15-Hydroxy-4-oxo-10-pentadecynoic acid lactone (2i): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.38 (6 H, m), 1.50–1.77 (4 H, m, C6-H_2 and C14-H_2), 2.12 (4 H, m, C9-H_2 and C12-H_2), 2.43 (2 H, t, J = 6.0 Hz, C5-H_2), 2.50 (2 H, t, J = 5.8 Hz, C2-H_2 or C3-H_2), 2.68 (2 H, t, J = 5.8 Hz, C3-H_2 or C2-H_2), 4.03 (2 H, t, J = 6.8 Hz, C15-H_2); ^{13}C NMR (75 MHz, ppm) 18.3 (CH_2), 18.5 (CH_2), 23.3 (CH_2), 24.8 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 28.7 (CH_2), 37.6 (CH_2), 42.0 (CH_2), 64.2 (CH_2), 80.0 (C), 80.9 (C), 172.2 (*C*=O), 208.9 (*C*=O); IR (neat) ν_{max} 2932, 2212 (C≡C), 1736, 1412, 1256, 1164 cm^{-1}; EIMS, m/e (relative intensity) 93 (44), 79 (94), 67 (39), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 251 (M^+ + H); EIHRMS, m/e 250.1567 ($C_{15}H_{22}O_3$ requires 250.1569).

(*Z*)-15-Hydroxy-4-oxo-8-pentadecenoic acid lactone (2j): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.36 (6 H, m), 1.56–1.77 (4 H, m), 2.02 (4 H, m, C7-H_2 and C10-H_2), 2.46 (2 H, t, J = 6.0 Hz, C5-H_2), 2.59 (2 H, t, J = 5.9 Hz, C2-H_2 or C3-H_2), 2.75 (2 H, t, J = 5.9 Hz, C3-H_2 or C2-H_2), 4.15 (2 H, t, J = 5.3 Hz, C15-H_2), 5.40 (2 H, m, C*H*=C*H*); IR (neat) ν_{max} 2928, 1736, 1460, 1410, 1260, 1178, 1084, 1054 cm^{-1}; EIMS, m/e (relative intensity) 252 (2, M^+), 234 (2), 136 (17), 121 (15), 111 (24), 98 (40), 80 (50), 67 (91), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 253 (base, M^+ + H); EIHRMS, m/e 252.1724 ($C_{15}H_{24}O_3$ requires 252.1725).

(*Z*)-15-Hydroxy-8-methyl-4-oxo-8-pentadecenoic acid lactone (2k): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.33 (6 H, br s), 1.54 (4 H, m), 1.71 (3 H, s, C8-CH_3), 1.95 (4 H, m, C7-H_2 and C10-H_2), 2.45 (2 H, t, J = 5.9 Hz, C5-H_2), 2.58 (2 H, t, J = 5.8 Hz, C2-H_2 or C3-H_2), 2.77 (2 H, t, J = 5.8 Hz, C3-H_2 or C2-H_2), 4.17 (2 H, t, J = 5.3 Hz, C15-H_2), 5.15 (1 H, t, J = 7.0 Hz, C9-H); IR (neat) ν_{max} 2928, 2858, 1736, 1460, 1258, 1182, 1142, 1048, 998, 846 cm^{-1}; EIMS, m/e (relative intensity) 266 (7, M^+), 248 (5, $M^+ - H_2O$), 123 (8), 111 (base, $C_7H_{11}O^+$), 95 (16), 81 (31), 67 (36), 55 (69); CIMS (isobutane), m/e 266.1888 ($C_{16}H_{26}O_3$ requires 266.1882).

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 42056).

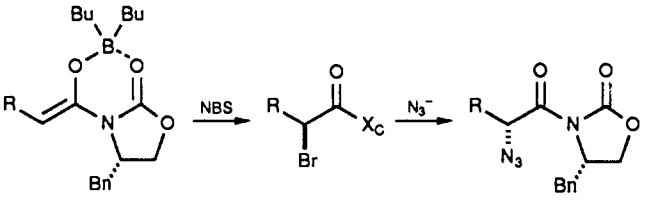
Supplementary Material Available: Full details of the preparation and characterization of the precursor ω-hydroxy carboxylic acids that serve as precursors to the phenyl selenoesters **1g–k** and full characterization of the ω-hydroxy phenyl selenides and **1a,c–k** are provided (13 pages). Ordering information is given on any current masthead page.

The Asymmetric Synthesis of α-Amino Acids. Electrophilic Azidation of Chiral Imide Enolates, a Practical Approach to the Synthesis of (*R*)- and (*S*)-α-Azido Carboxylic Acids

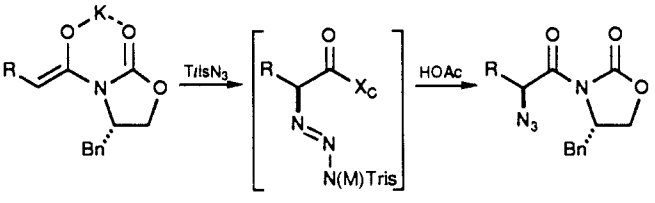
David A. Evans,* Thomas C. Britton, Jonathan A. Ellman,[1] and Roberta L. Dorow

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received August 18, 1989*

Abstract: Two complementary approaches to the asymmetric synthesis of α-amino acids have been achieved. In the initially investigated reaction sequence, the diastereoselective bromination of the illustrated boron enolate with *N*-bromosuccinimide was followed by stereospecific azide displacement by tetramethylguanidinium azide. The resulting α-azido carboximides may be readily purified to high diastereomeric purity by chromatography on silica.



In the second reaction sequence, the illustrated potassium enolate was treated with 2,4,6-triisopropylbenzenesulfonyl azide, and the intermediate sulfonyl triazene was decomposed through an acetic acid quench to give the α-azido carboximide. The diastereoselection of the reaction as a function of R is as follows: R = Me, CH_2Ph, 97:3; R = $CHMe_2$, 98:2; R = CMe_3, >99:1; R = Ph, 91:9. The important parameters of this azidation process were evaluated, and experiments were conducted to help elucidate the mechanism of the reaction.

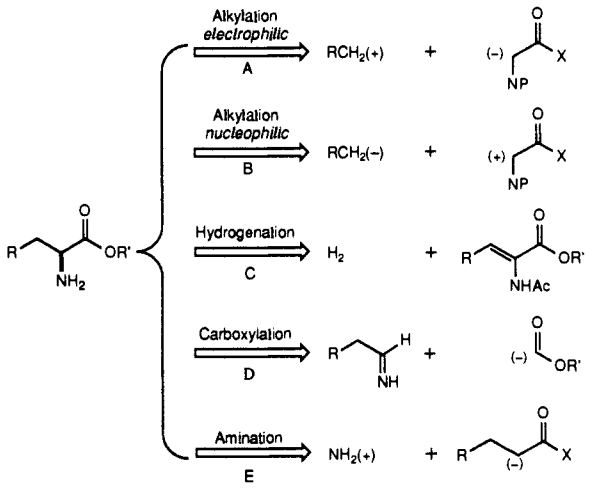


The α-azido carboximide products have been shown to be versatile α-amino acid synthons that may be readily converted to α-amino acids as well as to N-protected α-amino acid derivatives. The racemization-free removal of the chiral auxiliary was achieved in high yield both by saponification and transesterification, either before or after reduction and acylation of the azide functionality.

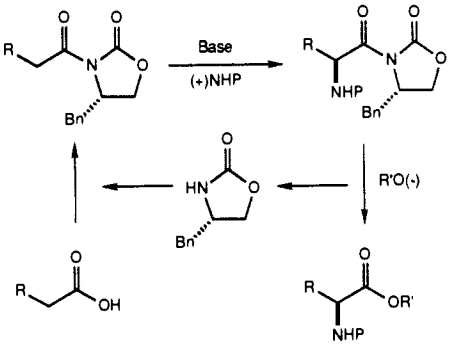
As a consequence of the importance of enantiomerically pure α-amino acids, the development of new reaction methodology which provides an expedient, general approach to the synthesis of this family of compounds continues to be an active area of

0002-7863/90/1512-4011$02.50/0

Scheme I

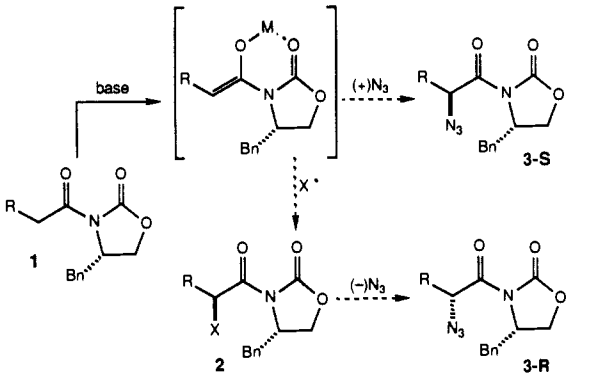


Scheme II



investigation.[2] The established methods for the asymmetric synthesis of α-amino acids can be categorized according to the nature of the stereodifferentiating event. The analysis provided in Scheme I indicates five recognized ways of stereoselectively constructing the α-stereogenic center of a simple α-amino acid. While methods for effecting the stereoselective alkylation (transforms A and B), hydrogenation (transform C), and carboxylation (transform D) of the corresponding α-amino acid precursors had been well documented, at the outset of this project practical asymmetric enolate amination reactions (transform E) remained unexplored (vide infra). In principle, this enolate-based bond construction should possess a broader degree of generality than the ubiquitous glycine enolate electrophilic alkylation option (transform A)[3] since the latter reaction is subject to the limitations of alkyl halide reactivity, which in certain situations, will effectively shut down the bond construction. These limitations are obviously not relevant to the synthesis of β-hydroxy α-amino acids, where the aldehyde–glycine enolate-based bond constructions analogous to transform A represent one of the most expedient methods of assemblage to date.[4]

Scheme III



Prior reports from these laboratories have documented the utility of oxazolidone-derived carboximides for the construction of enantiomerically pure compounds. Their derived enolates have demonstrated good levels of diastereoselection in asymmetric enolate alkylation,[5] acylation,[6] hydroxylation,[7] and aldol addition reactions.[4b,c,8] In conjunction with our interests in amino acid derived natural products, we anticipated that these enolates might be attractive precursors to enantiomerically pure α-amino acids if effective electrophilic aminating agents could be developed. The simple strategy that was envisioned (Scheme II) held the potential for a useful collection of desirable features, making it complementary to existing methodologies. First, the required starting materials would be the corresponding carboxylic acids, which in most cases would be commercially available or readily prepared by standard methods. Second, mild methods for installing and removing the oxazolidone chiral auxiliary that tolerate a range of protecting groups and sensitive functionality in complex cases which might even include esters are available. Third, the scope of the amination transform need not be defined by the nature of the amino acid R group, as it is in the alkylation route, thereby affording access to classes of targets, e.g., arylglycines and *tert*-alkylglycines, that are unavailable by other enolate-based methodology. Finally, precedent would indicate that any stereochemical defect in the amination process could be corrected by chromatographic resolution of the diastereomeric products, thereby providing access to products of high enantiomeric purity after the nondestructive removal of the chiral auxiliary.[9,10]

The successful implementation of the above amination strategy was necessarily predicated on the availability of a suitable electrophilic nitrogen source. The literature pertaining to potential (+)-NR_2 synthons is extensive, and the topic has been comprehensively reviewed on more than one occasion.[11] One self-imposed

(1) National Science Foundation Predoctoral Fellow 1984–1987.

(2) For reviews, see: (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, DC, 1976; Chapter 7. (b) Harada, K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Chapter 10. (c) α-Amino Acid Synthesis, Martin J. O'Donnell, Ed.; Tetrahedron Symposia *Tetrahedron*, **1988**, *44*, 5253–5605. (d) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

(3) See ref 2c for a recent overview of a number of the glycine enolate based methods. In addition, see: (a) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R. Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 125–259. (b) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091. (c) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799–1806. (d) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403–3406. (e) Jacquier, R.; Lazaro, R.; Ranirisehenо, H.; Viallefont, P. *Tetrahedron Lett.* **1984**, *25*, 5525–5528.

(4) See ref 2c for a recent overview of a number of the glycine enolate based methods. In addition, see: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (c) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42. (d) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406. (e) Seebach, D.; Juaristi, E.; Miller, D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237–261. (f) Schöllkopf, U.; Nozulak, J.; Grauert, M. *Synthesis* **1985**, 55–56. (g) Belokon', Y. N.; et al. *J. Am. Chem. Soc.* **1985**, *107*, 4252–4259.

(5) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(6) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156.

(7) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

(8) (a) Evans, D. A.; Bartroli, J.; Shih, T. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957–4960.

(9) In both the prior alkylation and hydroxylation studies of these imide enolates the diastereomers were readily separated by either MPLC or flash chromatography on silica gel. See ref 5 and 7.

(10) Both enantiomers of the 4-(phenylmethyl)-2-oxazolidone auxiliary are readily prepared (ref 4b), and are also commercially available: Aldrich Chemical Co., Cat. #29, 464-0 (4(*S*) isomer) and #30, 097-7 (4(*R*)-isomer).

constraint which was instrumental to reagent selection was that the electrophilic nitrogen be introduced in *protected* form so that this transformation would be rendered unnecessary in subsequent steps. For reasons which will be outlined later, electrophilic enolate azidation with (+)-N_3 synthons (**1** → **3-*S***) and the complementary one-pot halogenation/azide displacement reactions (**1** → **3-*R***) were chosen for development (Scheme III). The underlying premise for the selection of this course of action was predicated on our initial observations indicating that the enantiomerically pure α-azido carboxylic acids were versatile N-protected α-amino acid derivatives (vide infra).

The following study documents our efforts to develop conditions for both diastereoselective enolate halogenation[12]/azide displacement and electrophilic enolate azidation in conjunction with the development of asymmetric syntheses of (*R*)- and (*S*)-α-azido carboxylic acids. The syntheses of all of the *N*-acyl carboximides used during the course of this study have been detailed in a prior paper from this laboratory.[13]

Halogenation of Imide Enolates

Prior to the present halogenation study, which has been reported in preliminary form,[14] no chiral auxiliary-based enol or enolate halogenation reactions had been described in the literature. During the course of this investigation, Oppolzer and co-workers reported the halogenation of representative camphor-derived silyl ketene acetals.[15] Effective asymmetric induction has also been reported in the bromination of chiral ketals derived from tartaric acid.[16] Our choice of electrophiles for the diastereoselective halogenation of chiral imide enolates was guided by a general investigation of diastereoselective halogenation and those reaction parameters which influence stereoselectivity.[17] This study revealed that the α-iodo carboximides **2** (X = I) were not configurationally stable at room temperature, thus eliminating diastereoselective iodination as a viable option. A survey of both brominating and chlorinating agents revealed that bromination, in general, provided higher diastereoselection, presumably because of the greater steric requirements of the larger halogen atom. We therefore chose to focus on diastereoselective bromination, a reaction which provides a product of acceptable S_N2 reactivity for subsequent displacement reactions with nucleophiles such as azide ion.

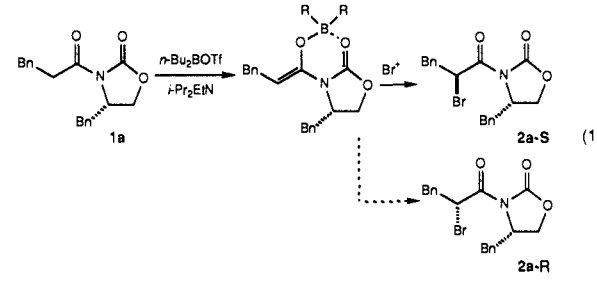
To assay the inherent diastereoselection of the different bromination methods, we employed hydrocinnamyl carboximide **1a** (R = Bn) as the substrate. A variety of brominating agents and metal enolates were screened.[18] The halogenation method that provided the highest diastereoselectivity was the reaction of *N*-bromosuccinimide (NBS) with the dibutylboryl enolate derived from **1a**, which provided a 90:10 ratio of α-bromo diastereomers

Table I. Bromination of the Boron Enolate of Carboximide **1a** (R = Bn) with NBS (Eq 1)[a]

entry	boron triflate	amine base	solvent	diastereoselection[b]
A	*n*-Bu_2BOTf (1.1 equiv)	Et_3N (1.2 equiv)	CH_2Cl_2	90:10
B	*n*-Bu_2BOTf (1.1 equiv)	Et_3N (1.2 equiv)	THF	70:30
C	*n*-Bu_2BOTf (1.1 equiv)	*i*-Pr_2NEt (1.2 equiv)	CH_2Cl_2	95:5
D	*n*-Bu_2BOTf (1.1 equiv)	*i*-Pr_2NEt (1.7 equiv)	CH_2Cl_2	95:5
E	*n*-Bu_2BOTf (1.7 equiv)	*i*-Pr_2NEt (0.8 equiv)	CH_2Cl_2	86:14
F	*n*-Bu_2BOTf (1.4 equiv)	*i*-Pr_2NEt (1.8 equiv)	CH_2Cl_2	89:11
G	*n*-Bu_2BOTf (1.05 equiv)	*i*-Pr_2NEt (1.2 equiv)	CH_2Cl_2	95:5
H	9-BBNOTf (1.05 equiv)	*i*-Pr_2NEt (1.2 equiv)	CH_2Cl_2	90:10

[a] In all experiments 1.1 equiv of NBS was employed. [b] Ratios of the α-bromo imide diastereomers were determined by HPLC analysis of the unfractionated product.

2-*S* and **2-*R*** (R = Bn), readily separable by silica gel chromatography, in 98% overall yield (eq 1).[19] Both α-bromo imides were indefinitely stable at 0 °C. The diastereomeric nature of the two isomers was readily confirmed by their interconversion with LiBr in refluxing THF.



(1)

A summary of the experiments which resulted in the optimization of diastereoselectivity is provided in Table I. As shown in entry B, when THF rather than CH_2Cl_2 was employed as the solvent the diastereoselection dropped to 70:30. Changing the base from triethylamine to diisopropylethylamine resulted in an increase in the diastereoselectivity to 95:5 (entry C). The effect of excess base was then probed by employing 1.7 equiv of diisopropylethylamine in the enolization reaction; no change in the diastereoselectivity was observed (entry D). In contrast, when excess dibutylboryl triflate (1.7 equiv) was employed, the diastereoselectivity decreased to 86:14 (entry E). Even when additional diisopropylethylamine (1.8 equiv) was added to complex with the excess boryl triflate (1.4 equiv), the diastereoselectivity of the reaction remained low at 89:11 (entry F). These results indicate that the excess boryl triflate may disrupt the presumed chelated boryl enolate (illustrated in eq 3). When less than 1.1 equiv of dibutylboryl triflate was employed in the reaction, the diastereoselectivity in the bromination reaction remained at 95:5 (entry G). In addition, the use of 9-BBN triflate rather than dibutylboryl triflate in the enolization of the carboximide resulted in a diminished bromination diastereoselectivity of 90:10 (entry H). It thus appears that any reaction constituent, such as solvent or Lewis base, which disrupts the chelated boryl enolate, will result in the reduction of reaction stereoselectivity. *Thus, the optimized conditions for the enolization of the carboximide were determined to be 1.05 equiv of dibutylboryl triflate, 1.2 equiv of diisopropylethylamine, with CH_2Cl_2 as the solvent.* Employing these

(11) For reviews on electrophilic amination, see: (a) Krohn, K. *Nachr. Chem., Tech. Lab.* **1987**, *35*, 1047–1052. (b) Sheradsky, T. In *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives, Part 1*; Patai, S., Ed.; Wiley: New York, 1982; pp 395–401. (c) Wallace, R. G. *Aldrichimica Acta* **1980**, *13*, 3–11. (d) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1–17. (e) Schmitz, E. *Russ. Chem. Rev. (Engl. Transl.)* **1976**, *45*, 16–24. (f) Fahr, E.; Lind, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 327–384. A partial review of electrophilic aminating agents may also be found in a recent general treatment of electrophilic reagents: Effenburger, F. *Angew. Chem., Int. Ed. Eng.* **1980**, *19*, 151–171.

(12) A number of different methods for halogenating ketone and ester enolates have been documented. (a) House, H. O. *Modern Synthetic Reactions, 2nd ed.*; W. A. Benjamin: Menlo Park, CA, 1972; Chapter 8, pp 459–478. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, NY, 1985; Chapter 12, pp 529–532.

(13) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525–5540.

(14) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123–1126.

(15) Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831–834.

(16) Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018–3027; Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 259–260.

(17) Dorow, R. L. Masters Thesis, Harvard University, 1985.

(18) The halogenating agents that were screened were bromine, benzenesulfonyl bromide, *N*-bromosuccinimide, carbon tetrabromide, isopropylidene dibromomalonate, cupric bromide, *N*-bromoacetamide, 1,3-dibromo-5,5-dimethylhydantoin, bromoisopropylsulfonium bromide, and 2,4,4,6-tetrabromocyclohexa-2,5-dienone. Both the lithium and boron enolates were employed.

(19) In accord with the protocol for oxidatively degrading the di-*n*-butylboron aldolate produced in the diastereoselective aldol reaction of dibutylboryl imide enolates, we initially employed an oxidative workup, H_2O_2, pH 7 buffer, 0 °C, 1 h, (ref 8a). Upon employing these work-up conditions, the diastereomeric α-bromo carboximides were obtained in 65–85% yield along with several side products each in <5% yield each.

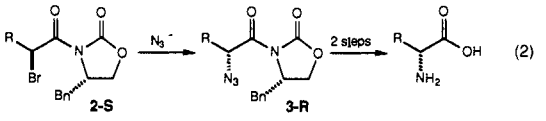
Table II. Diastereomeric Purity after Individual Steps for Synthesis of α-Azido Carboximides **3-*R*** through Consecutive Bromination and Azide Displacement (Eq 5)

entry	carboximide **1**	bromination[a] 2*S*:2*R*	azidation[a] 2*S*:2*R*	yield, % **3-*R***[b,c]
A	R = $CH_2C_6H_5$	95:5	6:94	83 (**3a-*R***)
B	R = CH_2CHMe_2	95:5	5:95	86 (**3b-*R***)
C	R = $CH_2CH{=}CH_2$	94:6	6:94	82 (**3c-*R***)
D	R = C_6H_5	78:22	22:78	67 (**3d-*R***)
E	R = $CHMe_2$	96:4	6:94	80 (**3e-*R***)
F	R = CMe_3	>96:4	–	–

[a] Ratios of bromide and azide diastereomers were determined by HPLC analysis. [b] Values reported represent the overall yield of diastereomerically pure azide from imide **1** for both the bromination and azide displacement steps. [c] Diastereomeric purity >99%.

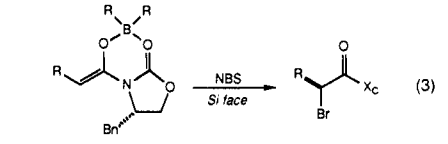
enolization conditions, we again screened a number of different brominating agents; none of the reagents tried provided diastereoselectivity comparable to that observed with NBS.[20]

The assignment of absolute stereochemistry to the major product diastereomer **2-*S*** was made by correlation with α-amino acids of known configuration (eq 2); vide infra.

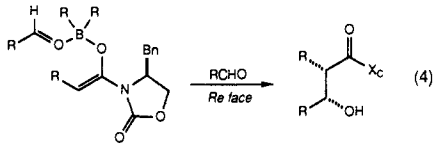


(2)

It is interesting that the sense of asymmetric induction in this reaction can be rationalized via electrophile attack on the *chelated* boryl enolate, a stereochemical outcome which is *opposite* to the asymmetric induction observed in the aldol reaction of the same enolate (eq 3,4).[21]



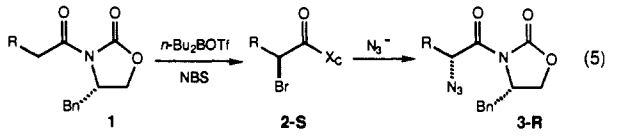
(3)



(4)

Synthesis of α-Azido Carboximides

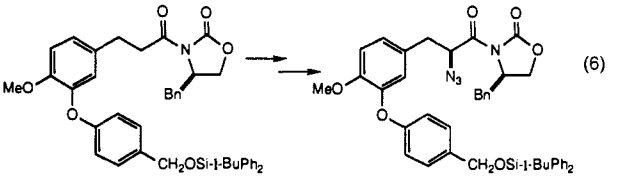
With a highly diastereoselective method for the preparation of α-bromo carboximides **2** in hand, the development of appropriate conditions to convert the unpurified α-bromo carboximide **2** to the α-azido carboximide **3** with minimal epimerization was undertaken (eq 5). When the unpurified α-bromo carboximide



(5)

2a-*S* (R = Bn) was treated with sodium azide in DMSO at 0 °C, 9% epimerization was observed during the course of azide displacement. On the other hand, upon treatment of the α-bromo carboximide **2a-*S*** with tetramethylguanidinium azide (TMGA)[22] in CH_2Cl_2 at 0 °C, ≤1% epimerization was observed. Employing TMGA in the azide displacement reaction, the diastereomerically pure α-azido carboximide **3a-*R*** (R = Bn) was isolated in 83% overall yield for the combined bromination and azide displacement steps after chromatographic purification. The generality of this two-step synthesis of α-azido carboximides is evident from the cases provided in Table II.

For each substrate, the diastereomeric purity of the α-bromo carboximide **2-*S*** and α-azido carboximide **3-*R*** was determined by HPLC analysis. An authentic mixture of α-bromo carboximide epimers was prepared by reaction of the α-bromo carboximide with lithium bromide in refluxing THF. In all but one case, the bromination step was found to be highly diastereoselective. The only noted exception was the bromination of the phenylacetic acid derived carboximide **1d** (R = Ph). The diminished diastereoselectivity observed with this substrate is consistent with previous studies on the enolate oxygenation of the same compound.[7] In all cases, the azide displacement step was uniformly high-yielding and displayed ≤1% epimerization, even with the racemization-prone phenylacetic acid derivative **2d-*S*** (R = Ph) (entry D). Not surprisingly, the neopentyl bromide **2f-*S*** (R = CMe_3) was resistant to azide substitution. Treatment of this substrate with sodium azide in DMSO at 55 °C over a prolonged time period did result in azide displacement, although in poor yield. Thus, this case defined one of the limitations of this two-step procedure for the synthesis of α-azido carboxylic acids. This reaction sequence can also be extended to more complex substrates as illustrated in eq 6. In this example, the α-azido carboximide is isolated as a single

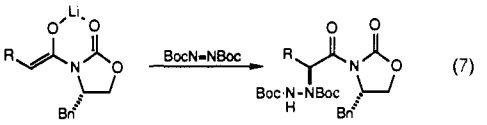


(6)

diastereomer in 83% overall yield after chromatography with an observed diastereoselection of 96:4 for the two steps.

Direct Azidation of Carboximide Enolates

In parallel with the preceding studies, considerable effort was directed toward the development of a one-step enolate amination reaction, and in the process a number of (+)-NH_2 synthons were investigated. Reagents such as oxygen-activated hydroxylamine derivatives, which have proven to be popular in the electrophilic amination of carbon nucleophiles,[23] did not perform well in our hands. The first successful enolate amination which we developed was the reaction of imide enolates with di-*tert*-butyl azodicarboxylate (DBAD) (eq 7). This reagent provided access to



(7)

a wider range of targets, e.g., *tert*-alkyl and arylglycines than were available by the halogenation and azide displacement methodology.[13,24,25] The major liability in the use of this amination protocol is in the "packaging" of the nitrogen as delivered to the substrate. Although the hydrazide may be successfully degraded to the amine by treatment with trifluoroacetic acid followed by reduction of the hydrazine moiety with H_2 (500 psi, Raney nickel catalyst), the α-azido carboximides were found to be much more versatile protected α-amino acids (vide infra). As a consequence of these complementary studies, we decided to investigate the utility of (+)-N_3 synthons in the direct electrophilic azidation of

(20) The reagents that were screened were benzenesulfonyl bromide, cupric bromide, bromine, *N*-bromoacetamide, isopropylidene dibromomalonate, and 1,3-dibromo-5,5-dimethylhydantoin.

(21) This facial selectivity has also been observed with other noncoordinating electrophiles. (a) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675–4676. (b) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749–5759.

(22) TMGA can readily be prepared (Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426–1430) and is also commercially available: Lancaster Synthesis, Cat. #0282.

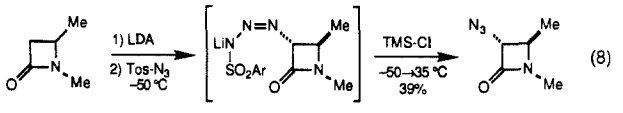
(23) For a review of hydroxylamine-*O*-sulfonic acids as electrophilic aminating agents, see ref 11c. See also: Boche, G.; Schrott, W. *Tetrahedron Lett.* **1982**, *23*, 5403–5406.

(24) (a) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397.

(25) For related studies, see: (a) Gennari, C.; Columbo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395. (b) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399. (c) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923–1926.

the enolates under study, thus incorporating the most desirable features of both of these enolate-based approaches (Scheme III).

There are a limited number of literature citations documenting the electrophilic azide transfer to enolates by sulfonyl azides; however, these reagents are also known to function as (+)-N_2 synthons in the more commonly utilized diazo transfer reaction.[26] Although both azide[27] and diazo transfer had been achieved with resonance stabilized enolates, only a few examples of direct azide transfer to nonstabilized enolates had been reported prior to the present study.[28,29] All of these cases were based on the method developed by Kühlein and Jensen in their seminal investigations with β-lactam enolates.[29] In this important study, the lithium enolate of the azetidinone, generated with lithium diisopropylamide (LDA), was treated with tosyl azide to afford an intermediate adduct, which was isolated and characterized by IR spectroscopy as the lithium salt of the acyclic tosyl triazene (eq 8). Treatment

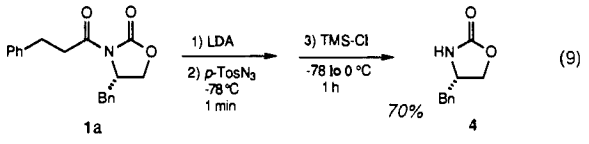


(8)

diastereoselection 60:40

of this intermediate, generated in situ, with excess chlorotrimethylsilane (TMS-Cl) and subsequent heating afforded the desired α-azide in modest yield as a 3:2 ratio of stereoisomers. All of the subsequently reported examples of direct azide transfer to unstabilized enolates have employed this "TMS-Cl quench" procedure with lithium enolates.[28,29]

Azide vs Diazo Transfer: Reaction Optimization Studies. Our initial efforts to effect direct azide transfer to carboximide enolates were modeled closely after the Kühlein and Jensen procedure. The lithium enolate derived from imide **1a** generated with LDA in the usual manner, was treated with 1.3 equiv of tosyl azide at −78 °C (eq 9). After the exothermic reaction subsided (~1 min),



(9)

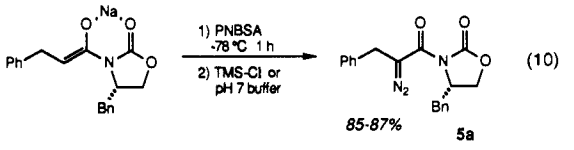
the reaction was "quenched" with the usual 2 equiv of TMS-Cl and warmed to 0 °C for 1 h. Careful analysis of the reaction mixture revealed that only traces (<3%) of the desired α-azido imide or of the α-diazo imide byproduct were present, even though the imide starting material had been completely consumed. The only other product that was identified in the complex product mixture was the free oxazolidone auxiliary, which was isolated in 70% yield.

Following several minor modifications of the Kühlein and Jensen azide transfer procedure which produced qualitatively similar results,[30] we concluded that a significant departure from established procedures was in order. Since reactions of enolates with sulfonyl azides were generally known to be sensitive to both the enolate counterion and sulfonyl azide structure, both of these variables were modified in an attempt to change the course of the reaction. In accordance with literature precedent concerning the use of trifluoromethanesulfonyl azide as an (+)-N_3 synthon,[27b] other highly electron deficient sulfonyl azides were considered as alternatives to this highly explosive reagent. This analogy led us to investigate the use of *p*-nitrobenzenesulfonyl azide (PNBSA) as an (+)-N_3 synthon.[31] The reaction of the sodium enolate derived from **1a**, generated with 1.2 equiv of sodium hexamethyldisilazide as previously described,[7] with PNBSA (1.3 equiv) at −78 °C for 1 h, followed by treatment with TMS-Cl (2.3 equiv) at −78 °C for 1 h, cleanly afforded the *diazo* transfer product **5a** in 87% yield, with no trace of the desired azide being detected (eq 10). It was subsequently determined that TMS-Cl was not

Table III. Enolate Metal and Quench Dependence on Direct Azidation (Eq 11)

entry	metal[a]	reaction time (A), min	quench reagent[b]	yield, % **3a-*S***[a]
A	Li	2 min	TMS-Cl (2.3 equiv)	8
B	Na	2 min	TMS-Cl (2.3 equiv)	30
C	Na	0.5 min	TMS-OTf (2.3 equiv)	–
D	Na	0.5 min	HOAc (4.6 equiv)	59
E	K	0.5 min	HOAc (4.6 equiv)	92
F	K	−78 to 25 °C/3 h	none	–
G	K	30 min	HOAc (4.6 equiv)	78
H	Li	1 min	HOAc (4.6 equiv)[d]	74

[a] The Li enolate was generated with LDA (1.1 equiv) in THF as described in ref 13. The Na and K enolates were prepared from NaHMDS and KHMDS, respectively, in similar fashion. [b] The quench reagent was added at −78 °C, the cooling bath was removed, and the solution stirred for 3 h while warming to 25 °C. The exception was Entry H, which was allowed to stir for 12 h. [c] Isolated yield of the **2-*S*** diastereomer. [d] The quench was added at −78 °C, and the solution was immediately warmed to 25 °C and stirred for 12 h.



(10)

essential for this transformation, since the same product was obtained in 85% yield if the reaction was quenched instead with pH 7 phosphate buffer. This unexpected diazo-transfer reaction is particularly surprising in light of the fact that PNBSA had previously been reported to be inferior to tosyl azide as a diazo-transfer reagent.[32]

Several key points emerged from the above observations which encouraged us to pursue the azide transfer objective. First, the initial reaction of these carboximide enolates with the sulfonyl azides was very rapid at −78 °C. Second, the course of the overall reaction proved to be very responsive to variation in the structure of the azide electrophile. Third, the formation of the isolated products could be rationalized by the formation of a primary enolate–electrophile adduct which might function as a precursor to the desired azide product, but whose breakdown was following alternate and undesired pathways. Literature precedent suggested that the mode of breakdown of such a primary adduct might be controlled through appropriate modification of reaction parameters.

The next significant perturbation in electrophile structure that was investigated was the use of a sterically demanding sulfonyl azide, of which 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide)[33] was the most readily available example. The motivation behind this choice of reagent was that the formation of free oxazolidone **4** from the reaction of the lithium enolate with tosyl azide (eq 9) implicated the involvement of a nonproductive cyclic intermediate (vide infra) whose formation might be retarded or whose ring opening might be promoted if the aryl moiety were suitably bulky. The encouraging results obtained with trisyl azide

(26) For reviews on diazo transfer, see: (a) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*; Academic: New York, 1986; Chapter 13. (b) Regitz, M. *Synthesis* **1972**, 351–373. (c) Regitz, R. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 733–749.

(27) (a) Weininger, S. J.; Kohen, S.; Mataka, S.; Koga, G.; Anselme, J.-P. *J. Org. Chem.* **1974**, *39*, 1591–1592. (b) Hakimelahi, G. H.; Just, G. *Synth. Commun.* **1980**, *10*, 429–435.

(28) (a) Wasserman, H. H.; Hlasta, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 6780–6781. (b) Golding, B. T.; Smith, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 702–703. (c) Bevilacqua, P. F.; Keith, D. D.; Roberts, J. L. *J. Org. Chem.* **1984**, *49*, 1430–1434. (d) Nishida, A.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1984**, *25*, 765–768. (e) Nitta, H.; Hatanaka, M.; Ishimaru, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51–52.

(29) Kühlein, K.; Jensen, H. *Liebigs Ann. Chem.* **1974**, 369–402.

(30) Only minor amounts of the desired α-azido imide were detected in the reaction of the corresponding sodium enolate with tosyl azide under similar conditions.

(31) Reagan, M. T.; Nickon, A. *J. Am. Chem. Soc.* **1968**, *90*, 4096–4105.

(32) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610–3611.

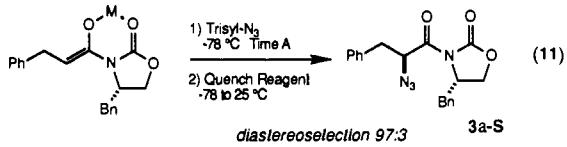
(33) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11–16.

Table IV. Effect of Sulfonyl Azide Structure on Azide vs Diazo Transfer (Eq 12)

entry	sulfonyl azide	yield, % **3a-S**[a]	yield, % **5a**[a]	kinetic ratio[b] 2S:2R
A	PNBSA[c]	15	70	-
B	*p*-TosN$_3$[d]	51	26	96:4
C	Trisyl-N$_3$[e]	91	-[f]	97:3

[a] Isolated yield. [b] Diastereomer ratios determined by HPLC. [c] *p*-Nitrobenzenesulfonyl azide. [d] *p*-Toluenesulfonyl azide. [e] 2,4,6-Triisopropylbenzenesulfonyl azide. [f] None detected.

prompted a systematic study of the effect of the enolate counterion, as well as the quench reagent, on the yield of azide transfer product, **3a** (eq 11). The results of this study are summarized in Table III.



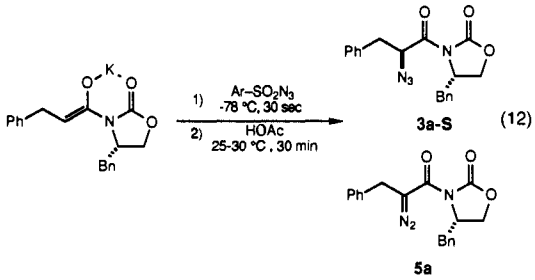
(11)

diastereoselection 97:3 **3a-S**

The use of trisyl azide, rather than tosyl azide, under standard Kühlein and Jensen conditions afforded small amounts (8%) of the desired azide transfer product, **3a-*S*** (entry A). A substantial improvement in the yield of azidation was realized when the sodium, rather than lithium, enolate was employed under otherwise identical conditions (entry B). At this point, the effect of the quench reagent was examined since its function in the overall azide-transfer process was unclear. When the reaction was quenched with the more reactive silylating reagent, trimethylsilyl triflate (TMS-OTf), the THF solvent was polymerized, and none of the desired product was obtained (entry C). However, the yield of **3a-*S*** increased to 59% when the reaction was quenched with an excess of the simple proton source, glacial acetic acid (HOAc) (entry D). An additional marked improvement resulted when this quenching protocol was combined with use of the corresponding potassium enolate, which was generated with potassium hexamethyldisilazide (KHMDS) in an analogous fashion (entry E). A 92% yield of the major 2(*S*)-azide diastereomer **3a-*S*** was realized from this reaction, for which the kinetic diastereoselection was determined to be 97:3 by HPLC analysis.

The importance of this acetic acid quench step for the overall azide-transfer process is further emphasized by entries F–H. When this step was omitted (entry F), none of the desired product was produced. If the quench step was delayed for 30 min, a decrease in the yield of azide product from 92% to 78% resulted (entry G). Finally, a respectable yield of **3a-*S*** (74%) could even be obtained from the corresponding lithium enolate when the optimum quenching procedure was employed (entry H). However, in this case a much longer time period (12 h) was required for the primary adduct to completely break down.

The effect of sulfonyl azide structure on the partitioning of the reaction between the azide- and diazo-transfer pathways was next evaluated (eq 12, Table IV). For this study, the potassium enolate and acetic acid quench protocol were employed. Since earlier



(12)

3a-S **5a**

studies indicated that these reaction parameters afforded maximum yields of the azide-transfer product, the relative importance of these parameters compared to sulfonyl azide structure in determining the reaction outcome might be ascertained. *The results of this study, summarized in Table IV, clearly indicate that the structure of the sulfonyl azide electrophile has a major influence on the product distribution.* Under otherwise identical conditions, the use of PNBSA resulted in predominant formation of the *diazo*-transfer product, **5a** (70% yield) (entry A), whereas use of trisyl azide resulted in the exclusive formation of the azide-transfer product, **3a-*S*** (91% yield) (entry C). The use of tosyl azide (entry B) afforded an intermediate result, in which azide transfer predominated over diazo transfer by a ratio of 2:1. However, the sensitive interplay between the quench reagent and electrophile structure in determining the reaction outcome was demonstrated by an additional experiment, differing from that in entry B only in the use of a stronger acid, trifluoroacetic, in the quench step. *In this case a 57% yield of the diazo-transfer product **5a** was obtained, and none of the azide **3a** could be detected.*

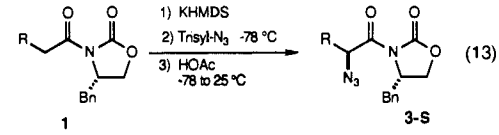
Although a logical analysis led us to examine trisyl azide as a potential azide transfer reagent toward carboximide enolates, our observation that this electrophile afforded maximum *azide* transfer with minimal competing *diazo* transfer is ironic if viewed in the context of literature precedent. The only general method for effecting direct *diazo* transfer to unstabilized enolates employs trisyl azide as the (+)-N$_2$ synthon under phase-transfer conditions.[34] In the cited study, *trisyl azide was found to be superior to both tosyl azide and PNBSA as a diazo-transfer reagent!* Collectively, these independent observations underscore the lack of mechanistic sophistication which currently surrounds these reactions.

Table V. Electrophilic Azide Transfer to *N*-Acyloxazolidones **1** (Eq 13)

entry	imide **1**	kinetic ratio[a] 2S:2R	yield, %[b] **3-*S***
A	R = CH_2Ph	97:3	91 (**3a-*S***)
B	R = Me	97:3	74 (**3b-*S***)
C	R = $CH_2CH{=}CH_2$	97:3	78 (**3c-*S***)
D	R = C_6H_5	91:9[c]	82 (**3d-*S***)
E	R = $CHMe_2$	98:2	77 (**3e-*S***)
F	R = CMe_3	>99:1	90 (**3f-*S***)

[a] Diastereomer ratios determined by HPLC. [b] Values refer to isolated yields of product with a diastereomeric purity >200:1. [c] Ratios determined by ^{1}H NMR spectroscopy.

Direct Azide Transfer to Imide Enolates: Reaction Generality. Having achieved excellent yield and high stereoselectivity in the direct azidation of the potassium enolate derived from **1a** (R = Bn) with the (+)-N$_3$ synthon, trisyl azide, the generality of the optimized conditions was explored. The results of this study are summarized in Table V (eq 13). The potassium enolates derived



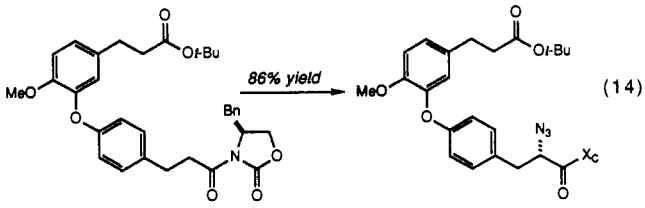
(13)

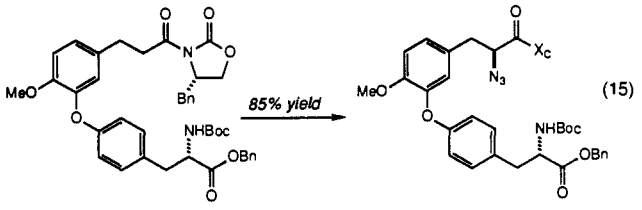
1 **3-S**

from a representative series of imides **1**, formed by treatment with 1.1 equiv of KHMDS in THF (−78 °C, 30 min), were allowed to react with 1.2–1.3 equiv of trisyl azide at −78 °C for 1–2 min. After the solution was quenched at −78 °C with 4.6 equiv of glacial acetic acid, the reactions were either warmed slowly to room temperature (10–12 h, 25 °C) or heated gently (30 min, 25–30 °C). The resultant α-azido carboximides **3-*S*** were isolated in the indicated yields as single diastereomers [2*S*:2*R* >200:1] after chromatographic purification on silica gel (Table V). From the data in the table it is evident that this azidation reaction enjoys considerable scope while displaying a high level of stereoselectivity. For the α-azido carboximide diastereomers **3-*S*** and **3-*R***, it was noted that the major 2*S* diastereomer **3-*S*** in each case exhibited the greater mobility on silica gel chromatography upon elution with CH_2Cl_2–hexane mixtures. Such stereoregular chromatographic behavior has previously been observed for other series of imide enolate–electrophile adducts.[35]

(34) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368–369.

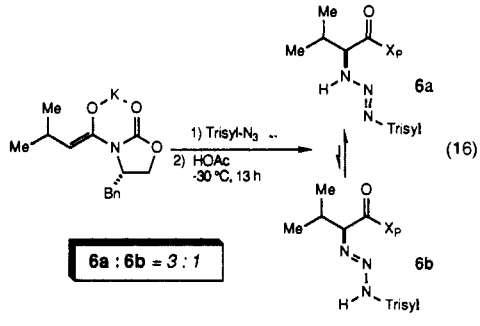
During the course of our recent syntheses of the cyclic tripeptides K-13 and OF-4949-III,[36] we applied the direct enolate azidation protocol with trisyl azide to substrates containing functional groups that could have easily compromised the desired reaction (eq 14, 15). In the first case it is clear that selective





enolization of the imide moiety in the presence of the ester ensures the success of the reaction.[37] The diastereoselection (97:3) was found to be the same as that found for the simpler phenylalanine analogue (Table V, entry A). In the more complex case containing a pendant N-protected α-amino ester (eq 15), an extra equivalent of KHMDS was employed to scavenge the acidic amide proton. These examples clearly demonstrate that the electrophilic azidation process can be applied successfully to polyfunctional imide substrates without a compromise in yield or selectivity.

Mechanistic Studies of Direct Azide (Diazo) Transfer. During the course of the above direct azidation studies, an intermediate was detected by TLC during the warming period after the addition of the acetic acid quenching reagent. Furthermore, this intermediate appeared to be a precursor to the product azide since its disappearance coincided with the formation of the α-azido carboximide. In order to gain some insight into the reaction mechanism, we attempted to isolate this compound and identify its structure. The reaction chosen for this investigation was the conversion of **1e** to **3e-*S*** (R = *i*-Pr), since preliminary observations indicated that the breakdown of the "intermediate" in this case was somewhat sluggish. The isolated yield of this presumed intermediate was highest when the following conditions were employed. The potassium enolate derived from **1e**, generated with KHMDS in the standard fashion, was treated with trisyl azide (1.3 equiv) under the usual conditions (−78 °C, 2 min). Following the standard quench with glacial acetic acid (4.6 equiv, −78 °C), the solution was held at −30 °C for 13 h prior to isolation by CH_2Cl_2 extraction and purification by silica gel chromatography (eq 16). In this manner the sulfonyl triazene **6** was obtained in



56% yield as a 3:1 ratio of the two tautomeric forms, **6a** and **6b**, as determined by 300-MHz ^1H NMR spectroscopy in $CDCl_3$.[38]

(35) For an explanation of the stereoregular elution behavior, see ref 13.
(36) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063–1072.
(37) For other examples of related selective enolization reactions, see ref 7 and 8a.

Scheme IV

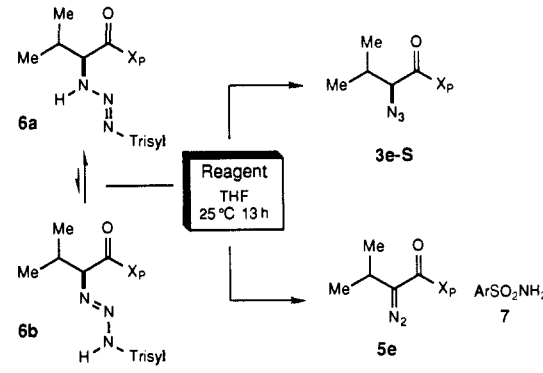


Table VI. Decomposition Studies on Sulfonyl Triazene 6 (Scheme IV)

		yield, %		
entry	reagent[a]	**3e-*S***	**5e**	**7**
A	KHMDS, 1.1 equiv[b] HOAc, 4.8 equiv[c]	76	–	–
B	KHMDS, 1.1 equiv[b] TMS-Cl, 2.0 equiv[c]	23	23	72
C	HMDS, 1.1 equiv[c] HOAc, 4.8 equiv[c]	23	48	82
D	HOAc, 4.6 equiv[d]	0	0	0
E	KOAc, 4.6 equiv[d]	84	0	16

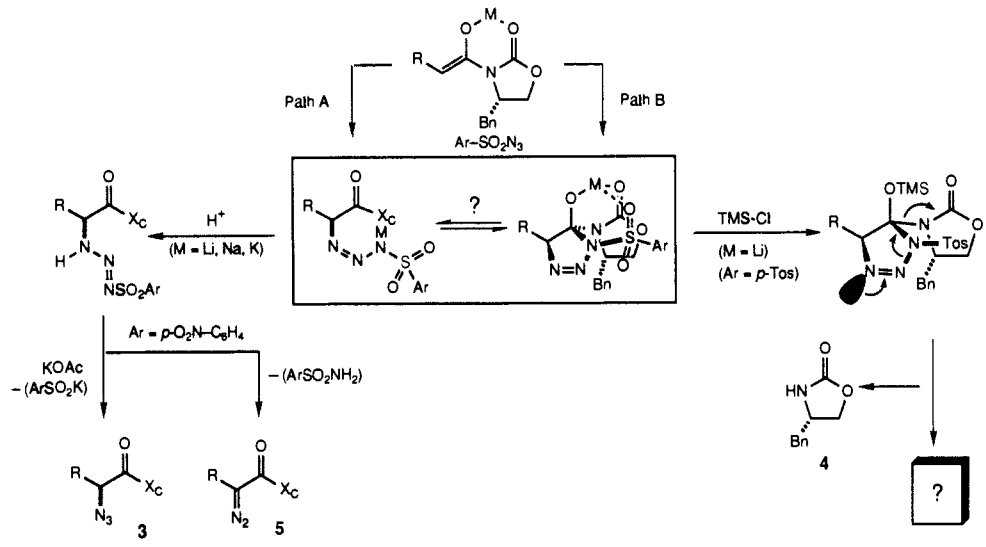
[a] A 0.08 M solution of 6 in THF was treated with indicated reagents. [b] Solution of 6 treated with KHMDS at −78 °C (2 min) prior to addition of "quench" reagent. [c] Reagent added at −78 °C, and stirred 13–15 h at 25 °C. [d] Stirred at 25 °C (13 h).

Proton NMR saturation transfer experiments further established that these tautomers were interconverting at an approximate rate of 0.1–1 s^{-1} in $CDCl_3$ at 25 °C.[39] Once purified, this compound could be stored for weeks at −20 °C without significant decomposition. It is presumed that the geometry of the triazene is *E*, as illustrated, but the experiments described above provide no information on this stereochemical issue. In order to further establish that triazene **6** was, in fact, an intermediate in the reaction, an additional experiment was performed, differing from that described above in that following the "aging" period at −30 °C, the reaction was held at 25 °C for 22 h prior to product isolation. In this manner the corresponding azide **3e-*S*** was obtained in 86% yield, a significant improvement over the result obtained under the "standard" conditions (Table V, entry E).

We next subjected the isolated triazene **6** to reagents which might promote its fragmentation (Scheme IV). One of our objectives was to establish which constituents of the reaction mixture promoted its conversion to the azide **3e-*S***. The results of this series of experiments are summarized below (Table VI). A control experiment was first performed in which **6** was resubjected to conditions designed to mimic those under which it was formed and subsequently decomposed during an actual azide-transfer experiment (Table VI, entry A). Following its deprotonation with KHMDS (1.1 equiv) in THF at −78 °C (2 min), the triazene **6** was immediately treated with acetic acid (4.6 equiv), and the resulting solution was warmed to 25 °C (13 h). The α-azido imide **3e-*S*** was thereby obtained in 76% yield, which is identical with the yield of **3e-*S*** obtained from imide **1e** via a standard azide-transfer experiment (Table V, entry E). In a similar experiment (Table VI, entry B), the potassium salt of the

(38) The indicated structure of these tautomers was further supported by IR and MS data. No information is available concerning the azo linkage stereochemistry in either isomer.
(39) Irradiation (direct saturation) of the α-proton (2-H) in **13b** (d, J = 3.8 Hz, 5.59 δ) resulted in a 42% reduction in the normalized integrated signal of the corresponding α-proton in **13a** (dd, J = 5.1, 5.8 Hz, 6.00 δ) after correction for spillover saturation from the irradiating frequency. For a leading reference to the technique of saturation transfer NMR, see: Serianni, A. S.; Pierce, J.; Huang, S.-G.; Barker, R. *J. Am. Chem. Soc.* **1982**, *104*, 4037–4044.

Scheme V



triazene was treated at −78 °C with TMS-Cl (2.0 equiv). After the solution was warmed to 25 °C for 13 h, a 1:1 ratio of the azide and diazo transfer products **3e-*S*** and **5e** was obtained in modest yield, confirming the inferiority of the TMS-Cl quench procedure in promoting the formation of the azide. When **6** was treated with hexamethyldisilazane (HMDS, 1.1 equiv) and acetic acid (4.6 equiv) under similar conditions, formation of the diazo compound **5e** was favored over the azide **3e-*S*** by a 2:1 margin (entry C). No significant decomposition of **6** was noted on treatment with acetic acid alone for 13 h at 25 °C (entry D). However, the use of KOAc (2.0 equiv) under identical conditions resulted in formation of the azide **3e-*S*** in 84% yield, with none of the corresponding diazo imide being detected (entry E).

Having established that the weak, insoluble base, KOAc, was the key ingredient which effected the fragmentation of the intermediate triazene **6** to the azide **3e-*S***, we next subjected **6** to a series of related reagents in order to compare their effectiveness in promoting this mode of breakdown. The procedure that was followed was the same in every case: a solution of triazene **6** in THF was treated with the reagent (2.0 equiv), and the resulting solution was stirred at 25 °C for 13 h. The results of this study are summarized in Table VII. A comparison of entries A–D clearly reveals a pronounced counterion effect for the series of acetate salts. The most ionic salt in the series, tetramethylammonium acetate (entry A), was the most effective in promoting formation of the azide, whereas the most covalent salt, lithium acetate, was clearly the least effective (entry D). Surprisingly, the lithium acetate–12-crown-4 complex was only marginally more effective than LiOAc alone in effecting this transformation. This final set of observations now reveals why the potassium enolate, which provides the potassium acetate after the acetic acid quench, affords the optimal yield of azide product. Of all the reagents examined, pyridine proved most effective in promoting the decomposition of **6** to the diazo compound **5e** (82%) (entry H), while the insoluble base, $KHCO_3$ (entry G), and the soluble base, triethylamine (entry F), afforded increasingly greater amounts of the azide. The data therefore indicate that *there is no correlation between the reaction product distribution and either the solubility of the reagent, or its basicity.* An explanation for these results is not readily apparent.

Inspection of entries A–E in Table VII and entries B–C in Table VI reveals another interesting observation. There is generally not a 1:1 correspondence between the amount of the diazo compound produced relative to the amount of sulfonamide **7** formed. This suggests that, in addition to the two modes of decomposition illustrated in Scheme IV, another as yet unidentified pathway may be operative that affords the sulfonamide, but not the diazo compound. An alternative explanation for this observation is that the diazo compound, once formed, might be further degraded by the reagent, a possibility which has not been pursued.

Table VII. Decomposition Studies on Sulfonyl Triazene 6 (Scheme IV)

		yield, %		
entry	reagent[a]	**3e-*S***	**5e**	**7**
A	$Me_4N^+{}^-OAc$	91	0	8
B	KOAc	84	0	16
C	NaOAc	45	0	46
D	LiOAc	35	5	45
E	LiOAc, 12-Cr-4	42	8	52
F	Et_3N	57	38	47
G	$KHCO_3$	22	71	77
H	C_5H_5N	6	82	86

[a] A 0.08 M solution of 6 in THF was treated with 2.0 equiv of the indicated reagent at 25 °C for 13 h.

A mechanistic rationale for our observations concerning the reaction of the above imide enolates with sulfonyl azide electrophiles, as well as the decomposition of the initial adduct, is presented in Scheme V. The initial enolate–electrophile adduct could be either an acyclic sulfonyl triazene salt resulting from nucleophilic attack of the enolate on the terminal azide nitrogen (path A),[40] or the cyclic triazoline resulting from a cycloaddition of the azide dipole on the enolate (path B).[41] The mode of addition might even vary, depending on the enolate metal and the identity of the sulfonyl azide electrophile. The formation of the triazoline (path B) could be favored when the metal is strongly coordinating (e.g., M = Li), due to the opportunity for intramolecular metal ligation in the resulting adduct, as illustrated. Alternatively, the reaction of a relatively ionic enolate (M = K) with a sterically demanding electrophile (trisyl azide) may prefer the acyclic mode of addition (path A). Regardless of the nature of the primary adduct, the possibility exists that both species might be readily accessible by their subsequent interconversion, either before or after the addition of the quench reagent. We have established that when the electrophile is trisyl azide and when the reaction is quenched with acetic acid, an acyclic intermediate results, regardless of the nature of the enolate counterion.[42] We have demonstrated that such sulfonyl triazines can fragment either to the α-azido imide **3** or the corresponding diazo imide **5**. Our

(40) For the analogous reactions of Grignard reagents with azides, see: (a) Dimroth, O. *Chem. Ber.* **1903**, *36*, 909. *Ibid.* **1905**, *38*, 607. *Ibid.* **1905**, *38*, 2328. *Ibid.* **1906**, *39*, 3905. (b) Bertho, A. *J. Prakt. Chem.* **1927**, *116*, 101. (c) Itoh, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 635. (d) Smith, P. A. S.; Rowe, C.; Bruner, L. B. *J. Org. Chem.* **1969**, *34*, 3430. (e) Reed, J. O.; Lwowski, W. *J. Org. Chem.* **1971**, *36*, 2864. Please also see ref 44.

(41) For a general reference to 1,3-dipolar cycloadditions with azides, see: Lwowski, W. In *1,3 Dipolar Cycloaddition Chemistry*; Padwa, A.; Ed.; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 5.

(42) Triazine **6** was identified as the intermediate formed in the reaction of the lithium enolate derived from **1e** and trisyl azide after quenching with acetic acid.

Table VIII. Direct Azide (Diazo) Transfer to Benzyl Dihydrocinnamate **8** (Eq 19)

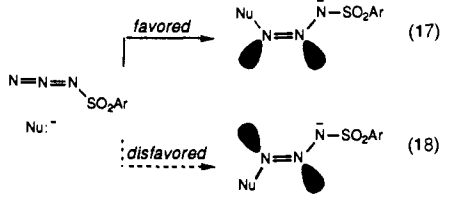
entry	metal[a]	reagent	time A, min	quench reagent	time B, h	yield, % 9	10	11	8
A	K	Trisyl-N_3	1	HOAc	0.5	48	20	-	15
B	K	Trisyl-N_3[b]	1	HOAc	0.5	72	8	-	-
C	Li[c]	Trisyl-N_3	2	HOAc[d]	12	73	-	1	2
D	Li	*p*-Tosyl-N_3	0.5	HOAc	15	43	-	27	2
E	Li	*p*-Tosyl-N_3	0.5	TMS-Cl[d]	11[e]	48	-	24	2
F	Li	PNBSA	15	pH 7[f]	-	5	-	68	0

[a] The K enolate was prepared by treatment with KHMDS (1.1 equiv) in THF at −78 °C (30 min). The Li enolate was prepared in a similar manner from LDA. [b] Inverse addition of the enolate solution to a solution of trisyl azide was employed. [c] 1.0 equiv of LDA was employed to generate the enolate. [d] 2 equiv was used. [e] After addition of TMSCl, solution was warmed to 0 °C for the indicated time. [f] Excess phosphate buffer was used to quench reaction.

data also indicate that the mode of fragmentation of these triazines is dramatically influenced by the steric and electronic features of the aryl moiety, as well as the identity of "reagents", e.g., KOAc, which may be present in the reaction medium. Fragmentation to the diazo imide **5** is strongly favored when the aryl moiety is *p*-nitrophenyl, whereas the formation of the azide **3** is favored when the aryl group is trisyl. Although these trends for triazene breakdown appear to be general, their underlying causes are not clear at present.

When the Kühlein and Jensen procedure (M = Li, tosyl azide, TMS-Cl quench) was employed, the only product that could be identified in the resulting reaction mixture was the oxazolidone **4**. This observation is most readily explained by the formation of the cyclic triazoline (path B), which is subsequently trapped in this form by O-silylation on treatment with TMS-Cl. The stereoelectronically assisted fragmentation of this intermediate with initial formation of a diazonium salt and loss of a leaving group (oxazolidone **4** in this case) has ample literature precedent.[43] Further degradation of the resultant diazonium salt would explain our inability to identify the fate of the acyl residue in the overall reaction.

One of the principal issues associated with the discussion of the azidation mechanism deals with the details of the initial union of sulfonyl azide and enolate. Both options are illustrated in Scheme V. What had *not* been previously discussed is the fact that a stepwise nucleophilic addition could give rise to isomeric *E*- or *Z*-triazenyl anions such as those illustrated in eq 17, 18.

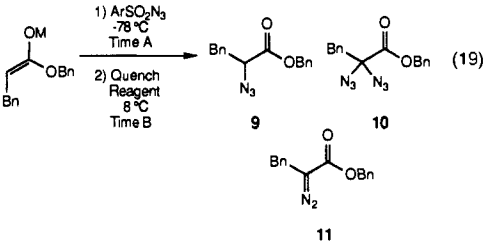


Using steric arguments one might readily conclude that the *E* anion (eq 18) might be formed preferentially, while a stereoelectronic argument which implicates antiperiplanar overlap of developing σ-bonds (antibonds) and the vicinal nonbonding electron pair could be used to support the preferential formation of the *Z* anion (eq 17). Trost and Pearson have recently documented that Grignard reagents add preferentially to thioalkyl azides to give the *less stable Z*-triazenyl anion adducts.[44] This stereoelectronic argument was suggested to account for the observed results. If these observations prove to be general, the *Z*-triazenyl anion illustrated in Scheme V might be produced either directly via path A or indirectly through the cycloadduct through path B.

(43) (a) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1982**, *47*, 5042–5044. (b) Goldsmith, D. J.; Soria, J. J. *Tetrahedron Lett.* **1986**, *27*, 4701–4704. (c) Abramovitch, R. A.; Ortiz, M.; McManus, S. P. *J. Org. Chem.* **1981**, *46*, 330. (d) Also see ref 26 and 41.

(44) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 1054–1056.

Direct Azide (Diazo) Transfer to Esters. Although the Kühlein and Jensen direct-azidation protocol failed when applied to carboximide enolates, its utility for direct azide transfer to β-lactam enolates has been amply documented.[28,29] A recent report has described the successful application of this method for the direct azidation of a γ-lactone lithium enolate.[28e] We therefore decided to determine whether the trends which had been observed during our azidation studies of imide enolates were applicable to other types of substrates. Benzyl dihydrocinnamate (**8**) was chosen as a prototypical ester substrate for this investigation (eq 19). The results of this study are summarized in Table VIII.



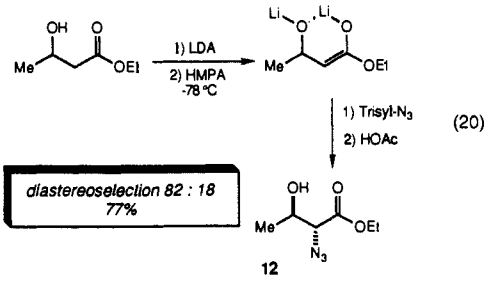
Our first attempt to effect direct azide transfer to the dihydrocinnamate ester **8** utilized the reaction of its derived potassium enolate, generated with KHMDS (1.1 equiv) by the standard enolization procedure (−78 °C, THF, 30 min), with trisyl azide followed by an acetic acid quench (Table VIII, entry A). Under these conditions, which were determined to be optimum for direct azidation of the corresponding carboximide, a 48% yield of the azide **9** was obtained, along with 20% of the bis-azide **10** and a 15% recovery of the starting ester. This result implicated a rapid proton transfer between the potassium enolate of **8** and the initial adduct with the sulfonyl azide. In a subsequent, otherwise identical, experiment (entry B), inverse addition of the enolate to the electrophile was employed in an attempt to minimize this side reaction. In accordance with the hypothesis, the yield of azide **9** increased to 72%, with a corresponding decrease in the amount of the bis-azide. An almost identical yield (73%) of azide **9** was obtained when the corresponding lithium enolate, generated with 1.0 equiv of LDA, was employed by using the normal mode of addition, followed by an acetic acid quench (entry C). In this case, none of the bis-azide was detected. The use of Me_4NOAc (2 equiv) along with acetic acid (2 equiv) as the quench reagent in an experiment that was otherwise identical to that in entry C afforded no improvement in the yield of the azide. Tosyl azide reacted with the lithium enolate to afford a 2:1 ratio of azide transfer to diazo transfer, regardless of whether the reaction was quenched with acetic acid or TMS-Cl (entries D and E). Finally, the *reaction of p-nitrobenzenesulfonyl azide (PNBSA) with the lithium enolate resulted in predominant diazo transfer (68% yield) with minimal azide transfer (5%) (entry F)*. This latter result represents an important transformation of some value to synthesis if it should prove to be general. In this regard, the recent report by Schöllkopf documenting the use of tosyl azide in the successful diazo transfer to lithiated diketopiperazine bislactim ethers is noteworthy.[45]

The above data show that the reactions of ester enolates with sulfonyl azide electrophiles are less sensitive to the nature of the enolate metal than are the corresponding imide enolate reactions. Unlike the imide enolates, both lithium and potassium ester enolates can perform with comparable levels of efficiency in the azide-transfer reaction under appropriate conditions. For esters, lithium enolates may even be preferable in situations where competing proton transfer becomes a severe problem. For the analogous carboximides, such competing proton transfer processes are unimportant due to the low kinetic acidity of the α-protons in the initial enolate–electrophile adduct. However, the effect of the sulfonyl azide electrophile structure on the partitioning of the reaction between azide transfer and diazo transfer is the same for both ester enolates and imide enolates. *The use of trisyl azide*

(45) Schöllkopf, U.; Hauptreif, M.; Dippl, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 192–93.

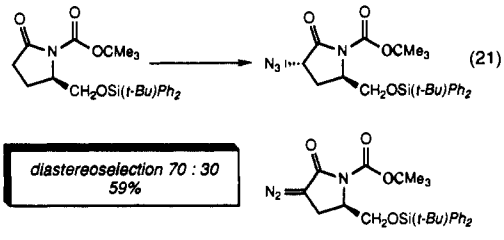
affords maximum yields of azide transfer in both series, while diazo transfer is maximized when PNBSA is employed as the electrophile.

Once we had established that trisyl azide could be used to effect direct azide transfer to ester enolates, we investigated the application of this method to the synthesis of β-hydroxy-α-azido esters. For this preliminary investigation, we employed the dilithium conjugate of racemic ethyl 3-hydroxybutyrate (eq 20).



The optimum yield and diastereoselectivity for direct azide transfer to this substrate was obtained when the following conditions were employed. The lithium aldolate enolate, generated with 2.2 equiv of LDA (−78 to −20 °C, 10 min), was treated at −78 °C with HMPA (5.5 equiv) followed by trisyl azide (1.2 equiv). After 30 s, the reaction was quenched with acetic acid (6.9 equiv) and warmed to 25 °C for 3 h. The α-azido-β-hydroxy ester was thereby obtained in 77% yield as an inseparable 82:18 ratio of anti and syn diastereomers, respectively. Lower yields of **12** (60–66%) resulted when the HMPA was omitted, or when 2.0 equiv of LDA was employed to generate the enolate. Inverse addition of the enolate to the electrophile afforded no improvement in the diastereoselectivity. Although the yield for this direct azidation was acceptable, the low stereoselectivity was surprising in view of the much higher stereoselectivity (≥96%) that has been reported for the analogous alkylation reactions of this substrate.[46]

We have also had the opportunity to apply the azidation reaction, as developed for imides, to cyclic imides where the enolate diastereofacial bias presents the opportunity for intraannular 1,3-asymmetric induction (eq 21).[47] We were surprised to observe



only modest levels of asymmetric induction (2.4:1) in the enolate azidation. This reaction was also accompanied by minor amounts of bis-azidation (1%) and diazo transfer (10%). From these two cases (eq 20, 21) we conclude that the steric requirements for azide transfer are modest, in fact, even smaller than an analogous enolate methylation. Evidence for such anticipated levels of internal asymmetric induction were apparent, but unappreciated, in the original Kühlein and Jensen study (see eq 8).[29]

Derivatization of α-Azido Carboximides

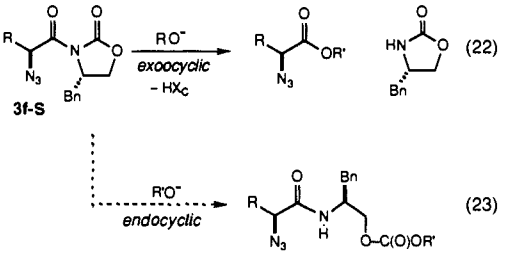
N-Acyloxazolidones undergo transesterification and aminolysis approximately 1000 times faster than the corresponding benzyl esters.[48] This places the imide carbonyl reactivity on par with that of a phenyl ester.[49] In most cases, where the R moiety is less sterically demanding than *tert*-butyl, nucleophilic attack occurs preferentially at the desired exocyclic imide carbonyl, affording the liberated carboxylic acid (ester) and recovered oxazolidone

Table IX. Hydrolysis and Transesterification of Carboximide **3-*R*** (Eqs 24 and 25)

entry	carboximide	reagent	yield, %[a]	ratio *R*:*S*[b]
A	R = $CH_2C_6H_5$	LiOH	97	>99.5:0.5
B	R = CH_2CHMe_2	LiOH	96	>99.5:0.5
C	R = $CHMe_2$	LiOH	88	>99.5:0.5
D	R = C_6H_5	LiOH	97	99:1
E	R = $CH_2C_6H_5$	$Ti(OBn)_4$	93	>99.5:0.5
F[c]	R = C_6H_5	$Ti(OBn)_4$	83	>99:1

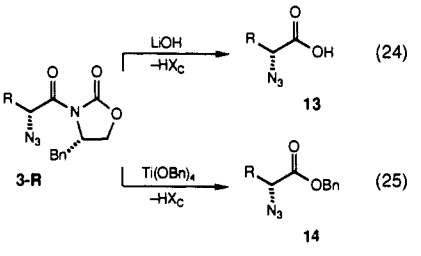
[a] Values refer to isolated yields of product. [b] Enantiomer ratios determined by conversion to (+)-MTPA amide methyl or benzyl esters followed by GLC analysis. [c] **3d-*S*** (R = C_6H_5) prepared by direct azidation was employed in this reaction.

(eq 22). This intrinsic preference for exocyclic nucleophilic attack may be overridden if the R substituent on the *N*-acyl moiety becomes excessively sterically demanding (eq 23).[50]



Saponification of the α-azido imides **3-*R*** was carried out with 2 equiv of lithium hydroxide in 3:1 THF–H_2O (eq 24). The reaction was complete in less than 30 min at 0 °C for every substrate. As shown in Table IX, entries A–D, the α-azido acids **13** could readily be isolated in analytically pure form and in high yields by a straighforward extractive workup. Most of the derivatization studies were carried out before the direct azide transfer reaction was optimized and were thus performed with the 2*R* diastereomer of α-azido carboximides **3-*R*** prepared by the bromination–azide displacement method. To confirm the analogous behavior of the *R*- and *S*-azide diastereomers toward hydrolysis, we also submitted the 2*S* diastereomer of α-azido carboximides **3a-*S*** (R = Bn) and **3d-*S*** (R = Ph), prepared by direct azide transfer, to the identical saponification conditions. The corresponding α-azido acids were isolated in quantitative yield and in high enantiomeric purity (≥99%).

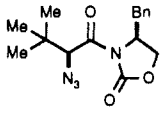
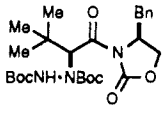
In addition to a viable saponification procedure, we also sought to define an appropriate transesterification protocol for removal of the oxazolidone from the α-azido carboximides.[51] The titanium(IV) alkoxide catalyzed transesterification method developed by Seebach proved to be ideal.[52] In evaluating this transesterification procedure (eq 25), we chose to study substrates **3a-*R*** (R = Bn) and **3d-*S*** (R = Ph) (entries E and F of Table IX). The



former substrate was chosen to represent a "conventional" amino acid precursor, while the latter substrate was selected as a highly racemization-prone case. Transesterification of **3a-*R*** and **3d-*S***

(46) Frater, G. *Helv Chim. Acta* **1979**, *62*, 2825–2832.
(47) Lundy, K. M., Harvard University. Unpublished results.
(48) Weber, A. E., Harvard University. Unpublished results.
(49) Gordon M.; Miller, J. G.; Day, A. R. *J. Am. Chem. Soc.* **1948**, *70*, 1946–1953.
(50) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
(51) Preliminary studies in this laboratory had shown that 4% racemization had occurred in the transesterification of α-azido carboximide **3a** (R = Bn) with magnesium methoxide. See ref 17.
(52) Seebach, D.; Hungerbuhler, E.; Naef, R.; Schurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138–141.

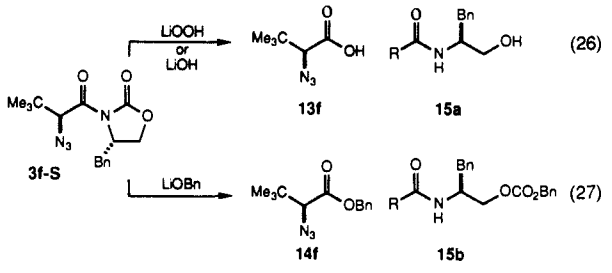
Table X. Hydrolysis (Transesterification) of *tert*-Butylglycyl Oxazolidone Derivatives (Eqs 26 and 27)

substrate	reagent[a]	conditions	cleavage path, yield, %[b] 13f(14f)	15a(15b)
	LiOOH	0 °C/0.5 h	98	1
	LiOBn	−70 °C/36 h	52	33
	LiOH	0 °C/1.5 h	42	52
	LiOOH	0 °C/3.2 h	91[c]	6
	LiOBn	−50 °C/50 h	51	
	LiOH	0 °C/16 h	16[c]	83

[a] LiOOH hydrolyses were performed as indicated in ref 50. LiOH hydrolyses were conducted under directly analogous conditions in the absence of HOOH. LiOBn transesterifications were conducted in THF as previously described (ref 13). [b] Isolated yield of enantiomerically (diastereomerically) pure (>99:1) product. [c] The carboxylic acid was characterized as its derived methyl ester following diazomethane treatment (ref 13). Yields quoted are for overall conversion to the ester.

(prepared by direct azidation) by treatment with $Ti(OBn)_4$ (1.5–2.0 equiv) and benzyl alcohol (50 equiv) in accord with literature analogy (65–80 °C, 7 h) provided the α-azido benzyl esters in 93% and 83% yields, respectively. Both **3a-*R*** and **3d-*S*** showed little if any racemization; thus, this transesterification method is suitable for both "conventional" α-azido carboximides and the more labile arylglycine derivatives.

While the saponification of the α-azido carboximides listed in Table IX proceeded in high yield, the hydrolysis of the sterically demanding substrate, **3f-*S*** proved problematic (Table X, eqs 26, 27), since cleavage occurred predominantly at the endocyclic



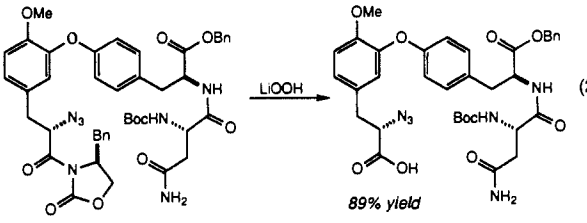
(26)

(27)

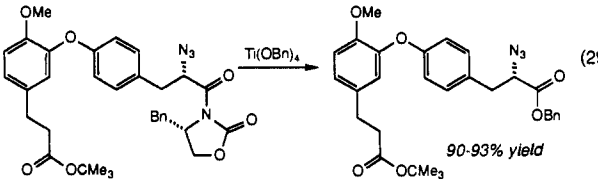
oxazolidone carbonyl, rather than the desired reaction at the exocyclic azidoacyl moiety. Similar results were also observed with lithium benzyloxide transesterification, a reaction which, in previous studies, had exhibited good exocyclic carbonyl cleavage regioselectivity.[13] *However, a dramatic improvement in selectivity was achieved in the hydrogen peroxide mediated hydrolysis of this substrate.* The desired enantiomerically pure α-azido acid **13f** was thereby obtained in 98% yield along with a 98% recovery of the oxazolidone chiral auxiliary following a simple extraction procedure. Similar observations have been made not only with the *tert*-butylglycine hydrazide derived oxazolidone illustrated in Table X but with a range of other imides as well.[50]

We surmise that the dramatic difference in product distribution for the hydroxide- and peroxide-mediated saponifications is probably tied to the fact that the rate-determining steps for the two processes are different. Since the reactivity of these imides may be placed in the category of "activated esters" (such as phenyl esters), the rate-determining attack of hydroxide ion at the competing acyl carbons dictates the product composition.[53] In the case of peroxide, we postulate that nucleophilic attack is reversible, and product composition is dictated by the relative rates of breakdown of the two possible tetrahedral intermediates. Given this postulate, the observed results can only be accounted for by asserting that the cyclic oxazolidone, which must be ejected during the exocyclic cleavage mode, is a *better* leaving group than the acyclic amide which is ejected during the alternative endocyclic cleavage. This assertion has now been confirmed. It is noteworthy that the pK_a of 4-benzyl-2-oxazolidone is 20.5 in DMSO, only 2.5 pK_a units less acidic than phenol in the same solvent.[54] This value places the acidity of 2-oxazolidone very close to that of hydrogen peroxide and nearly 4 pK_a units more acidic than noncyclic amides or urethanes.

The acyl-transfer reactions involving the selective hydrolysis or transesterification of the imide chiral auxiliary in the presence of other potentially vulnerable esters have proven to be quite successful. Two representative transformations which have recently been published from this laboratory are illustrated in eqs 28 and 29.[36] In both cases, the desired transformation, either hydrolysis or transesterification, could be effected on the imide acyl moiety without compromising the other carboxylic acid derivatives present in the molecule.

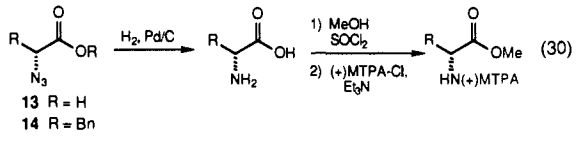


(28)



(29)

The optical purities of the α-azido acids **13** and α-azido esters **14** produced from the saponification and transesterification reactions were determined as outlined in eq 30.[55] Each α-azido



(30)

acid or ester was reduced with hydrogen at atmospheric pressure (5% Pd-C, HOAc–HOH). The resulting amino acid was then esterified in the conventional manner with $SOCl_2$ in methanol to provide the methyl ester hydrochloride.[56] The α-amino methyl ester was then acylated with both (+)-MTPA and (−)-MTPA acid chlorides[57] with triethylamine as base. Subsequent gas chromatographic analysis of the resulting MTPA amide methyl esters provided the overall diastereomeric purity for the hydrolysis and derivatization sequence. The validity of this diastereomer purity assay was confirmed by performing the esterification and (+)-MTPA chloride acylation sequence on an authentic sample of enantiomerically pure phenylglycine, the most racemization-prone amino acid to be tested. The phenylglycine (+)-MTPA amide methyl ester prepared by this derivatization sequence showed slightly less than 1% of the diastereomer by GLC analysis (vide

(53) Jencks, P. W.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637.

(54) This measurement has been carried out by F. G. Bordwell. For a general tabulation of acidity data in DMSO see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. The surprising fact that 4-benzyl-2-oxazolidone is ca. 4 pK_a units *more* acidic than related noncylic amides and urethanes may be attributed to the same effects which have been identified in enhancing the C–H acidity of lactones over related ester substrates. For a discussion of this issue, see: Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872–1874.

(55) The optical purity of the α-azido ester **14** (R = C_6H_5) was initially determined by reduction of the azide, without concomitant hydrogenolysis of the benzyl ester, with hydrogen and W-2 Raney nickel as catalyst in acetic acid–CH_2Cl_2, followed by acylation with (+)-MTPA–Cl to provide the appropriate derivative for GLC analysis. This assay showed 36% racemization, with the racemization presumably occurring in the reduction step.

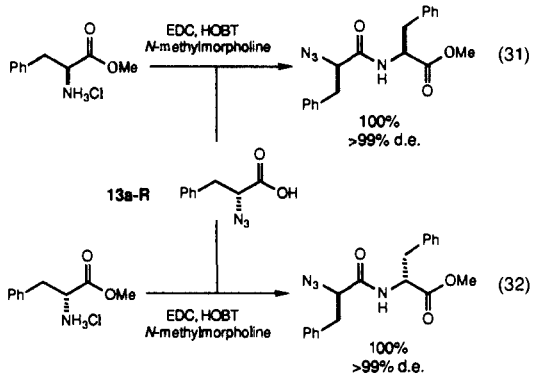
(56) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.

(57) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

supra). On the other hand, more conventional amino acids, such as phenylalanine, exhibited no detectable levels of racemization.[58]

As shown in Table IX, no racemization (<1%) was observed in the saponification and subsequent derivatization of any of the α-azido carboximides **3-*R*** except for the highly labile α-azido carboximide **3d-*R*** (R = Ph) where 2% overall racemization was observed. It should be noted that this is the same amount of racemization that was observed in the control reaction in processing (*S*)-phenylglycine through the reaction sequence illustrated in eq 30. We have thus concluded that the maximum level of racemization which occurs in the saponification step in the synthesis of arylglycine derivatives is less than 2%. From the racemization assay, the sense of asymmetric induction in the bromination and azidation reactions was unambiguously determined, both from the optical rotations of the intermediate amino acids as well as by correlation of the (+)-MTPA amide methyl esters.

With a general method for preparing the enantiomerically pure α-azido acids in hand, we evaluated the viability of the azide moiety as an amine-protecting group in conventional peptide coupling reactions. Accordingly, 2(*R*)-azidohydrocinnamic acid (**13a-*R***) was coupled with (*S*)-phenylalanine methyl ester with use of EDC,[59] hydroxybenzotriazole, and *N*-methylmorpholine to afford the dipeptide product, mp 66–67 °C, in quantitative yield (eq 31). The analogous coupling reaction was also carried out with (*R*)-phenylalanine methyl ester to afford the diastereomeric dipeptide, mp 87.5–88.5 °C, in quantitative yield (eq 32).



(31) (32)

HPLC analysis of the dipeptide products from each experiment did not reveal any of the diastereomeric cross-contaminant (>99% diastereomeric purity).[60] From these and related experiments concerned with the synthesis the cyclic tripeptides OF-4949 and K-13,[36] we have concluded that α-azido acids are effective α-amino acid derivatives which may be employed directly in peptide synthesis.

From the above studies it is apparent that the α-azido carboximides undergo selective saponification and, for conventional substrates, transesterification in high yield without racemization. In order to extend the versatility of these intermediates, nitrogen derivatization *prior* to removal of the chiral auxiliary was also investigated. The ease with which one can reduce and acylate α-azido esters belies one major problem which must be addressed in the reduction and acylation of these substrates: the α-amino carboximide which is produced upon reduction of the azide will rapidly cyclize (<5 min) to give the imidazolone **17** (Scheme VI) if it is not protected as the acid salt. However, when the acid salt of the amine is neutralized in the presence of a reactive acylating agent such as carbobenzyloxy chloride or acetyl chloride, the acylation is much faster than intramolecular cyclization.[61] This protocol is nicely demonstrated in the two examples shown in eq 33, with the derivatization of both substrates occurring in ≥96% overall yield.[62] It is noteworthy that the standard acylating

Scheme VI

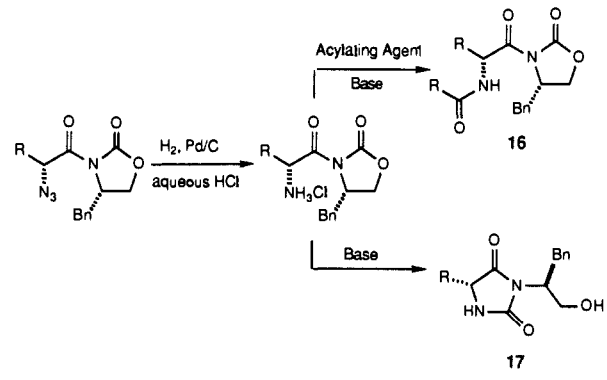
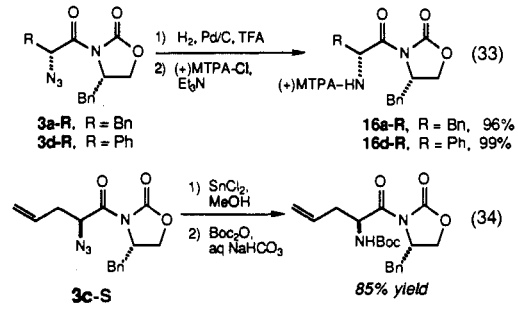


Table XI. Hydrolysis and Transesterification of **16-*R*** (Eqs 35 and 36)

entry	carboximide **16a-*R*–16d-*R***	reagent	yield, % (product)	ratio *R*:*S*[a]
A	R = $CH_2C_6H_5$	LiOH	97 (**18a-*R***)	>99.5:0.5
B	R = C_6H_5	LiOH	100 (**18d-*R***)	99:1
C	R = $CH_2C_6H_5$	$Ti(OBn)_4$	89 (**19a-*R***)	>99.5:0.5
D	R = C_6H_5	$Ti(OBn)_4$	81 (**19d-*R***)	98:2

[a] Diastereomer ratios were determined by GLC analysis.

reagents to prepare *N*-Boc derivatives, such as *tert*-butyl pyrocarbonate[63] or 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (BOC-ON),[64] are not sufficiently reactive to compete with the intramolecular cyclization under the above conditions. Recently, conditions have been discovered to achieve this transformation in good yield.[65] Under this protocol, the azide is reduced with $SnCl_2$ in methanol (2 h, 0 °C), and the resulting amine is then acylated with *tert*-butyl pyrocarbonate in dioxane–aqueous bicarbonate. A typical transformation is illustrated in eq 34 (see Experimental Section for general conditions).



(33) (34)

In comparing the two competing reactions illustrated in Scheme VI, superficially, one might find it surprising that *intermolecular acylation* could ever compete with *intramolecular acyl transfer*. We attribute this relatively slow internal acylation rate to the fact that imide resonance must be broken in order to bring the amine moiety within reacting distance with the urethane carbonyl.

As a complement to the earlier studies on the α-azido carboximides **3**, we also evaluated the saponification and transesterification of the α-acylamino carboximides **16a-*R*** (R = Bn) **16d-*R*** (R = Ph) (eqs 35, and 36, Table XI). Saponification and transesterification of **16a-*R*** (R = Bn) and **16d-*R*** (R = Ph) employing the conditions described earlier occurred in high yield with less than 1% racemization as determined by GLC analysis (Table XI, entries A, C). Saponification of the more highly racemization prone substrate **16d-*R*** (R = Ph) afforded the desired acid in

(58) From our own experience, this analytical method is probably ineffective in detecting ≤0.5% racemization.

(59) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

(60) An α-azido acid has also successfully been employed in a peptide cyclization reaction. See ref 36.

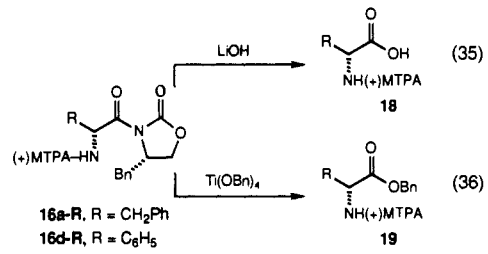
(61) Illig, C. R., Harvard University. Unpublished results, 1984.

(62) The reduction and acylation to prepare **16b** was performed on the enantiomer of **3d-*R*** (R = Ph).

(63) Tarbell, D. F.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730–732.

(64) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, *12*, 4393–4394.

(65) These experimental conditions have been developed by Mr. John Lynch of this laboratory.



quantitative yield with only 2% racemization (entry B), while the $Ti(OBn)_4$ promoted transesterification of this substrate resulted in 4% racemization (entry D). Thus, the chiral auxiliary can be removed without racemization by saponification or transesterification before or after reduction and acylation of the azide moiety, even for the stereochemically labile **3d** (R = Ph) derivatives.

Conclusions

In attempting to pass judgment on the reaction methodology which has been developed for the asymmetric synthesis of α-amino acids, it is instructive to not only address the issue of "production economics", the overall cost of producing the material, but it is also important to consider the reliability, generality, and ease of execution of the given process. Reactions meeting these latter criteria, irrespective of cost, are of considerable value to the research investigator who is interested in synthesizing, with minimal time investment, laboratory-scale quantities of the desired target substance. One might coin the term "research economics" to categorize this latter situation. It is an arguable point that *no* current general approach to the asymmetric synthesis of amino acids has yet been developed which meets the needs of *both* production and research scale. It has been our experience to date that the enolate azidation reaction developed in this study provides access to nonconventional amino acid derivatives with a minimal time investment. Furthermore, in contrast to the alkylation of chiral glycine enolates, this methodology provides access to both arylglycines and hindered amino acid derivatives such as *tert*-alkylglycines, both of which are not directly accessible via enolate alkylation.

Experimental Section

General Experimental. Tetrahydrofuran (THF) was dried by distillation under N_2 from sodium benzophenone. Lithium diisopropylamide (LDA) was generated in situ by treating dry diisopropylamine (0.33 M in THF) with 0.96 equiv of *n*-butyllithium (~1.6 M in hexane) at −78 °C for 30 min. *N*-Bromosuccinimide was recrystallized from H_2O and dried over P_2O_5. Dibutylboryl triflate was prepared according to the published procedure.[66] Sodium hexamethyldisilazide (NaHMDS) was purchased from Aldrich Chemical Co. as a 1.0 M solution in THF and was used as received. *p*-Toluenesulfonyl azide[67] (tosyl azide) and *p*-nitrobenzenesulfonyl azide[31] (PNBSA) were prepared as previously described. Potassium hexamethyldisilazide (KHMDS) was purchased from Callery Chemical Co. as an approximate 0.57 M solution in toluene. These solutions of KHMDS and NaHMDS were titrated prior to use with 2,6-di-*tert*-butyl-4-methylphenol 0.25 M in dry THF, at 0 °C using fluorene as the indicator according to a modification of a literature procedure.[68] Flash chromatography was performed as previously described[69] 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.[70] Michel-Miller columns (Ace Glass, Inc.) drypacked with the above 230–400-mesh silica gel were used in conjunction with this apparatus. Analytical HPLC was performed on an Hewlett-Packard HP 1090 chromatograph equipped with a 4.6 mm × 25 cm Du Pont Zorbax 5 μ silica gel column. Capillary GLC analyses were performed on a Hewlett-Packard 5880A gas chromatograph equipped with a 30 m × 0.25 mm fused-silica DB-1 column. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AM-500, AM-300, or AM-250 spectrometer at ambient temperature. Mass spectra (MS) were determined on a Kratos MS-50 spectrometer. Fast-atom bombardment mass spectra (FAB MS) were obtained on solutions in the indicated solvent with xenon as the ionization gas.

Preparation of the *N*-Acyloxazolidinones. (4*S*)-4-(Phenylmethyl)-2-oxazolidinone (**4**) is available from Aldrich Chemical Co, or can be prepared according to the procedure of Evans and Weber.[4b] A detailed procedure for the synthesis of this chiral auxiliary has recently been described.[71] The *N*-acyloxazolidinones **1** were prepared in 87–98% yields by reaction of the corresponding acyl chloride with lithiated oxazolidinone. The full experimental details of these preparations are provided in a prior paper from this laboratory.[13] A detailed procedure for these types of acylations has also recently been described.[72] The *N*-acyloxazolidinones can also be prepared directly from the corresponding acids employing a one-pot procedure: formation of the mixed anhydride of the acid by treatment with pivaloyl chloride and triethylamine followed by reaction with the lithiated oxazolidinone. The preparation of the *N*-acyloxazolidinones employed in the synthesis of OF4949-III (eqs 14, 15) were prepared in this way in 90–95% yields.[36] The procedures for these experiments are described in full detail in the prior report on the synthesis of OF4949-III. The full experimental details of the direct azidations of these substrates (eqs 14, 15), as well as the subsequent saponifications (eq 27) and transesterifications (eq 28) were also published in the report on the synthesis of OF4949-III.[36]

General Procedure for the Bromination and Subsequent Azide Displacement of *N*-Acyloxazolidinones 1 (Table II). The indicated acyloxazolidinone is added to a flame-dried flask equipped with magnetic stirring bar. The flask is flushed with nitrogen and freshly distilled CH_2Cl_2 is added. The resulting clear solution (0.1–0.5 M) is cooled to −78 °C. Freshly distilled diisopropylethylamine (1.2 equiv) is added followed by dropwise addition of dibutylboryl triflate[66] (1.05 equiv). The resulting colorless or pale yellow solution is stirred at −78 °C for 15 min and then at 0 °C for 1 h. To a flame-dried flask equipped with magnetic stirring bar is added 1.1 equiv of *N*-bromosuccinimide (NBS). The flask is flushed with nitrogen and cooled to −78 °C. Freshly distilled CH_2Cl_2 (0.5–2.0 mL/mmol NBS) is added to form a slurry (NBS is completely insoluble in CH_2Cl_2 at this temperature). The boron enolate solution, precooled to −78 °C, is added rapidly by Teflon cannula to the NBS slurry. The resulting purple slurry is stirred at −78 °C for 1.25 h and is quenched by pouring into 0.5 N aqueous sodium bisulfate–brine. The solution is extracted three times with ethyl acetate, and the combined organic layers are washed twice with 0.5 N aqueous sodium thiosulfate–brine and once with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Diastereomerically pure α-bromo carboximide **2** can be isolated by flash chromatography and is stable for several months at −16 °C. The diastereomer analysis of **2** was performed with an analytical high-performance liquid chromatography with a Du Pont Zorbax column (4.6 mm × 25 mm, 5-μm silica gel) and *tert*-butyl methyl ether–isooctane or dichloromethane–isooctane as eluent. The minor epimer is prepared by lithium bromide epimerization (5 equiv, THF, 2 h, reflux) of **2**.

Unpurified α-bromo carboximide **2** is then added to a round-bottom flask equipped with stirring bar. The flask is flushed with nitrogen and CH_2Cl_2 is added. The resulting pale yellow solution (0.1–0.3 M) is cooled to 0 °C and tetramethylguanidinium azide[22] (3.0 equiv) is added in one portion. The solution is stirred 3 h at 0 °C and is quenched by addition of saturated aqueous sodium bicarbonate. The resulting mixture is extracted three times with CH_2Cl_2, and the combined organic extracts are washed once with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting α-azido carboximide **3** is purified by flash chromatography (ethyl acetate–hexane or dichloromethane–hexane). The diastereomer analysis of the α-azido carboximides is carried out by use of a high-performance liquid chromatography with a Du Pont Zorbax column (4.6 mm × 25 mm, 5-μm silica gel) and either *tert*-butyl methyl ether–isooctane or dichloromethane–isooctane as eluent. Minor diastereomers were isolated and characterized by ^1H NMR and IR.

(3(2*S*),4*S*)-3-(2-Bromo-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (2a-*S*, R = $CH_2C_6H_5$). The boron enolate formed from 1.50 g (4.85 mmol) of acyloxazolidinone **1a** (R = Bn), 1.40 g (5.09 mmol, 1.05 equiv) of dibutylboryl triflate,[66] and 0.752 g (5.82 mmol, 1.2 equiv) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added to 1.04 g (5.82 mmol, 1.2 equiv) of NBS in 10 mL of CH_2Cl_2. After the reaction was stirred for 1.25 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (20:80 *tert*-butyl methyl ether–isooctane, 2 mL/min) afforded a 4.6:95.4 ratio of 2*R* and 2*S* diastereomers (t_R 4.17 and 4.94 min, respectively).

(66) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
(67) Regitz, M.; Hocker, J.; Liedhegener *Organic Synthesis*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. 5, p 179.
(68) Brown, C. A. *Synthesis* **1974**, 427–428.
(69) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(70) Peterson, E. A.; Sober, H. A. *Anal. Chem.* **1959**, *31*, 857.
(71) Gage, J. R.; Evans, D. A. in *Org. Synth.* **1989**, *68*, 77–82.
(72) Gage, J. R.; Evans, D. A. in *Org. Synth.* **1989**, *68*, 83–90.

R_f 0.43 (30:70 ethyl acetate–hexane). Unpurified **2a-*S*** (R = Bn) was used directly in the subsequent azide displacement reaction.

(3(2*R*),4*S*)-3-(2-Azido-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (3a-*R*, R = $CH_2C_6H_5$). To 4.85 mmol of unpurified bromide **2a-*S*** (R = Bn) in 20 mL of CH_2Cl_2 was added 1.15 g (7.28 mmol, 1.5 equiv) of tetramethylguanidinium azide TMGA[22] in 15 mL of CH_2Cl_2. The reaction was stirred for 0.5 h at 0 °C and for 1.0 h at 25 °C. The product was isolated according to the general procedure to give a yellow solid. HPLC diastereomer analysis (20:80 *tert*-butyl methyl ether–isooctane, 2 mL/min) afforded a 94:6 ratio of 2*R* and 2*S* diastereomers (t_R 5.98 and 7.26 min, respectively). Purification by flash chromatography (using eluent gradient 20:80 hexane–dichloromethane to CH_2Cl_2) yielded 1.41 g (>99% diastereomeric purity) of the title compound as a white crystalline solid in a 83% overall yield for the bromination and azide displacement steps: R_f 0.30 (30:70 ethyl acetate–hexane); mp 116–117 °C; IR (CH_2Cl_2) 2118, 1784, 1707 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36–7.13 (m, 10 H, aromatic Hs), 5.24 (q, 1 H, *J* = 4.9 Hz, C_2-C*H*N_3), 4.77–4.69 (m, 1 H, C_4-C*H*CH_2O), 4.32–4.19 (m, 2 H, C_5-CH_2O), 3.31 (dd, 1 H, *J* = 4.9, 13.6 Hz, C_3-C*H*HPh), 3.21 (dd, 1 H, *J* = 3.3, 13.5 Hz, C*H*HPh), 3.04 (dd, 1 H, *J* = 9.4, 13.6 Hz, C_3-*H*HPh), 2.70 (dd, 1 H, *J* = 9.4, 13.4 Hz, C*H*HPh); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.3, 152.8, 135.9, 129.4, 129.0, 128.6, 127.5, 127.3, 66.6, 61.2, 55.1, 47.8, 47.7; $[\alpha]_D$ + 68.0° (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.12; H, 5.19. Found: C, 65.20; H, 5.26.

(3(2*S*),4*S*)-3-(2-Bromo-4-methyl-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone (2b-*S*, R = CH_2CHMe_2). The boron enolate formed from 1.059 g of acyloxazolidinone **1b** (R = CH_2CHMe_2), 1.089 g (3.96 mmol, 1.05 equiv) of dibutylboryl triflate,[66] and 0.597 g (4.61 mmol, 1.2 equiv) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added to 0.753 g (4.23 mmol, 1.1 equiv) of NBS in 10 mL of CH_2Cl_2. After the reaction was stirred for 1.25 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (20:80 *tert*-butyl methyl ether–hexane, 2 mL/min) afforded a 5.2:94.8 ratio of 2*R* and 2*S* diastereomers (t_R 3.73 and 4.71 min, respectively). R_f 0.61 (10:90 hexane–dichloromethane). Unpurified **2b-*S*** (R = CH_2CHMe_2) was used directly in the subsequent azide displacement reaction.

(3(2*R*),4*S*)-3-(2-Azido-4-methyl-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone (3b-*R*, R = CH_2CHMe_2). To 3.85 mmol of unpurified bromide **2b-*S*** (R = CH_2CHMe_2) in 20 mL of CH_2Cl_2 was added 1.83 g (11.5 mmol, 3.0 equiv) of tetramethylguanidinium azide (TMGA).[22] The reaction was stirred 3.0 h at 0 °C. The product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (10:90 hexane–dichloromethane, 1.5 mL/min) afforded 95:5 ratio of 2*R* and 2*S* diastereomers (t_R 5.98 and 7.26 min, respectively). Purification by medium-pressure chromatography (using eluent gradient 20:80 hexane–dichloromethane to 10:90 hexane–dichloromethane) yielded, after rechromatography of mixed fractions, 1.41 g (>99% diastereomeric purity) of the title compound as a white crystalline solid in 86% overall yield for the bromination and azide displacement reactions: mp 50–51 °C; R_f 0.35 (30:70 ethyl acetate–hexane); IR (neat) 3125–2840, 2111, 1788, 1705, 1395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5 H, aromatic Hs), 4.92 (dd, 1 H, *J* = 3.8, 10.4 Hz, C_2-C*H*N_3), 4.76–4.70 (m, 1 H, C_4-C*H*CH_2O), 4.31–4.20 (m, 2 H, C_5-CH_2O), 3.28 (dd, 1 H, *J* = 3.3, 13.4 Hz, C*H*HPh), 2.80 (dd, 2 H, *J* = 9.5, 13.4 Hz, C*H*HPh), 1.93–1.89 (m, 1 H, C_4-C*H*$(CH_3)_2$), 1.89–1.62 (m, 2 H, C_3-CH_2CH$(CH_3)_2$), 1.04 (d, 3 H, *J* = 3.8 Hz, CH-(CH_3)(CH_3)), 1.02 (d, 3 H, *J* = 3.7 Hz, CH(CH_3)(CH_3)); ^{13}C (75.5 MHz, $CDCl_3$) δ 171.7, 152.7, 134.7, 129.4, 129.0, 127.5, 66.8, 58.8, 55.1, 39.6, 37.8, 25.4, 23.1, 21.0; $[\alpha]_D$ +20.0 (*c* 1.08, CH_2Cl_2). Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.74; H, 6.37. Found: C, 60.81; H, 6.43.

(3(2*S*),4*S*)-3-(2-Bromo-1-oxo-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (2c-*S*, R = $CH_2CH{=}CH_2$). The boron enolate formed from 0.975 g (3.76 mmol, 1.0 equiv) of acyloxazolidinone **1c** (R = $CH_2CH{=}CH_2$), 1.11 g (4.05 mmol, 1.08 equiv) of dibutylboryl triflate,[66] and 0.598 g (4.63 mmol, 1.2 equiv) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added to 0.721 g (4.05 mmol, 1.08 equiv) of NBS in 10 mL of CH_2Cl_2. After the reaction was stirred for 1 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (85:15 isooctane–*tert*-butyl methyl ether, 2 mL/min) afforded a 6.4:93.6 ratio of 2*R* and 2*S* diastereomers (t_R 4.54 and 7.23 min, respectively). R_f 0.25 (20:80 ethyl acetate–hexane). Unpurified **2c** (R = $CH_2CH{=}CH_2$) was used directly in the subsequent azide displacement reaction.

(3(2*R*),4*S*)-3-(2-Azido-1-oxo-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (3c-*R*, R = $CH_2CH{=}CH_2$). To 3.76 mmol of unpurified bromide **2c-*S*** (R = $CH_2CH{=}CH_2$) in 10 mL of CH_2Cl_2 was added 1.78 g (11.3 mmol, 3.0 equiv) of TMGA.[22] The reaction was stirred 2 h at 0 °C. The product was isolated according to standard procedure to give a yellow oil. HPLC diastereomer analysis (10:90 isooctane–CH_2Cl_2, 1.5 mL/min) afforded a 93.5:6.5 ratio of 2*R* and 2*S* diastereomers (t_R 6.88 and 8.35 min, respectively). Purification by flash chromatography (using eluent gradient 50:50 dichloromethane–hexane to dichloromethane) yielded, after rechromatgraphy of mixed fractions, 0.922 g (>99% diastereomeric purity) of the title compound as a clear colorless oil in 82% overall yield for the bromination and azide displacement steps: R_f 0.39 (10:90 hexane–dichloromethane); IR (neat) 2860–3100, 2110, 1785, 1708, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5 H, aromatic Hs), 5.94–5.80 (m, 1 H, C_4-C*H*$=CH_2$), 5.28 (d, 1 H, *J* = 17.1 Hz, C_5-CH=C*H*H), 5.22 (d, 1 H, *J* = 9.8 Hz, C_5-CH=CH*H*), 5.02 (dd, 1 H, *J* = 5.3, 8.2 Hz, C_2-C*H*N_3), 4.76–4.68 (m, 1 H, C_4-C*H*CH_2O), 4.32–4.20 (m, 2 H, C_5-CH_2O), 3.29 (dd, 1 H, *J* = 3.3, 13.3 Hz, C*H*HPh), 2.80–2.57 (m, 3 H, C*H*HPh overlapping with C_3-CHN$_3$CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.3, 152.8, 134.7, 132.0, 129.3, 129.0, 127.5, 119.4, 66.8, 59.4, 55.3, 37.9, 35.8; $[\alpha]_D$ +38.7 (*c* 1.51, CH_2Cl_2). Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37. Found: C, 59.85; H, 5.32.

(3(2*S*),4*S*)-3-(2-Bromo-1-oxo-2-phenylethyl)-4-(phenylmethyl)-2-oxazolidinone (2d-*S*, R = C_6H_5). The boron enolate formed from 1.50 g (5.08 mmol) of acyloxazolidinone **1d** (R = C_6H_5), 1.46 g (5.33 mmol, 1.05 equiv) of dibutylboryl triflate,[66] and 0.788 g (6.10 mmol, 1.2 equiv) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added to 0.800 g (5.33 mmol, 1.05 equiv) of NBS in 10 mL of CH_2Cl_2. After the reaction was stirred for 1 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (85:15 isooctane–*tert*-butyl methyl ether, 2 mL/min) afforded a 22:78 ratio of 2*R* and 2*S* diastereomers (t_R 4.54 and 7.23 min, respectively). R_f 0.39 (90:10 dichloromethane–hexane). Unpurified **2d-*S*** (R = Ph) was used directly in the subsequent azide displacement reaction.

(3(2*R*),4*S*)-3-(2-Azido-1-oxo-2-phenethyl)-4-(phenylmethyl)-2-oxazolidinone (3d-*R*, R = C_6H_5). To 5.08 mmol unpurified bromide **2d-*S*** (R = C_6H_5) in 50 mL of CH_2Cl_2 was added 2.41 g (15.2 mmol, 3.0 equiv) of TMGA.[22] The reaction was stirred 1 h at −23 °C. The product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (10:90 isooctane–CH_2Cl_2, 1.5 mL/min) afforded a 78:22 ratio of 2*R* and 2*S* diastereomers (t_R 5.11 and 8.35 min, respectively). Purification by flash chromatography (using eluent gradient 20:80 dichloromethane–hexane to dichloromethane) yielded, after rechromatography of mixed fractions, 1.19 g (>99% diastereomeric purity) of the title compound as a clear, colorless oil in 67% overall yield for the bromination and azide displacement steps: R_f 0.32 (10:90 hexane–dichloromethane); IR (neat) 2860–3110, 2100, 1785, 1705, 1500, 1458, 1390, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.53–7.43 (m, 5 H, aromatic Hs), 7.25–7.19 (m, 3 H, aromatic Hs), 7.03–6.99 (m, 2 H, aromatic Hs), 6.12 (s, 1 H, C_2-C*H*N_3), 4.83–4.75 (m, 1 H, C_4-C*H*CH_2O), 4.23 (t, 1 H, *J* = 9.1 Hz, C_5-C*H*HO), 4.12 (dd, 1 H, *J* = 3.2, 9.2 Hz, C_5-C*H*HO), 3.20 (dd, 1 H, *J* = 3.5, 13.4 Hz, C*H*HPh), 2.61 (dd, 1 H, *J* = 9.1, 13.4, C*H*HPh); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.1, 152.5, 134.4, 132.9, 129.5, 129.3, 129.1, 128.9, 128.7, 127.4, 66.5, 63.5, 54.9, 37.3; $[\alpha]_D$ −100.3 (*c* 0.57, CH_2Cl_2). Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79. Found: C, 64.34; H, 4.80.

(3(2*S*),4*S*)-3-(2-Bromo-3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (2e-*S*, R = $CHMe_2$). The boron enolate formed from 0.500 g (1.91 mmol) of acyloxazolidinone **1e** (R = $CHMe_2$), 0.551 g (2.01 mmol, 1.05 equiv) of dibutylboryl triflate,[66] and 0.296 g (2.39 mmol, 1.2 equiv) of diisopropylethylamine in 10 mL of CH_2Cl_2 was added to 0.374 g (2.10 mmol, 1.1 equiv) of NBS in 10 mL of CH_2Cl_2. After the reaction was stirred for 1.25 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (90:10 isooctane–*tert*-butyl methyl ether, 2 mL/min) afforded a 4.4:95.6 ratio of 2*R* and 2*S* diastereomers (t_R 6.09 and 10.16 min, respectively). R_f 0.37 (30:70 ethyl acetate–hexane). Unpurified **2e-*S*** (R = $CHMe_2$) was used in the subsequent azide displacement reaction.

(3(2*R*),4*S*)-3-(2-Azido-3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (3e-*R*, R = $CHMe_2$). To 1.91 mmol of unpurified bromide **2e** (R = $CHMe_2$) in 3 mL of CH_2Cl_2 was added 0.907 g (5.73 mmol, 3.0 equiv) of TMGA.[22] The reaction was stirred 9 h at 25 °C. The product was isolated according to the general procedure to give a yellow oil. HPLC diastereomer analysis (10:90 *tert*-butyl methyl ether–isooctane, 2 mL/min) afforded a 94.1:6.9 ratio of 2*R* and 2*S* diastereomers (t_R 7.71 and 13.34 min, respectively). Purification by flash chromatography (using eluent gradient 10:90 ethyl acetate–hexane to 15:85 ethyl acetate–hexane) yielded 0.464 g (>99% diastereomeric purity) of the title compound as a white crystalline solid in 80% overall yield for the bromination and azide displacement steps: mp 52 °C; R_f 0.41 (30:70 ethyl acetate–hexane); IR ($CHCl_3$) 3100–2860, 2112, 1784, 1710, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5 H, aromatic Hs), 4.91 (d, 1 H, *J* = 6.4 Hz, C_2C*H*N_3), 4.81–4.71 (m, 1 H, C_4C*H*CH_2O),

4.29–4.17 (m, 2 H, C_5CH_2O), 3.37 (dd, 1 H, J = 3.4, 13.2 Hz, CHHPh), 2.71 (dd, 1 H, J = 10.1, 13.2 Hz, CHHPh), 2.40–2.26 (m, 1 H, C_3CH-$(CH_3)_2$), 1.10 (d, 3 H, J = 4.4 Hz, $CH(CH_3)(CH_3)$), 1.07 (d, 3 H, J = 4.4 Hz, $CH(CH_3)(CH_3)$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.3, 152.9, 134.9, 129.7, 129.0, 127.5, 66.7, 65.4, 55.3, 38.1, 31.2, 19.5, 17.6; $[\alpha]_D$ +32.7 (c 1.42, CH_2Cl_2). Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00. Found: C, 59.77; H, 6.02.

(3(2*S*),4*S*)-3-(2-Bromo-3,3-dimethyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (2f-*S*, R = CMe_3). The boron enolate formed from 500 mg (1.82 mmol) of acyloxazolidinone **1f** (R = *tert*-butyl), 499 mg (1.91 mmol, 1.05 equiv) of dibutylboryl triflate,[66] and 282 mg (2.18 mmol, 1.2 equiv) of diisopropylethylamine in 5 mL of CH_2Cl_2 was added to 356 mg (2.00 mmol, 1.10 equiv) of NBS in 2 mL of CH_2Cl_2. After the reaction was stirred for 1 h at −78 °C, the product was isolated according to the general procedure to give a yellow oil. Purification by flash chromatography (3 × 25 cm silica gel, 20:80 ethyl acetate–hexane) provided the pure product as a clear and colorless oil: R_f 0.46 (30:70 ethyl acetate–hexane); IR (neat) 3100–2876, 1780 (b), 1709 (b), 1607, 1498, 1480, 1465, 1455, 1375 (b), 1270, 1210, 1108 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5 H, aromatic *H*s), 5.77 (s, 1 H, CHBr), 4.75–4.70 (m, 1 H, $CHCH_2O$), 4.22–4.18 (m, 2 H, CH_2O), 3.28 (dd, 1 H, J = 3.2, 13.5 Hz, CHHPh), 2.79 (dd, 1 H, J = 9.4, 13.5 Hz, CHHPh), 1.20 (s, 9 H, $C(CH_3)_3$); $[\alpha]_D$ +77.7° (c 0.655, CH_2Cl_2). Anal. Calcd for $C_{16}H_{20}NO_3Br$: C, 54.25; H, 5.69. Found: C, 54.30; H, 5.72.

(4*S*)-3-(2-Diazo-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidone (5a, R = $CH_2C_6H_5$). Method A. A solution of 1.00 mmol (1.15 equiv) of sodium hexamethyldisilazide (NaHMDS) in THF (4.0 mL), stirred at −78 °C under dry N_2, was treated via rapid cannulation with a precooled (−78 °C) solution of 269 mg (0.87 mmol) of **1a** in 3 mL of dry THF. Residual **1a** was rinsed in with two 1-mL portions of dry THF, and the resulting solution was stirred at −78 °C for 15 min. To the above solution of the sodium enolate was added via rapid cannulation a precooled (−78 °C) solution of *p*-nitrobenzenesulfonyl azide (PNBSA) (251 mg, 1.10 mmol, 1.26 equiv) in 3 mL of dry THF. Residual PNBSA was rinsed in with two 1-mL portions of THF, and the resulting yellow-orange solution was stirred at −78 °C for 60 min. Trimethylsilyl chloride (TMS-Cl) (0.25 mL, 210 mg, 2.0 mmol, 2.3 equiv) was added, and the pale yellow solution was stirred at −78 °C for 1 h and was then poured into ice-cold aqueous pH 7 phosphate buffer. The mixture was extracted with 3 portions of CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was flash chromatographed on 40 g of silica gel eluting with hexane–EtOAc (80:20) to yield 253 mg (87%) of **5a** (R = $CH_2C_6H_5$) as a viscous yellow oil: TLC R_f = 0.38 (silica, toluene–Et_2O (10:1)); IR (neat) 2090, 1774, 1735 (w), 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 10 H, aromatics), 4.879–4.784 (sym m, 1 H, NCH), 4.281 (apparent t, J = 8.4 Hz, 1 H, NHC*H*HO), 4.107 (dd, J = 7.7, 8.8 Hz, 1 H, NHCH*H*O), 3.786 (s, 2 H, CH_2N_2), 3.271 (dd, J = 3.8, 13.5 Hz, 1 H, 4-CH*H*C_6H_5), 2.809 (dd, J = 8.7, 13.5 Hz, 1 H, 4-CH*H*C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.47 (s), 152.85 (s), 136.34 (s), 134.84 (s), 129.12 (d), 128.70 (d), 128.31 (d), 127.14 (d), 127.09 (d), 66.91 (t), 63.87 (s), 55.42 (d), 37.68 (t), 30.23 (t); $[\alpha]_D^{25}$ +126° (c = 1.26, $CHCl_3$). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11. Found: C, 67.95; H, 4.96.

Method B. In an experiment otherwise identical with that described above, the sodium enolate was treated with the PNBSA at −78 °C for 30 min prior to the addition of 5 mL of aqueous pH 7 phosphate buffer. The resulting solution was warmed to 25 °C and the product was isolated as described above to afford 250 mg (85% yield) of **5a**.

General Optimized Procedure for the Direct Azide Transfer to the Carboximide Potassium Enolates (Table V). To 3 mL of dry THF, stirred at −78 °C under N_2, was added 2.00 mL (0.960 mmol, 1.1 equiv) of potassium hexamethyldisilazide (KHMDS) (0.48 M in toluene). To the resulting solution was added via cannula a precooled (−78 °C) solution of 0.87 mmol of the imide **1** in 3 mL of dry THF. Residual imide was rinsed in with two 1-mL portions of THF, and stirring was continued at −78 °C for 30 min.

To the above solution of potassium enolate, stirred at −78 °C, was added via cannulation a precooled (−78 °C) solution of 330–340 mg (1.07–1.10 mmol, 1.23–1.26 equiv) of trisyl azide[33] in 3 mL of THF. After 1–2 min the reaction was quenched with 0.23 mL (4.0 mmol, 4.6 equiv) of glacial acetic acid. The cooling bath was removed, and the reaction was stirred at room temperature for 10–12 h (method A) or, alternately, warmed immediately to 25–30 °C for 30 min with a warm water bath (method B). The solution was partitioned between CH_2Cl_2 (40 mL) and dilute brine (40 mL). The aqueous phase was washed with CH_2Cl_2 (×3). The organic phases were combined, washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated in vacuo. Diastereomeric ratios of the resulting crude product, purified by filtration of an approximate 20-mg aliquot dissolved in CH_2Cl_2–EtOAc (8:2) through 0.5 g of silica gel, were determined by HPLC analysis on a 4.6 mm × 25 cm 5 μ Zorbax silica column eluting with the indicated solvent at 2.0 mL/min. The crude product was purified by medium-pressure chromatography (MPLC) on Michel-Miller columns packed with silica gel (Merck Si 60, 230–400 mesh) with typical column loadings of 0.3–1 g of material per 100 g of adsorbant (see below for solvent).

(3(2*S*),4*S*)-3-(2-Azido-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (3a-*S*, R = $CH_2C_6H_5$). As described above (method B, 1 min reaction time), 269 mg (0.87 mmol) of **1a** (R = $CH_2C_6H_5$) afforded 278 mg (91%) of **3a-*S*** (R = $CH_2C_6H_5$) as a white solid after purification by MPLC (50 g of silica gel; 1-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2). Diastereomer analysis [HPLC; CH_2Cl_2–isooctane (80:20)] of the unpurified product gave a 2*S* (t_R = 4.59 min):2*R* (minor diastereomer, t_R = 6.65 min) ratio of 97:3. The chromatographed product gave a 2*S*:2*R* ratio >200:1. The analytical sample was recrystallized from Et_2O–hexane: mp 86–87.5 °C; IR ($CHCl_3$) 2105, 1780, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 10 H, aromatics), 5.279 (dd, J = 5.7, 9.1 Hz, 1 H, 2-H), 4.62–4.55 (m, 1 H, 4-H), 4.18 (dd, J = 2.7, 9.1 Hz, 1 H, OC*H*H), 4.08 (dd, J = 7.7, 9.2 Hz, 1 H, OCH*H*), 3.33 (dd, J = 3.2, 13.4 Hz, 1 H, 4-CH*H*C_6H_5), 3.21 (dd, J = 5.7, 13.5 Hz, 1 H, CH*H*CHN_3), 3.07 (dd, J = 9.1, 13.5 Hz, 1 H, CH*H*CHN_3), 2.82 (dd, J = 9.6, 13.4 Hz, 1 H, 4-CH*H*C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.43, 152.72, 135.65, 134.73, 129.37, 129.29, 129.01, 128.65, 127.50, 127.28, 66.52, 61.20, 55.39, 37.59; $[\alpha]^{25}_D$ +108.0° (c = 1.02, $CHCl_3$). Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18. Found: C, 64.95; H, 5.18.

(3(2*S*),4*S*)-3-(2-Azido-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (3b-*S*, R = CH_3). As described above (method B, 1 min reaction time), 203 mg (0.87 mmol) of **1b** (R = CH_3) afforded 176 mg (74%) of **3b-*S*** (R = CH_3) as a faintly yellow oil after purification by MPLC (50 g of silica gel; 1-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2 followed by 0.5 L of CH_2Cl_2). Diastereomer analysis [HPLC; CH_2Cl_2–isooctane (90:10)] of the unpurified product gave a 2*S* (t_R = 5.72 min):2*R* (minor diastereomer, t_R = 7.31 min) ratio of 97:3. The purified product gave a 2*S*:2*R* ratio >200:1: IR (neat) 2115, 1782, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5 H, aromatics), 5.045 (q, J = 6.9 Hz, 1 H, 2-H), 4.73–4.65 (m, 1 H, 4-H), 4.31–4.22 (m, 2 H, OCH_2), 3.345 (dd, J = 3.3, 13.4 Hz, 1 H, CH*H*C_6H_5), 2.831 (dd, J = 9.5, 13.4 Hz, 1 H, CH*H*C_6H_5), 1.563 (d, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.30, 152.66, 134.64, 129.27, 128.89, 127.35, 66.49, 55.81, 55.19, 37.37, 16.27; $[\alpha]^{25}_D$ +146° (c = 1.11, $CHCl_3$). Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14. Found: C, 57.07; H, 5.09.

(3(2*S*),4*S*)-3-(2-Azido-1-oxo-4-pentenyl)-4-(phenylmethyl)-2-oxazolidinone (3c-*S*, R = $CH_2CH{=}CH_2$). As described above (method B, 1 min reaction time), 226 mg (0.87 mmol) of **1c** (R = $CH_2CH{=}CH_2$) afforded 205 mg (78%) of **3c-*S*** (R = $CH_2CH{=}CH_2$) as a faintly yellow, viscous oil after purification by MPLC [50 g of silica gel; 1-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2]. Diastereomer analysis [HPLC; CH_2Cl_2–isooctane (90:10)] of the unpurified product gave a 2*S* (t_R = 4.13 min):2*R* (minor diastereomer, t_R = 5.96 min) ratio of 97:3. The purified product gave a 2*S*:2*R* ratio >200:1: IR (neat) 2105, 1782, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5 H, aromatics), 5.860 (ddt, J_{cis} = 10.0 Hz, J_{trans} = 17.1, J_{allyl} = 7.0, 1 H, $H_2C{=}CH$), 5.258 (dm, J_{trans} = 17.1 Hz, 1 H, $H_cC{=}CHCH_2$), 5.204 (dm, J_{cis} = 10.0 Hz, 1 H, $H_tC{=}CHCH_2$), 5.084 (dd, J = 5.5, 8.3 Hz, 1 H, 2-H), 4.72–4.64 (m, 1 H, 4-H), 4.29–4.22 (m, 2 H, OCH_2), 3.342 (dd, J = 3.3, 13.4 Hz, 1 H, CH*H*C_6H_5), 2.837 (dd, J = 9.5, 13.4 Hz, 1 H, CH*H*C_6H_5), 2.72–2.54 (m, 2 H, $H_2C{=}CHCH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.27, 152.85, 134.73, 132.11, 129.40, 129.07, 127.54, 119.39, 66.63, 59.60, 55.39, 37.65, 35.62; $[\alpha]^{25}_D$ +112° (c = 1.19, $CHCl_3$). Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37. Found: C, 59.81; H, 5.27.

(3(2*S*),4*S*)-3-(2-Azido-2-phenyl-1-oxoethyl)-4-(phenylmethyl)-2-oxazolidinone (3d-*S*, R = C_6H_5). As described above (method B, 1 min reaction time), 257 mg (0.87 mmol) of **1d** (R = C_6H_5) afforded 241 mg (82%) of **3d-*S*** (R = C_6H_5) as a white solid after purification by MPLC (50 g of silica gel; 1-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2). Diastereomer analysis [500-MHz ^{1}H NMR integration of the benzylic protons (4-$CH_2C_6H_5$)] of the unpurified product gave a 2*S*:2*R* ratio of 91:9. Diastereomer analysis [HPLC; CH_2Cl_2–isooctane (90:10)] of the chromatographed product gave a 2*S* (t_R = 3.61):2*R* (t_R = 6.24) ratio >200:1. The analytical sample was recrystallized from hexane–EtOAc to give fine white needles: mp 107.5–108.5 °C; IR ($CHCl_3$) 2107, 1785, 1707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.23 (m, 10 H, aromatics), 6.145 (s, 1 H, 2-H), 4.69–4.61 (m, 1 H, 4-H), 4.195–4.077 (AB m of ABX system, 2 H, OCH_2), 3.420 (dd, J = 3.2, 13.4 Hz, 1 H, 4-CH*H*C_6H_5), 2.854 (dd, J = 9.7, 13.4 Hz, 1 H, 4-CH*H*C_6H_5); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.39, 152.41, 134.81, 132.97, 129.54, 129.43, 129.15, 129.09, 128.62, 127.56, 66.46, 63.72, 55.72, 37.75; $[\alpha]^{25}_D$ +278° (c = 1.02, $CHCl_3$). Anal. Calcd for

$C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79. Found: C, 64.40; H, 4.75.

(3(2*S*),4*S*)-3-(2-Azido-3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (3e-*S*, R = $CH(CH_3)_2$). As described above (method A, 2 min reaction time), 277 mg (0.87 mmol) of **1e** (R = $CH(CH_3)_2$) afforded 201 mg (77%) of **3e-*S*** (R = $CH(CH_3)_2$ as a colorless oil after purification by MPLC (50 g of silica gel; 1-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2). Diastereomer analysis [HPLC; CH_2Cl_2–isooctane (80:20)] of the unpurified product gave a 2*S* (t_R = 4.42 min):2*R* (t_R = 6.47 min) ratio of 98:2. The purified product gave a 2*S*:2*R* ratio >200:1: IR (neat) 2107, 1785, 1703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5 H, aromatics), 4.933 (d, J = 7.0 Hz, 1 H, 2-H), 4.75–4.67 (m, 1 H, 4-H), 4.29–4.22 (m, 2 H, OCH_2), 3.345 (dd, J = 3.2, 13.4 Hz, 1 H, 4-C*H*HC_6H_5), 2.861 (dd, J = 9.4, 13.4 Hz, 1 H, 4-CH*H*C_6H_5), 2.253 (d of septets, J = 7.0, 6.8 Hz, 1 H, C*H*$(CH_3)_2$), 1.075 (d, J = 6.7 Hz, 3 H, $CH(CH_3)$, 1.039 (d, J = 6.7 Hz, 3 H, $CH(CH_3)$; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.26, 152.88, 134.79, 129.43, 129.04, 127.53, 66.48, 65.55, 55.47, 37.65, 30.90, 19.43, 17.90; $[\alpha]^{25}_D$ +97.2° (c = 1.01, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00. Found: C, 59.53; H, 6.04.

(3(2*S*),4*S*)-3-(2-Azido-3,3-dimethyl-1-oxobutyl)-1-(phenylmethyl)-2-oxazolidinone (3f-*S*, R = $C(CH_3)_3$). Following a 10-fold scaleup of the general procedure (method A, 2 min reaction time), 2.40 g (8.70 mmol) of **1f** (R = $C(CH_3)_3$) afforded 2.49 g (90%) of **3f-*S*** (R = $C(CH_3)_3$) as a faintly yellow, viscous oil after purification by MPLC (320 g of silica gel; 5-L linear gradient from CH_2Cl_2–hexane (6:4) to CH_2Cl_2). Diastereomer analysis [HPLC; isooctane–*t*-BuOMe (85:15)] of the unpurified product gave a 2*S* (t_R = 6.48 min):2*R* (t_R = 3.55 min) ratio of >99:1. The purified product gave a 2*S*:2*R* ratio >200:1: IR (neat) 2107, 1785, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5 H, aromatics), 5.255 (s, 1 H, 2-H), 4.76–4.69 (m, 1 H, 4-H), 4.25–4.19 (m, 2 H, OCH_2), 3.335 (dd, J = 3.1, 13.4 Hz, 1 H, 4-C*H*HC_6H_5), 2.868 (dd, J = 9.4, 13.4 Hz, 1 H, 4-CH*H*C_6H_5), 1.089 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.09, 153.07, 134.81, 129.40, 129.01, 127.48, 66.74, 66.21, 55.59, 37.65, 36.78, 26.27; $[\alpha]^{25}_D$ +45.9° (c = 1.48, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.74; H, 6.37. Found: C, 60.92; H, 6.42.

Isolation of the Intermediate (3(2*S*),4*S*)-3-[2-[3-[[2,4,6-tris(1-methylethyl)phenyl]sulfonyl]triazino]-3-methyl-1-oxobutyl]-4-(phenylmethyl)-2-oxazolidinone (6). In a procedure that was otherwise identical with the preparation of **3e-*S*** (R = $CH(CH_3)_2$), following the acetic acid quench, the reaction was warmed to −30 °C for 13 h. The cold solution was partitioned between half-saturated aqueous NaCl and CH_2Cl_2. The aqueous phase was rapidly extracted with two additional portions of CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo without heating. The pale-yellow residual oil was chromatographed (gradient elution MPLC) on one size B Michel-Miller column (~50 g of silica gel) eluting with a 1-L linear gradient from hexane–EtOAc (80:20) to hexane–EtOAc (50:50) at a rate of 27 mL/min. Fractions 13–19 (25 mL each), found to contain 6 along with a minor, faster moving impurity, were rechromatographed as described above to afford 279 mg (56% yield) of 6 as a colorless glass foam: TLC R_f = 0.23 (silica, hexane–EtOAc (70:30)); IR (CCl_4) 3445, 3300, 2970, 2935, 2875, 1793, 1710, 1603, 1468, 1387, 1335, 1210, 1195, 1165, 1155, 1108, 700, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (br s, 0.2 H, NH (**6b**)), 8.78 (d, J = 5.9 Hz, 0.8 H, NH (**6a**)), 7.35–7.14 (m, 7 H, aromatics), 6.00 (dd, J = 5.8, 5.1 Hz, 0.8 H, CHC=O (**6a**)), 5.59 (d, J = 3.8 Hz, 0.2 H, CHC=O (**6b**)), 4.68–4.60 (m, 1 H, NC*H*CH_2O), 4.26–4.21 (m, 2 H, NCHC*H*$_2$O), 4.18–3.98 (m, 2 H, aromatic C*H*$(CH_3)_2$), 3.33–3.23 (m, 1 H, C*H*HC_6H_5), 2.93–2.69 (m, 2 H, aromatic C*H*$(CH_3)_2$ and CH*H*C_6H_5), 2.41–2.30 (m, 0.8 H, $(CH_3)_2CHCHN_3$ (**6a**)), 2.29–2.15 (m, 0.2 H, $(CH_3)_2CHCHN_3$ (**6b**)), 1.30–1.18 (m, 18 H, aromatic $CH(CH_3)_2$), 1.10 (d, J = 6.9 Hz, 2.3 H, CH_3CHC=O (**6a**)), 1.05 (d, J = 7.0 Hz, 2.3 H, CH_3CHC=O (**6a**)), 0.901 (d, J = 6.8 Hz, 0.7 H, CH_3CHC=O (**6b**)), 0.851 (d, J = 6.9 Hz, 0.7 H, CH_3CH-C=O (**6b**)); FAB MS (glycerol–nitrobenzyl alcohol) m/e 571 (M + H^+), 543, 277 (base peak).

Preparation of an Authentic Sample of (4*S*)-3-(2-Diazo-3-methyl-1-oxobutyl)-4-(phenylmethyl)-2-oxazolidinone (5e-*R*, = $CH(CH_3)_2$). A solution of 0.96 mmol (1.1 equiv) of sodium hexamethyldisilazide (NaHMDS) in THF (4.0 mL), stirred at −78 °C under dry N_2 was treated via rapid cannulation with a precooled (−78 °C) solution of 277 mg (0.87 mmol) of **1e** (R = $CH(CH_3)_2$) in 3 mL of dry THF. Residual **1e** was rinsed in with two 1-mL portions of dry THF, and the resulting solution was stirred at −78 °C for 30 min. To the above solution of the sodium enolate was added via rapid cannulation a precooled (−78 °C) solution of PNBSA (251 mg, 1.10 mmol, 1.26 equiv) in 3 mL of dry THF. The resulting yellow-orange solution was stirred at −78 °C for 30 min. The reaction was quenched at −78 °C by the addition of 5 mL of pH 7 aqueous phosphate buffer. The reaction was warmed to 25 °C, diluted with pH 7 aqueous phosphate buffer, and extracted with three portions of CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), and evaported in vacuo. The residue was flash chromatographed on 50 g of silica gel eluting with CH_2Cl_2. Fractions containing the yellow band were rechromatographed (gradient elution MPLC) on one size B Michel-Miller column (~50 g of silica gel) eluting with a 1-L linear gradient from hexane–*tert*-butyl methyl ether (90:10) to hexane–*tert*-butyl methyl ether (70:30) to yield 82 mg (34%) of **5e** (R = $CH(CH_3)_2$) as a viscous yellow oil: TLC R_f = 0.36 [silica, hexane–*tert*-butyl methyl ether (1:1)]; IR (neat) 3030, 2970, 2930, 2870, 2085, 1775, 1645, 1455, 1390, 1367, 1345, 1295, 1212, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 3 H, aromatics), 7.18–7.15 (m, 2 H, aromatics), 4.873–4.802 (sym m, 1 H, CH_2CHN), 4.287 (t, J = 8.6 Hz, 1 H, OC*H*H), 4.109 (dd, J = 7.4, 8.6 Hz, 1 H, OCH*H*), 3.264 (dd, J = 4.0, 13.5 Hz, 1 H, C*H*HC_6H_5), 2.954 (septet, J = 6.9 Hz, 1 H, C*H*$(CH_3)_2$), 2.828 (dd, J = 8.6, 13.5 Hz, 1 H, CH*H*C_6H_5), 1.195 (d, J = 6.9 Hz) and 1.188 (d, J = 6.9 Hz) (6 H total, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.29, 152.85, 135.04, 129.20, 128.78, 127.23, 68.52, 66.99, 55.44, 38.03, 24.13, 20.20, 19.84; $[\alpha]^{23}_D$ +181° (c = 1.08, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.70; H, 5.96. Found: C, 62.80; H, 5.87.

General Procedure for Studies of the Decomposition of Intermediate 6 (Table VII). A solution of 57.1 mg (0.10 mmol) of 6 in 1.25 mL of dry THF was treated with 0.20 mmol of the indicated reagent and stirred under N_2 at 25 °C for 13 h. The resulting solution was partitioned between half-saturated aqueous NaCl and CH_2Cl_2. The aqueous phase was extracted with three portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography of the residue on 12 g of silica gel eluting with 100 mL of hexane–EtOAc (90:10) followed by 100 mL of hexane–EtOAc (80:20) afforded a mixture of **3e**, **5e** and **7**, the respective molar ratios of which were determined by 300 MHz ^1H NMR. This mixture was rechromatographed on 10 g of silica gel eluting with 75 mL of CH_2Cl_2–hexane (1:1) followed by 100 mL of CH_2Cl_2–hexane (1:1) to afford a baseline separation of **3e** in the indicated yield. Yields for **5e** and **7** (entries A–F) were calculated from the ratios in the mixture and the isolated yield of **3e**. For entries G and H, elution was continued with CH_2Cl_2 to afford **7** in the indicated isolated yield. Yields for **3e** and **5e** (entries G and H) were calculated from the ratios in the mixture and the isolated yield of **7**.

Direct Azide (Diazo) Transfer to Benzyl Dihydrocinnamate (8) (Table VIII). Preparation of the Potassium Enolate Derived from 8. To a solution of 2.00 mL (0.96 mmol, 1.1 equiv) of KHMDS (0.48 M in toluene) and 3.0 mL of dry THF, stirred at −78 °C under dry N_2, was added via cannula a precooled (−78 °C) solution of 210 mg (0.87 mmol) of **8** in 3 mL of dry THF. Residual **8** was rinsed in with two 1-mL portions of THF, and the resulting solution was stirred at −78 °C for 30 min.

Preparation of the Lithium Enolate Derived from 8. To a solution of 0.96 mmol (1.1 equiv) of LDA, prepared from 0.14 mL (1.0 mmol) of diisopropylamine and 0.62 mL (0.96 mmol, 1.1 equiv) of *n*-butyllithium (1.54 M in hexane) in 3.0 mL of dry THF, stirred at −78 °C under dry N_2, was added via cannula a precooled (−78 °C) solution of 210 mg (0.87 mmol) of **8** in 3 mL of dry THF. Residual **8** was rinsed in with two 1-mL portions of THF, and the resulting solution was stirred at −78 °C for 30 min.

Benzyl 2-Azidodihydrocinnamate (9) (Entry C). A stirred solution of the lithium enolate, prepared as described above from 210 mg (0.873 mmol) of **8** and 0.874 mmol (1.00 equiv) of LDA, was treated via rapid cannulation at −78 °C with a precooled (−78 °C) solution of 325 mg (1.05 mmol, 1.2 equiv) of trisyl azide[33] in 3 mL of dry THF. After 2 min the reaction was quenched with 0.11 mL (120 mg, 1.9 mmol, 2.2 equiv) of glacial acetic acid. The cooling bath was removed, and the reaction was stirred at 25 °C for 12 h. Following the standard workup (vide supra), the CH_2Cl_2 extracts were flash chromatographed on 40 g of silica gel eluting with hexane–*tert*-butyl methyl ether (96:4) to afford 186 mg of pale-yellow oil found by 300-MHz ^1H NMR to be a mixture of **8**, **9**, and **11** in the respective molar ratios of 1.89:70.9:1.00. Calculated yields: **8** (2% recovery), **9** (73%), **11** (1%).

Benzyl 2-Diazodihydrocinnamate (11) (Entry F). A stirred solution of the lithium enolate, prepared as described above from 210 mg (0.873 mmol) of **8** and 0.954 mmol (1.10 equiv) of LDA, was treated via rapid cannulation at −78 °C with a precooled (−78 °C) solution of 249 mg (1.09 mmol, 1.2 equiv) of PNBSA in 3 mL of dry THF. Immediately the reaction turned a deep wine color. After 15 min the reaction was quenched with 5 mL of aqueous pH 7 phosphate buffer and warmed to 25 °C. Following the standard workup, the CH_2Cl_2 extracts were flash chromatographed on 40 g of silica gel eluting with hexane–*tert*-butyl methyl ether (96:4) to afford 172 mg of a yellow oil found by 300-MHz ^1H NMR to be a mixture of **9** and **11** and in the respective molar ratio of 1.00:13.2. Calculated yields: **9** (5%), **11** (68%). This material was rechromatographed (MPLC) on one size B Michel-Miller column (50

g of silica gel) eluting with a 1-L linear gradient from hexane–CH_2Cl_2 (8:2) to hexane–CH_2Cl_2 (1:1) to afford 136 mg (58% isolated yield) (baseline separation was not achieved) of pure 2-diazo ester **11** as a yellow oil: TLC R_f = 0.34 (silica, CH_2Cl_2–hexane (6:4); IR ($CHCl_3$) 3065, 3030, 2085, 1693, 1497, 1455, 1383, 1335, 1295, 1253, 1173, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.22 (m, 10 H, aromatics), 5.230 (s, 2 H, CH_2O), 3.648 (s, 2 H, CH_2CN_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.93, 137.10, 136.04, 128.75, 128.48, 128.29, 128.14, 127.98, 128.29, 128.14, 127.98, 127.08, 66.46, 29.34; high-resolution MS *m/e* calcd for $C_{16}H_{14}N_2O_2$ 266.1055, found 266.1050.

(3*R,2*R**)-2-Azido-3-hydroxybutanoic Acid, Ethyl Ester and (3*R**,2*S**)-2-Azido-3-hydroxybutanoic Acid, Ethyl Ester (12).** To a solution of 4.23 mmol (2.2 equiv) of LDA, prepared in the usual manner from 0.62 mL (4.4 mmol, 2.3 equiv) of diisopropylamine and 2.66 mL (4.23 mmol, 2.2 equiv) of *n*-butyllithium (1.59 M in hexane) in 19 mL of dry THF, stirred at −78 °C under dry N_2, was added dropwise 250 μL (254 mg, 1.92 mmol) of ethyl 3-hydroxybutyrate (Aldrich, 99%). The resulting solution was warmed to −20 °C for 10 min and was then recooled to −78 °C. Hexamethylphosphoric triamide (HMPA) (1.84 mL, 1.90 g, 10.6 mmol, 5.5 equiv) was added in one portion. The reaction was warmed slightly until the frozen HMPA dissolved, and the solution was recooled to −78 °C. To the above enolate solution, stirred at −78 °C, was added via rapid cannulation a precooled (−78 °C) solution of 714 mg (2.31 mmol, 1.2 equiv) of trisyl azide[33] in 6 mL of dry THF. After 30 s, the reaction was quenched with 0.76 mL (796 mg, 13.3 mmol, 6.9 equiv) of glacial acetic acid. The resulting mixture was stirred at 25 °C for 3 h and was then partitioned between pH 7 aqueous phosphate buffer and CH_2Cl_2. The aqueous phase was extracted with three portions of CH_2Cl_2. The organic extracts (350 mL) were combined, dried ($MgSO_4$), and evaporated in vacuo. The residue was flash chromatographed on 50 g of silica gel, eluting with hexane–EtOAc (70:30) to remove the HMPA. The eluant was rechromatographed (MPLC) on one size B Michel-Miller column (50 g of silica gel) eluting with a 1-L linear gradient from CH_2Cl_2–hexane–CH_3CN (70:30:6) to CH_2Cl_2–hexane–CH_3CN (70:30:10) to afford 255 mg (77% yield) of **12** as a colorless oil, found by 300-MHz ^1H NMR to be an 82:18 ratio of anti and syn diastereomers, respectively: TLC R_f = 0.22 (silica, CH_2Cl_2–hexane–CH_3CN (70:30:7)); IR ($CHCl_3$) 3450 (br OH), 2982, 2935, 2105, 1740, 1375, 1263, 1197, 1095, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.302 (q, *J* = 7.1 Hz, CH_2O major isomer), 4.309 (q, *J* = 7.1 Hz, CH_2O minor isomer) and 4.30–4.22 (m, C*H*OH minor isomer) (2.2 H total), 4.192–4.088 (sextet, $J \approx 6.2$ Hz, 0.8 H, C*H*OH major isomer), 3.954 (d, *J* = 5.6 Hz, 0.8 H, CHC=O major isomer), 3.819 (d, *J* = 3.8 Hz, 0.2 H, CHC=O minor isomer), 2.418 (d, *J* = 6.4 Hz, 0.8 H, OH major isomer), 2.231 (d, *J* = 6.5 Hz, 0.2 H, OH minor isomer), 1.343 (t, *J* = 7.1 Hz, CH_2CH_3) and 1.318 (d, *J* = 6.3 Hz, $CHOHCH_3$ minor isomer) (3.6 H total), 1.279 (d, *J* = 6.3 Hz, 2.4 H, $CHOHCH_3$ major isomer); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.96 (*C*=O minor isomer), 168.77 (*C*=O major isomer), 68.16 (minor isomer), 67.96 (major isomer), 67.20 (minor isomer), 67.13 (major isomer), 61.90, 19.68 (minor isomer), 18.81 (major isomer), 13.94. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40. Found: C, 41.41; H, 6.55.

Saponification and Transesterification of α-Azido Carboximides. General Procedure for the Saponification of α-Azido Carboximides 3 (Table IX). A 0.05–0.10 M solution of α-azido carboximide **3** in 3:1 THF–H_2O stirred at 0 °C under nitrogen, is treated with 2.0 equiv of solid lithium hydroxide. After stirring for 30 min, excess 0.5 N aqueous sodium bicarbonate is added, and the THF is removed in vacuo. The residual mixture is extracted with four portions of CH_2Cl_2. The organic extracts are combined, dried (Na_2SO_4), and evaporated in vacuo to afford the recovered chiral auxiliary in 95–100% yield. The aqueous phase is acidified to pH 1–2 with 3 N aqueous HCl and extracted successively with four portions of EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo to afford the α-azido acid **13** (90–100%) which was generally found to be pure by ^1H NMR spectroscopy and combustion analysis. If necessary, **13** could be purified by flash chromatography on silica gel eluting with hexane–ethyl acetate–acetic acid (50:50:1). The single exception was azido acid **13** (R = Ph) which racemized to the extent of 5–10% under these conditions.

General Procedure for the Determination of Enantiomeric Purity of the α-Azido Acids (Table IX). The azido acids were reduced to their corresponding amino acids (10% Pd–C, 15 psi hydrogen). These samples were converted into both the (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetamide (MTPA amide) methyl esters in order to secure authentic samples of the diastereomeric MTPA amide methyl esters. The diastereomeric purity of both (+)- and (−)-MTPA amide methyl esters are then determined by capillary GLC analysis using a 30 m × 0.25 mm fused silica capillary column wall-coated with DB-1 or DB-1701. The response factors of the MTPA amide methyl ester diastereomers are assumed to be the same. The detailed procedure for the analyses are provided in the supplementary material.

2(*R*)-Azido-3-phenylpropanoic Acid (13-*R*, R = $CH_2C_6H_5$). To 103 mg (0.293 mmol) of azide **3a-*R*** (R = $CH_2C_6H_5$) dissolved in 11 mL of 3:1 THF–H_2O was added 24 mg (0.57 mmol, 2.0 equiv) of lithium hydroxide monohydrate. The reaction was stirred for 0.5 h at 0 °C. Extraction according to the general procedure yielded 54 mg of the analytically pure title compound as a clear oil (97%): R_f 0.21 (40:60:1 ethyl acetate–hexane–acetic acid); IR (neat) 3600–2400, 2115, 1720, 1608, 1500, 1456 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 11.2–10.4 (br s, 1 H, O*H*), 7.38–7.25 (m, 5 H, aromatic Hs), 4.20–4.14 (m, 1 H, C_2-*H*), 3.25 (dd, 1 H, *J* = 4.7, 14.7 Hz, C_3-C*H*H), 3.05 (dd, 1 H, *J* = 8.8, 14.0 Hz, C_3-C*H*H); $[\alpha]_D$ +68.6 (*c* 1.40, $CHCl_3$). Anal. Calcd for $C_9H_9O_2N_3$: C, 56.55; H, 4.75. Found: C, 56.39; H, 4.78.

General Procedure for the Determination of Enantiomeric Purity of the α-Azido Acids (Table IX). A 0.05–0.10 M solution of α-azido acid **13** in 3:1 HOH–HOAc is treated with 15–30% by weight 10% Pd/C and stirred under an atmosphere of hydrogen for 3–7 h. The reaction contents are then filtered through Celite 545, and the filtrate is concentrated in vacuo to give a white solid. The product amino acid is redissolved in water and concentrated to azeotrope out the remaining acetic acid. The product is placed under vacuum (<0.1 mm) over P_2O_5 for 12 h. A sample of the indicated amino acid is converted into both the (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetamide (MTPA amide) methyl esters in order to secure authentic samples of the diastereomeric MTPA amide methyl esters. The diastereomeric purity of both (+)- and (−)-MTPA amide methyl esters is then determined by capillary GLC analysis using a 30-m × 0.25-mm fused silica capillary column wall coated with DB-1 or DB-1701. The response factors of the MTPA amide methyl ester diastereomers are assumed to be the same. The General Procedure for the preparation of the MTPA amide methyl esters is as follows. The indicated amino acid (1.0 equiv) is added to a flame-dried flask fitted with stirring bar. The flask is flushed with nitrogen, and freshly distilled MeOH (1 mmol/5–10 mL) is added by syringe. The resulting slurry is cooled to 0 °C, and 2–5 equiv of $SOCl_2$ is added. The solution is stirred for 15 min at 0 °C and then is heated at reflux for 2–3 h. The volatiles are then removed in vacuo to yield the unpurified amino ester hydrochloride as a white solid. The unpurified amino acid methyl ester hydrochloride (1.0 equiv) in freshly distilled CH_2Cl_2 (approximately 10 mL/mmol) is treated with triethylamine (4.0 equiv) and (+)- or (−)-MTPA chloride (2.0 equiv).[57] The solution is stirred at 0 °C for 15 min at ambient temperature for 2–5 h and is then quenched by addition of 1 N aqueous $NaHSO_4$. The solution is extracted with three portions of ether, and the combined organic extracts are washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The unpurified MTPA amide methyl ester is then eluted through a short plug of silica gel with ether to remove baseline contaminants prior to the GLC assay.

Racemization Assay. Azide **13-*R*** (R = Bn), 25 mg (0.132 mmol), and 10 mg of 10% Pd–C in 3:1 H_2O–HOAc were stirred under 150 psi of hydrogen for 1 h. Isolation according to the general procedure yielded 21 mg (97%) of D-phenylalanine: IR (KBr) 3600–2400, 2100, 1608, 1590, 1500, 1410, 1329 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 7.27–7.06 (m, 10 H, aromatic Hs), 3.76 (t, 1 H, *J* = 5 Hz, C_2-*H*), 3.08 (dd, 1 H, *J* = 4.4, 12.6 Hz, C_3-CH*H*), 2.90 (dd, 1 H, *J* = 6.3, 12.6 Hz, C_3-CH*H*); $[\alpha]_D$ = +4.36 (*c* 1.00, 5 N HCl). Both the (+)- and (−)-MTPA amide methyl esters of the synthetic D-phenylalanine were prepared according to the general procedure. Capillary GLC analysis (DB-1, 200 °C, 10 psi) revealed the ratio of (+)-MTPA amide methyl ester of D-phenylalanine (t_R = 7.27 min) to (+)-MTPA amide methyl ester of L-phenylalanine (t_R = 7.57 min) to be greater than 99.8:0.2.

2(*R*)-Azido-4-methylvaleric Acid (13-*R*, R = $CH_2CH(CH_3)_2$). To 195 mg (0.613 mmol) of azide **3b-*R*** (R = $CH_2CH(CH_3)_2$) dissolved in 13 mL of 3:1 THF–H_2O was added 51 mg (1.2 mmol, 2.0 equiv) of lithium hydroxide monohydrate. The reaction was stirred for 0.5 h at 0 °C. Extraction according to the general procedure yielded 93 mg of the title compound as an analytically pure clear oil (96%): R_f 0.25 (40:60:1 ethyl acetate–hexane–acetic acid); IR (neat) 3600–2400, 2112, 1722, 1470, 1420 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.88 (dd, 1 H, *J* = 5.9, 8.6 Hz, C_2-*H*), 1.87–1.79 (m, 1 H, C_4-*H*), 1.77–1.69 (m, 2 H, C_3-H_2), 0.99 (t, 6 H, *J* = 6.0 Hz, $CH(CH_3)_2$); $[\alpha]_D$ +36.3 (*c* 1.13, methanol). Anal. Calcd for $C_6H_{11}O_2N_3$: C, 45.85; H, 7.05. Found: C, 45.75; H, 7.16.

Racemization Assay. Azide **13-*R*** (R = $CH_2CH(CH_3)_2$), 85 mg (0.539 mmol), and 15 mg of 10% Pd–C in 3:1 H_2O–HOAc were stirred under 1 atm of hydrogen for 4 h. Isolation according to the general procedure yielded 65 mg (92%) of D-leucine: IR (KBr) 3500–2300, 2115, 1590, 1585, 1520, 1408, 1389, 1362, 1318, 1300 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 3.56 (t, 1 H, *J* = 8.2 Hz, C_2-*H*), 1.65–1.45 (m, 3 H, C_3-H_2 overlapping with C_4-*H*), 0.86–0.72 (m, 6 H, $CH(CH_3)_2$); $[\alpha]_D$ = −14.7 (*c* 0.275, 5 N HCl). Both the (+)- and (−)-MTPA amide methyl esters of the synthetic D-leucine were prepared according to the general procedure. Capillary GLC analysis (DB-1701, 175 °C, 10 psi) revealed the

ratio of (+)-MTPA amide methyl ester of D-leucine (t_R = 9.49 min) to (+)-MTPA amide methyl ester of L-leucine (t_R = 10.12 min) to be greater than 99.8:0.2.

2(*R*)-Azido-3-methylbutanoic Acid (13-*R*, R = CH(CH$_3$)$_2$). To 139 mg (0.457 mmol) of azide **3e-*R*** (R = CH(CH$_3$)$_2$) dissolved in 11 mL of 3:1 THF–H$_2$O was added 38 mg (0.92 mmol, 2.0 equiv) of lithium hydroxide monohydrate. The reaction was stirred for 0.5 h at 0 °C. Extraction according to the general procedure yielded 54 mg of the title compound as an analytically pure clear oil (96%): R_f 0.23 (40:60:1 ethyl acetate–hexane–acetic acid); IR (neat) 3600–2400, 2110, 1718, 1470, 1420, 1390, 1372 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 11.0–10.2 (br s, 1 H, O*H*), 3.76 (d, 1 H, *J* = 5.0 Hz, C$_2$-*H*), 2.28–2.17 (m, 1 H, C$_3$-C*H*), 1.05 (d, 3 H, *J* = 6.7 Hz, CH(C*H*$_3$)(CH$_3$)), 1.00 (d, 3 H, *J* = 6.7 Hz, CH(CH$_3$)(C*H*$_3$)); [α]$_D$ +71.5 (*c* 1.89, methanol). Anal. Calcd for C$_5$H$_9$O$_2$N$_3$: C, 41.95; H, 6.34. Found: C, 41.85; H, 6.42.

Racemization Assay. Azide **13-*R*** (R = CH(CH$_3$)$_2$), 49 mg (0.342 mmol), and 10 mg of 10% Pd–C in AcOH–H$_2$O were stirred under 1 atm of hydrogen for 3 h. Isolation according to the general procedure yielded 41 mg (99%) of D-valine: IR (KBr) 3600–2300, 2100, 1590, 1510, 1395, 1330 cm^{-1}; ^{1}H NMR (300 MHz, D$_2$O) δ 3.40 (d, 1 H, *J* = 4.3 Hz, C$_2$-*H*), 2.13–2.00 (m, 1 H, C$_3$-*H*), 0.83 (d, *J* = 7.0 Hz, 3 H, CH(CH$_3$)(C*H*$_3$)), 0.78 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)(CH$_3$)); [α]$_D$ = −25.5 (*c* 0.750, 5 N HCl). Both the (+)- and (−)-MTPA amide methyl esters of the synthetic D-valine were prepared according to the general procedure. Capillary GLC analysis (DB-1701, 175 °C, 7.5 psi) revealed the ratio of (+)-MTPA amide methyl ester of D-valine (t_R = 9.89 min) to (+)-MTPA amide methyl ester of L-valine (t_R = 10.16 min) to be greater than 99.8:0.2.

2(*R*)-Azidophenylacetic Acid (13-*R*, R = C$_6$H$_5$). To 163 mg (0.486 mmol) of azide **3e-*R*** (R = C$_6$H$_5$) dissolved in 11 mL of 3:1 THF–H$_2$O is added 41 mg (0.97 mmol, 2.0 equiv) of lithium hydroxide monohydrate. The reaction was stirred for 0.5 h at 0 °C. Extraction according to the general procedure yielded 83 mg of the title compound as an analytical pure crystalline solid (97%): mp 50–51 °C; R_f 0.20 (50:50:1 ethyl acetate–hexane–acetic acid); IR (CH$_2$Cl$_2$) 3600–2400, 2115, 1765, 1730, 1500, 1460 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 9.00–9.70 (br s, 1 H, O-*H*), 7.42 (s, 5 H, aromatic Hs), 5.05 (s, 1 H, C$_2$-*H*); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 174.4, 133.1, 129.5, 129.1, 127.6, 65.3; [α]$_D$ −169° (*c* 1.40, CHCl$_3$). Anal. Calcd for C$_8$H$_7$O$_2$N$_3$: C, 54.24; H, 3.98. Found: C, 54.02; H, 3.95.

This compound exhibits ca. 10% racemization when flash chromatographed (SiO$_2$) with 50:50:1 ethyl acetate–hexane–acetic acid as eluent.

Racemization Assay. Azide **13-*R*** (R = C$_6$H$_5$), 35 mg (0.198 mmol), and 9 mg of 10% Pd–C in 11 mL of AcOH–H$_2$O were stirred under 1 atm of hydrogen for 3 h. Isolation according to the general procedure yielded 31 mg (97%) of D-phenylglycine: IR (KBr) 3600–2400, 2100, 1610, 1585, 1555, 1510, 1466, 1398, 1355 cm^{-1}; ^{1}H NMR (300 MHz, D$_2$O) δ 7.20–7.35 (m, 5 H, aromatic Hs), 4.60 (t, 1 H, *J* = 5 Hz, C$_2$-*H*); [α]$_D$ −154.8 (*c* 0.79, 5 N HCl). The methyl ester was prepared by employing thionyl chloride (2.0 equiv, methanol, 0.5 mL, reflux, 2 h). Longer reaction times, or additional equivalents of thionyl chloride resulted in >1% racemization. The (+)- and (−)-MTPA amide methyl esters were prepared according to the general procedure. Capillary GLC analysis (DB-1, 200 °C, 10 psi) revealed the ratio of (+)-MTPA amide methyl ester of D-phenylglycine (t_R = 5.30 min) to (+)-MTPA amide methyl ester of L-phenylglycine (t_R = 5.64 min) to be 99.2:0.8.

2(*S*)-Azido-3-phenylpropanoic Acid (13-*S*, R = CH$_2$C$_6$H$_5$). The LiOH hydrolysis of 176 mg (0.500 mmol) of **3a-*S*** (R = CH$_2$C$_6$H$_5$) as described above afforded 96 mg (100%) of **13-*S*** (R = CH$_2$C$_6$H$_5$) as a faintly yellow oil: IR (neat) 3610–2400 (v br), 2115, 1722 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.3 (v br s, 1 H, CO$_2$H), 7.38–7.25 (m, 5 H, aromatics), 4.159 (dd, *J* = 5.0, 9.0 Hz, 1 H, 2-H), 3.244 (dd, *J* = 4.9, 14.1 Hz, 1 H, 3-C*H*H), 3.042 (dd, *J* = 9.0, 14.1 Hz, 1 H, 3-CH*H*); [α]$^{25}_D$ −67.9° (*c* = 107, CHCl$_3$). The optical purity of this material was determined according to the general procedure to be >99% ee by capillary GLC diastereomer analysis of its derived (+)-MTPA amide methyl ester.

2(*S*)-Azidophenylacetic Acid (13-*S*, R = C$_6$H$_5$). The LiOH hydrolysis of 169 mg (0.500 mmol) of **3d-*S*** (R = C$_6$H$_5$) as described above afforded 89 mg (100%) of **13-*S*** (R = C$_6$H$_5$) as a light tan solid: mp 47–51 °C (lit.[5] mp 50–51 °C); IR (CHCl$_3$) 3600–2400 (v br), 2115, 1730 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.1 (v br s, 1 H, CO$_2$H), 7.417 (s, 5 H, aromatics), 5.040 (s, 1 H, 2-H); [α]$^{25}_D$ +175° (*c* = 1.06, CHCl$_3$) (lit.[5] [α]$_D$ −169° (*c* = 1.40, CHCl$_3$) for the 2*R* enantiomer). The optical purity of this material was determined according to the general procedure to be >99% ee by capillary GLC diastereomer analysis of its derived (+)-MTPA-amide methyl ester.

General Procedure for the Titanium Tetrabenzyl Oxide Transesterification of the α-Azido Carboximides 3 (Table IX). To a flame-dried flask fitted with stirring bar was added titanium tetraisopropoxide (1.5–2.0 equiv) and benzyl alcohol (30–50 equiv) by syringe. The solution was stirred under vacuum (1.0 mm) for 30 min in order to remove the 2-propanol and was then transferred by cannula to the respective acyloxazolidinone **3** under nitrogen atmosphere in a flame-dried flask fitted with stirring bar. The solution was heated to 65–75 °C for 7–10 h and was subsequently quenched by the addition of aqueous 1 N HCl. The solution was extracted with three portions of ethyl acetate, and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo to yield a pale yellow oil. On small scale the product was purified by flash chromatography. Alternatively, the benzyl alcohol may be removed by Kugelrohr distillation prior to chromatographic purification.

Benzyl 2(*R*)-Azido-3-phenylpropionic Acid (14-*R*, R = CH$_2$C$_6$H$_5$). Titanium tetraisopropoxide, 73 mg (0.257 mmol, 1.5 equiv), and 648 mg (6.0 mmol, 35 equiv) of benzyl alcohol were stirred under vacuum for 0.5 h. The solution was added to 61 mg (0.174 mmol) of **3a-*R*** (R = CH$_2$C$_6$H$_5$) and the resulting solution was heated to 68 °C for 7 h. Workup according to the general procedure yielded a yellow oil. Flash chromatography (7:93 ethyl acetate–hexane) yielded 46 mg (93%) of **14-*R*** (R = CH$_2$C$_6$H$_5$) as a clear, colorless oil: R_f 0.32 (10:90 ethyl acetate/hexane); IR (CH$_2$Cl$_2$) 2860–3120, 2114, 1745, 1608, 1500, 1468 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36–7.16 (m, 10 H, aromatic Hs), 5.17 (s, 2 H, OC*H*$_2$Ph), 4.08 (dd, 1 H, *J* = 5.7, 8.5 Hz, C$_2$-C*H*), 3.17 (dd, 1 H, *J* = 5.7, 14.0 Hz, C$_3$-C*H*H), 3.02 (dd, 1 H, *J* = 8.5, 14.0 Hz, C$_3$-C*H*H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 169.7, 135.8, 135.0, 129.1, 128.6, 128.5, 128.4, 127.2, 67.5, 63.2, 37.6; [α]$_D$ +34.1 (*c* 1.70, CH$_2$Cl$_2$). Anal. Calcd for C$_{16}$H$_{15}$O$_2$N$_3$: 68.32; H, 5.38. Found: C, 68.50; H, 5.29.

The extent of racemization during transesterification was determined according to the general procedure for the α-azido acids **13**: Hydrogenation and hydrogenolysis (10% Pd–C, 1:3 acetic acid–water), conversion to the methyl ester (thionyl chloride, 5.0 equiv, methanol, reflux, 3 h), and acylation with (+)-MTPACl (2.0 equiv) with triethylamine (4.0 equiv, CH$_2$Cl$_2$) yielded the (+)-MTPA amide methyl ester of phenylalanine. Capillary GLC analysis (DB-1, 200 °C, 9 psi) revealed the ratio of (+)-MTPA amide methyl ester of (*R*)-phenylalanine (t_R = 7.72) to the (+)-MTPA amide methyl ester of (*S*)-phenylalanine (t_R = 7.92) to be greater than 99.5:0.5.

Benzyl 2(*S*)-Azidophenylacetate (14-*S*, R = C$_6$H$_5$). Titanium tetraisopropoxide, 169 mg (0.595 mmol, 2.0 equiv), and 1.29 g (11.9 mmol, 40 equiv) of benzyl alcohol were stirred under vacuum for 1.5 h. The solution was added to 100 mg (0.297 mmol) of **3d-*S*** (R = C$_6$H$_5$) (prepared by direct azidation) and the resulting solution was heated to 65 °C for 8.5 h. Isolation according to the general procedure yielded a yellow oil. Flash chromatography (7:93 ethyl acetate–hexane) yielded 65 mg (83%) of **14** (R = C$_6$H$_5$) as a clear, colorless oil: R_f 0.32 (10:90 ethyl acetate–hexane); IR (CH$_2$Cl$_2$) 3120–2860, 2109, 1748, 1500, 1468 cm^{-1}; ^{1}H NMR (300 MHz, CHCl$_3$) δ 7.41–7.23 (m, 10 H, aromatic Hs), 5.25 (d, 1 H, *J* = 12.3 Hz, OC*H*HPh), 5.17 (d, 1 H, *J* = 12.3 Hz, OC*H*HPh), 5.00 (s, 1 H, C$_2$-C*H*); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 168.9, 135.0, 133.9, 129.3, 129.0, 128.6, 128.5, 128.2, 127.7, 67.6, 65.4. Anal. Calcd for C$_{15}$H$_{13}$O$_2$N$_3$: C, 67.41; H, 4.90. Found: C, 67.46; H, 4.94.

The extent of racemization during transesterification was determined according to the general procedure for α-azido acids: Hydrogenation and hydrogenolysis (10% Pd–C, 1:3 acetic acid–water), conversion to the methyl ester (thionyl chloride, 2.0 equiv, methanol, reflux, 2 h), and acylation with (−)-MTPACl (2.0 equiv) with triethylamine (4.0 equiv, CH$_2$Cl$_2$) yielded the (−)-MTPA amide methyl ester of L-phenylglycine. Capillary GLC analysis (DB-1, 200 °C, 10.5 psi) revealed the ratio of (−)-MTPA amide methyl ester of (*S*)-phenylalanine (t_R = 4.72) to the (−)-MTPA amide methyl ester of (*R*)-phenylalanine (t_R = 4.97) to be greater than 99.5:0.5.

Hydrolysis and Transesterification of Sterically Hindered Carboximides (Table X). 2(*S*)-Azido-3,3-dimethylbutanoic Acid (13-*S*, R = C(CH$_3$)$_3$). A solution of 159 mg (0.50 mmol) of **3f-*S*** (R = C(CH$_3$)$_3$) in 10 mL of 3:1 THF–H$_2$O, stirred at 0 °C under N$_2$, was treated with 24 mg (1.00 mmol, 2.0 equiv) of LiOH (anhydrous powder). The resulting reaction was stirred at 0 °C for 1.5 h. Following the addition of 3 mL of 0.5 N NaHCO$_3$, the THF was evaporated in vacuo. The aqueous residue was diluted to 40 mL with H$_2$O and extracted with four 25-mL portions of CH$_2$Cl$_2$. The organic extracts were combined, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was chromatographed by gradient elution MPLC (50 g of silica gel eluting with a 1-L linear gradient from hexane–EtOAc (70:30) to hexane–EtOAc (30:70) to yield 75.2 mg (52%) of **15a** (R = C(CH$_3$)$_3$) as a white solid: IR (CHCl$_3$) 3620, 3400, 2110, 1668, 1515 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33–7.20 (m, 5 H, C$_6$H$_5$), 6.40 (br d, *J* = 7.1 Hz, 1 H, NH), 4.271–4.166 (sym m, 1 H, NC*H*CH$_2$), 3.76–3.64 (m, C*H*$_2$OH) and 3.641 (s, C*H*C=O) (3 H total), 2.983–2.787 (8 line AB portion of an ABX system, J_{AB} = 13.9 Hz, J_{AX} = 6.7 Hz, J_{BX} = 8.4 Hz, ν_A = 2.94 δ, ν_B = 2.83 δ, 2 H, CHC*H*$_2$C$_6$H$_5$), 2.58 (br s, 1 H, OH), 0.874 (s, 9 H, C-

$(CH_3)_3$); ^{13}C NMR (75.5 MHz; $CDCl_3$) δ 168.75, 137.41, 129.07, 128.62, 126.67, 74.80, 64.11, 52.79, 36.97, 35.87, 26.41. The analytical sample was recrystallized from acetone–hexane: mp 73.5–74.5 °C; $[\alpha]^{25}_D$ −133° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}N_4O_2$: C, 62.05; H, 7.64. Found: C, 61.96; H, 7.76.

The aqueous phase was acidified to pH 1–2 with 3 N HCl and extracted with four 40-mL portions of EtOAc. The EtOAc extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to yield 33.4 mg (42%) of the azido acid **13f** as a white solid (see below for characterization data). The optical purity of this material, determined by capillary GLC diastereomer analysis of its derived (+)-MTPA-amide methyl ester was found to be >99% ee.

2(*S*)-Azido-3,3-dimethylbutanoic Acid, Phenylmethyl Ester (14f-*S*, R = C(CH$_3$)$_3$). A solution of 155 μL (162 mg, 1.50 mmol, 3.0 equiv) of redistilled benzyl alcohol in 3.0 mL of dry THF, stirred at −78 °C under dry N_2, was treated with 0.65 mL (1.00 mmol, 2.0 equiv) of *n*-butyl lithium (1.54 M in hexanes). The solution was warmed to 0 °C and immediately recooled to −78 °C. To the above solution of LiOBn, stirred at −78 °C, was added via cannula a solution of 158.5 mg (0.500 mmol) of the azido imide **3f-*S*** (R = C(CH$_3$)$_3$) in 2.0 mL of dry THF. Residual imide was rinsed in with two 1.0-mL portions of THF, and the resulting solution was stirred at −70 °C for 36 h. The reaction was quenched at −70 °C with 5 mL of pH 7 phosphate buffer concentrate, warmed to 25 °C, and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with three additional portions of CH_2Cl_2. The CH_2Cl_2 extracts were combined, 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 0.4 L of hexane–EtOAc (90:10) followed by a 1-L linear gradient from hexane–EtOAc (90:10) to hexane–EtOAc (70:30). Early fractions afforded 64.1 mg (52% yield) of the ester **14f** as a colorless oil: IR ($CHCl_3$) 2965, 2100, 1740, 1267, 1202, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5 H, C_6H_5), 5.220 (s, 2 H, OCH_2), 3.714 (s, 1 H, C*H*C=O), 1.002 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.99, 135.10, 128.58, 128.51, 71.69, 67.10, 35.77, 26.52; $[\alpha]^{25}_D$ −43.0° (*c* = 1.07, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.25; H, 6.96.

The optical purity of this material, determined by capillary GLC (150 °C, 6 PSI) diastereomer analysis of its derived (+)-MTPA amide methyl ester, L-derivative (t_R = 17.00 min) and D-derivative (t_R = 16.31 min), was found to be >99% ee.

Later fractions yielded 69.3 mg (33%) of the mixed benzyl carbonate **15b** (R = C(CH$_3$)$_3$), as a white solid: IR ($CHCl_3$) 3417, 2110, 1749, 1676, 1512, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.17 (m, 10 H, aromatics), 6.355 (d, *J* = 8.4 Hz, 1 H, NH), 5.192 (s, 2 H, $OCH_2C_6H_5$), 4.531–4.425 (sym m, 1 H, NC*H*CH$_2$O), 4.258–4.146 (8 line AB portion of ABX system, J_{AB} = 11.1 Hz, J_{AX} = 3.9 Hz, J_{BX} = 4.5 Hz, 2 H, NCHCH_2O), 3.600 (s, 1 H, CHC=O), 2.876 (d, *J* = 7.7 Hz, 2 H, CHC$H_2C_6H_5$), 0.864 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.89, 155.07, 136.68, 135.01, 129.04, 128.62, 128.37, 126.84, 74.71, 69.97, 68.14, 49.58, 37.12, 35.81, 26.43. The analytical sample was recrystallized from Et_2O–hexane: mp 71.5–72.5 °C; $[\alpha]^{23}_D$ −94.1° (*c* = 1.01, $CHCl_3$). Anal. Calcd for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65. Found: C, 65.05; H, 6.68.

General Procedure for the LiOOH-Mediated Hydrolysis of the α-Azido Carboximides 3. A stirred solution of 1.00 mmol of the α-azido carboximide **3** in 15 mL of THF[73] and 4.6 mL of H_2O, cooled to 0 °C, was treated with 0.40 mL (4.1 mmol, 4 equiv) of 31% H_2O_2 followed by 48 mg (2.00 mmol, 2.0 equiv) of solid LiOH. After stirring at 0 °C for 30 min, the reaction was treated with a solution of 0.55 g (4.4 mmol) of Na_2SO_3 in 3 mL of H_2O followed by 10 mL of 0.5 N $NaHCO_3$. Following removal of the THF in vacuo on the rotary evaporator, the residue was diluted to 80 mL with H_2O and extracted with four portions of CH_2Cl_2 (200 mL total). The aqueous phase was acidified to pH 1–2 with 5 N HCl and extracted with four portions of EtOAc (400 mL total). The EtOAc extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to yield the pure α-azido acid **13**. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), and evaporated in vacuo to afford the chiral auxiliary **4**, which could be purified further, if necessary, by recrystallization or chromatography.

2(*S*)-Azido-3,3-dimethylbutanoic Acid (13f-*S*, R = C(CH$_3$)$_3$). As described above, the LiOOH mediated hydrolysis of 317 mg (1.00 mmol) of **3f-*S*** (R = C(CH$_3$)$_3$) afforded 155 mg (98%) of **7f** (R = *t*-Bu) as a white crystalline solid that was homogeneous on TLC: R_f = 0.3 (silica; hexane–EtOAc–HOAc (50:50:1)); IR ($CHCl_3$) 3500–2500, 2105, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.3 (v br s, 1 H, CO_2H), 3.755 (s, 1 H, 2-H), 1.078 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.06, 71.79, 35.67, 26.55. The optical purity of the unrecrystallized material, determined by capillary GLC diastereomer analysis of its derived (+)-MTPA amide methyl ester, was found to be >99% ee. The analytical sample was recrystallized from hexane: mp 71–72.5 °C; $[\alpha]^{25}_D$ −72.4° (*c* = 1.02, $CHCl_3$). Anal. Calcd for $C_6H_{11}N_3O_2$: C, 45.85; H, 7.05. Found: C, 45.92; H, 7.22.

The CH_2Cl_2 extracts were chromatographed (MPLC) on 50 g of silica gel [1-L linear gradient from hexane–EtOAc (7:3) to hexane–EtOAc (2:8)] to afford 2.8 mg (1%) of the β-hydroxyethyl amide **15a** (R = C(CH$_3$)$_3$) (R_f = 0.25; silica, hexane–EtOAc (1:1)) and 175 mg (98% recovery) of the chiral auxiliary **4**, X_PH [R_f = 0.15; silica, hexane–EtOAc (1:1)].

(3(2*R*),4*S*)-3-[2-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-1-oxo-3-phenylpropyl]-4-(phenylmethyl)-2-oxazolidinone (16a-*R*, R = $CH_2C_6H_5$). To 203 mg (0.579 mmol) of azide **3a-*R*** (R = $CH_2C_6H_5$) dissolved in 15 mL of 10:8:1 methanol–tetrahydrofuran–trifluoroacetic acid was added 50 mg of 10% Pd–C. The reaction flask was flushed with nitrogen and then stirred under a hydrogen atmosphere (1 atm) for 3 h. Upon completion of the reaction, the solution was passed through Celite 545. The filter cake was then washed with methanol (3 × 10 mL), and the solvent was removed in vacuo to yield the trifluoroacetate salt of the (aminoacyl)oxazolidinone. To the unpurified (aminoacyl)oxazolidinone in a 25-mL flask fitted with stirring bar under a nitrogen atmosphere was added 5 mL of distilled CH_2Cl_2 by syringe. The solution was cooled to 0 °C, and 263 mg of (+)-MTPA chloride (1.04 mmol, 1.8 equiv) followed by 176 mg of triethylamine (1.74 mmol, 3.0 equiv) was added by syringe. The pale yellow solution was stirred 15 min at 0 °C and 45 min at ambient temperature. The reaction was quenched by the addition of 1 N aqueous bisulfate solution, and after addition of CH_2Cl_2, the organic extract was washed successively with saturated aqueous bicarbonate and brine, dried (Na_2SO_4), and concentrated in vacuo to yield a viscous yellow oil. Purification by flash chromatography (70:30 hexane–ethyl acetate) afforded 301 mg (96%) of **16a** (R = $CH_2C_6H_5$) as a white solid: mp 152.5–153.5 °C; R_f = 0.29 (30:70 ethyl acetate–hexane); IR (CH_2Cl_2) 3420, 3120–2860, 1787, 1699, 1608, 1513, 1500, 1455, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.71–7.68 (m, 3 H, aromatic Hs), 7.43–7.11 (m, 14 H, aromatic Hs), 7.37–6.12 (m, 16 H, aromatic Hs and N-*H*), 6.99 (dt, 1 H, *J* = 3.9, 9.3 Hz, C_2-CN*H*), 4.74–4.68 (m, 1 H, C_4-C*H*CH$_2$O), 4.31–4.19 (m, 2 H, C_5-CH_2O), 3.43–3.36 (m, 4 H, OCH_3 and CNHC*H*H), 3.25 (dd, 1 H, *J* = 3.4, 13.4 Hz, C*H*HPh), 2.84–2.74 (m, 2 *H*, C*H*HPh and CNHC*H*H); $[\alpha]_D$ +24.4 (*c* 1.03, CH_2Cl_2). Anal. Calcd for $C_{29}H_{27}N_2O_5F_3$: C, 64.44; H, 5.03. Found: C, 64.48; H, 5.00.

(3(2*R*),4*S*)-3-[2-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-1-oxo-2-phenylethyl]-4-(phenylmethyl)-2-oxazolidinone (16d-*R*, R = C_6H_5). To a solution of **3d-*R*** (R = C_6H_5), (100 mg, 0.31 mmol) in 5.0 mL of methanol was added trifluoroacetic acid (71.5 mL, 0.93 mmol, 3.0 equiv) and 10% Pd–C (ca. 20 mg). After thoroughly purging with hydrogen, the reaction was stirred under 1.0 atm H_2 for 3 h at room temperature. The solution was then filtered through cotton to remove the catalyst and concentrated in vacuo to give a white solid. This material was treated sequentially with CH_2Cl_2 (3 mL), (+)-MTPA chloride (0.120 mL, 0.62 mmol) and triethylamine (0.260 mL, 1.86 mmol) and the resulting homogeneous solution stirred for 1 h at 25 °C. The reaction solution was poured into 100 mL of 75:25 petroleum ether–CH_2Cl_2, washed successively with 20 mL of 10% aqueous HCl and 20 mL of brine, dried (Na_2SO_4), and concentrated in vacuo to afford a clear oil. This material was filtered through 20 g of silica gel with 3:1 ethyl acetate–hexane to afford the title compound **16d-*R*** (R = C_6H_5) 159 mg (99%) of a clear colorless foam: R_f = 0.44 (25% ethyl acetate–hexane); IR (CH_2Cl_2) 3420, 1790, 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60–7.10 (m, 15 H, arom), 6.92 (m, 1 H, N*H*-MTPA), 6.77 (d, 1 H, *J* = 6.8 Hz, 1 H, C*H*NH-MTPA), 4.78 (m, 1 H, NC*H*CH$_2$O), 4.20–4.10 (m, 2 H, NCHCH_2O), 3.35 (q, J_{HF} = 1.1 Hz, 3 H, CH_3O), 3.10 (d of d, *J* = 3.4, 13.7 Hz, 1 H, NCHCH_2Ph), 2.63 (d of d, *J* = 8.4, 13.7 Hz, 1 H, NCHCH_2Ph). Anal. Calcd for $C_{28}H_{25}F_3N_2O_5$: C, 63.88, H, 4.79. Found: C, 63.70; H, 4.76.

General Procedure for the Formation of *N*-Boc Carboximides (Eq 34). A 500-mL flame-dried round-bottom flask was charged with 170 mL of anhydrous methanol followed by 7.6 g (40 mmol, 2 equiv) of $SnCl_2$. The flask was swept with nitrogen, stirred at room temperature for 10 min, and then cooled to 0 °C. Azido imide **3c-*S*** (6 g, 20 mmol) in 30 mL of anhydrous MeOH was then added via syringe, stirred at 0 °C for 5 min and then allowed to warm to room temperature for an additional 2 h. The methanol was then removed in vacuo to yield a light yellow-cream colored foam. To this foam was added 160 mL of dioxane followed by 6.5 g of BOC_2O (30 mmol, 1.5 equiv) in 20 mL of dioxane. Finally, a slurry of 6.7 g (80 mmol, 4 equiv) of $NaHCO_3$ in 20 mL of distilled water was added while swirling the reaction mixture. The resulting white slurry

(73) The THF for these experiments was Fisher Certified Grade, which is stabilized with 0.025% BHT, and used as received. We have some evidence that the stabilizer might be important in suppressing radical-mediated side reactions during these hydrolysis experiments.

was stirred rapidly at room temperature for 12 h. This reaction mixture was diluted with 300 mL of EtOAc and 100 mL of H_2O and acidified to pH 1 with 2 N $NaHSO_4$. The layers were separated, and aqueous layer was extracted with an additional 300 mL of EtOAc. The organic extracts were combined, washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (MPLC) using a Michel Miller column size D (ACE Glass, 47 × 450 mm), gradient elution 4:1 to 1:1 hexane–EtOAc afforded 6.4 g (85%) of the desired N-protected carboximide as a white solid: $[\alpha]_D$ +42° (c = 0.007, $CHCl_3$); IR ($CHCl_3$) 3455, 3025, 2940, 1775–1800, 1700–1720, 1500, 1370–1400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 330 K) δ 7.19–7.34 (m, 5 H, aromatics), 5.70–5.85 (ddt, 1 H, J_{allyl} = 7.1, J_{cis} = 9.5, J_{trans} = 17.9 Hz, CH_2=C*H*R), 5.46–5.53 (m, 1 H, α-*H*), 5.06–5.16 (m, 3 H, CH_2= CHR, N*H*), 4.58–4.66 (m, 1 H, NC*H*Bn), 4.15–4.21 (m, 2 H, OCH_2), 3.31 (dd, J = 3.3, 13.6 Hz, C*H*HPh), 2.76–2.84 (dd, 1 H, J = 9.4, 13.6 Hz, CH*H*Ph), 2.53–2.62 (m, 1 H), 2.35–2.45 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, 330 K) δ 172.90, 152.79, 135.42, 132.68, 129.46, 129.04, 127.42, 118.78, 80.01, 66.60, 55.67, 53.05, 37.91, 36.73, 28.41. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.16; H, 7.00. Found: C, 64.33; H, 6.72. This procedure has proven to be quite general for other α-azido carboximides as well.

Saponification and Transesterification of α-Acylamino Carboximides 16-*R* (Table XI). Methyl 2(*R*)-2-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-3-phenylpropionate (Methyl Ester of 18a-*R*, R = $CH_2C_6H_5$). To carboximide **16a-*R***, (R = $CH_2C_6H_5$), 80 mg (0.148 mmol) dissolved in 11 mL of 3:1 THF–H_2O was added 12 mg (0.29 mmol, 2.0 equiv) of lithium hydroxide monohydrate. The reaction was stirred 0.5 h at 0 °C. Product isolation according to the general procedure for the hydrolysis of **3** provided **18a-*R*** (R = $CH_2C_6H_5$) as a clear oil. The oil was diluted with 5 mL of ethyl acetate, and a CH_2N_2–ether solution was added dropwise with stirring until a yellow color persisted. The reaction was quenched by the dropwise addition of acetic acid until the disappearance of the yellow color. The solution was washed successively with saturated aqueous bicarbonate and brine, then dried (Na_2SO_4), and concentrated in vacuo to afford 55 mg (96%) of the title compound as a clear oil judged to be a single compound by ^1H NMR spectroscopy: R_f = 0.36 (30:70 ethyl acetate–hexane); IR (neat) 3420, 3360, 3120–2850, 1750, 1700, 1515, 1453, 1360 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4 H, aromatic Hs), 7.25–7.13 (m, 3 H, aromatic Hs), 7.02 (d, 1 H, J = 8.4 Hz, N-*H*), 6.91–6.87 (m, 2 H, aromatic Hs), 5.03–4.95 (m, 1 H, C_2-C*H*), 3.75 (s, 3 H, CO_2CH_3), 3.43 (q, 3 H, J_{HF} = 1.4 Hz, CF_3OCH_3), 3.15 (dd, 1 H, J = 5.3, 14.0 Hz, C*H*HPh), 3.03 (dd, 1 H, J = 7.0, 14.0 Hz, C*H*HPh); $[\alpha]_D$ −44.6° (c = 2.23, CH_2Cl_2). Capillary GLC analysis (DB-1, 200 °C, 10 PSI) revealed the ratio of (+)-MTPA-amide methyl ester of (*R*)-phenylalanine (t_R = 6.64 min) to the (+)-MTPA amide methyl ester of (*S*)-phenylalanine (t_R = 6.90 min) to be >99.2:0.2. Anal. Calcd for $C_{20}H_{20}O_4NF_3$: C, 60.76; H, 5.10. Found: C, 60.90; H, 4.99.

Methyl 2(*R*)-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-2-phenylacetate (Methyl Ester of 18d-*S*, R = C_6H_5). To a cooled (0 °C) solution of **16d-*R***, (R = C_6H_5) (13.1 mg, 25.5 mmol) in 0.5 mL 2:1 dioxane–water was added lithium hydroxide (6.0 mg, 0.254 mmol, 10 equiv) in one portion. After stirring 0.5 h at this temperature, the solution was acidified to pH 1 with 10% aqueous HCl and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried over sodium sulfate, concentated in vacuo, and treated immediately with excess diazomethane–ether. Product isolation and chromatography on 15 g of silica gel with 4:1 ethyl acetate–hexane afforded 9.7 mg (100%) of the desired 2*R*-(+)-MPTA amide methyl ester as a clear colorless oil. Capillary GLC analysis (DB-1, 200 °C, 5.0 psi) revealed this material to contain 2*R*-(+)-MTPA amide methyl ester (t_R = 10.01 m) and 2*S*-(+)-MTPA amide methyl ester (t_R = 10.60 m) in a ratio of 99:1. R_f = 0.44 (25% ethyl acetate–hexane); IR (neat) 3540, 3360, 1780, 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.55 (d(b), J = 7.2 Hz, 1 H, N*H*), 7.40–7.10 (m, 10 H, aromatic Hs), 5.53 (d, J = 7.2 Hz, 1 H, C*H*Ph), 3.68 (s, 3 H, CO_2CH_3), 3.48 (d, J = 1.4 Hz, 3 H, CF_3OCH_3). Anal. Calcd for $C_{28}H_{25}F_3N_2O_5$: C, 63.88; H, 4.79. Found: C, 63.70; H, 4.76.

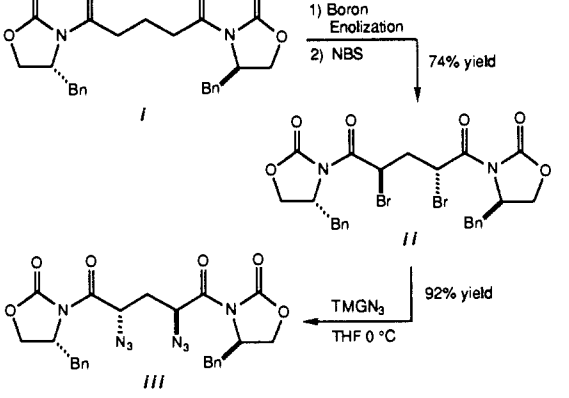
Benzyl 2(*R*)-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-3-phenylpropionate (19b-*R*, R = $CH_2C_6H_5$). Titanium tetraisopropoxide, 126 mg (0.444 mmol, 3.0 equiv), and 800 mg (7.40 mmol, 50 equiv) of benzyl alcohol were stirred under vacuum for 0.5 h. The resulting solution was added to 80 mg (0.148 mmol) of **16a-*R*** (R = $CH_2C_6H_5$), and the reaction mixture was heated at 85 °C for 7 h. Product isolation according to the general procedure afforded a yellow oil. Benzyl alcohol was removed by Kugelrohr distillation (0.1–0.3 mm) and flash chromatography (1:4 ethyl acetate–hexane) of the residue yielded 62 mg (89%) of **19a-*R*** (R = $CH_2C_6H_5$) as a clear, colorless oil: R_F = 0.25 (20:80 ethyl acetate–hexane); IR (CH_2Cl_2) 3420, 3120–2855, 1745, 1700, 1515, 1500, 1460 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39–6.77 (m, 16 H, aromatic Hs and NH), 5.22 (d, 1 H, J = 12.1 Hz, OC*H*HPh), 5.1 (d, 1 H, J = 12.1 Hz, OC*H*HPh), 5.07–4.98 (m, 1 H, C_2-C*H*), 3.38 (d, 1 H, J = 1.6 Hz, CF_3OCH_3), 3.12 (dd, H, J = 5.5, 14.0 Hz, C_3-C*H*H), 3.01 (dd, 1 H, J = 6.7, 14.0 Hz, C_3-C*H*H); $[\alpha]_D$ = −8.8 (c = 1.22, CH_2Cl_2). Anal. Calcd for $C_{26}H_{24}O_4NF_3$: C, 66.24; H, 5.13. Found: C, 66.04; H, 5.21.

The extent of racemization during transesterification was determined as follows: **19a-*R*** (R = $CH_2C_6H_5$) was hydrogenated at 1 atm (10% Pd–C, 10 mg, MeOH, 1 h), and the unpurified product was esterified with diazomethane–ether to yield the (+)-MTPA amide methyl ester of phenylalanine. Capillary GLC analysis (DB-1, 200 °C, 10 psi) of the unpurified product revealed the ratio of (+)-MTPA amide methyl ester of D-phenylalanine (t_R = 6.62) to the (+)-MTPA amide methyl ester of L-phenylalanine (t_R = 6.88) to be 99.8:0.2.

Benzyl 2(*R*)-[[(+)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl]amino]-2-phenylacetate (19d-*R*, R = C_6H_5). To a solution of titanium tetrabenzyl oxide as described above from 0.30 mL (1.0 mmol) of titanium tetraisopropoxide and 0.81 mL (7.92 mmol) benzyl alcohol was added (+)-MTPA amino carboximide (**16d-*R***, (R = C_6H_5) (46 mg, 91 mmol) in 2.0 mL THF via cannula in one portion. The solution was then heated at 70 °C (allowing the tetrahydrofuran to evaporate) with stirring for 7 h. The product was separated from the excess benzyl alcohol by chromatography on 25 g silica eluting with 100-mL portions of 0, 10, 20, 30% ethyl acetate–hexane. This operation afforded 32.1 mg (81%) of the desired benzyl ester as a clear colorless oil. Capillary GLC analysis (DB-1, 225 °C, 10.0 psi) revealed this material to contain 2*S*-(+)-MTPA-amide benzyl ester (t_R = 11.88 m, 2.4%) and 2*R*-(+)-MTPA-amide benzyl ester (t_R = 12.21 m, 97.6%): R_f = 0.63 (30% ethyl acetate–hexane); IR (neat) 3420, 1745, 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.60–7.10 (m, 15 H, aromatic), 5.65 (d, J = 6.8 Hz, 1 H, C*H*NH), 5.13 (s, 2 H, CH_2Ph), 3.33 (d, J = 1.1 Hz, 3 H, CH_3O). Anal. Calcd for $C_{18}H_{18}O_3NF_3$: C, 67.13; H, 5.16. Found: C, 66.87; H, 4.87.

Acknowledgment. Support has been provided by the National Institutes of Health, the National Science Foundation, and Merck. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

Note Added in Proof. Since submission of this manuscript, we have had the occasion to carry out the diastereoselective two-step bis-amination of the illustrated bis-carboximide i derived from glutaric acid. Although the direct azidation procedure employing trisyl azide on the potassium enolate failed, probably due to competing internal enolate acylation, the bromination–azide displacement alternative provided the illustrated crystalline dibromide ii (mp 157–158.5 °C) in 74% yield after purification. Subsequent azide displacement provided the desired bis-azide iii (mp 133.5–134.5 °C) in 92% yield. This precedent suggests that related diamino diacids might also be accessible by a similar strategy. The experimental details of this study will be reported shortly (*J. Org. Chem.*, manuscript in preparation).



i *ii* *iii*

Supplementary Material Available: Selected experimental procedures not essential to the execution of the synthesis methodology including the detailed procedure for the enantiomeric purity of the α-azido acids, the general procedure for direct azide transfer, and studies of the decomposition of intermediate **6** (5 pages). Ordering information is given on any current masthead page.