the electrophile.



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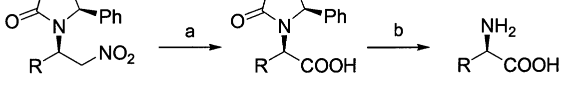
From a single-crystal X-ray analysis of adduct **19g**, which is derived from (*R*)-4-phenyl-2-oxazolidinone, the newly created stereogenic center was shown to have an *R* absolute configuration.[4a] Chemical correlations of the adducts **19d** and **19e** agreed with this observation,[4a] and thus we assumed that the diastereoface selection occurred in the same way in the other reactions with the nitroalkenes; this was later confirmed by the results from the amino acid syntheses.

The origin of the observed diastereoselection in the conjugate addition is not clear. Nitroalkenes that contain some *Z*-stereoisomer proportion nevertheless afforded single adducts. Seebach et al.[13] have described examples of diastereoselective additions of carbon nucleophiles (enolates and enamines) to either *Z*-nitroalkenes or *E*-nitroalkenes that afforded products of the same configuration.

Preparation of D-α-Amino Acids

Various examples of **19** were converted into the corresponding D-α-amino acids **23** in a two-step sequence, as shown in Scheme 6 and Table 3. Several methods to oxidize a nitromethyl function to a carboxylic acid have been described.[14] Compound **19** was oxidized by treatment with sodium nitrite (3 equiv) and acetic acid (10 equiv) in DMSO at 40 °C for 18–30 hours.[14a] Acids **22** were isolated in 25–89% yield, and in all cases, only one diastereomer was observed by ^{1}H- and ^{13}C NMR spectroscopy, indicating that no epimerization of the stereogenic center had occurred during the reaction. The yield was not very good for compounds in which the residue R is not bulky, especially for **22a** (R = Me). A possible explanation may be a loss of acid in the aqueous phase during the extraction, although we could not get a better yield of **22a** in an experiment where continuous extraction was used to recover the product. No other oxidation method was tested.



19 **22** **23**

Scheme 6. Reagents and conditions: (a) $NaNO_2$ (10 equiv), AcOH (3 equiv), DMSO, 18–30 h, 40 °C; (b) Li/NH_3, THF, *t*BuOH, −78 °C, then purification on DOWEX 50WX4–400 ion-exchange resin (elution: H_2O, then aq NH_4OH)

A Birch reduction of the oxazolidinone ring of compounds **22**, to generate the corresponding unprotected amino group, was then carried out. This method was recently employed in the synthesis of L-methionine from a precursor containing an oxazolidinone moiety which was prepared by asymmetric carboxylation.[15] Thus, treatment of oxazolidinones **22** with lithium/ammonia in THF and *t*BuOH at −78 °C for 30 min afforded D-α-amino acids **23**, which were isolated after ion-exchange resin purification, in 62–99%

Table 3. Preparation of D-α-amino acids **23** from nitro compounds **19**

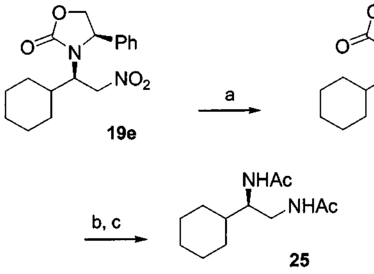
Entry	R (in **19** and **22**)	Yield (%) (**22**)	R (in **23**)	Yield (%) (**23**)	ee (%) (**23**)
1	Me	25	Me	99	> 96[a]
2	*n*Pr	48	*n*Pr	96	> 96[a]
3	$BnOCH_2$	43	$HOCH_2$	94	> 96[a]
4	*i*Pr	51	*i*Pr	62	> 96[a]
5	*t*Bu	89	*t*Bu	88	95[b]

[a] Evaluated by HPLC using a Crownpak CR(+) column; in each case, it was not possible to detect the L-enantiomer. – [b] Evaluated by examination of the ^{19}F NMR of the corresponding Mosher amide.

yield (Table 3). The protecting benzyl group in **22c** was concomitantly removed, leading to D-serine (**23c**) (entry 3). The enantiomeric purity of the α-amino acids was evaluated by HPLC using a Crownpak CR(+) column or, in the case of *tert*-leucine (**23f**) (entry 5), by examining the ^{19}F NMR of the corresponding Mosher amide.

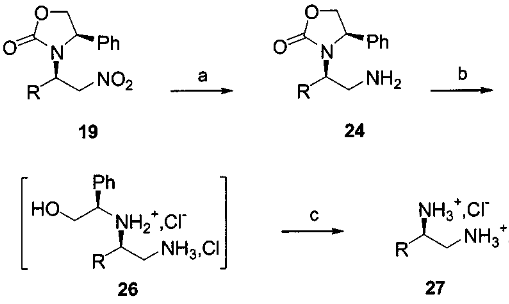
Preparation of Monosubstituted 1,2-Diamines

To convert compounds **19** to the corresponding 1,2-diamines, the nitro function must be reduced and the oxazolidinone needs to be cleaved off. Several reagents are known to reduce the nitro group to an amine.[16,17,18] We employed either catalytic hydrogenation or catalytic transfer hydrogenation (ammonium formate as hydrogen source)[19] for this purpose. The two methods afforded the corresponding amine with similar yields. The preparation of diacetamide **25**, an enantiomer of a known compound,[20] is shown in Scheme 7.[4a]



Scheme 7. Reagents and conditions: (a) HCO_2NH_4, Pd/C, MeOH; (b) Li/NH_3, THF, *t*BuOH, −78 °C; (c) AcCl, pyridine, 46% overall yield from **19e**

However, when other compounds **19** were used, this procedure did not give reproducible yields of diacetamide, because of the formation of 2-imidazolinone-containing products during the reductive cleavage. To cleave the oxazolidinone ring of several compounds **24**, obtained by reduction of **19**, a two-step procedure (Scheme 8, Table 4) was used. Treatment of **24** in 12 N HCl at 120 °C for 3–5 days, followed by catalytic hydrogenation over palladium hydroxide in a methanol/1 N HCl mixture for 2–7 days afforded the diamines as their hydrochloride salts **27**. The intermediates **26** were not isolated, because they were contaminated with variable amounts of the final products **27**. Prolonged treatment (7 days) with HCl was employed to generate **27f** directly from **24f**. The enantiomeric purity of the diamines was assessed by ^{19}F NMR of the corresponding diamides **28** and **29** respectively derived from the (*S*)- and (*R*)-enantiomers of Mosher's acid chloride.



Scheme 8. Reagents and conditions: (a) HCO_2NH_4, Pd/C, MeOH; (b) 12 N HCl, sealed tube, 120 °C; (c) H_2 (10 bar), $Pd(OH)_2$/C, MeOH/1 N HCl

Table 4. Preparation of 1,2-diamine hydrochlorides **27** from nitro compounds **19**

R	Yield (%) (**24**)	Yield (%) (**27**)	ee (%)[b] (**27**)
Me	69[a]	66	98.9
*n*Pr	100	52	97.5
cyclohexyl	98	58	98.7
*t*Bu	91	64	98.6

[a] Prepared by catalytic hydrogenation. – [b] Evaluated by examination of the ^{19}F NMR of the corresponding Mosher diamide.

In conclusion, after studying the reactivity of several nitrogen nucleophiles in the conjugate addition to monosubstituted nitroalkenes, we selected the potassium salt of 4-phenyl-2-oxazolidinone, which led essentially to single diastereomers. Moreover, both enantiomers of **17** are commercially available, or easily synthesized from the corresponding enantiomer of phenylglycine, and it is easy to cleave off the 4-phenyl-substituted oxazolidinone ring to generate an amino group. To the best of our knowledge, **17** had not previously been employed in conjugate additions.[21] Several adducts of (*R*)-4-phenyl-2-oxazolidinone were converted in two steps to either D-α-amino acids or monosubstituted (*R*)-1,2-diamines of high enantiomeric purity.

Experimental Section

General: THF was freshly distilled from sodium benzophenone ketyl. Conjugate additions were performed under an argon atmosphere. − TLC: Silica gel $60F_{254}$ plates (Merck), with detection by UV light or with an acidic solution of ninhydrin in *t*BuOH. − Column chromatography: 40−63 μm Merck silica gel. − IR: Perkin−Elmer 2000. − Optical rotations: Jobin-Yvon micropolarimeter RJ or Perkin−Elmer 341 micropolarimeter. Melting points (uncorrected): Büchi 535. − NMR: Bruker AM 300 (300.13 and 75.47 MHz for ^{1}H- and ^{13}C NMR spectra, respectively). − MS: Finnegan−Mat 4600 (70 eV).

Typical Procedures for the Preparation of Nitro Alcohols 7

Method A (Sodium Hydroxide Catalysis). − Nitro Alcohol 7e: To a solution of cyclohexanecarboxaldehyde (5.5 mL, 45.4 mmol) and nitromethane (2.5 mL, 46.2 mmol) in EtOH (10 mL) cooled at 0°C was added dropwise, under vigorous stirring (necessary to prevent the formation of a solid mass) an aqueous 10 M sodium hydroxide solution (4.54 mL, 45.4 mmol). After 10 min, the reaction mixture became yellow. Acetic acid (2.6 mL, 45.4 mmol) was added. The aqueous phase was extracted with ether (2×500 mL). The combined organic phases were washed with water until the pH of the washings was 6. After drying over magnesium sulfate, filtration, and concentration in vacuo, 6.43 g (82%) of nitro alcohol **7e** was obtained.

Method B (Potassium Fluoride Catalysis). − Nitro Alcohol 7a: To a solution of acetaldehyde (5.16 mL, 0.92 mol) and nitromethane (10.0 mL, 0.185 mol) in 2-propanol (50 mL), cooled at 0°C, was added potassium fluoride (0.70 g, 12 mmol). The reaction mixture was allowed to warm to room temperature. After stirring for 15 h, water (50 mL) was added, the aqueous phase was extracted with ether (3×50 mL). The combined organic phases were washed with water (50 mL), dried over magnesium sulfate, and then filtered. Concentration in vacuo afforded 9.2 g (95%) of nitro alcohol **7a**, which was not purified further.

7a: Oil. − IR (film): $\tilde{\nu}$ = 3395 cm^{-1}, 2982, 2938, 1551, 1459, 1424, 1387, 1139. − ^{1}H NMR ($CDCl_3$): δ = 4.41 (br. s, 1 H, OH), 4.40−4.20 (m, 2 H), 3.70 (m, 1 H), 1.20 (d, *J* = 6.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 81.4, 64.7, 19.5.

7b: Oil. − IR (film): $\tilde{\nu}$ = 3419 cm^{-1}, 2964, 2877, 1557, 1385. − ^{1}H NMR ($CDCl_3$): δ = 4.40−4.20 (m, 3 H), 3.03 (br. s, 1 H, OH), 1.50−1.35 (m, 4 H), 0.91 (t, *J* = 6.9 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 80.7, 68.4, 35.7, 18.3, 13.6.

7c: Oil. − ^{1}H NMR ($CDCl_3$): δ = 7.45−7.20 (m, 5 H), 4.65−4.35 (m, 5 H), 3.65−3.45 (m, 2 H), 3.12 (s, 1H, OH). − ^{13}C NMR ($CDCl_3$): δ = 137.1, 128.4, 127.8, 127.7, 78.1, 73.3, 70.5, 67.5.

7d: Oil. − ^{1}H NMR ($CDCl_3$): δ = 4.42 (m, 2 H), 4.09 (m, 1 H), 2.59 (m, 1 H, OH), 1.78 (m, 1 H), 0.98 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 79.0, 73.1, 31.5, 18.2, 17.2.

7e: Oil. − ^{1}H NMR ($CDCl_3$): δ = 4.50−4.30 (m, 2 H), 4.10−4.00 (m, 1 H), 2.79 (br. s, 1 H, OH), 1.45−1.35 (m, 1 H), 1.80−1.60 (m, 5 H), 1.30−0.95 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 79.3, 72.8, 41.4, 28.7, 27.9, 26.0, 25.8, 25.7.

7f: Oil. − IR (film): $\tilde{\nu}$ = 3500 cm^{-1}, 2963, 2875, 1557, 1480, 1382, 1286, 1025, 881. − ^{1}H NMR ($CDCl_3$): δ = 4.49 (dd, *J* = 12.8, 2.2 Hz, 1 H), 4.34 (dd, *J* = 12.8, 10.1 Hz, 1 H), 4.00 (dd, *J* = 10.1, 2.2 Hz, 1 H), 3.05 (br. s, 1 H, OH), 0.94 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 78.1, 76.0, 34.0, 25.3.

Typical Procedures for the Preparation of Nitroalkenes 8

Method C (with DCC−CuCl). − Nitroalkene 8d: To a solution of dicyclohexylcarbodiimide (11.1 g, 54.1 mmol) and copper(I) chloride (110 mg, 1.1 mmol) in anhydrous diethyl ether (15 mL), was added a solution of nitro alcohol **7d** (5.53 g, 41.6 mmol) in anhydrous diethyl ether (10 mL). After stirring for 12 h, pentane (50 mL) was added and the reaction mixture was kept at 4°C. Compounds derived from the DCC precipitated. After filtration, the organic phase was concentrated in vacuo, then pentane (70 mL) and a solution of acetic acid (3.8 mL) in water (10 mL) were added. After several hours, the residual DCC had disappeared (TLC), and the mixture was filtered. The organic phase was washed with water (20 mL) and dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (93:7 pentane/Et_2O), afforded 2.23 g (47%) of nitroalkene **8d** (as a 90/10 mixture of *E*- and *Z*-isomers).

Method D [with $(CF_3CO)_2O-Et_3N$]. − Nitroalkene 8c: To a solution of nitro alcohol **7c** (6.18 g, 29.2 mmol) in dichloromethane (60 mL), cooled at 0°C, were added successively trifluoroacetic acid anhydride (4.34 mL, 30.7 mmol) and then, dropwise, triethylamine (8.56 mL, 61.4 mmol). The reaction mixture was allowed to warm to room temperature; after stirring for 1 h, dichloromethane (40 mL) was added. The organic phase was washed successively with water (20 mL), saturated aqueous ammonium chloride (20 mL) and brine (20 mL), then dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (90:10 pentane/AcOEt) afforded 4.65 g (82%) of nitroalkene **8c**.

8a: Oil. − ^{1}H NMR ($CDCl_3$): δ = 7.24 (dq, *J* = 13.2, 7.3 Hz, 1 H), 6.97 (d, *J* = 13.2, 1.6 Hz, 1 H), 1.90 (dd, *J* = 7.3, 1.6 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 140.2, 138.1, 13.5.

8b: Oil. − ^{1}H NMR ($CDCl_3$): δ = 7.25 (dt, *J* = 13.5, 7.4 Hz, 1 H), 6.96 (dt, *J* = 13.5, 1.5 Hz, 1 H), 2.23 (qd, *J* = 7.4, 1.5 Hz, 2 H), 1.53 (dq, *J* = 13.2, 7.3 Hz, 1 H), 1.90 (m, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 142.0, 139.5, 30.1, 20.8, 13.2.

8c: Oil. − IR (film): $\tilde{\nu}$ = 3124 cm^{-1}, 3064, 2864, 1658, 1527, 1357, 1122, 742, 699. − ^{1}H NMR ($CDCl_3$): δ = 7.45−7.30 (m, 6 H), 7.25 (d, *J* = 13.5 Hz, 1 H), 4.60 (s, 2 H), 4.25 (s, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 139.5, 138.3, 136.9, 128.4, 128.3, 127.5, 73.0, 65.4. − $C_{10}H_{11}NO_3$ (193.2): calcd. C 62.17, H 5.74, N 7.25; found C 62.32, H 5.71, N 7.15.

8d: Oil (83/17 mixture of *E*- and *Z*-isomers). *E*-isomer. ^{1}H NMR ($CDCl_3$): δ = 7.20 (dd, *J* = 13.4, 7.0 Hz, 1 H), 6.89 (d, *J* = 13.4 Hz, 1 H), 2.60−2.45 (m, 1 H), 1.09 (d, *J* = 6.7 Hz, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 148.2, 137.9, 28.1, 20.7. *Z*-isomer. ^{1}H NMR ($CDCl_3$): δ = 6.77 (d, *J* = 9.0 Hz, 1 H), 5.87 (t, *J* = 9.0 Hz, 1 H), 3.65−3.45 (m, 1 H), 1.05 (d, *J* = 6.7 Hz, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 147.9, 135.6, 27.0, 21.6.

8e: Oil (83/17 mixture of *E*- and *Z*-isomers). *E*-isomer. ^{1}H NMR ($CDCl_3$): δ = 7.19 (dd, *J* = 13.5, 7.2 Hz, 1 H), 6.90 (dd, *J* = 13.5, 1.2 Hz, 1 H), 2.30−2.15 (m, 1 H), 1.80−1.05 (m, 10 H). − ^{13}C NMR ($CDCl_3$): δ = 146.7, 138.1, 37.2, 31.5, 25.3, 25.1, 24.9. *Z*-isomer. ^{1}H NMR ($CDCl_3$): δ = 6.79 (d, *J* = 9.2 Hz, 1 H), 5.89 (t, *J* = 9.2 Hz, 1 H), 3.29 (m, 1 H), 1.80−1.05 (m, 10 H). − ^{13}C NMR ($CDCl_3$): δ = 145.4, 136.0, 35.9, 31.2, 25.3, 25.1, 24.9.

8f: Oil. − ^{1}H NMR ($CDCl_3$): δ = 7.22 (d, *J* = 13.6 Hz, 1 H), 6.86 (d, *J* = 13.6 Hz, 1 H), 1.12 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 151.5, 137.0, 32.3, 28.2.

Typical Procedure for the Conjugate Addition of 4-Phenyl-2-oxazolidinone to Nitroalkenes: THF (5 mL) was added to a mixture of (*R*)-4-phenyl-2-oxazolidinone (100 mg, 0.61 mmol), potassium *tert*-butoxide (68.8 mg, 0.61 mmol), and 18-crown-6 (162 mg, 0.61 mmol), which were cooled at 0 °C and under argon. After 1 h at 0 °C, the resulting solution (in several cases a white solid had precipitated) was cooled to −78 °C and a solution of nitroalkene **8d** (78.4 mg, 0.61 mmol) in THF (2 mL) was added by syringe. After 15 min, saturated aq NH_4Cl (2.5 mL) was added and, after warming to room temperature, the mixture was extracted with ether (2 × 10 mL). The combined organic phases were then washed with water and dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (70:30 pentane/AcOEt) afforded 154.8 mg (87%) of nitro compound **19d**.

19a: Oil. − $[\alpha]_D = -105$ ($c = 2.70$, $CHCl_3$). − IR (KBr): $\tilde{\nu} = 3463$ cm^{-1}, 3054, 2981, 2932, 1740, 1556, 1368, 1340, 768, 701. − ^1H NMR ($CDCl_3$): $\delta = 7.41-7.25$ (m, 5 H), 4.93 (dd, $J = 12.5, 8.6$ Hz, 1 H), 4.80 (t, $J = 8.8$ Hz, 1 H), 4.57 (t, $J = 8.8$ Hz, 1 H), 4.47 (dd, $J = 12.5, 5.5$ Hz, 1 H), 4.09 (t, $J = 8.8$ Hz, 1 H), 4.00 (m, 1 H), 1.17 (d, $J = 7.1$ Hz, 3 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.3$, 137.2, 129.3, 129.2, 127.1, 76.5, 70.2, 59.7, 48.4, 14.5. − $C_{12}H_{14}N_2O_4$ (250.3): calcd. C 57.59, H 5.64, N 11.19; found C 57.15, H 5.68, N 11.04.

19b: Oil. − $[\alpha]_D = -62.0$ ($c = 0.68$, CH_3OH). − IR (film): $\tilde{\nu} = 3035$ cm^{-1}, 2963, 2875, 2933, 1748, 1557, 1363, 766, 704. − ^1H NMR ($CDCl_3$): $\delta = 7.46-7.28$ (m, 5 H), 4.92 (dd, $J = 12.4, 9.0$ Hz, 1 H), 4.80 (dd, $J = 8.7, 7.6$ Hz, 1 H), 4.62 (t, $J = 8.7$ Hz, 1 H), 4.44 (dd, $J = 12.4, 5.0$ Hz, 1 H), 4.20 (dd, $J = 8.8, 7.6$ Hz, 1 H), 3.92−3.82 (m, 1 H), 1.71−1.63 (m, 1 H), 1.48−1.23 (m, 3 H), 0.86 (t, $J = 7.1$ Hz, 3 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.4$, 137.5, 129.6, 129.4, 127.4, 75.8, 70.3, 60.8, 53.0, 31.9, 19.4, 13.5. − $C_{14}H_{18}N_2O_4$ (278.3): calcd. C 60.42, H 6.52, O 22.99; found C 60.16, H 6.51, O 22.77.

19c: Oil. − $[\alpha]_D = -93.6$ ($c = 3.48$, $CHCl_3$). − IR (film): $\tilde{\nu} = 3034$ cm^{-1}, 2918, 2871, 1755, 1556, 1363, 765, 701. − ^1H NMR ($CDCl_3$): $\delta = 7.41-7.23$ (m, 10 H), 4.98 (dd, $J = 12.9, 8.9$ Hz, 1 H), 4.93 (t, $J = 8.3$ Hz, 1 H), 4.54 (t, $J = 8.3$ Hz, 1 H), 4.40 (d, $J = 11.8$ Hz, 1 H), 4.34 (d, $J = 11.8$ Hz, 1 H), 4.15 (m, 2 H), 3.74 (dd, $J = 9.5, 7.3$ Hz, 1 H), 3.39 (dd, $J = 9.5, 6.2$ Hz, 1 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.4$, 138.1, 129.3, 129.1, 128.3, 127.8, 127.4, 127.2, 73.3, 73.0, 70.3, 67.1, 60.9, 52.1. − $C_{19}H_{20}N_2O_4$ (340.4): calcd. C 64.04, H 5.66, N 7.86; found: C 63.89, H 5.66, N 7.75.

19d: White solid, mp 91−92 °C. − $[\alpha]_D = -72.4$ ($c = 1.00$, CH_3OH). − IR (KBr): $\tilde{\nu} = 3047$ cm^{-1}, 2977, 2919, 1750, 1553, 1424, 1034, 766, 701. − ^1H NMR ($CDCl_3$): $\delta = 7.50-7.20$ (m, 5 H), 5.10 (dd, $J = 12.6, 9.7$ Hz, 1 H), 4.82 (t, $J = 8.1$ Hz, 1 H), 4.64 (t, $J = 8.8$ Hz, 1 H), 4.48 (dd, $J = 12.6, 3.7$ Hz, 1 H), 4.25 (t, $J = 9.1$ Hz, 1 H), 3.55−3.40 (m, 1 H), 2.25−2.00 (m, 1 H), 1.02 (d, $J = 6.6$ Hz, 3 H), 0.92 (d, $J = 6.7$ Hz, 3 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.1$, 136.7, 129.5, 129.2, 127.5, 74.4, 69.9, 61.7, 58.8, 29.4, 19.9, 19.4. − $C_{14}H_{18}N_2O_4$ (278.3): calcd. C 60.42, H 6.52, N 10.06; found C 60.71, H 6.28, N 10.21.

19e: White solid, mp 107−108 °C. − $[\alpha]_D = -55.4$ ($c = 0.91$, CH_3OH). − ^1H NMR ($CDCl_3$): $\delta = 7.40-7.25$ (m, 5 H), 4.99 (dd, $J = 12.6, 9.3$ Hz, 1 H), 4.79 (dd, $J = 8.8, 7.3$ Hz, 1 H), 4.58 (t, $J = 8.8$ Hz, 1 H), 4.47 (dd, $J = 8.8, 7.3$ Hz, 1 H), 4.17 (dd, $J = 12.6, 4.1$ Hz, 1 H), 3.55 (td, $J = 10.0, 3.5$ Hz, 1 H), 1.80−1.50 (m, 6 H), 1.25−0.90 (m, 5 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.2$, 137.0, 129.3, 129.0, 127.5, 74.5, 69.9, 61.4, 57.9, 38.7, 30.0, 29.7, 25.5, 25.4. − $C_{17}H_{22}N_2O_4$ (318.4): calcd. C 64.13, H 6.97, N 8.80; found C 64.29, H 6.82, N 8.74.

ent-**19e**: $[\alpha]_D = +57.2$ ($c = 1.68$, CH_3OH).

ent-**20e**: White solid, mp 120−121 °C. − $[\alpha]^{21}_D = +8.8$ ($c = 1.13$, CH_3OH). − ^1H NMR ($CDCl_3$): $\delta = 7.45-7.35$ (m, 5 H), 4.76 (dd, $J = 13.0, 10.0$ Hz, 1 H), 4.66 (t, $J = 8.0$ Hz, 1 H), 4.59 (t, $J = 8.0$ Hz, 1 H), 4.41 (dd, $J = 13.0, 3.5$ Hz, 1 H), 3.61 (td, $J = 9.3, 4.1$ Hz, 1 H), 1.90 (m, 1 H), 1.70−1.55 (m, 5 H), 1.25−0.75 (m, 4 H), 0.44 (m, 1 H). − ^{13}C NMR ($CDCl_3$): $\delta = 156.7$, 136.7, 129.5, 129.0, 128.2, 74.3, 69.3, 61.4, 57.8, 37.3, 30.1, 29.9, 25.5, 25.4.

19f: White solid, mp 97.5−98 °C. − ^1H NMR ($CDCl_3$): $\delta = 7.37-7.19$ (m, 5 H), 5.37 (dd, $J = 12.4, 8.9$ Hz, 1 H), 4.80 (dd, $J = 8.8, 5.7$ Hz, 1 H), 4.60 (t, $J = 8.8$ Hz, 1 H), 4.41 (dd, $J = 12.8, 3.4$ Hz, 1 H), 4.19 (dd, $J = 8.8, 5.7$ Hz, 1 H), 3.43 (dd, $J = 8.9, 3.4$ Hz, 1 H), 0.98 (s, 9 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.0$, 137.3, 129.4, 129.2, 127.4, 72.9, 69.6, 62.9, 61.4, 37.5, 27.5. − $C_{15}H_{20}N_2O_4$ (292.3): calcd. C 61.63, H 6.90, O 21.89; found C 61.57, H 7.08, O 22.07.

ent-**19f**: $[\alpha]_D = +69.8$ ($c = 1.03$, CH_3OH).

19g: White solid, mp 119−120 °C. − $[\alpha]_D = -65.9$ ($c = 1.06$, CH_3OH). − ^1H NMR ($CDCl_3$): $\delta = 7.45-7.28$ (m, 10 H), 5.83 (dd, $J = 13.5, 9.4$ Hz, 1 H), 4.78 (dd, $J = 13.5, 5.8$ Hz, 1 H), 4.63−4.47 (m, 3 H), 4.11 (t, $J = 8.2$ Hz, 1 H). − ^{13}C NMR ($CDCl_3$): $\delta = 157.7$, 135.7, 134.7, 129.6−127.2 (6 peaks), 75.2, 70.1, 60.7, 56.1. − $C_{17}H_{16}N_2O_4$ (312.3): calcd. C 65.38, H 5.16, N 8.97, found C 65.48, H 5.31, N 8.85.

Typical Procedure for the Oxidation of Nitro Compounds 19: A solution of nitro compound **19f** (1.06 g, 3.62 mmol), sodium nitrite (0.75 g, 3 equiv), and acetic acid (2.07 mL, 10 equiv) in DMSO (25 mL) was heated at 40 °C for 28 h. After cooling to room temperature, 1 N HCl (30 mL) was added to the yellow solution; after 15 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were then washed with water and dried over magnesium sulfate. After filtration and concentration in vacuo, chromatography on silica gel (95:5 CH_2Cl_2/CH_3OH) afforded 890 mg (89%) of acid **22f**.

22a: Oil. − $[\alpha]_D = -99$ ($c = 0.61$, $CHCl_3$). − IR (film): $\tilde{\nu} = 3414$ cm^{-1}, 3009, 2921, 1731, 1651, 1459, 1407, 1230, 1020, 769, 704. − ^1H NMR ($CDCl_3$): $\delta = 12.00$ (s, 1 H), 7.51−7.38 (m, 5 H), 5.15 (dd, $J = 8.8, 6.7$ Hz, 1 H), 4.72 (t, $J = 8.8$ Hz, 1 H), 4.39 (q, $J = 7.4$ Hz, 1 H), 4.09 (dd, $J = 8.8, 6.7$ Hz, 1 H), 1.13 (d, $J = 7.4$ Hz, 3 H). − ^{13}C NMR ($CDCl_3$): $\delta = 172.4$, 158.7, 141.1, 129.5, 129.1, 127.7, 71.1, 59.3, 52.6, 15.5.

22b: Oil. − $[\alpha]_D = -56.1$ ($c = 3.00$, $CHCl_3$). − IR (film): $\tilde{\nu} = 3467$ cm^{-1}, 2963, 2034, 2874, 1740, 1423, 1222, 765, 702. − ^1H NMR ($CDCl_3$): $\delta = 10.70$ (s, 1 H), 7.40−7.32 (m, 5 H), 5.04 (dd, $J = 8.8, 6.7$ Hz, 1 H), 4.69 (t, $J = 8.8$ Hz, 1 H), 4.34 (dd, $J = 9.3, 4.7$ Hz, 1 H), 4.22 (dd, $J = 8.8, 6.7$ Hz, 1 H), 1.70−1.63 (m, 1 H), 1.35−1.10 (m, 3 H), 0.60 (t, $J = 7.2$ Hz, 3 H). − ^{13}C NMR ($CDCl_3$): $\delta = 174.9$, 159.2, 138.8, 128.9, 128.2, 70.8, 59.4, 56.9, 30.9, 19.4, 13.0.

22c: Oil. − $[\alpha]_D = -73.2$ ($c = 2.70$, $CHCl_3$. − IR (film): $\tilde{\nu} = 3459$ cm^{-1}, 3032, 2920, 1752, 1415, 1217, 1076, 765, 700. − ^1H NMR ($CDCl_3$): $\delta = 10.45$ (s, 1 H), 7.33−7.13 (m, 10 H), 5.13 (dd, $J = 8.9, 6.5$ Hz, 1 H), 4.65 (t, $J = 8.9$ Hz, 1 H), 4.52 (dd, $J = 7.2, 3.4$ Hz, 1 H), 4.09 (dd, $J = 8.9, 6.5$ Hz, 1 H), 4.04 (s, 2 H), 3.76 (dd, $J = 9.9, 7.2$ Hz, 1 H), 3.48 (dd, $J = 8.9, 3.4$ Hz, 1 H). − ^{13}C NMR ($CDCl_3$) $\delta = 171.8$, 159.1, 139.3, 137.3, 128.8, 128.5, 128.1, 127.4, 127.2, 126.9, 126.8, 72.5, 71.2, 66.9.

22d: Oil. − $[\alpha]_D = -49.5$ ($c = 1.94$, $CHCl_3$). − IR (film): $\tilde{\nu} = 3423$ cm^{-1}, 3038, 2968, 2877, 1739, 1690, 1428, 1255, 1202, 699. − ^1H NMR ($CDCl_3$): $\delta = 9.70$ (s, 1 H), 7.36−7.25 (m, 5 H), 4.98 (dd,

J = 8.8, 5.8 Hz, 1 H), 4.57 (t, J = 8.8 Hz, 1 H), 4.15 (dd, J = 8.8, 5.8 Hz, 1 H), 3.86 (d, J = 9.3 Hz, 1 H), 2.11−2.01 (m, 1 H), 0.89 (d, J = 6.3 Hz, 3 H), 0.87 (d, J = 6.3 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 172.5, 159.0, 137.8, 129.2, 129.0, 127.3, 70.9, 64.1, 61.1, 27.9, 19.4. − $C_{14}H_{17}NO_4$ (263.3): calcd. C 63.86, H 6.51, N 5.32; found C 63.53, H 6.51, N 5.08.

22f: Oil. − $[\alpha]_D$ = −34.9 (c = 0.76, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2962 cm^{-1}, 1752, 1732, 1428, 1220, 763, 701. − ^{1}H NMR ($CDCl_3$): δ = 11.07 (s, 1 H), 7.40−7.30 (m, 5 H), 4.96 (dd, J = 8.7, 5.4 Hz, 1 H), 4.69 (t, J = 8.7 Hz, 1 H), 4.20 (dd, J = 8.7, 5.4 Hz, 1 H), 3.57 (s, 1 H), 1.02 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 170.9, 159.2, 137.8, 129.1, 127.4, 71.0, 66.1, 62.7, 26.2, 27.7. − $C_{15}H_{19}NO_4$ (277.3): calcd. C 64.97, H 6.91, N 5.05; found C 64.62, H 6.95, N 5.03.

Typical Procedure for the Reductive Cleavage of Oxazolidinones 22: To a solution of oxazolidinone **22f** (0.35 g, 1.26 mmol), in THF (75 mL) and *tert*-butyl alcohol (10 mL) was added lithium (88 mg, 10 equiv). After cooling the reaction mixture to −78 °C, NH_3 (about 110 mL) was added by condensation. The resulting deep-blue solution was stirred at −78 °C for 30 min, then NH_4Cl (1.5 g) was added. The reaction mixture was allowed to warm to room temperature, then concentrated in vacuo. The residue was purified using a DOWEX 50WX4−400 ion-exchange resin washed beforehand with water. The resin was eluted with water, then with 0.5 M NH_4OH, then with 1 M NH_4OH. The content of each fraction was checked by thin-layer chromatography (80/20 EtOH/10% aq NH_4OH, ninhydrin, R_f = 0.65). D-*tert*-leucine **23f** was obtained as a white solid (0.145 g, 88%).

Determining the Enantiomeric Purity of α-Amino Acids 23 by Chiral-Phase HPLC: Both an authentic racemic mixture and the synthetic sample were analyzed by HPLC using a Crownpak CR(+) column. Mobile phase: pH 1.5 aq $HClO_4$; flow rate: 0.4 mL/min; λ = 200 nm. Compounds **23c,d** were analyzed at 0 °C. Retention times: R_t(D-enantiomer)/R_t(L-enantiomer) = 3.7 min/4.8 min (alanine); 5.9 min/9.2 min (norvaline); 3.9 min/4.9 min (serine); 5.8 min/7.4 min (valine).

Determining the Enantiomeric Purity of α-Amino Acid 23f: Both authentic racemic *tert*-leucine and synthetic **23f** were converted into their Mosher′s amide, derived from (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride, according to the procedure described by Lander and Hegedus.[22]

D-Alanine 23a: $[\alpha]_D^{31}$ = −13.5 (c = 0.30, 5 N HCl); ref.[23a] $[\alpha]_D$ = −12.7 (c = 0.51, 5 N HCl). − ^{1}H NMR (D_2O): δ = 3.98 (q, J = 7.2 Hz, 1 H), 1.68 (d, J = 7.2 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 176.2, 51.0, 16.6.

D-Norvaline 23b: $[\alpha]_D^{38}$ = −22.2 (c = 0.82, 6 N HCl); ref.[23b] $[\alpha]_D^{25}$ = −23.0 (c = 2−3, 6 N HCl). − ^{1}H NMR (D_2O): δ = 3.94 (t, J = 6.2 Hz, 1 H), 2.02 (m, 2 H), 1.58 (m, 2 H), 1.15 (t, J = 7.3 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 175.5, 55.2, 33.0, 18.3, 13.4.

D-Serine 23c: $[\alpha]_D^{28}$ = −13 (c = 0.30, 5 N HCl); ref.[23c] $[\alpha]_D^{23}$ = −15.0 (c = 4, 1 N HCl). − ^{1}H NMR (D_2O): δ = 4.19 (m, 2 H), 4.07 (t, J = 4.2 Hz, 1 H). − ^{13}C NMR (D_2O): δ = 172.8, 60.6, 56.8.

D-Valine 23d: $[\alpha]_D^{26}$ = −27.5 (c = 0.80, 6 N HCl); ref.[23d,e] $[\alpha]_D^{25}$ = −29.04 (6 N HCl). − ^{1}H NMR (D_2O): δ = 3.81 (d, J = 5.4 Hz, 1 H), 2.48 (m, 1 H), 1.24 (d, J = 7.0 Hz, 3 H), 1.19 (d, J = 7.0 Hz, 3 H). − ^{13}C NMR (D_2O): δ = 177.1, 60.8, 29.5, 18.4, 17.1.

D-*tert*-Leucine 23f: $[\alpha]_D^{32}$ = −29.0 (c = 1.00, AcOH); ref.[23f] $[\alpha]_D^{25}$ = −31.4 (c = 1.0, AcOH). − ^{1}H NMR (D_2O): δ = 3.65 (s, 1 H), 1.24 (s, 9 H). − ^{13}C NMR (D_2O): δ = 173.9, 64.5, 32.4, 26.3.

Typical Procedures for the Reduction of Nitro Compounds 19 to Amines 24

Procedure with Ammonium Formate. − Amine 24b: To a solution of nitro compound **19b** (51.3 mg, 0.18 mmol) in dry methanol (0.5 mL) was added successively, under an argon atmosphere, ammonium formate (61 mg, 0.97 mmol) and 10% palladium on carbon (13 mg). The reaction mixture was stirred for 2 h at room temperature, then filtered through a short pad of celite; the celite was then washed with methanol (10 mL). Concentration of the combined organic phases in vacuo afforded 45.8 mg (quantitative) of amine **24b**, which was used without purification in the next step.

Procedure with Hydrogen. − Amine 24d: To a solution of nitro compound **19d** (355 mg, 1.28 mmol) in dry methanol (20 mL) was added 20% palladium hydroxide on carbon (36 mg). The suspension, placed in an autoclave, was purged with hydrogen (2 × 10 bar), and then stirred under hydrogen (30 bar) for 14 h. Hydrogen was then evacuated and nitrogen was flushed into the autoclave prior to its opening. The suspension was then filtered through a short pad of celite, which was then washed with methanol (10 mL). After concentrating the combined organic phases in vacuo, chromatography on silica gel (95:5:1 CH_2Cl_2/MeOH/Et_3N), afforded 268.5 mg (85%) of amine **24d**.

24a: White solid, mp 94 °C. − $[\alpha]_D^{25}$ = −53.0 (c = 1.04, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.31−7.26 (m, 5 H), 4.81 (dd, J = 9.0, 6.6 Hz, 1 H), 4.58 (t, J = 8.8 Hz, 1 H), 4.05 (dd, J = 8.5, 6.4 Hz, 1 H), 3.59−3.51 (m, 1 H), 2.90 (dd, J = 13.2, 9.2 Hz, 1 H), 2.74 (dd, J = 13.2, 5.3 Hz, 1 H), 2.32 (br. s, 2 H), 0.81 (d, J = 7.1 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 158.7, 139.8, 129.3, 129.1, 127.4, 70.4, 59.1, 53.2, 44.8, 16.3. − MS (CI, NH_3); m/z (%): 221 [M^+ + H], 238 [M^+ + NH_4]. − $C_{12}H_{16}N_2O_2$: calcd. 220.1212, found 220.122 (MS).

24b: Oil. − $[\alpha]_D^{25}$ = −18.8 (c = 1.00, MeOH). − ^{1}H NMR (CD_3OD): δ = 7.45−7.35 (m, 5 H), 4.90 (dd, J = 8.6, 6.4 Hz, 1 H), 4.77 (br. s, 2 H), 4.69 (t, J = 8.6 Hz, 1 H), 4.20 (dd, J = 8.6, 6.4 Hz, 1 H), 3.50−3.40 (m, 1 H), 2.89 (dd, J = 13.2, 9.8 Hz, 1 H), 2.70 (dd, J = 13.2, 4.5 Hz, 1 H), 1.25−1.15 (m, 2 H), 1.12−1.00 (m, 2 H), 0.67 (t, J = 7.1 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 161.0, 141.1, 130.2, 130.1, 128.8, 71.8, 60.6, 58.7, 43.6, 33.8, 20.6, 14.0. − MS (CI, NH_3); m/z (%): 249 [M^+ + H], 266 [M^+ + NH_4]. − $C_{13}H_{16}NO_2$ [M^+ − CH_2NH_2]: calcd. 218.1018, found 218.119 (MS).

24d: White solid, mp 88−89 °C. − $[\alpha]_D^{25}$ = −10.5 (c = 1.00, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.40 (br. s, 5 H), 4.86 (t, J = 7.7 Hz, 1 H), 4.67 (t, J = 7.7 Hz, 1 H), 4.67 (t, J = 7.7 Hz, 1 H), 3.10−2.85 (m, 3 H), 1.98 (br. s, 2 H), 1.65−1.45 (m, 1 H), 0.88 (d, J = 6.5 Hz, 1 H), 0.79 (d, J = 6.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 158.9, 138.9, 128.8, 127.7, 69.8, 63.8, 60.1, 40.4, 28.9, 20.4, 19.6. − MS (CI, NH_3); m/z (%): 249 [M^+ + H], 266 [M^+ + NH_4]. − $C_{13}H_{16}NO_2$ [M^+ − CH_2NH_2]: calcd. 218.1018, found 218.1188 (MS).

24e: White solid, mp 73.5−74 °C. − $[\alpha]_D^{25}$ = −18.1 (c = 1.00, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.32−7.27 (m, 5 H), 4.78 (dd, J = 8.8, 7.0 Hz, 1 H), 4.58 (t, J = 8.8 Hz, 1 H), 4.17 (dd, J = 8.8, 7.0 Hz, 1 H), 3.02−2.79 (m, 3 H), 1.71−0.75 (m, 11 H). − ^{13}C NMR ($CDCl_3$): δ = 158.7, 139.0, 128.8, 127.6, 69.7, 62.7, 60.2, 40.4, 38.3, 30.5, 29.9, 25.9, 25.6, 25.4. − MS (CI, NH_3); m/z (%): 289 [M^+ + NH_4]. − $C_{17}H_{26}N_2O_3$ (**24e** + H_2O, 306.4): calcd. C 66.64, H 8.55, N 9.14; found C 66.21, H 8.22, N 9.06.

24f: White solid, mp 110°C. − $[\alpha]_D$ = +8.5 (c = 0.97, MeOH). − ^{1}H NMR ($CDCl_3$): δ = 7.42−7.32 (m, 5 H), 4.77 (dd, J = 8.7, 4.5 Hz, 1 H), 4.66 (t, J = 8.7 Hz, 1 H), 4.31 (dd, J = 8.7, 4.5 Hz, 1 H), 3.37 (m, 1 H), 2.76 (m, 2 H), 0.88 (s, 9 H). − ^{13}C NMR ($CDCl_3$): δ = 158.2, 139.5, 129.0, 127.9, 69.5, 67.0, 62.1, 37.7, 36.0, 27.7. − MS (CI, NH_3); m/z (%): 263 [M^+ + H]. − $C_{15}H_{22}N_2O_2$ (262.4): calcd. C 68.67, H 8.45, N 10.68; found C 68.22, H 8.08, N 10.62.

Typical Procedure for the Preparation of Diamine Dihydrochlorides 27 from Amines 24

Procedure with Hydrogen. − Diamine Dihydrochloride 27f: A solution of amine **24f** (285 mg, 1.09 mmol) in 12 N HCl, placed in a heavy-walled tube, was heated at 120°C for 3.5 days. Concentration in vacuo afforded a brown powder, which was then dissolved in a 1/1 methanol/1 N HCl mixture (20 mL). Palladium hydroxide (20% on carbon, 36 mg) was added. The suspension was placed in an autoclave which was purged with hydrogen (2 × 5 bar), then stirred under hydrogen (10 bar) for 5 days. Hydrogen was then evacuated and nitrogen was flushed into the autoclave prior to its opening. The suspension was then filtered through a short pad of celite, which was then washed with methanol (10 mL). The residue obtained after concentration of the combined phases in vacuo was recrystallized (EtOH), affording 132 mg (64%) of diamine dihydrochloride **27f**.

27a: Beige solid, mp 234−235°C. − $[\alpha]_D^{25}$ = +8.0 (c = 1.05, MeOH). − ^{1}H NMR (CD_3OD): δ = 4.82 (br. s, 6 H), 3.64 (m, 1 H), 3.26 (m, 1 H), 3.11 (dd, J = 13.3, 7.2 Hz, 1 H), 1.40 (d, J = 6.7 Hz, 3 H). − ^{13}C NMR (CD_3OD): δ = 46.6, 43.3, 16.6. − MS (CI, NH_3); m/z (%): 75 [M^+ + H], 92 [M^+ + NH_4].

27b: White solid. − $[\alpha]_D^{25}$ = +10.5 (c = 1.00, MeOH). − ^{1}H NMR (CD_3OD): δ = 4.87 (br. s, 6 H), 3.60−3.45 (m, 1 H), 3.30−3.20 (m, 2 H), 1.80−1.35 (m, 4 H), 0.97 (t, J = 7.3 Hz, 3 H). − ^{13}C NMR (CD_3OD): δ = 50.7, 42.2, 33.6, 19.2, 13.8.

27e: White solid, mp 249−250°C. − $[\alpha]_D^{25}$ = +5.1 (c = 1.06, MeOH). − ^{1}H NMR (CD_3OD): δ = 4.81 (br. s, 6 H), 3.36−3.12 (m, 3 H), 1.83−1.06 (m, 11 H). − ^{13}C NMR (CD_3OD): δ = 55.6, 40.7, 39.6, 29.5, 28.7, 26.9, 26.8. − MS (CI, NH_3); m/z (%): 143 [M^+ + H], 160 [M^+ + NH_4].

27f: White solid, mp 290−291°C. − $[\alpha]_D^{25}$ = −5.9 (c = 1.03, MeOH). − ^{1}H NMR (CD_3OD): δ = 5.89 (br. s, 6 H), 3.47−3.24 (m, 3 H), 1.05 (s, 9 H). − ^{13}C NMR (CD_3OD): δ = 60.1, 40.9, 34.4, 26.6. − MS (CI, NH_3); m/z (%): 117 [M^+ + H], 134 [M^+ + NH_4]. − $C_6H_{18}Cl_2N_2$ (189.1): calcd. C 38.10, H 9.59, N 14.81; found C 37.92, H 9.34, N 14.52.

Typical Procedure for the Preparation of Mosher Diamides 28 and 29. − Diamide 28a: Triethylamine (22 μL, 0.16 mmol) was added to a suspension of compound **27a** (9.8 mg, 0.067 mmol) in THF (1 mL). After stirring for 1 h, (S)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (Mosher′s acid chloride; 29 μL, 0.15 mmol) and triethylamine (22 μL, 0.16 mmol) were successively added. After stirring for 12 h, dichloromethane (10 mL) was added, the organic phase was washed with water (2 × 5 mL) and dried over magnesium sulfate. After filtration and concentration in vacuo, 31.8 mg diamide **28a** was obtained. The enantiomeric excesses were determined by examination of the ^{19}F NMR of the crude diamides **28** and **29** derived respectively from (S)- and (R)-Mosher's acid chloride. Chemical shifts observed for CF_3 in the ^{19}F NMR spectra of **28** and **29** ($CDCl_3$): **28a**: δ = 34.01; **29a**: δ = 33.81, 33.82; **28b**: δ = 34.02; **29b**: δ = 33.85, 33.89; **28e**: δ = 34.02, 34.07; **29e**: δ = 33.86, 34.06; **28f**: δ = 34.01, 34.11; **29f**: δ = 33.81, 34.33.

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[1] Reviews: [1a] R. M. Williams, *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, **1989**. − [1b] R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539−1650.

[2] Selected recent references: [2a] A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656−673. − [2b] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445−446. − [2c] C. P. Decicco, P. Grover, *Synlett* **1997**, 529−530. − [2d] M. Calmes, J. Daunis, N. Mai, F. Natt, *Tetrahedron Lett.* **1996**, *37*, 379−380. − [2e] C. J. Moody, A. P. Lightfoot, P. T. Gallagher, *Synlett* **1997**, 659−660. − [2f] J. Liang, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 3154−3155. − [2g] L. Meyer, J.-M. Poirier, P. Duhamel, L. Duhamel, *J. Org. Chem.* **1998**, *63*, 8094−8095. − [2h] V. Ferey, L. Toupet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1996**, *108*, 475−477; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 430−432. − [2i] V. Ferey, P. Vedrenne, L. Toupet, T. Le Gall, C. Mioskowski, *J. Org. Chem.* **1996**, *61*, 7244−7245.

[3] D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724−2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580−2627.

[4] For preliminary communications on this work, see: [4a] D. Lucet, L. Toupet, T. Le Gall, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 2682−2683. − [4b] S. Sabelle, D. Lucet, T. Le Gall, C. Mioskowski, *Tetrahedron Lett.* **1998**, *39*, 2111−2114.

[5] [5a] C. A. Sprang, E. F. Degering, *J. Am. Chem. Soc.* **1942**, *64*, 1063−1064. − Review: [5b] G. Rosini, "The Henry (Nitroaldol) Reaction" in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**; Vol. 2, pp. 321−340.

[6] P. Knochel, D. Seebach, *Synthesis* **1982**, 1017−1018.

[7] S. E. Denmark, C. B. W. Senanayake, *Tetrahedron* **1996**, *52*, 11579−11600.

[8] R. Ballini, R. Castagnani, M. Petrini, *J. Org. Chem.* **1992**, *57*, 2160−2162.

[9] [9a] R. L. Heath, J. D. Rose, *J. Chem. Soc.* **1947**, 1486−1489. − [9b] P. Bitha, Y. Lin, *J. Heterocyclic Chem.* **1988**, *25*, 1035−1036. − [9c] J. Ville, *Bull. Soc. Chim. Fr.* **1959**, 1407−1410. − [9d] M. S. Akhtar, V. L. Sharma, M. Seth, A. P. Bhaduri, *Indian J. Chem.* **1988**, *27B*, 448−451. − [9e] D. Ranganathan, S. Ranganathan, C. B. Rao, K. Kesavan, *Synthesis* **1980**, 884−886.

[10] [10a] D. Ranganathan, S. Ranganathan, S. Bamezai, *Tetrahedron Lett.* **1982**, *23*, 2789−2792. − [10b] A. Barco, S. Benetti, G. P. Pollini, G. Spalluto, *Synthesis* **1991**, 479−480. − [10c] M. L. Morris, M. A. Sturgess, *Tetrahedron Lett.* **1993**, *34*, 43−46. − [10d] M. A. Sturgess, D. J. Yarberry, *Tetrahedron Lett.* **1993**, *34*, 4743−4746. − [10e] D. Enders, J. Wiedemann, *Synthesis* **1996**, 1443−1450.

[11] D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1985**, *26*, 3783−3786.

[12] [12a] I. Ojima, H.-J. C. Chen, X. Qiu, *Tetrahedron* **1988**, *44*, 5307−5318. − [12b] J. W. Fisher, J. M. Dunigan, L. D. Hatfield, R. C. Hoying, J. E. Ray, K. L. Thomas, *Tetrahedron Lett.* **1993**, *34*, 4755−4758. − [12c] P.-J. Colson, L. S. Hegedus, *J. Org. Chem.* **1993**, *58*, 5918−5924.

[13] R. Häner, T. Laube, D. Seebach, *Chimia* **1984**, *38*, 255−257.

[14] [14a] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234−235. − [14b] M. R. Galobardes, H. W. Pinnick, *Tetrahedron Lett.* **1981**, *22*, 5235−5238. − [14c] E. A. Saville-Stones, S. D. Lindell, *Synlett* **1991**, 591−592. − [14d] S. D. Lindell, R. M. Turner, *Tetrahedron Lett.* **1990**, *31*, 5381−5384. − [14e] T. Urbanski, *J. Chem. Soc.* **1949**, 3374−3376. − [14f] N. Kornblum, R. K. Blackwood, D. D. Mooberry, *J. Am. Chem. Soc.* **1956**, *78*, 1501−1504. − [14g] G. Calderari, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 1592−1604.

[15] F. Jeanjean, N. Pérol, J. Goré, G. Fournet, *Tetrahedron Lett.* **1997**, *38*, 7547−7550.

[16] Reviews: [16a] G. W. Kabalka, R. S. Varma, "Reduction of Nitro and Nitroso Compounds" in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**; Vol. 8, pp. 363−379. − [16b] *Methoden Org. Chem.* (Houben-Weyl), **1992**; Vol. E16d, II, pp. 815−865.

[17] Recent methods: [17a] A. S. Kende, J. S. Mendoza, *Tetrahedron*

Lett. **1991**, *32*, 1699−1702. − [17b] B. Fischer, L. Sheihet, *J. Org. Chem*. **1998**, *63*, 393−395.

[18] For stereoselective syntheses of 1,2-diamines that use the reduction of nitro compounds, see ref.[10d], ref.[10e], and also: H. Adams, J. C. Anderson, S. Peace, A. M. K. Pennell, *J. Org. Chem*. **1998**, *63*, 9932−9934.

[19] S. Ram, R. E. Ehrenkaufer, *Tetrahedron Lett*. **1984**, *25*, 3415−3418.

[20] H. Reihlen, L. Knöpfle, W. Sapper, *Liebigs Ann. Chem*. **1938**, *534*, 247−275.

[21] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev*. **1996**, *96*, 835−875.

[22] P. A. Lander, L. S. Hegedus, *J. Am. Chem. Soc*. **1994**, *116*, 8126−8132.

[23] [23a] T. Eguchi, T. Koudate, K. Kakinuma, *Tetrahedron* **1993**, *49*, 4527−4540. − [23b] M. S. Patel, M. Worsley, *Can. J. Chem*. **1970**, *48*, 1881−1884. − [23c] V. E. Price, J. B. Gilbert, J. P. Greenstein, *J. Biol. Chem*. **1949**, *179*, 1169−1174. − [23d] E. Fischer, *Chem. Ber*., **1906**, *39*, 2320. − [23e] U. E. Diner, M. Worsley, J. W. Lown, J.-A. Forsythe, *Tetrahedron Lett*. **1972**, 3145−3148. − [23f] J. Viret, H. Patzelt, A. Collet, *Tetrahedron Lett*. **1986**, *27*, 5865−5868.

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