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The Asymmetric Synthesis of α-Amino and α-Hydrazino Acid Derivatives via The Stereoselective Amination of Chiral Enolates with Azodicarboxylate Esters.

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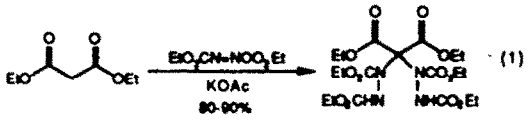
Abstract: The utility of azodicarboxylate esters as (+)NH_2 and (+)NH–NH_2 synthons in highly diastereoselective reactions with chiral carboximide-derived enolates has been demonstrated. The lithium enolates derived from 4-substituted N-acyl 2-oxazolidinones were found to react with di-*tert*-butyl azodicarboxylate (DBAD) to afford the derived 2-hydrazido carboxylic acid derivatives in yields in excess of 90 %. The diastereoselectivities of these reactions ranged from 97% to greater than 99%. The subsequent transformation of these adducts to both α–hydrazino and α–amino acids in enantiomeric purities in excess of 99% is described.

Introduction

Although the exceptional electrophilic reactivity of azodicarboxylate esters has been widely recognized,[1,2,3,4,5] the application of this reagent to the electrophilic amination of carbon nucleophiles has remained largely undeveloped. This is somewhat surprising since the first documented example of this process, the reaction of diethyl malonate with diethyl azodicarboxylate (DEAD), appeared in 1924 (eq 1).[6] The subsequent applications of this reagent as an (+)NH_2 synthon has been limited to a few reports concerning the reaction of DEAD with electron-rich aromatics[7] and enol ethers (eq 2).[8] At the time that this study was initiated, the single example illustrating the use of an organometallic reagent as a carbon nucleophile in this context was the reaction of *tert*-butylmagnesium chloride with di-*tert*-butyl azodicarboxylate (DBAD).[9,10]



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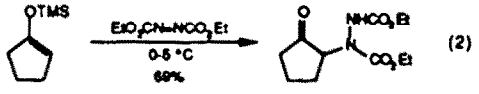

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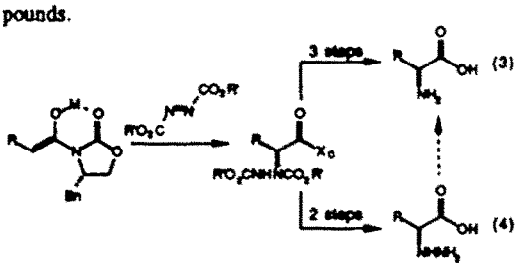
The above precedents suggested that azodicarboxylates possessed a desirable combination of high reactivity toward nucleophiles coupled with good shelf stability. Accordingly, the present investigation describes the reactions of azodicarboxylate esters with the illustrated chiral enolate system (eq 3,4) as a general route to both α-hydrazino and α-amino acids.[11,12] Currently available methods for obtaining α-hydrazino acids in enantiomerically pure form are limited either to classical resolution,[13] or to multistep procedures starting from the requisite enantiomerically pure α-amino acid precursors.[14,15,16] A convenient, general method for the asymmetric synthesis of these compounds based on the illustrated reaction of chiral carboximide enolates with a suitable azodicarboxylate electrophile would have obvious value, and could greatly facilitate the development of the biological potential offered by this class of compounds.

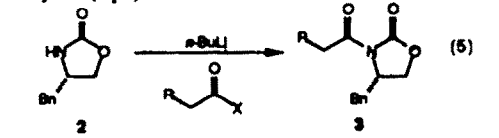


In preliminary studies, the suitability of azodicarboxylates as (+)NH_2 synthons toward carboximide enolates was established. Our selection of Di-*tert*-butyl azodicarboxylate (DBAD) (1) as the reagent of choice was motivated by several factors. First, it is a stable, crystalline yellow solid (mp 90-92 °C) that is readily prepared,[9] and is also commercially available.[17] Second, since the *tert*-butoxycarbonyl (Boc) group is widely used as a protecting group in peptide chemistry, methods for its removal under mild, nonracemizing conditions were well established, and are complementary to known methods for N-N bond cleavage. This offered the potential for convenient access to either α-amino or α-hydrazino acids from a common intermediate. Finally, preliminary data suggested that this reagent possessed a unique combination of high reactivity and high diastereoface selection in reaction with chiral imide enolates.

Results and Discussion

Electrophilic Amination of Chiral Imide Enolates. The carboximide substrates 3a-h chosen for this study were prepared as previously described *via* re-

action of the lithiated oxazolidone 2 and either the desired acid chloride[18] or the analogous mixed pivalic acid anhydride, which was generated *in situ* (eq 5). Initial electrophilic amination studies were conducted on the dihydrocinnamate derivative 3c (R=CH_2Ph) which was chosen as a representative substrate. The reaction of its derived lithium enolate, generated with lithium diisopropylamide (LDA) (1.05 equiv) in THF as previously described,[19] with DBAD (1.2 equiv) at -78 °C was found to be instantaneous, as evidenced by the immediate decoloration of the cooled (-78 °C) solution of DBAD in CH_2Cl_2 upon its addition to the enolate solution by rapid cannulation. Following an almost immediate quench (1 min) with glacial acetic acid (2.6 equiv) and conventional isolation, the adduct 4c (R=CH_2Ph) was obtained in excellent yield (eq 6).



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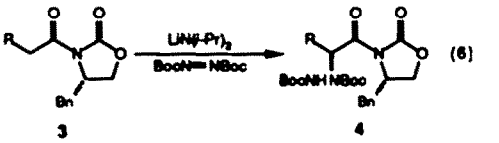
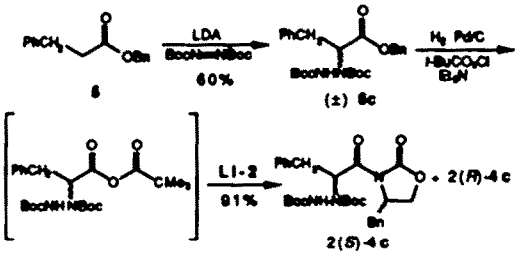


(6)

The ^1H NMR spectrum ($CDCl_3$, 300 MHz) of 4c obtained at 23 °C was largely uninterpretable due to hindered rotation about the Boc groups; however, the corresponding spectrum obtained at 57 °C was dramatically simplified and readily analyzed. This analytical method revealed only one product diastereomer; however, significant broadening of the spectral lines even at this temperature made it impossible to verify the presence of small but significant quantities of the minor diastereomeric impurity. In order to accurately determine the diastereoselectivity in these reactions, an unambiguous method for the production of both diastereomers was developed. One such method which proved to be viable is outlined in Scheme 1.

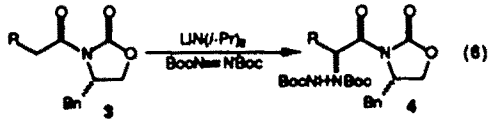
Scheme 1



The lithium enolate of the corresponding benzyl ester 5 was treated with DBAD in a similar fashion, to afford the racemic α-hydrazido ester 6c in 60% yield. Following benzyl ester hydrogenolysis, formation of the mixed pivalic acid anhydride, and subsequent treatment with the lithiated oxazolidone (2.1 equiv), the desired carboximide 4c was obtained in 91% overall yield (from 6c) as a 1:1-mixture of C_2 diastereomers. These compounds proved to be readily separable by both TLC as well as by HPLC (α =1.66). The faster-eluting component of this diastereomeric mixture was found to correspond to the major diastereomer from the imide-DBAD reaction, and was subsequently shown to possess the 2(*S*) configuration by correlation with L-phenylalanine (*vide infra*). HPLC analysis of the unfractionated imide-derived sample of 4a afforded a 2(*S*):2(*R*) ratio of 97:3, which was increased to >200:1 (91% yield) on a ten-gram scale following a single chromatographic purification on a standard grade of silica.

In order to facilitate the diastereomer analysis for other enolate-DBAD reactions, a more convenient method for obtaining hydrazido imide samples enriched in the minor diastereomer was developed. It was subsequently discovered that base-catalyzed epimerization of 4 could be achieved under the proper conditions. For example, when a solution of the 2(*S*) diastereomer of hydrazido imide 4c (0.09 M in THF) and 2 equiv of 1,1,3,3-tetramethylguanidine was heated at reflux for 4.5 h, a 45:55 mixture of the 2(*S*) and 2(*R*) diastereomers respectively was obtained in 63% yield. With appropriate adjustments for differing substrate epimerization rates,[20] this method was generally employed to independently verify the identity of the minor 2(*R*) diastereomer in those cases where sufficient quantities could not be isolated directly from the amination reaction for spectral characterization.

The results obtained for the reaction of DBAD with the lithium enolates derived from imides 3a-f under reaction conditions similar to that employed above are listed in Table 1 below.



(6)

Table 1. Selective "Amination" of Carboximide Enolates (eq 6).

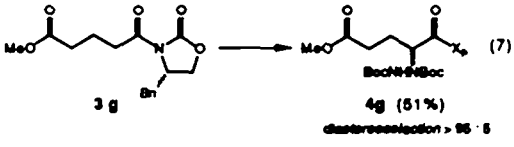
Entry	Imide	Substituent (R)	Kinetic Ratio[a] 2(S) : 2(R)	Product	Yield,[b] %
A	3a	Me	98 : 2[c]	4a	92
B	3b	$CH_2CH{=}CH_2$	98 : 2	4b	94
C	3c	CH_2Ph	97 : 3	4c	91
D	3d	Ph	97 : 3	4d	96
E	3e	$CHMe_2$	98 : 2	4e	95
F	3f	CMe_3	>99 : 1	4f	96

[a] Ratios determined by HPLC analysis. [b] Values refer to isolated yields of pure adduct, 2(S) : 2(R)> 200:1. [c] Isolated yield of the diastereomer mixture.

Minor modifications of the above chromatographic procedure afforded diastereomerically pure hydrazides 4b-f [2(*S*):2(*R*)>200:1] in 91-96% yields. The chiral auxiliary proved to be not only an effective directing ligand in the amination reaction, but it also performed as an efficient chiral chromatographic resolving moiety as well. *In accord*

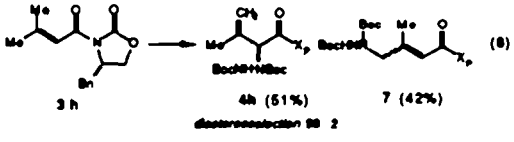
with previous studies, a stereoregular elution order was observed with the illustrated series of hydrazides, with the major 2(S) diastereomer exhibiting the greater mobility (vide infra).

In addition to the cases summarized in the Table, the direct amination of several less conventional substrates was also examined (eq 7, 8). The glutaryl imide **3g** was selectively deprotonated with 1.0 equiv of LDA (-78 °C, 5 min), and the resulting solution was treated with a slight excess of DBAD at -78 °C for 40 s prior to the usual acetic acid quench. Following a conventional isolation and chromatographic purification, the amination product **4g** was obtained in 51% yield (diastereomeric purity ≥95%) along with a 16% recovery of the imide starting material **3g**.[21] This is the only case that we have encountered in which the product diastereomers did not afford a baseline separation on analytical HPLC. In this instance, the reaction diastereoselection was conservatively estimated to be ≥95:5 from the 300 MHz ^{1}H NMR (331 °K) spectrum of the unfractionated product.



(7)

The lithium dienolate of the β,β-dimethylacryloyl imide **3h** was similarly treated with DBAD to afford a 51% of the 1,2-adduct **4h** along with 42% of the 1,4-addition product **7** as a 6:4 mixture of *E*:*Z* isomers (eq 8). Again, the 1,2-adduct was formed with high stereoselectivity (98:2), and the major product could be isolated in >200:1 diastereomeric purity (48% yield) on a multigram scale after chromatographic purification.

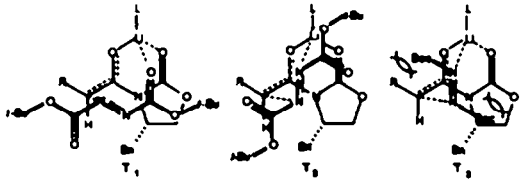


(8)

The amination reaction of these carboximide lithium enolates with DBAD show striking similarities, as well as significant differences, to analogous imide enolate-electrophile reactions that have been investigated in these laboratories. As in the analogous alkylation,[24] acylation,[22] hydroxylation,[21] halogenation,[23] and azidation[24] studies, the sense of asymmetric induction observed in this study is consistent with preferential attack of DBAD on the least hindered diastereoface of the chelated (*Z*) enolate.

Of all of the above imide enolate-electrophile reactions investigated, these amination reactions have simultaneously proven to be among the fastest, highest yielding, and most uniformly stereoselective of any yet encountered. The broad scope of this reaction is obvious from the data in Table 1. Unlike the analogous alkylation reactions, the reactivity of DBAD toward these enolates was not perceptibly attenuated as the steric requirements of the enolate substituent (R) are increased. In fact, not only was a high level of reactivity maintained, but the stereoselectivity was significantly improved. A striking illustration of these facts is provided in Entry F, in which the *tert*-butylacetyl derivative **4f** was obtained in 96% isolated yield, with >200:1 kinetic stereoselection, after a 3-min reaction time at -78 °C. In studies of the reactions of these chiral imide enolates with other heteroatomic electrophiles, it has been generally observed that the kinetic stereoselectivity is amplified with increasing steric requirements of the enolate R group. However this dependence of the reaction stereoselection on the structure of the imide enolate acyl residue is significantly attenuated in the corresponding reactions with DBAD. These results are in direct contrast to analogous halogenation,[23] hydroxylation,[21] and azidation studies,[24] in which a significant decrease in reaction stereoselection has been observed for phenylacetate-derived imide substrates (e.g. 3, R = Ph) as compared to the corresponding propionate (R = Me) and butyrate (R = Et) derivatives.

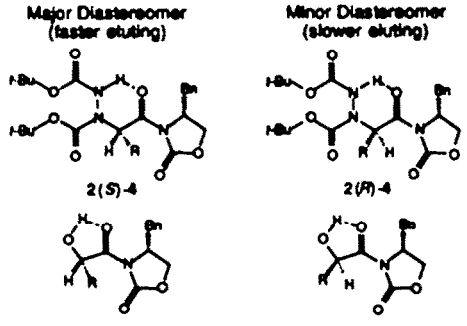
Mechanistic Considerations. We speculate that these highly exothermic reactions proceed through an early reactant-like, but highly ordered, transition state. Since DBAD can be considered a nitrogen analog of a conventional α,β-unsaturated ester, e.g. di-*tert*-butyl fumarate, these reactions probably bear a strong mechanistic relationship to the Michael addition reactions of enolates to such esters, a reaction which is the focal point of some current interest. Several models for this reaction have recently been extended to explain the diastereoselectivity observed in acyclic systems. Studies have recently appeared in support of a pericyclic process,[25] in which the enone carbonyl is coordinated to the enolate metal while an alternative open transition structure, involving no metal ion organization, has also been proposed.[26] Although much of the data that has been accumulated can be rationalized with either model, cases have been reported that are most readily explained in terms of a pericyclic transition state. In accord with the above precedent, we favor an analogous pericyclic transition state for the reaction of DBAD with imide enolates. Several possible transition structures for this reaction are illustrated below. It is evident that a high degree of organization can be achieved through coordination of the lithium atom with either the ester carbonyl (structure T_1) or the azo nitrogen of DBAD (structures T_2 and T_3).



In the former case, an 8-centered pericyclic transition state is thereby involved, while in the latter cases, 6-centered pericyclic structures which are directly analogous to the now commonly accepted Zimmerman-Traxler aldol transition state[27] appear plausible. In these latter two cases, al-

though DBAD could, in principle, assume two possible orientations as illustrated in T_2 and T_3, it appears that the former transition structure T_2 might be favored on steric grounds.

The chromatographic parameters for the α-hydrazido carboximide diastereomers prepared during this study are summarized in Table 2. As in the examples cited above, the major 2(*S*) product diastereomer is seen to elute first in each case. The separation factors (α) were found to be large enough so that diastereomer resolution could be effected on silica gel with little difficulty. The possible ground state conformations which may be employed to rationalize the stereoregular chromatographic behavior displayed by the diastereomeric α-hydrazido carboximide adducts are illustrated below. It is suggested that the major, faster-eluting diastereomer 2(S)-4 adopts the illustrated conformation in which the lipophilic moieties, R and Bn, "shield" both faces of the molecule from the polar adsorbant.



It is felt that the minor diastereomer 2(R)-4, on the other hand, might adopt the corresponding conformation in which these substituents reside on the *same* molecular face. Since the opposite, more polar face is exposed to the adsorbant, this diastereomer is more strongly retained. In each case, conformational organization is achieved by a combination of both intramolecular hydrogen bonding and the preferential opposition of the carbonyl dipoles.[28]

Table 2. HPLC Resolution of α-Hydrazidoacyl Diastereomers 4.[a]

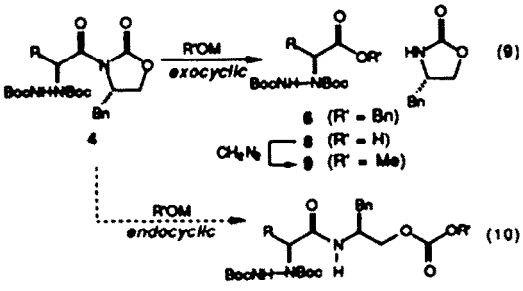
Imide	Substituent (R)	k'[b] 2(S)-4	k'[b] 2(R)-4	Sep. Factor[c] (α)
4a	Me	2.35	3.27	1.39
4b	$CH_2CH{=}CH_2$	2.97	4.64	1.56
4c	CH_2Ph	3.84	6.37	1.66
4d	Ph	2.88[d]	4.97[d]	1.73[d]
4e	$CHMe_2$	2.95	4.53	1.54
4f	CMe_3	2.65	4.29	1.62
4h	$C(Me){=}CH_2$	3.02	4.14	1.37

[a] Analyses carried out on a Waters 5 micron Radial-Pak column eluting with CH_2Cl_2-hexane-MeCN (70:30:5). [b] HPLC capacity factor defined as $(t - t_0)/t_0$. [c] HPLC separation factors for product diastereomers defined as the ratio of the capacity factors. [d] Eluting solvent: CH_2Cl_2-hexane-MeCN (70:30:7.5).

This "adsorption" model may also be applied to the α-hydroxy carboximides,[21] and it also predicts the elution order for other diastereomeric oxazolidones as well.[29]

Imide Hydrolysis and Transesterification. With a general method for the preparation of enantiomerically pure α-hydrazido carboximides in hand, attention was directed to the development of methods appropriate to the mild hydrolysis and alcoholysis of the hydrazide adducts (eq 9). At the outset, it was unclear how difficult this would be to achieve for a broad range of substrates. Although the exocyclic imide carbonyl is electronically activated by the α-heteroatom substituent, in the present case that substituent is also sterically demanding. From previous studies in these laboratories, it was known that the reactivity of the exocyclic imide carbonyl moiety toward nucleophilic attack is suppressed with increasing steric demands of the exocyclic acyl substituent. In such instances, competing attack of the nucleophile at the endocyclic auxiliary carbonyl function can dominate, resulting in the preferential formation of oxazolidone ring cleavage products (eq 10).

In order to compare the effectiveness of several reagents that had previously been used to effect carboximide hydrolysis or transesterification, four prototype hydrazido imides were studied. Hydrazide 4c (R=CH_2Ph) was chosen to represent a conventional substrate, while the isovalerate (4e, R=$CHMe_2$) and *tert*-butylacetate (4f, R=CMe_3) derivatives were chosen to test the steric limitations regarding the positional selectivity of these reagents. Finally, the phenylacetate derivative (4d, R=Ph) provided a sensitive test of the potential for racemization which might occur during these processes.



For this study, only enantiomerically pure (2*S*:2*R* > 200:1) imide samples were employed so that even minor amounts of racemization could be detected with high precision by subsequent capillary gas chromatographic analysis of the derived α-amino methyl ester (+)-MTA amides (*vide infra*). The results of this study reveal several interesting trends (Table 3). For the conventional substrate 4c (Entries A-C), all three methods examined, hydrolysis, methanolysis, and benzyl ester transesterification,[19] provided the acid (ester) derivative, 8c, 9c, and 6c, respectively, in good to excellent yield with no detectable racemization, along with a corresponding recovery of the chiral auxiliary. However, varying amounts of racemization were observed for the phenylacetate derivative 4d depending upon the reagent employed (Entries D-F). The preferred method for removing the chiral auxiliary in this

case proved to be LiOH hydrolysis, which provided the corresponding acid in good yield (84%) with minimal (≤2%) racemization. On the other hand, magnesium methoxide methanolysis afforded the corresponding methyl ester **9d** in 93% ee, while the benzyl ester **6d** obtained following treatment with LiOBn was almost totally racemic. A comparison of Entries G and H, and Entries I and J reveals the substantially improved exocyclic carbonyl positional selectivity displayed by LiOBn as compared to both LiOH and BrMgOMe for imide deacylation reactions when the steric interactions in the substrate become more severe. These results are in accord with prior precedent established in this laboratory. Although the yield of the isovalerate benzyl ester **6e** obtained with LiOBn was still very good (82%) (Entry H), the *tert*-butylacetate derivative **4f** (Entry J), suffers from an elevation of the undesired mode of cleavage (eq 10) resulting in significantly reduced yield (51%) of the desired product **6f**. *However, even in this extreme case, excellent exocyclic carbonyl cleavage regioselectivity could be restored with LiOOH*, which afforded the desired acid **8f** in 91% yield (>99% ee) along with a 91% recovered yield of the oxazolidone chiral auxiliary **2** (Entry K). It should be noted that in none of the transesterification and hydrolysis experiments conducted on the sterically hindered substrates **4e** and **4f** was any racemization detected (Entries H-K).

Table 3. Hydrolysis & Transesterification of Hydrazide Adducts (eq 9).

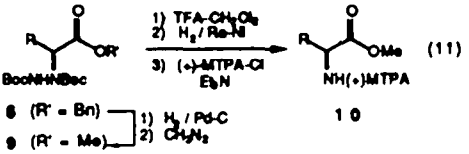
Entry	Compnd.	Reagent	Conditions[a]	Product	Yield, %[b]	ee, %[c]
A	**4c** R=Bn	LiOH	0 °C; 3 h	**8c**[d]	82[d]	> 99
B	**4c**	BrMgOMe	0 °C; 0.5 h	**9c**	89	> 99
C	**4c**	LiOBn	0 °C; 2 h	**6c**	96	> 99
D	**4d** R=Ph	LiOH	0 °C; 2 h	**8d**[d]	84	98
E	**4d**	BrMgOMe	0 °C; 1.5 h	**9d**	71	93
F	**4d**	LiOBn	0 °C; 4.8 h	**6d**	89	22
G	**4e** R=i-Pr	BrMgOMe	0 °C; 22 h	**9e**	12	...
H	**4e**	LiOBn	0 °C; 15.5 h	**6e**	82	> 99
I	**4f** R=t-Bu	LiOH	0 °C; 16 h	**8f**[d]	16	> 99
J	**4f**	LiOBn	0 °C; 50 h	**6f**	51	> 99
K	**4f**	LiOOH	0 °C; 3.2 h	**8f**[d]	91	> 99

[a] LiOH hydrolyses conducted in 2:1 THF-HOH with 2.3 equiv of LiOH (substrate conc. 0.17 M). Methanolyses were conducted with 2.0 equiv of MeOMgBr in MeOH (substrate conc. 0.04 M). Benzyl ester transesterifications were conducted with 2.0 equiv of LiOBn/ 1.0 equiv of HOBn in THF (substrate conc. 0.14 M). Peroxide-mediated hydrolyses were performed with 2.0 equiv of LiOH/ 4.0 equiv of HOOH in 3:1 THF-HOH (substrate conc. 0.05 M). [b] Yields quoted are for the overall conversion to **8**. [c] The ee values were determined by capillary GLC of the derived MTPA amides. [d] Carboxylic acids **8** were characterized as their methyl esters **9**.

The unparalleled reactivity and exocyclic carbonyl regioselectivity displayed by LiOOH in carboximide hydrolysis (Entry K) has been found to be quite general, and as a consequence, it has proven to be the reagent of choice for removal of these chiral auxiliaries from sterically demanding carboximide substrates. These results have been discussed in some detail elsewhere.[30]

α-Amino Acid Synthesis and Optical Purity Assay.

Having established that these chiral imide enolates could be employed in a general route for the preparation of enantiomerically pure N-protected α-hydrazino esters and acids, a practical protocol for the conversion of these substrates to α-amino acid derivatives was developed. Ideally the preferred mode of degradation might involve the direct N-N bond cleavage of the urethane-protected hydrazine to afford the N-Boc α-amino acids (esters), since these products would be convenient and versatile, N-protected α-amino acid synthons. However, in earlier studies conducted in these laboratories, attempts to effect this transformation on the diacyl hydrazides *via* Raney nickel hydrogenolysis, or dissolving-metal reduction proved unsuccessful.[31] However, an alternative method consisting of prior removal of the Boc groups followed by hydrogenolysis of the resulting hydrazino esters over Raney nickel did provide a useful route to the desired α-amino products.[32] The overall process was combined with an acylation step with (+) MTPA chloride[33] (eq 11). Diastereomer analysis of the resulting (+)-MTPA amide derivatives **10** by capillary GLC provided a sensitive assay of the stereochemical fidelity of the entire sequence (*vide infra*). The representative substrates were first converted to the corresponding methyl esters **9**. In the case of the benzyl esters **6**, this was achieved in quantitative yield *via* hydrogenolysis over 5% Pd-C (1 atm H_2, EtOAc, 25 °C) followed by diazomethane treatment.



(11)

The remaining steps in the sequence are illustrated by the following representative example (Table 4, Entry A). Hydrazido ester **6c** (R=CH_2Ph) was deprotected to the free hydrazine and the resulting solution was directly hydrogenated over Raney nickel catalyst (500 psi of H_2, 4 h, 25 °C).

Table 4. Reduction and Acylation of α-Hydrazido Esters (eq 11).

Entry	Hydrazide	(R)	H_2 time (h)	Product	Yield %	Ratio[a] 2(S) : 2(R)
A	**6c**	CH_2Ph	4	**10c**	94	>200 : 1
B	**9d**	Ph	4	**10d**	99	99 : 1
C	**6e**	$CHMe_2$	16	**10e**	83	>200 : 1
D	**6f**	CMe_3	16	**10f**	89	>200 : 1

[a] Determined by capillary GLC of the product(+)-MTPA amides **10**.

The unpurified α-amino ester, obtained after filtration through Celite and solvent removal, was acylated with (+)-MTPA chloride to afford the (+)-MTPA amide **10c** in 94% overall yield for the three steps. This material was found to be identical to the (+)-MTPA amide derived from authentic L-phenylalanine, thereby establishing the 2(*S*) absolute configuration in the synthetic phenylalanine intermediate. Analysis by capillary GLC revealed the ratio of 2(*S*):2(*R*) diastereomers to be >200:1. The additional

examples provided in Table 4 were subjected to the identical reaction sequence, differing only in the longer Raney nickel hydrogenolysis time (16 h) employed for the hindered substrates **6e**, and **6f** (Entries C and D). From the tabulated data, it is apparent that a wide variety of α-amino acids can be obtained in this fashion in good yield with insignificant racemization.[34]

In conclusion, the electrophilic amination of chiral imide enolates with DBAD provides an expedient approach to the asymmetric synthesis of both α-hydrazino and α-amino acid derivatives. A wide range of target structures of predictable absolute configuration are accessible in high enantiomeric purity, and excellent overall yield. This includes classes of α-amino and hydrazino acid derivatives such as aryl and *tert*-alkyl glycines and their *N*-amino congeners which are not readily accessible by complementary methods. This approach to the electrophilic amination of carboxylic acid enolate synthons is highly complementary, although not quite as efficient, as the electrophilic azidation of these same enolate systems recently reported from this laboratory.[24] In view of the efficiency with which the azidation process may now be carried out, the present methodology should be principally exploited within the context of asymmetric α-hydrazino acid synthesis.

Experimental Section

General. Di-*tert*-butyl azo-dicarboxylate (1) (DBAD) was purchased from Fluka AG and used as received. The imides **3** were prepared as previously described from the corresponding acid chlorides or mixed pivalic acid anhydrides and (4*S*)-4-Phenylmethyl-2-oxazolidinone (2) (XpH).[35] Lithium diisopropylamide (LDA) was generated *in situ* by treating dry diisopropylamine (0.38 M in THF) with 0.92 equiv of *n*-butyllithium (1.6 M in hexane) at -78 °C for 30 min. High pressure Raney Ni hydrogenolyses were performed in a magnetically stirred, glass-lined, stainless-steel autoclave. Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh). Solvent gradients for medium pressure preparative chromatography (MPLC) were constructed with a simple two-chamber apparatus[36] which supplied, by gravity feed, a single high-capacity pump. Michel-Miller columns dry-packed with 230-400 mesh silica gel were used in conjunction with this apparatus.

(4*S*)-3-(1-oxo-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (3b, R = $CH_2CH{=}CH_2$). To a mechanically stirred solution of 5.61 mL (5.61 g, 55.0 mmol, 1.1 equiv) of 4-pentenoic acid and 9.21 mL (6.68 g, 66.7 mmol, 1.33 equiv) of triethylamine (freshly distilled from CaH_2 under N_2) in 100 mL of dry THF, cooled to -78 °C under N_2, was added 7.08 mL (6.93 g, 57.5 mmol, 1.15 equiv) of pivaloyl chloride. The mixture was warmed to 0 °C for 60 min and then recooled to -78 °C. A solution of 8.86 g (50.0 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) and 15 mg of triphenylmethane (indicator) in 90 mL of dry THF, stirred at -30 °C to -45 °C under N_2, was treated dropwise with *n*-butyllithium (2.48 M in hexane) until an orange color persisted (20.2 mL, 1.00 equiv required). The resulting solution was cooled to -78 °C and then added, via rapid cannulation, to the above stirred mixture containing the mixed anhydride. The residual metalated oxazolidone was rinsed in with two 10-mL portions of dry THF and the resulting mixture was stirred at -78 °C for 30 min. After warming to 0 °C, the mixture was partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The CH_2Cl_2 phase washed with 5% aqueous $NaHCO_3$ followed by half-saturated aqueous NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residual oil was chromatographed on two size D Michel-Miller columns (660 g of silica gel) eluting with 3: 1 hexane-EtOAc. Mixed fractions (~2 g) were rechromatographed as described above to give a baseline separation of **3b** as a colorless, viscous oil (11.5 g) that was homogeneous on TLC: R_f 0.27 (silica, 3: 1 hexane-EtOAc). Kugelrohr distillation (150 °C/ 8 millitorr) yielded 11.4 g (87%) of pure material: IR (neat) 3065, 3025, 2975, 2920, 1782, 1702, 1387, 1352, 1210 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37-7.19 (m, 5H, C_6H_5), 5.884 (ddt, J_{cis} = 10.3 Hz, J_{trans} = 17.0 Hz, J_{allyl} = 6.5 Hz, 1H, $H_2C{=}CHCH_2$), 5.108 (dm, J_{trans} = 17.0 Hz, 1H, $H_cC{=}CHCH_2$), 5.032 (dm, J_{cis} = 10.3 Hz, 1H, $H_tC{=}CHCH_2$), 4.716-4.622 (sym m, 1H, CH_2CHN), 4.227-4.123 (m, 2H, CH_2O), 3.288 (dd, J = 3.3, 13.4 Hz, 1H, $CHHC_6H_5$), 3.169-2.935 (AB quartet of triplets, ν_A = 3.091, ν_B = 3.011, J_{AB} = 17.3 Hz, J_t = 7.4 Hz, 2H, $CHHC{=}O$), 2.762 (dd, J = 9.6, 13.4 Hz, 1H, $CHHC_6H_5$), 2.502-2.411 (m, 2H, $H_2C{=}CHCH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.44, 153.30, 136.69, 135.35, 129.31, 128.85, 127.24, 115.51, 66.19, 55.09, 38.02, 34.80, 28.21; $[\alpha]_D^{25}$ +62.0° (*c* = 1.13, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.57; H, 6.59.

(4*S*)-3-(1-oxo-3-phenylpropyl)-4-(phenylmethyl)-2-oxazolidinone (3c, R = $CH_2C_6H_5$). A solution of 22.55 g (127.3 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) and 50 mg of triphenylmethane (indicator) in 250 mL of dry THF, stirred at -78 °C under N_2, was treated dropwise with *n*-butyllithium (1.55 M in hexane) until an orange color persisted (82 mL, 1.00 equiv required); the solution being kept at -65 to -78 °C during the addition. After recooling to -78 °, the solution was treated with 21.0 mL (23.8, 141 mmol, 1.10 equiv) of dihydrocinnamoyl chloride over a 2-min period. The resulting mixture was warmed to 0 °C, treated with 100 mL of saturated aqueous $NaHCO_3$, and stirred at 20 °C for 30 min. The mixture was extracted with three portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined and successively washed with 5% aqueous Na_2CO_3 and saturated aqueous NaCl, dried ($MgSO_4$), and evaporated *in vacuo* to afford an off-white solid. This material was recrystallized from 450 mL of 2: 1 hexane-EtOAc to yield 36.4 g (92%) of glistening white needles: TLC R_f 0.27 (silica, 3: 1 hexane-EtOAc); mp 109-109.5 °C; IR ($CHCl_3$)

1780, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 10H, aromatics), 4.700-4.622 (sym m, 1H, CH_2CHN), 4.209-4.126 (m, 2H, CH_2O), 3.382-3.187 (m, 3H, $CH_2C{=}O$ and 4-$CHHC_6H_5$), 3.102-2.952 (m, 2H, $CH_2CH_2C{=}O$), 2.751 (dd, J = 9.5, 13.4 Hz, 1H, 4-$CHHC_6H_5$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.41, 153.42, 140.73, 135.57, 129.57, 129.05, 128.77, 128.60, 127.43, 126.40, 66.19, 55.25, 38.05, 37.27, 30.60; $[\alpha]_D^{25}$ +78.6° (*c* = 1.00, CH_2Cl_2). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.75; H, 6.20. Found: C, 73.70; H, 6.21.

(4*S*)-3-(phenylacetyl)-4-(phenylmethyl)-2-oxazolidinone (3d, R = C_6H_5). A solution of 12.4 g (70.0 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) and 25 mg of triphenylmethane (indicator) in 130 mL of dry THF, stirred at -78 °C under N_2, was treated dropwise with *n*-butyllithium (2.55 M in hexane) until an orange color persisted (27.5 mL, 1.00 equiv required); the solution being kept at -65 to -78 °C during the addition. After recooling to -78 °C, the solution was treated with 10.0 mL (11.5 g, 74.1 mmol, 1.06 equiv) of phenylacetyl chloride (98%) over a 2-min period. The resulting mixture was warmed to 25 °C, treated with 100 mL of saturated aqueous $NaHCO_3$, and stirred at 25 °C for 30 min. The mixture was extracted with three portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with 5% aqueous Na_2CO_3, washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residual yellow oil was triturated with three portions of Et_2O to afford, after thorough air drying, 8.73 g (42%) of 3d as a cream-colored solid found by TLC to contain a trace of XpH. The triturate liquors were combined and evaporated *in vacuo*. The residual yellow oil (11.1 g) was chromatographed on two size D Michel-Miller columns (660 g of silica gel) eluting with 3: 1 hexane-EtOAc to yield an additional 7.05 (34%) of 3d, found by TLC (hexane-EtOAc (65: 35)) to contain a trace faster moving impurity. The two lots were combined and recrystallized from Et_2O-hexane to afford 11.6 g of 3d (white needles) that was homogeneous on TLC: R_f 0.54 (silica, 1: 1 hexane-EtOAc); mp 71.5-72.5 °C. IR ($CHCl_3$) 3030, 1783, 1700, 1498, 1454, 1385, 1362, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.12 (m, 10H, aromatics), 4.719-4.641 (sym m, 1H, CH_2CHN), 4.388-4.294 (AB quartet, ν_A = 4.343, ν_B = 4.277, J_{AB} = 15.7 Hz, 2H, $CH_2C{=}O$), 4.21-4.15 (m, 2H, CH_2O), 3.275 (dd, J = 3.2, 13.4 Hz, 1H, 4-$CHHC_6H_5$), 2.756 (dd, J = 9.5 13.4 Hz, 1H, 4-$CHHC_6H_5$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.93, 153.19, 135.01, 133.47, 129.61, 129.24, 128.71, 128.37, 127.09, 127.03, 65.90, 55.02, 41.33, 37.48; $[\alpha]_D^{22}$ +72.4° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80. Found: C, 73.02; H, 5.72.

(4*S*)-3-(3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (3e, R = $CH(CH_3)_2$). A solution of 8.86 g (50.0 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) and 15 mg of triphenylmethane (indicator) in 90 mL of dry THF, stirred at -50 °C under N_2, was treated dropwise with *n*-butyllithium (~2.5 M in hexane) until an orange color persisted (19.9 mL, 1.00 equiv required); the solution warming to -30 °C during the addition. After recooling to -78 °C, the solution was treated with 6.71 mL (6.64 g, 55.0 mmol, 1.10 equiv) of redistilled isovaleryl chloride in one portion. The resulting solution was stirred at -78 °C for 15 min, warmed to 0 °C, and treated with 100 mL of saturated aqueous $NaHCO_3$. The mixture was stirred vigorously at 20 °C for 45 min, and was then partitioned between CH_2Cl_2 and H_2O containing 15 mL of 10% aqueous Na_2CO_3. The aqueous phase was extracted with three additional portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated *in vacuo* to give 13.5 g of a pale-yellow oil. This material was crystallized from Et_2O-hexane to yield, in three crops, 12.0 g (92%) of 3e as fine white needles: TLC R_f 0.40 (silica, 7: 3 hexane-EtOAc); mp 50.0-51.0 °C; IR ($CHCl_3$) 3030, 2962, 2870, 1782, 1698, 1390, 1385, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.21 (m, 5H, C_6H_5), 4.725-4.646 (sym m, 1H, CH_2CHN), 4.225-4.133 (m, 2H, CH_2O), 3.316 (dd, J = 3.3, 13.3 Hz, 1H, $CHHC_6H_5$), 2.936-2.738 (8-line AB portion of ABX system, ν_A = 2.891, ν_B = 2.784, J_{AB} = 16.2 Hz, J_{AX} = 6.7 Hz, J_{BX} = 6.9 Hz, $CH_2C{=}O$) and 2.752 (dd, J = 9.7 13.3 Hz, $CHHC_6H_5$) (3H total), 2.225 (sym 9-line m, J = 6.7 Hz, 1H, $CH(CH_3)_2$), 1.025 (d, J = 6.7 Hz) and 1.009 (d, J = 6.7 Hz) (6H total); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.52, 153.30, 135.34, 129.29, 128.81, 127.20, 66.01, 55.02, 43.87, 37.93, 24.96, 22.42, 22.31; $[\alpha]_D^{25}$ +55.8° (*c* = 1.01, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.87; H, 7.30.

(4*S*)-3-(3,3-dimethyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (3f, R = $C(CH_3)_3$). A solution of 6.44 g (36.3 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) in 70 mL of dry THF, stirred at -78 °C under N_2, was treated dropwise with 23.1mL (1.0 equiv) of *n*-butyllithium (1.56 M in hexane) over a 5-min period. The solution was stirred at -78 °C for 15 min, and then treated dropwise with 5.50 mL (5.33 g, 39.6 mmol, 1.09 equiv) of *t*-butylacetyl chloride. After stirring at -78 °C for 20 min, the solution was warmed to 25 °C over a 1-h period and treated with 10 mL of saturated aqueous NH_4Cl. The THF was evaporated *in vacuo*. The aqueous residue was extracted with three 80-mL portions of Et_2O. The Et_2O extracts were combined, washed with 1 N NaOH, washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated *in vacuo*. The residual white solid was recrystallized from Et_2O to yield, in two crops, 9.23 g (92%) of 3f as fine white needles: mp 112.5-113.5 °C; IR ($CHCl_3$) 3020, 2960, 2870, 1780, 1690, 1385, 1362, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H, C_6H_5), 4.738-4.695 (sym m, 1H, CH_2CHN), 4.192-4.122 (m, 2H, CH_2O), 3.350 (dd, J = 3.3, 13.3 Hz, 1H, $CHHC_6H_5$), 3.023-2.836 (AB quartet, ν_A = 2.994, ν_B = 2.866, J_{AB} = 14.9 Hz, 2H, $CH_2C{=}O$), 2.713 (dd, J = 10.0, 13.3 Hz, 1H, $CHHC_6H_5$), 1.096 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.79, 153.39, 135.43, 129.32, 128.84, 127.20, 65.73, 55.25, 46.08, 38.01, 31.32, 29.53; $[\alpha]_D^{22}$ +42.5° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69. Found: C, 69.98; H, 7.75.

(4*S*)-3-(1,5-dioxo-5-methoxypentyl)-4-(phenylmethyl)-2-oxazolidinone (3g, R = $CH_2CH_2CO_2Me$). A solution of 8.86 g (50.0 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) and 15 mg of triphenylmethane (indicator) in 90 mL of dry THF, stirred at -50 °C under N_2, was treated dropwise with *n*-butyllithium (~2.5 M in hexane) until an orange color persisted (19.9 mL, 1.00 equiv required); the solution warming to -30 °C during the addition. After recooling to -78 °C, the solution was treated with 7.60 mL (9.05, 55.0 mmol, 1.10 equiv) of methyl 4-(chloroformyl)butyrate in one portion. The resulting solution was stirred at -78 °C for 15 min, warmed to 0 °C, and treated with 100 mL of saturated aqueous $NaHCO_3$. The mixture was stirred vigorously at 20 °C for 45 min, and was then partitioned between CH_2Cl_2 and H_2O containing 15 mL of 10% aqueous Na_2CO_3. The aqueous phase was extracted with three additional portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated *in vacuo* to give 15.9 g of a pale-yellow oil which solidified on standing. One recrystallization from hexane-EtOAc yielded 10.8 g (71%) of white solid (first crop) that was homogeneous on TLC: R_f 0.23 (silica, CH_2Cl_2-hexane-CH_3CN (70: 30: 5)); mp 72.5-74.0 °C; IR ($CHCl_3$) 3030, 3020, 2955, 1782, 1732, 1700, 1385, 1355 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5H, C_6H_5), 4.718-4.624 (sym m, 1H, CH_2CHN), 4.250-4.142 (m, 2H, CH_2O), 3.690 (s, 3H, CO_2CH_3), 3.300 (dd, *J* = 3.3, 13.3 Hz, 1H, $CHHC_6H_5$), 3.107-2.895 (sym m, 2H, CH_2CH_2CON), 2.771 (dd, *J* = 9.6, 13.3 Hz, 1H, $CHHC_6H_5$), 2.443 (t, *J* = 7.3 Hz, 2H, $CH_2CO_2CH_3$, 2.094-1.640 (m, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.07, 172.25, 153.22, 135.18, 129.21, 128.73, 127.13, 66.13, 54.92, 51.29, 37.79, 34.51, 32.91, 19.38; $[\alpha]_D^{22}$ +51.0° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27. Found: C, 62.88; H, 6.36.

(4*S*)-3-(3-methyl-1-oxo-2-butenyl)-4-(phenylmethyl)-2-oxazolidinone (3h). A solution of 8.93 g (50.4 mmol, 1.00 equiv) of (4*S*)-(phenylmethyl)-2-oxazolidone (2) (XpH) in 100 mL of dry THF, stirred at -78 °C under N_2, was treated dropwise with 20.9 mL (53.9 mmol, *n*-butyllithium (2.58 M in hexane) over a 5-min period. The solution was stirred at -78 °C for an additional 5 min, and then treated with 6.00 mL (6.39 g, 53.9 mmol, 1.07 equiv) of 3,3-dimethylacryloyl chloride (97%) in one portion. The resulting solution was stirred at -78 °C for 5 min, warmed to 25 °C, and treated with 5 mL of saturated aqueous NH_4Cl. The THF was evaporated *in vacuo* , and the residue was partitioned between 300 mL of 1:1 CH_2Cl_2-hexane and 100 mL of saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated *in vacuo* to yield 13.1 g of white solid. This material was recrystallized from hexane-EtOAc to yield, in two crops, 11.5 g (88%) of **3h** as fine white needles: TLC R_f 0.60 (silica, 1:1 hexane-EtOAc); mp 79.5-80.5 °C; IR ($CHCl_3$) 3020, 2920, 1772, 1677, 1630, 1385, 1360, 1350, 1257, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (m, 5H, C_6H_5), 6.966-6.950 (m, 1H, C=C<u>H</u>C=O), 4.762-4.684 (sym m, 1H, CH_2CHN), 4.213-4.118 (m, 2H, CH_2O), 3.347 (dd, *J* = 3.3, 13.3 Hz, 1H, $CHHC_6H_5$), 2.775 (dd, *J* = 9.7, 13.3 Hz, 1H, $CHHC_6H_5$), 2.250 (d, *J* = 1.2 Hz, 3H, CH_3C=CH), 2.016 (d, *J* = 1.2 Hz, 3H, CH_3C=CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.93, 159.24, 153.33, 135.56, 129.40, 128.84, 127.17, 115.79, 65.84, 55.14, 38.01, 28.00, 21.31; $[\alpha]_D^{22}$ +60.4° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61. Found: C, 69.56; H, 6.63.

General Procedure for the Formation of the Carboximide (Z) Lithium Enolates and Their Subsequent Reaction with Di-*t*-butyl Azodicarboxylate. To a freshly prepared solution of 1.05 mmol of lithium diisopropylamide in 3 mL of THF, stirred at -78 °C under N_2, was added via cannula a precooled (-78 °C) solution of 1.00 mmol of the imide, **3**, in 3 mL of THF. Residual **3** was rinsed in with two 1 mL portions of THF and stirring continued at -78 °C for 30 min. A precooled (-78 °C) solution of 265 mg (1.15 mmol) of DBAD in 6 mL of dry CH_2Cl_2 was added via cannula to the above enolate solution and after an additional 30-180 sec the reaction was quenched with 2.6 mmol of glacial acetic acid. The mixture was partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The aqueous phase was washed with three portions of CH_2Cl_2. The CH_2Cl_2 phases were combined, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. Diastereomeric ratios of the resulting unpurified product were obtained by HPLC analysis on a Waters, 8mm x 10 cm 5 micron silica gel Radial-Pak^R column (UV detection at 235 nm) eluting with either CH_2Cl_2-hexane-CH_3CN (70:30:5) (Solvent A) or CH_2Cl_2-hexane-CH_3CN (70:30:7.5) (Solvent B) (*vide infra*) at 2 mL/min. The unpurified product was purified by medium pressure chromatography (MPLC) on Michel-Miller columns (Ace Glass) packed with silica gel (Merck spectophotometer 230-400 mesh) with typical column loadings of 0.3 to 1 g of material per 100 g of adsorbent (see below for solvent):

(3(2*S*),4*S*)-3-(2-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (4a, R = CH_3) (Table I, Entry A). As described above, 233 mg (1.00 mmol) of **3a** (R = CH_3)[37] afforded 424 mg (92%) of **4a** (R = CH_3) as a colorless glass foam after purification by MPLC (50 g of silica gel; CH_2Cl_2-hexane-CH_3CN (70:30:7)). Recovery of **3a** : 13.2 mg (6%). Diastereomer analysis of the unpurified product (*vide supra*, solvent A) gave a 2(*S*) (t_r = 4.89 min): 2(*R*) (minor diastereomer, t_r = 6.24 min) ratio of 98:2. The purified product gave the same diastereomer ratio: IR ($CHCl_3$) 3400, 1788, 1747, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 329 °K) δ 7.35-7.19 (m, 5H, aromatics), 6.52 (br s, 1H, NH), 5.74 (br s, 1H, CHC=O), 4.63-4.56 (sym 8 line m, 1H, 4-H), 4.22-4.13 (m, 2H, OCH_2), 3.339 (dd, J_{vic} = 2.8 Hz, J_{gem} = 13.4 Hz, 1H, C<u>H</u>HPh), 2.754 (dd, J_{vic} = 9.9 Hz, J_{gem} = 13.4 Hz, 1H, CH<u>H</u>Ph), 1.482 (s, $OC(CH_3)_3$), 1.466 (s, $OC(CH_3)_3$) and 1.453 (s, $CHCH_3$)(21H total); $[\alpha]_D^{26}$ +37.7° (*c* = 1.05, $CHCl_3$). Anal. Calcd for $C_{23}H_{33}N_3O_7$: C, 59.60; H, 7.18. Found: C, 59.54; H, 7.13.

Preparation of the Minor Diastereomer (2(*R*)-4a, R = CH_3) Via Epimerization. A solution of 0.400 g (0.863 mmol) of 4a (R = CH_3) and 0.23 mL (0.21g; 1.83 mmol; 2.1 equiv) of 1,1,3,3-tetramethylguanidine in 9 mL of dry THF was refluxed under N_2 for 4.5 h. The solution as partitioned between aqueous pH 7 buffer and CH_2Cl_2. The aqueous phasewas washed with CH_2Cl_2 (x 2), and the organic phases were combined, dried ($MgSO_4$), and evaporated *in vacuo*. The unpurified product was purified by flash chromatography (45 g of silica gel, hexane-EtOAc (1:1)) to give 330 mg (82% recovery) of a colorless glass, assayed by HPLC (*vide supra*) to have a 2(*S*):2(*R*) ratio of 56:44. ^{1}H NMR (300 MHz, $CDCl_3$, 329 °K) integration of the low field diastereotopic benzylic protons afforded a 2(*S*):2(*R*) ratio of 54:46. Distinctive ^{1}H NMR signals attributed to the minor diastereomer (2(*R*)-4a) include the following: δ 4.71-4.62 (m, 1H, 4-H), 4.28-4.23 (low field half of AB m, OCHH), 3.223 dd, J_{vic} = 3.4 Hz, J_{gem} = 13.4 Hz, PhCHH), 2.788 (dd, J_{vic} = 9.2 Hz, J_{gem} = 13.5 Hz, PhCHH).

(3(2*S*),4*S*)-3-(2-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)-1-oxo-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (4b, R = $CH_2CH{=}CH_2$) (Table 1, Entry B). Following an exact scale up of the general procedure, 2.59 g (10.0 mmol) of 3b (R = $CH_2CH{=}CH_2$) gave 4.59 g (94%) of 4b (R = $CH_2CH{=}CH_2$) as a colorless glass foam after purification by MPLC (650 g of silica gel; Solvent A). HPLC analysis (*vide supra*, Solvent A) of the unpurified product gave a 2(*S*) (t_r = 5.79 min): 2(*R*) (t_r = 8.23 min) ratio of 98:2. HPLC analysis of the purified product gave a 2(*S*):2(*R*) ratio of >300:1 : IR (CH_2Cl_2) 3385, 1785, 1750, 1710 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.36-7.19 (m, 5H, aromatic), 6.52 (br s, 1H, NH), 5.932 (ddt, J_{cis} = 10.2 Hz, J_{trans} = 17.1 Hz, J_{allyl} = 6.9 Hz, 1H, C=CHCH$_2$), 5.88-5.80 (br m, 1H, CHC=O), 5.127 (dm, J = 17.1 Hz, 1H, H_cC=CHCH$_2$), 5.058 (dm, J = 10.2 Hz, 1H, H_tC=CHCH$_2$), 4.63-4.53 (sym m, 1H, 4-H), 4.154 (apparent d, J = 5.2 Hz, 2H, OCH$_2$), 3.335 (dd, J_{vic} = 3.0 Hz, J_{gem} = 13.3 Hz, 1H, CHHC$_6$H$_5$), 2.79- 2.52 (m, 3H, CHHC$_6$H$_5$ and C=CHCH$_2$)), 1.480 (s) and 1.471 (s) (18H, OC(CH$_3$)$_3$); $[\alpha]_D^{26}$ +48.6° (*c* = 1.03, $CHCl_3$). Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21. Found: C, 61.41; H, 7.26.

Later fractions gave 94 mg (1.9%) of the minor diastereomer 2(*R*)-4c (R = $CH_2CH{=}CH_2$) assayed by HPLC to have a 2(*R*):2(*S*) ratio of 99:1 : IR (CH_2Cl_2) 3385, 1785, 1755, 1710 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.35-7.16 (m, 5H, aromatic), 6.520 (br s, 1H, NH), 5.962 (ddt, J_{cis} = 10.1 Hz, J_{trans} = 17.1 Hz, J_{allyl} = 6.94 Hz, 1H, C=CHCH$_2$), 5.828 (apparent t, 1H, J = 6.7 Hz, CHC=O), 5.198 (dm, J = 17.1 Hz, 1H, H_cC=CHCH$_2$), 5.086 (dm, J = 10.1 Hz, 1H, H_tC=CHCH$_2$), 4.68-4.58 (sym m, 1H, 4-H), 4.23 (apparent t, J = 8.4 Hz, 1H, OCHH), 4.14 (dd, J = 3.3, 9.0 Hz, 1H, OCHH), 3.273 (dd, J_{vic} = 3.4 Hz, J_{gem} = 13.5 Hz, 1H, CHHC$_6$H$_5$), 2.76 -2.55 (m, 3H, CHHC$_6$H$_5$ and C=CHCH$_2$), 1.474 (s) and 1.451 (s) (18H, OC(CH$_3$)$_3$).

(3(2*S*),4*S*)-3-(2-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (4c, R = CH_2Ph) (Table 1, Entry C). Following a modification of the general procedure, a solution of 6.19 g (20.0 mmol) of 3c (R = $CH_2C_6H_5$) in 60 mL of THF was added via cannula over a 50 min period to a stirred, precooled (-78 °C) solution of 21.0 mmol of LDA in 20 mL of THF and 10 mL of hexane. Residual 3c was rinsed in with two 5 mL portions of THF and enolization continued at -78 °C for 30 min. The above precooled (-78 °C) solution of lithium enolate was added via cannula to a stirred, precooled (-78 °C) solution of 5.30 g (23.0 mmol) of DBAD in 120 mL of CH_2Cl_2 over a 9 min period. Residual enolate was rinsed in with two 10 mL portions of THF, and after an additional 60 sec the reaction was quenched with 3.0 mL (52 mmol) of glacial acetic acid. Following the standard workup (*vide supra*) and purification by MPLC (900 g of silica gel, Solvent A) 9.83 g (91%) of 2 (R = $CH_2C_6H_5$) was obtained as a colorless glass foam. HPLC analysis (*vide supra*, Solvent A) of the unpurified product gave a 2(*S*) (t_r = 7.07 min): 2(*R*) (t_r = 10.76) ratio of 97:3. HPLC analysis of the purified product gave a 2(*S*):2(*R*) ratio >400:1 : IR (CH_2Cl_2) 3390, 1785, 1750, 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 330 °K) δ 7.330-7.136 (m, 10H, aromatics), 6.50 (br s, 1H, NH), 6.15 (br s, 1H, CHC=O), 4.45-4.37 (sym m, 1H, 4-H), 4.008 (dd, J_{vic} = 2.8, J_{gem} = 8.9 Hz, 1H, OCHH), 3.832 (apparent t, J = 8.3 Hz, 1H, OCHH), 3.303 (dd, J_{vic} = 3.0 Hz, J_{gem} = 13.6 Hz, 1H, NCHCHHPh) 3.25-3.15 (AB m, 2H, PhCH$_2$CHC=O), 2.685 (dd, J_{vic} = 9.9 Hz, J_{gem} = 13.5 Hz, 1H, NCHCHHPh), 1.452 (s) and 1.444 (s) (18H, OC(CH$_3$)$_3$); $[\alpha]_D^{26}$ +84.4° (*c* = 1.01, $CHCl_3$). Anal. Calcd for $C_{29}H_{37}N_3O_7$: C, 64.55; H, 6.91. Found: C, 64.48; H, 6.90.

After several overlapping fractions (317 mg; 2.9%) there was obtained 254 mg (2.4%) of the minor diastereomer, 2(*R*)-4c (R = $CH_2C_6H_5$) which was found by HPLC (*vide supra*) to have a 2(*R*):2(*S*) ratio of 98:2 : IR (CH_2Cl_2) 3385, 1788, 1753, 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 329 °K) δ 7.34-7.08 (m, 10H, aromatics), 6.386 (br s, 1H, NH), 6.165 (br t, J = 6.8 Hz, 1H, CHC=O), 4.61-4.55 (m, 1H, 4-H), 4.205 (apparent t, J = 8.4 Hz, 1H, OCHH), 4.070 (dd, J_{vic} = 3.0 Hz, J_{gem} = 8.9 Hz, 1H, OCHH), 3.28- 3.13 (m, 3H, PhCH$_2$CHC=O and NCHCHHPh), 2.590 (dd, J_{vic} = 9.5 Hz, J_{gem} = 13.5 Hz), 1.409 (s, 18H, OC(CH$_3$)$_3$).

(3(2*S*),4*S*)-3-(2-(*N*,*N*'-bis-(*t*-butoxycarbonyl)hydrazino)phenylacetyl)-4-(phenylmethyl)-2-oxazolidinone (4d, R = Ph) (Table 1, Entry D). Following the general procedure, 295 mg (1.00 mmol) of 3d (R = Ph) afforded 503 mg (96%) of 4d (R = C_6H_5) as a colorless glass foam after purification by MPLC (170 g of silica gel, Solvent B). Diastereomer analysis of the unpurified product by HPLC (Solvent B, *vide supra*) gave a 2(*S*) (t_r = 5.66 min): 2(*R*) (t_r = 8.71 min) ratio of 97:3. HPLC analysis of the purified product gave a 2(*S*):2(*R*) ratio of >400:1 : IR

(CH_2Cl_2) 3400, 1788, 1750, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 329 °K) 7.38-7.22 (m, 10H, aromatics), 7.06 (s, 1H), 6.49 (br s, 1H), 4.65-4.57 (sym m, 1H, 4-H), 4.12-4.01 (m, 2H, OCH_2), 3.379 (br d, 1H, PhCHH), 2.848 (dd, J_{vic} = 9.7 Hz, J_{gem} = 13.3 Hz, 1H, PhCHH) 1.500 (s, 9H, $OC(CH_3)_3$), 1.191 (br s, 9H, $OC(CH_3)_3$); $[\alpha]_D^{26}$ +216° (*c* = 1.04, $CHCl_3$). Anal. Calcd for $C_{28}H_{35}N_3O_7$: C, 63.98; H, 6.71. Found: C, 64.07; H, 6.62.

Later fractions afforded 13 mg (2.4%) of the minor diastereomer 2(*R*)-4d (R = C_6H_5), shown by HPLC analysis to have a 2(*R*): 2(*S*) ratio of 97:3 : IR (CH_2Cl_2) 3405, 1785, 1750, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 330 °K) δ 7.43-7.22 (m, 8H, aromatics), 7.09-7.05 (m, 3H, 2 aromatics and NH or CHC=O), 6.50 (br s, 1H), 4.79-4.71 (sym m, 1H, 4-H), 4.190 (apparent t, J = 8.6 Hz, 1H, OCHH), 4.052 (dd, J_{vic} = 3.5 Hz, J_{gem} = 9.1 Hz, 1H, OCHH), 3.320 (dd, J_{vic} = 3.2 Hz, J_{gem} = 13.5 Hz, 1H, PhCHH), 2.590 (dd, J_{vic} = 9.7 Hz, J_{gem} = 13.2 Hz, 1H, PhCHH), 1.481 (s, 9H, $OC(CH_3)_3$), 1.194 (br s, 9H, $OC(CH_3)_3$).

(3(2*S*),4*S*)-3-(2-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (4e, R = *i*-Pr) (Table 1, Entry E). Following an exact scale up of the general procedure, 2.61 g (10.0 mmol) of 3e (R = *i*-Pr) gave 4.65 g (95%) of 4e (R = *i*-Pr) as a colorless glass foam after purification by MPLC (650 g of silica gel; Solvent A). HPLC analysis (*vide supra*, Solvent A) of the unpurified product gave a 2(*S*) (t_r = 5.77 min): 2(*R*) (t_r = 8.08 min) ratio of 98:2. HPLC analysis of the purified product gave a 2(*S*): 2(*R*) ratio >400: 1 : IR (CH_2Cl_2) 3390, 1785, 1750, 1708 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$; 331 °K) δ 7.35-7.19 (m, 5H, aromatics), 6.48 (br s, 1H, NH), 5.79 (br d, J = 8.2 Hz, 1H, CHC=O, 4.685-4.588 (m, 1H, 4-H), 4.192- 4.115 (m, 2H, OCH_2), 3.363 (br dd, J_{vic} = 3 Hz, J_{gem} = 13.5Hz, 1H, $CHHC_6H_5$), 2.718 (dd, J_{vic} = 9.9 Hz, J_{gem} = 13.5 Hz, 1H, $CHHC_6H_5$), 2.412-2.267 (m, 1H, $CH(CH_3)_2$), 1.478 (s) and 1.473 (s) (18H, $OC(CH_3)_3$), 1.099 (d, J = 6.7 Hz, 3H, $CHCH_3$), 1.000 (d, J = 6.9 Hz, 3H, $CHCH_3$); $[\alpha]_D^{26}$ +27.4° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{25}H_{37}N_3O_7$: C, 61.08; H, 7.59. Found: C, 60.90; H, 7.51.

Preparation of the minor diastereomer (2(*R*)-4e, R = *i*-Pr) via Epimerization. The protocol for carrying out the epimerization was the same as that described above for 4a, (R = Me). The reaction time was 19 h.

(3(2*S*),4*S*)-3-(2-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-3,3-dimethyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (4f, R = *t*-Bu) (Table 1, Entry F). Following a slightly modified (40 min enolization time) scale up of the general procedure, 2.75 g (10.0 mmol) of 3f (R = *t*-Bu) gave 4.83 g (96%) of 4f (R = *t*-Bu) as a colorless glass foam after purification by MPLC (*vide supra*, Solvent A). HPLC analysis (*vide supra*, Solvent A) of the unpurified product gave a 2(*S*) (t_r = 5.33 min): 2(*R*) (t_r = 7.73 min) ratio of 99.7:0.3. HPLC analysis of the purified product gave a 2(*S*):2(*R*) ratio >500:1 : IR (CH_2Cl_2) 3395, 1785, 1748, 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.34-7.20 (m, 5H, aromatics), very broad singlets at 6.45 and 6.07 (2H, NH and CHC=O), 4.71-4.61 (m, 1H, 4-H), 4.16-4.10 (m, 2H, OCH_2), 3.45-3.35 (unresolved m, 1H, $CHHC_6H_5$), 2.696 (dd, J_{vic} = 10.2 Hz, J_{gem} = 13.4 Hz, 1H, $CHHC_6H_5$), 1.491 (s) and 1.452 (s) (18H, $OC(CH_3)_3$), 1.116 (s, 9H, $CC(CH_3)_3$); $[\alpha]_D^{26}$ +13.4° (*c* = 1.01, $CHCl_3$). Anal.

(3(2*S*),4*S*)-3-(2-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-5-methoxy-1,5-dioxopentyl)-4-(phenylmethyl)-2-oxazolidinone (4g, R = $CH_2CH_2CO_2Me$) A solution of 305 mg (1.00 mmol, 1.00 equiv) of 3g in 3 ml of dry THF, stirred at -78 °C under N_2, was treated via rapid cannulation with a precooled (-78 °C) solution of 1.01 mmol of LDA (prepared as described above from 0.64 mL (1.01 mmol, 1.01 equiv) of *n*-butyllithium (1.58 M in hexane) and 0.15 mL (1.07 mmol) of diisopropyl amine in 3 mL of THF). Residual LDA was rinsed in with one 2-mL portion of THF, and the resulting solution was stirred at -78 °C for 5 min. To the above was added, via rapid cannulation, a precooled (-78 °C) solution of 265 mg (1.15 mmol, 1.15 equiv) of DBAD in 6 mL of CH_2Cl_2. After 40 sec the reaction was quenched with 0.15 mL (157 mg, 2.6 mmol) of glacial HOAc. The unpurified product obtained following the standard workup was purified by MPLC (106 g of silica gel; 2L linear gradient from Solvent A to CH_2Cl_2-hexane-CH_3CN (70: 30: 15)) to afford, in order of elution, 47.6 mg (16% recovery) of 3g followed by 267 mg (51% yield) of 4g as a colorless glass foam: IR ($CHCl_3$) 3385, 3060, 2973, 1785, 1750-1700 (br, max at 1735), 1480, 1393, 1369, 1353, 1235, 1197, 1173, 1152, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.36-7.17 (m, 5H, C_6H_5), 6.59 (br s, 1H, NH), 5.70 (br d, J = 8.6 Hz, 1H, CHC=O), 4.63-4.53 (sym m, 1H, CH_2CHN), 4.24-4.13 (m, 2H, CH_2O), 3.638 (s, 3H, CO_2CH_3), 3.30 (br d, J ~ 13.6 Hz, 1H, $CHHC_6H_5$), 2.88-2.73 (m, 2H, $CHHC_6H_5$ and $CHHCO_2CH_3$), 2.54 (ddd, 1H, J = 6.3, 9.7, 16.5 Hz, 1H, $CHHCO_2CH_3$), 2.29-1.97 (m, 2H, CH_2CH_2CHN), 1.475 (s, 18H, $OC(CH_3)_3$); $[\alpha]_D^{26}$ +46.9° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{26}H_{37}N_3O_9$: C, 58.31; H, 6.96. Found: C, 58.36; H, 7.09. This material was found to be homogeneous on HPLC: t_r 13.85 min (Solvent A), t_r 7.59 min (Solvent B). ^1H NMR analysis indicates a minimum diastereomeric purity of >95: 5 (*vide infra*).

Preparation of the minor diastereomer (2(*R*)-4g, R = $CH_2CH_2CO_2CH_3$) via Epimerization. The protocol for carrying out the epimerization was the same as that described above for 4a, (R = Me); the reaction time was 5 h.

(3(2*S*),4*S*)-3-(2-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-3-methyl-1-oxo-3-butenyl)-4-(phenylmethyl)-2-oxazolidinone (4h, R = C(=CH_2)Me and *E*- and *Z*-(4*S*)-3-(4-(*N*,*N'*-bis-(*t*-butoxycarbonyl)hydrazino)-3-methyl-1-oxo-2-butenyl)-4-(phenylmethyl)-2-oxazolidinone (7). Following an exact scale up of the general procedure, 2.59 g (10.0 mmol) of **4h** gave 2.25 g (47%) of **2S** (R = C(CH_3)=CH_2) as a colorless glass foam after purification by MPLC (650 g of silica gel; 6 L of Solvent A, 2 L linear gradient from Solvent A to CH_2Cl_2-hexane-CH_3CN (70: 30: 15), and finally 2 L of CH_2Cl_2-hexane-CH_3CN (70: 30: 15)). HPLC analysis (*vide supra*, Solvent A) of the unchromatographed product gave a 2(*S*) (t_r = 5.87 min): 2(*R*) (t_r =7.50 min) ratio of 98: 2. HPLC analysis of the purified product gave a 2(*S*): 2(*R*) ratio of >300: 1: IR (CH_2Cl_2) 3405, 1785, 1748, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 331 °K) δ 7.36-7.18 (m, 5H, aromatics), 6.64 (very broad s, 1H, NH), 6.262 (s, 1H, CHC=O), 5.019 (s, 1H, HHC=C), 4.696 (s, 1H, HHC=C), 4.70-4.56 (sym m, 1H, CH_2CHN), 4.20-4.13 (m ,2H, OCH_2), 3.298 (dd, J_{vic} = 3.0 Hz, J_{gem} = 13.7 Hz, 1H, CHHC$_6H_5$), 2.827 (dd, J_{vic} = 9.3 Hz, J_{gem} = 13.6 Hz, 1H, CHHC$_6H_5$), 2.002 (s, 3H, CH_3), 1.489 (s) and 1.445 (s) (18H, $OC(CH_3)_3$); $[\alpha]_D^{26}$ +209° (*c* = 1.04, $CHCl_3$). Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21. Found: C, 61.48; H, 7.13.

After several later fractions (149 mg, 3.0%) found by HPLC to be a 95: 5 mixture of 2(*S*) and 2(*R*) diastereomers, respectively, there was obtained 52 mg (1.1%) found by HPLC to be a 29: 71 mixture of 2(*S*)-**4h** and 2(*R*)-**4h**, respectively. ^1H NMR (250 MHz, $CDCl_3$, 331 °K) integration of this material gave a 2(*S*): 2(*R*) ratio of 30: 70. Distinctive signals attributed to the minor diastereomer (2(*R*)-**4h**) are: δ 6.208 (br s, CHC=O), 5.091 (s, HHC=C), 4.758 (s, HHC=C), 3.416 (dd, J_{vic} = 3.4 Hz, J_{gem} = 13.2 Hz, CHHC$_6H_5$), 2.036 (s, CH_3), 1.472 (s, $OC(CH_3)_3$).

Still later fractions yielded 2.24 g (42%) of the strongly UV absorbing 1,4-addition product **7** as a colorless glass foam. This material was found by HPLC and ^1H NMR to be a 6: 4 mixture of geometrical (E,Z) isomers: HPLC (Solvent B) t_r = 10.4, 11.8 min; TLC R_f 0.20 (silica, Solvent B); IR ($CHCl_3$) 3395 (br), 3063, 2980, 2935, 1780, 1745, 1713, 1685, 1643, 1480, 1455, 1393, 1385, 1368, 1350, 1173, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 330 °K) δ 7.34-7.17 (m, 5H, C_6H_5), 6.978 (q, J = 1.3 Hz, 0.4H, C=CH in minor isomer), 6.908 (q, J = 1.3 Hz, 0.4H, C=CH in major isomer), 4.76-4.65 (m, 1.8H, C=CH in minor isomer and CH_2CHN), 4.26-4.09 (m, 3.2H, CH_2NCO_2 in major isomer and CH_2O), 3.356 (dd, J = 3.4, 13.4 Hz) and 3.319 (dd, J = 3.4, 13.4 Hz) (1H total, CHHC$_6H_5$), 2.780 (dd, J = 9.5, 13.4 Hz) and 2.772 (dd, J = 9.5, 13.4 Hz) (1H total, CHHC$_6H_5$), 2.150 (d, J = 1.0 Hz, 1.8H, CH_3 in major isomer), 2.018 (d, J = 1.3 Hz, 1.2H, CH_3 in minor isomer), 1.478 (s), 1.472 (s), and 1.464 (s) (18H total, $OC(CH_3)_3$). Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21. Found: C, 61.35; H, 7.34.

General Procedure for the Magnesium Methoxide Methanolysis of Carboximides 4 To 4.0 mL of dry MeOH, cooled to 0 °C under N_2, was added dropwise 1.00 mmol of MeMgBr (0.315 mL of a 3.2 M solution in Et_2O). After stirring the above solution at 0 °C for 5 min, a solution of 0.50 mmol of the imide, **2**, in 4.0 mL in dry MeOH was added via cannula, residual **2** being rinsed in with two 2 mL-portions of dry MeOH. The above solution was stirred at 0 °C for an appropriate time (30-90 min, *vide infra*) and then quenched with 4 mL of pH 7 phosphate buffer. The mixture was partitioned between half-saturated aqueous NaCl/NH_4Cl and CH_2Cl_2. The aqueous phase was washed with CH_2Cl_2 (x 3). The CH_2Cl_2 phases were combined, dried ($MgSO_4$), and evaporated *in vacuo*. The residual unpurified product was purified by MPLC.

General Procedure for the Lithium Hydroxide Hydrolysis and Diazomethane Esterification of Carboximides 4. An ice cooled solution of 0.50 mmol of the imide, **2**, in 2.0 mL of THF was treated in one portion with a cold (0 °C) solution of 28 mg (1.2 mmol; 2.3 equiv) of LiOH in 1.0 mL of H_2O. The resulting two-phase mixture was stirred at 0 °C until the reaction was complete (*vide infra*) and was then worked up by one of the following methods:

Method A: The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20-30 mL) containing sufficient NaCl to break the emulsion. The aqueous phase was washed with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 phases were combined, dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the residue by MPLC afforded the chiral auxiliary, XpH. The aqueous phase was acidified with 1 N aqueous $NaHSO_4$ and extracted with CH_2Cl_2 (4 x 30 mL). The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo*. A CH_2Cl_2 solution of the residual unpurified acid was treated dropwise at 0 °C with ethereal diazomethane until a yellow color persisted. Following a standard workup (*vide infra*), the methyl ester was purified by MPLC.

Method B: The mixture was partitioned between 1 N aqueous $NaHSO_4$ and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (x 3), and the organic phases were combined, dried (Na_2SO_4), and evaporated *in vacuo*. A solution of the residue in CH_2Cl_2 (20 mL) was treated dropwise at 0 °C with ethereal CH_2N_2 until a yellow color persisted. The solution was decolorized with HOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by MPLC.

2*S*-(*N*,*N'*-Bis-(*t*-butoxycarbonyl)hydrazino)-3-phenyl-1-propanoic Acid, Methyl Ester (9c, R = CH_2Ph). Method A (Table 3, Entry A). Lithium Hydroxide hydrolysis (0 °C, 3 h; workup b) of 270 mg (0.500

mmol of 4c (R = CH_2Ph) afforded, after CH_2N_2 treatment, 161 mg (82%) of 9c (R = CH_2Ph) after purification by flash chromatography (10 g of silica gel; hexane-EtOAc (3:1)). The optical purity of this material was found by capillary gas chromatographic analysis of its derived (+)-MTPA amide, 10c (R = CH_2Ph), to be >99% ee (*vide infra*). The chiral auxiliary, XpH, was recovered in 85% yield by MPLC (50 g of silica gel; hexane-EtOAc (1:1)).

Method B (Table 3, Entry B). Magnesium methoxide methanolysis (0 °C, 30 min) of 270 mg (0.500 mmol) of 4c (R = CH_2Ph) afforded 176 mg (89%) of 9c (R = CH_2Ph) as a colorless, viscous oil after purification by MPLC (50 mg of silica gel; 2L linear gradient from hexane-EtOAc (9:1) to hexane-EtOAc (1:1)) : IR ($CHCl_3$) 3395, 1743, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 330 °K) δ 7.27-7.16 (m, 5H, aromatics), 6.240 (br s, 1H, NH), 5.00-4.95 (unresolved broad m, 1H, CHC=O), 3.656 (s, 3H, OCH_3), 3.169 (d, J = 7.2 Hz, 2H, CHC=O), 1.434 (s) and 1.421 (s) (18 H, $OC(CH_3)_3$); $[\alpha]_D^{22}$ -19.9° (*c* = 1.21, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}N_2O_6$: C, 60.90; H, 7.67. Found: C, 60.84; H, 7.76. The optical purity of the above material was found by capillary gas chromatographic analysis of its derived (+)-MTPA amide, 10c (R, = CH_2Ph), to be >99% ee (*vide infra*). Later fractions afforded 176 mg (89% recovery) of the chiral auxiliary, XpH.

2*S*-(*N*,*N'*-Bis-(*t*-butoxycarbonyl)hydrazino)phenylacetic Acid, Methyl Ester (9d, R = Ph) Method A.(Table 3, Entry D) Lithium hydroxide hydrolysis (0 °C, 120 min; workup b) of 263 mg (0.50 mmol) of 4d (R = Ph) afforded, after CH_2N_2 treatment, 160 mg (84%) of 9d (R = Ph) after purification by MPLC (50 g of silica gel; hexane-EtOAc (4:1)) : IR ($CHCl_3$) 3410, 1748, 1707 cm^{-1}; ^1H NMR (250 MHz; $CDCL_3$; 331 °K) δ 7.306 (s, 5H, aromatics), 6.40 (very broad s, 1H, NH), 5.95 (br s, 1H, CHC=O), 3.742 (s, 2H, OCH_2), 1.478 (s, 9H, $OC(CH_3)_3$), 1.193 (br s, 9H, $OC(CH_3)$; $[\alpha]_D^{22}$ +151.6° (*c* = 1.96, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.89; H, 7.42. Found: C, 60.17; H, 7.51. The optical purity of this material was found by capillary GLC analysis of its derived (+)-MTPA-amide, 10d, to be 98% ee.

Method B (Table 3, Entry E). Magnesium methoxide methanolysis (0 °C, 90 min) of 263 mg (0.50 mmol) of 4d (R = Ph) afforded 140 mg (71%) of 9d (R = Ph) after purification by MPLC. The optical purity of this material was found by capillary gas chromatographic analysis of its derived (+)-MPTA-amide, 10d (R = Ph), to be 93% ee (*vide infra*).

General Procedure for the Lithium Benzyloxide Transesterification[19] of Carboximides 4. To a cold (-78 °C) solution of 2.00 mmol of LiOBn (prepared as previously described from 310 μL (324 mg; 3.00 mmol) of redistilled benzyl alcohol and 2.00 mmol of *n*-butyl lithium (1.59 M in hexane)) in 6.0 mL of dry THF was added via cannula a precooled (-78 °C) solution of 1.00 mmol of the imide 2 in 4.0 mL of THF. Residual imide was rinsed in with two 2 mL-portions of THF, and the resulting solution stirred at -50 °C for 2.0-50 h (*vide infra*) prior to quenching with 6 mL of aqueous pH 7 phosphate buffer. The mixture was partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with three portions of CH_2Cl_2 and the organic phases were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The unpurified product was purified by MPLC:

2*S*-(*N*,*N'*-Bis-(*t*-butoxycarbonyl)hydrazino)-3-phenylpropanoic Acid, Benzyl Ester (6c, R = CH_2Ph) (Table 3, Entry C). As described above, lithium benzyloxide transesterification (-50 °C, 2.0 h) of 540 mg (1.00 mmol) of 4c (R = CH_2Ph) afforded 451 mg (96%) of 6c (R = CH_2Ph) as a colorless glass after purification by MPLC (50 g of silica gel; 0.5 L of hexane-EtOAc (9:1), 1.0 L linear gradient from hexane-EtOAc (9:1) to EtOAc, and finally EtOAc): IR ($CHCl_3$) 3395, 1743, 1713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.33-7.14 (m, 1OH, aromatics), 6.226 (br s, 1H, NH), 5.088 (s, 2H, $CHCH_2Ph$), 5.07-5.00 (unresolved m, 1H, CHC=O), 3.185 (d, J = 7.2 Hz, OCH_2Ph), 1.420 (s) and 1.399 (s) (18H, $OC(CH_3)_3$); $[\alpha]_D^{22}$ -4.16° (*c* = 1.99, $CHCl_3$). Anal. Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28. Found: C, 66.41; H, 7.18. The optical purity of the this material was found to be >99% ee by capillary GLC analysis of its derived (+)-MPTA-amide, 10c (R = CH_2Ph) (*vide infra*). Later fractions afforded 171 mg (96% recovery) of the

2*S*-(*N*,*N'*-Bis-(*t*-butoxycarbonyl)hydrazino)-3-methylbutanoic Acid, Benzyl Ester (6e, R = *i*-Pr) (Table 3, Entry H). In an exact scale up of the general lithium benzyloxide transesterification procedure (-50 °C, 15.5 h), 1.97 g (4.00 mmol) of 4e (R = *i*-Pr) gave 1.38 g (82%) of 6e (R = *i*-Pr) as a viscous oil after purification by MPLC (165 g of silica gel; 1 L of hexane-EtOAc (90:10), 1 L of hexane-EtOAc (75:25) and finally 1 L of EtOAc) : IR (Neat) 3335, 1742, 1713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.35-7.27 (m, 5H, aromatics), 6.354 (br s, 1H, NH), 5.152 (s, 2H, OCH_2), 4.534 (br d, J = 6.6 Hz, 1H, CHC=O), 2.36-2.22 (sym 6 line m, 1H, $CH(CH_3)_2$), 1.456 (s) and 1.431 (s) (18H, $OC(CH_3)_3$), 1.048 (d, J = 6.8, 3H, $CHCH_3$), 1.023 (d, J = 6.8 Hz, 3H, $CHCH_3$); $[\alpha]_D^{22}$ -7.03° (*c* = 1.89, $CHCl_3$). Anal. Calcd for $C_{22}H_{34}N_2O_6$: C, 62.54; H, 8.11. Found: C, 62.70; H, 8.12. The optical purity of the above material was found to be >99% ee by capillary gas chromatographic analysis of its derived (+)-MTPA-amide 10e (*vide infra*).

2(*S*)-(*N*,*N'*-bis(*t*-butoxycarbonyl)hydrazino)-3,3-dimethylbutanoic acid, methyl ester (9f, R = *t*-Bu). Method A.(Table 3, Entry K). A solution of 253 mg (0.500 mmol) of 4f in 7.5 mL of THF and 2.3 mL of H_2O, stirred at 0 °C under N_2, was treated with 0.20 mL (2.0 mmol, 4.0 equiv) of 31% H_2O_2 followed by 24 mg (1.0 mmol, 2.0 equiv) of LiOH (anhydrous powder). The resulting mixture was stirred at 0 °C for 3.25 h, and was then treated

with a solution of 280 mg (2.2 mmol) of Na_2SO_3 in 1.5 mL of H_2O. Following the addition of 5 mL of 0.5 N aqueous $NaHCO_3$, the THF was evaporated *in vacuo*. The aqueous residue was acidified with 1 N aqueous $NaHSO_4$ and extracted with four portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting solution (15 mL) was treated dropwise at 0 °C with ethereal diazomethane until a yellow color persisted. The solution was decolorized with glacial HOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on one size B Michel-Miller column (50 g of silica gel) eluting with 0.5 L of hexane-EtOAc (85: 15) followed by a 1L linear gradient from hexane-EtOAc (60: 40) to EtOAc. Early fractions yielded 165 mg (91%) of the ester, **9f**, as a white solid: IR ($CHCl_3$) 3385 (br), 1745, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 331 °K) δ 6.45 (br s, 1H, NH), 4.658 (s, 1H, CHC=O), 3.707 (s, 3H, OCH_3), 1.468 (s) and 1.462 (s) (18H, $OC(CH_3)_3$), 1.124 (s, 9H, $CHC(CH_3)_3$); $[\alpha]_D^{23}$ -15.4° (*c* = 1.03, $CHCl_3$); mp 76.5-77.5 °C. Anal. Calcd for $C_{17}H_{32}N_2O_6$: C, 56.65; H, 8.95. Found: C, 56.68; H, 9.01. The optical purity of the above material was found to be >99% ee by capillary gas chromatographic analysis of its derived (+)-MTPA-amide **10f** (*vide infra*). Later fractions afforded 14.6 mg (6.1%yield) of the β-hydroxyethyl amide ring opened product followed by 80.6 mg (91% recovery) of the chiral auxiliary, 2 (XpH).

Method B (Table 3, Entry I). This is a modification of the general LiOH hydrolysis procedure. A solution of 253 mg (0.500 mmol) of **4f** in 7.5 mL of THF and 2.5 mL of H_2O, stirred at 0 °C under N_2, was treated with 24 mg (1.0 mmol, 2.0 equiv) of LiOH (anhydrous powder). The resulting mixture was stirred at 0 °C for 16 h. Following the addition of 5 mL of 0.5 N aqueous $NaHCO_3$, the THF was evaporated *in vacuo*. The aqueous residue was acidified with 1 N aqueous $NaHSO_4$ and extracted with four portions of C_2HCl_2. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting solution (15 mL) was treated dropwise at 0 °C with ethereal diazomethane until a yellow color persisted. The solution was decolorized with glacial HOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed (MPLC) on one size B Michel-Miller column (50 g of silica gel) eluting with 0.5 L of hexane-EtOAc (90: 10) followed by a 1L linear gradient from hexane-EtOAc (60: 40) to EtOAc. Early fractions yielded 29.6 mg (16%) of the ester, **9f**, as a white solid. The optical purity of the above material was found to be >99% ee by capillary gas chromatographic analysis of its derived (+)-MTPA-amide **10f** (*vide infra*). Later fractions afforded 185.3 mg (76%yield) of the hydroxyethyl amide ring opened product.

2*S*-(*N*,*N'*-Bis-(*t*-butoxycarbonyl)hydrazino)-3,3-dimethylbutanoic Acid, Benzyl Ester (6f, R = *t*-Bu) (Table 3, Entry J). In an exact scale up of the general lithium benzyloxide transesterification procedure (-50 °C, 50 h), 2.75 g (5.44 mmol) of **4f** (R = *t*-Bu) gave 1.21 g (51%) of **6f** (R = *t*-Bu) as a viscous oil after purification by MPLC (in two portions on 165 g of silica gel; hexane-EtOAc (93:7)) : IR ($CHCl_3$) 3490, 1747, 1708 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 331 °K) δ 7.35-7.28 (m, 5H, aromatics), 6.39 (very br s, 1H, NH), 5.160 (s, 2H, OCH_2), 4.701 (br s, 1H, CHC=O), 1.454 (s) and 1.434 (s) (18H, $OC(CH_3)_3$), 1.119 (s, 9H, $CHC(CH_3)_3$); $[\alpha]_D^{22}$ -8.97° (*c* = 2.75, $CHCl_3$). Anal. Calcd for $C_{23}H_{36}N_2O_6$: C, 63.28; H, 8.31. Found: C, 63.38; H, 8.19. The optical purity of the this material was found to be >99% ee by capillary gas chromatographic analysis of its derived (+) MTPA-amide, **10f** (R = *t*-Bu) (*vide infra*).

General Procedure for the Deprotection, Hydrogenolysis and Acylation of the *N*,*N'*-Bis(*t*-butoxycarbonyl)-α-hydrazino Methyl Esters, 9: Assay for Optical Purity. A stirred solution of 0.100 mmol of the protected hydrazino ester **9** in 2.0 mL of CH_2Cl_2 was treated with 2.0 mL of trifluoroacetic acid (TFA) at 25 °C under N_2. After 30 min, the Raney Nickel[38] was added and the stirred mixture hydrogenated under 550 PSIG H_2 for 4-16 h (*vide infra*). The mixture was purged with N_2 and then filtered through Celite. The filter cake was washed with MeOH (x 4) and the filtrate evaporated *in vacuo*, residual TFA and MeOH being removed by azeotroping with toluene (x 3). The glassy green residue containing the α-amino ester was suspended in CH_2Cl_2 (3 mL/0.10 mmol) and acylated by treatment with 2.0 equiv of (+) MTPA-chloride [33] and 4.0 equiv of triethylamine at 25 °C. After stirring for 3 h at 25 °C, 2 mL of H_2O was added and stirring was resumed for 1 h additional. The mixture was diluted with CH_2Cl_2 and washed with 1 N HCl. The aqueous phase was back-extracted with CH_2Cl_2 (x 2). The CH_2Cl_2 phases were combined, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by careful flash chromatography such that no fractionation of diastereomers was effected. The diastereomeric purity of the resulting (+)-MTPA-amide, **10**, was determined by capillary GLC analysis on a 0.25 mm x 30 m DB-1 fused silica column (*vide infra*):

2*S*-((+)-α-Methoxy-α-trifluoromethylphenylacetylamino)-3-phenylpropionic Acid, Methyl Ester, 10c (R = CH_2Ph) (Table 4, Entry A). A sample (47.9 mg; 0.100 mmol) of **6c** (R = CH_2Ph), secured via LiOBn transesterification (*vide supra*), was converted to the corresponding methyl ester **9c** (R = CH_2Ph) by debenzylation (1 atm of H_2, 7 mg of 5% Pd/C, 1.5 mL of EtOAc, 3 h, 25 °C) and subsequent diazomethane treatment (CH_2Cl_2, 0 °C). Without purification, **9c** was subjected to the above deprotection, hydrogenolysis (4 h), and acylation ((+)-MTPA-chloride) [33] sequence. Purification by flash chromatography (6 g of silica gel; hexane-EtOAc (4:1)) afforded 37.7 mg (94%) of **10c** (R = CH_2Ph) as a white solid: IR ($CHCl_3$) 3415, 1747, 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.52-7.13 (m, 11H, aromatics and NH), 4.911 (ddd, *J* = 5.7, 6.7, 8.0 Hz, 1H, CHC=O), 3.734 (s, 3H, CO_2CH_3), 3.73-3.08 (AB m

and q at 3.215 (J_{HF} = 1.5 Hz), 5H, CH_2Ph and CF_3COCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.34, 165.96, 135.54, 132.09, 129.45, 129.15, 128.65, 128.45, 127.93, 127.24, 123.73 (q, J_{CF} = 290.2 Hz), 84.12 (q, J_{CF} = 26.1 Hz), 54.77, 53.16, 52.29, 37.72. Capillary GLC analysis (190 °C, 15 PSI) gave a 2(*S*)-**10c** (t_r = 7.04 min): 2(*R*)-**10c** (t_r = 6.64 min) ratio of 230:1. The above solid was recrystallized from acetone-hexane: mp 99.5-101 °C; $[\alpha]_D^{25}$ +6.77° (*c* = 1.00, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}F_3NO_4$: C, 60.75; H, 5.10. Found: C, 60.82; H, 5.22.

A sample of L-phenylalanine methyl ester hydrochloride (10.8 mg; 0.050 mmol) in CH_2Cl_2 (0.5 mL) was treated as described above with (+)-MTPA-chloride [33] (14.5 μL, 0.075 mmol, 1.5 equiv) and Et_3N (21 μL, 0.15 mmol, 3.0 equiv) for 2 h at 25 °C. Purification by flash chromatography afforded 18.6 mg (94%) of authentic **10c** (R = CH_2Ph), found by ^1H NMR and capillary GLC coinjection to be identical to the major diastereomer in the imide derived sample.
Acylation of L-phenylalanine methyl ester hydrochloride with (-)-MTPA-chloride[33] gave, after purification by flash chromotography, 19.0 mg (96%) of the (-)-MTPA-amide (R = CH_2Ph) as a colorless oil: ^1H NMR (250 MHz; $CDCl_3$) δ 7.40-7.13 (m, 8H, aromatics), 7.015 (br d, J = 8.3 Hz, 1H, NH), 6.91-6.87 (m, 2H, aromatics), 4.991 (ddd, J = 5.4, 7.0, 8.4 Hz, 1H, CHC=O), 3.757 (s, 3H, CO_2CH_3), 3.431 (q, J_{HF} = 1.6 Hz, 3H, CF_3COCH_3), 3.185-2.983 (8 line AB portion of ABX system, J_{AB} = 14.0 Hz, J_{AX} = 7.0 Hz, J_{BX} = 5.4 Hz, 2H, CH_2Ph). This material was shown by coinjection to have the same retention time on capillary GLC as the minor diastereomer, 2(*R*)-**10c** (R = CH_2Ph), in the imide derived sample.

2*S*-((+)-α-Methoxy-α-trifluoromethylphenylacetylamino)phenylacetic Acid, Methyl Ester, 10d (R = Ph) (Table 4, Entry B). A sample (38.4 mg; 0.10 mmol) of **9d** (R = Ph), secured via LiOH-hydrolysis/CH_2N_2-esterification (*vide supra*), was subjected to the above deprotection, hydrogenolysis (4 h) sequence. The unpurified amino ester was divided into two equal portions as a MeOH solution. Following solvent removal (*in vacuo*, toluene azeotrope) one portion was acylated as described above by treatment with 19.4 μL (0.10 mmol; 2.0 equiv) of (+)-MTPA-chloride[33] and 28 μL (0.20 mmol, 4.0 equiv) of triethylamine in 1.5 mL of CH_2Cl_2. The unpurified product was purified by flash chromatography (4 g of silica gel; hexane-EtOAc (85:15)) to afford 19.0 mg (99%) of **10d** (R = Ph) as a colorless, viscous oil : IR ($CHCl_3$) 3415, 1748, 1700 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) δ 7.771 (br d, J = 6.7 Hz, 1H, NH), 7.60-7.57 (m, 2H, aromatics), 7.45-7.34 (m, 8H, aromatics), 5.584 (d, J = 7.2 Hz, 1H, CHC=O), 3.733 (s, 3H, CO_2CH_3), 3.358 (q, J_{HF} = 1.3 Hz, CF_3COCH_3); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.68, 165.85, 135.68, 131.94, 129.54, 129.07, 128.77, 128.57, 128.03, 127.28, 123.76 (q, J_{CF} = 290.3 Hz), 84.14 (q, J_{CF} = 25.7 Hz), 56.60, 54.88, 52.78; $[\alpha]_D^{22}$ +80.9° (*c* = 0.90, $CHCl_3$); High Resolution MS. Calcd for $C_{19}H_{18}F_3NO_4$: m/e 381.11878. Found: m/e 381.11857. Capillary GLC diastereomer analysis (200 °C, 5 PSI) gave a 2(*S*)-**10d** (t_r = 10.65 min): 2(*R*)-**10d** (t_r = 9.8 min) ratio of 99:1.

The second portion of unpurified amino ester (*vide supra*) was acylated exactly as described above with (-)-MTPA-chloride[33] to afford 19.1 mg (99%) of the corresponding (-)-MTPA-amide (R = Ph) as a colorless glass: ^1H NMR (250 MHz; $CDCl_3$) δ 7.610 (br d, J = 6.5 Hz, 1H, NH), 7.41-7.25 (m, 10H, aromatics), 5.605 (d, J = 7.3 Hz, 1H, CHC=O), 3.753 (s, 1H, CO_2CH_3), 3.549 (q, J_{HF} = 1.6 Hz, 3H, CF_3COCH_3). This material was shown by coinjection with the above sample of **10d** (R = Ph) to have the same retention time on capillary GLC as the minor diastereomer, 2(*R*)-**10d**, in that sample.

2*S*-((+)-α-Methoxy-α-trifluoromethylphenylacetylamino)-3-methylbutanoic Acid, Methyl Ester, 10e (R = *i*-Pr) (Table 4, Entry C). A sample (135 mg; 0.319 mmol) of **6e** (R = *i*-Pr), secured via LiOBn transesterification (*vide supra*) was converted to the corresponding methyl ester **9e** by debenzylation (1 atm of H_2, 17 mg of 5% Pd/C, 5 mL of EtOAc, 3 h, 25 °C) and subsequent diazomethane treatment (CH_2Cl_2, 0 °C). Without purification, **9e** was subjected to the above deprotection (4 mL of CH_2Cl_2, 4 mL of TFA), hydrogenolysis (16 h), and acylation ((+)-MTPA-chloride)[33] sequence. Purification by flash chromatography (35 g of silica gel; hexane-EtOAc (85:15)) afforded 92.0 mg (83%) of **10e** (R = *i*-Pr) as a pale yellow oil: IR (Neat) 3430, 3350 (sh), 1746, 1705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.56-7.52 (m, 2H, aromatic), 7.46-7.37 (m, 4H, aromatic and NH), 4.597 (dd, J = 4.7, 9.1 Hz, 1H, CHC=O), 3.743 (s, 3H, CO_2CH_3), 3.387 (q, J_{HF} = 1.3 Hz, 3H, CF_3COCH_3), 2.281 (d of septets, J = 4.7, 6.9 Hz, 1H, $CH(CH_3)_2$), 0.994 (d, J = 6.9 Hz, 3H, $CH(CH_3)$), 0.947 (d, J = 6.9 Hz, 3H, $CH(CH_3)$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.70, 166.07, 131.97, 129.39, 128.46, 128.05, 123.85 (q, J_{CF} = 290.2 Hz), 84.29 (q, J_{CF} = 25.9 Hz), 57.25, 54.83, 52.01, 31.14, 18.90, 17.59; $[\alpha]_D^{25}$ -23.8° (*c* = 0.92, $CHCl_3$). High Resolution MS. Calcd for $C_{16}H_{20}F_3NO_4$: m/e 347.13443. Found: m/e 347.13369. Capillary GLC diastereomer ysis (150 °C, 7 PSI) gave a 2(*S*)-**10e** (t_r = 13.59 min): 2(*R*)-**10e** (t_r = 13.03 min) ratio of >500:1.

A sample of L-valine methyl ester hydrochloride (16.8 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was treated as described above with (+)-MTPA-Chloride[33] (29.1 μL, 37.9 mg, 0.15 mmol) and Et_3N (41.8 μL, 30.4 mg, 0.30 mmol) for 3 h at 25 °C. Purification by flash chromatography afforded 34.9 mg (100%) of **10e** (R = *i*-Pr) found by ^1H NMR and capillary GLC coinjection to be identical to the major diastereomer in the imide derived sample.

Acylation of L-valine methyl ester hydrochloride with (-)-MTPA-chloride[33] in an identical fashion gave, after purification by flash chromatography, 32.8 mg (95%) of the corresponding (-)-MTPA-amide (R = *i*-Pr) as a colorless oil: ^1H

NMR (250 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H, aromatic), 7.45-7.37 (m, 3H, aromatic), 7.051 (br d, J = 9.0 Hz, 1H, NH), 4.617 (dd, J = 4.6, 9.1 Hz, 1H, CHC=O), 3.764 (s, 3H, CO_2CH_3), 3.553 (q, J_{HF} = 1.7 Hz, 3H, CF_3COCH_3), 2.200 (d of septets, J = 4.7, 6.9 Hz, 1H, $CH(CH_3)_2$), 0.871 (d, J = 6.9 Hz, 3H, $CH(CH_3)$), 0.808 (d, J = 6.9 Hz, 3H, $CH(CH_3)$). This material was shown by coinjection to have the same retention time on capillary GLC as the minor diastereomer, 2(*R*)-**10e** (R = *i*-Pr), in the imide derived sample.

2*S*-((+)-α-Methoxy-α-trifluoromethylphenylacetylamino)-3,3-dimethylbutanoic Acid, Methyl Ester, 10f (R = *t*-Bu) (Table 4, Entry D). A sample (43.6 mg; 0.100 mmol) of **6f** (R = *t*-Bu), secured via LiOBn transesterification (*vide supra*), was converted to the corresponding methyl ester **9f** by debenzylation (1 atm of H_2, 7 mg of 5% Pd/C, 1.5 mL of EtOAc, 3 h, 25 °C) and subsequent diazomethane treatment (CH_2Cl_2, 0 °C). Without purification, **9f** was subjected to the above deprotection, hydrogenolysis (16 h) sequence. The unpurified amino ester was divided into two equal portions as a MeOH solution. Following solvent removal (*in vacuo*, toluene azeotrope), one portion was

[redacted]

mmol, 4.0 equiv) of triethylamine in 1.5 mL of CH_2Cl_2. The unpurified product was purified by flash chromatography (5 g of silica gel; hexane-EtOAc (9:1)) to afford 16.0 mg (89%) of **10f** (R = *t*-Bu) as a colorless viscous oil: IR (neat) 3430, 1744, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.48 (m, 3H, aromatic and NH), 7.43-7.38 (m, 3H, aromatic), 4.463 (d, J = 9.5 Hz, 1H, CHC=O), 3.727 (s, 3H, CO_2CH_3), 3.390 (q, J_{HF} = 1.4 Hz, 3H, CF_3COCH_3), 1.025 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 171.40, 165.86, 131.98, 129.45, 128.54, 128.05, 123.91 (q, J_{CF} = 290.1 Hz) 84.32 (q, J_{CF} = 25.9 Hz), 60.39, 54.95, 51.77, 34.87, 26.64; $[\alpha]_D^{25}$ -28.8° (*c* = 0.71, $CHCl_3$). High Resolution MS. Calcd for $C_{17}H_{22}F_3NO_4$: m/e 361.15008. Found: m/e 361.14596. Capillary GLC analysis (150 °C, 6 PSI) gave a 2(*S*)-**10f** (t_r = 17.00 min): 2(*R*)-**10f** (t_r = 16.31 min) ratio >500:1.

The second portion of unpurified amino ester (*vide supra*) was acylated exactly as described above with (-)-MTPA-chloride.[33] The unpurified product was purified as described above by flash chromatography to afford 15.2 mg (84%) of the corresponding (-)-MTPA-amide (R = *t*-Bu) as a colorless viscous oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 2H, aromatic), 7.43-7.38 (m, 3H, aromatic), 7.116 (br d, J = 9.7 Hz, 1H, NH), 4.483 (d, J = 9.7 Hz, 1H, CHC=O), 3.755 (s, 3H, CO_2CH_3), 0.903 (s, 9H, $C(CH_3)_3$). This material was shown by coinjection with **10f** (R = *t*-Bu) to have the same retention time on capillary GLC as the minor diastereomer, 2(*R*)-**10f** (R = *t*-Bu), in that sample.

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