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1-(2,4,6-Triisopropylphenyl)ethylamine: A New Chiral Auxiliary for the Asymmetric Synthesis of γ-Amino Acid Derivatives

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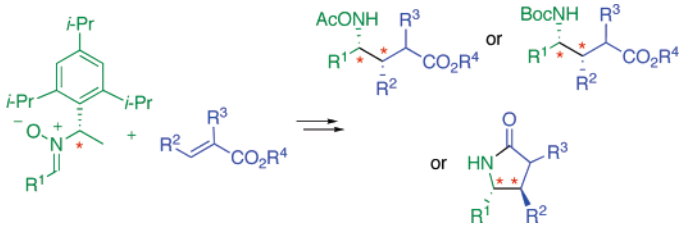
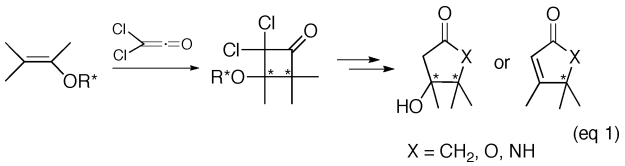


The title compound has proven to be an excellent chiral auxiliary for nitrones in SmI_2-mediated reductive coupling with α,β-unsaturated esters. A variety of such nitrones, prepared from aldehydes and enantiopure *N*-hydroxy-1-(2,4,6-triisopropylphenyl)ethylamine, afforded γ-*N*-hydroxyamino esters in high yields and diastereomeric purity. These adducts, readily available as either enantiomer, could be transformed into γ-*N*-acetoxyamino esters, *N*-Boc-γ-amino esters, and γ-lactams.

Introduction

Several years ago, an effective chiral control group was sought for use in an enol ether−dichloroketene cycloaddition approach to α,α-dichlorocyclobutanones, which are valuable precursors of cyclopentanone, γ-butyrolactone, and γ-butyrolactam derivatives.[1] A benzyloxy group seemed particularly desirable since it would allow a high degree of flexibility in the elaboration of intermediates: the resultant ether linkage would be relatively stable, yet easily transformed into a synthetically useful hydroxy group or double bond (eq 1).



(eq 1)

In an intial study,[2] the 1-(2,4,6-triisopropylphenyl)ethoxy group was shown to provide an excellent level of asymmetric induction, and the ether linkage was found to be sufficiently stable to permit elaboration of the cycloadduct prior to cleavage. A number of subsequent applications of this new chiral auxiliary[3] by us[4] and others[5] confirmed its usefulness in various areas of asymmetric synthesis.

In view of these results, the corresponding amine seemed worth examining as a possible chiral control group for asymmetric synthesis. An excellent test of its induction potential

(1) For reviews on dichloroketene, see: Hyatt, J. A.; Raynolds, P. W. *Org. Reac.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995. For reviews on the chemistry of cyclobutanones, see: Bellus, D.; Ernst, B. *Angew. Chem., Int. Ed.* **1988**, *27*, 797−827. Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485−1537.

(2) M. B. de Azevedo, M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940−4942.

(3) Delair, P.; Kanazawa, A. M.; M. B. de Azevedo, M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710.

(4) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210−5211. Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911−1912. Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660−4663. Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383−1386. Pourashraf, M.; Delair, P.; Rasmussen, M.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. Rasmussen, M.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443. Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741−1744. Muniz, M. N.; Kanazawa, A.; Greene, A. E. *Synlett* **2005**, 1328−1330. Ceccon, J.; Poisson, J.-F.; Greene, A. E. *Synlett* **2005**, 1413−1416. Roche, C.; Kadlecikova, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E.; Flot, D.; Burghammer, M. *J. Org. Chem.* **2005**, *70*, 8352−8356. Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 4739−4742.

(5) Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 7735−7738. Narkevitch, V.; Schenk, K.; Vogel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 1806−1808. Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 5080−5093. Bouchez, L. C.; Turks, M.; Dubbaka, S. R.; Fonquerne, F.; Craita, C.; Laclef, S.; Vogel, P. *Tetrahedron* **2005**, *61*, 11473−11487. Hamel, M.; Grach, G.; Abrunhosa, I.; Gulea, M.; Masson, S.; Vazeux, M.; Drabowicz, J.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3406−3415. See also: Pauling, H.; Wehrli, C. (Hoffmann-La Roche, F. and Co., A.-G., Switz) EP161580, 1985; *Chem. Abstr.* **1986**, *105*, 78765. Reeder, L. M.; Hegedus, L. S. *J. Org. Chem.* **1999**, *64*, 3306−3311.

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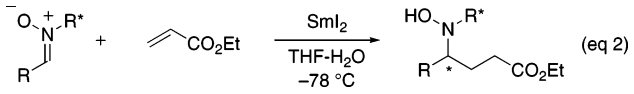
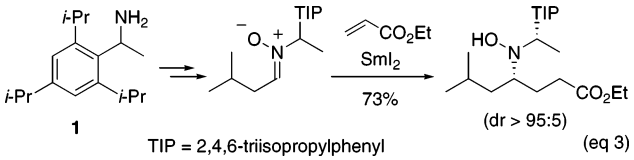
availed itself to us a few years ago during the study of the SmI_2-mediated nitrone−acrylate reductive coupling, which provides γ-amino ester derivatives.[6] Nitrones derived from several chiral amines and different aldehydes had been shown to produce only modest levels of asymmetric induction (60:40 to 85:15 diastereomeric ratios) in this novel transformation; for example, 1-phenylethylamine[7] provided a diastereomeric ratio of 75:25 (eq 2, R = isopropyl).



Racemic 1-(2,4,6-triisopropylphenyl)ethylamine (**1**) was prepared from the alcohol, via the azide,[8] in order to evaluate the level of induction that would be ultimately attainable with the chiral (nonracemic) amine. Most encouragingly, a single diastereomer (dr >95:5) was obtained in the reaction of ethyl acrylate with the nitrone derived from isovaleraldehyde (eq 3).

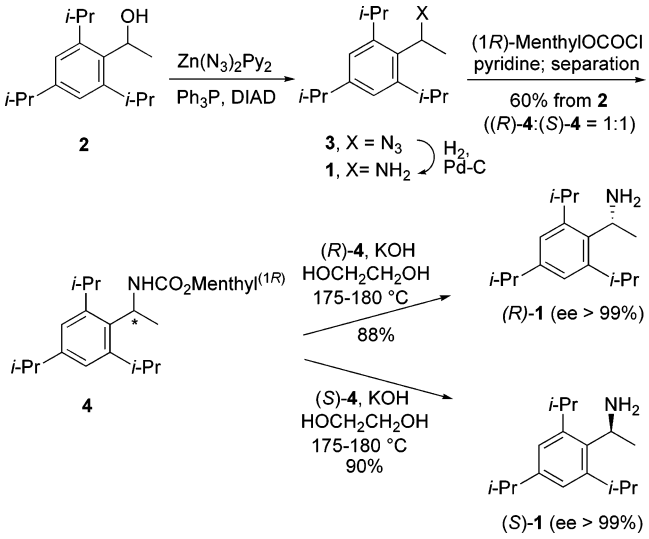


We now describe in this paper the preparation of the enantiopure *R* and *S* amines and their application for the synthesis of enantiopure γ-subtituted γ-amino acid derivatives, for which few effective approaches are currently available.[9]

Results and Discussion

An obvious starting point for the synthesis of the pure amine enantiomers was the corresponding, readily available, enantiopure alcohols. Disappointingly, however, all of the alcohol to azide protocols that were examined[10] produced low yields and/or a partially racemized product, which could not be effectively upgraded at the azide or amine stage by recrystallization. The problem was further exacerbated by the resistance of several diastereomeric salts of the racemic, as well as the enantioenriched, amine to efficient upgrading.[11] It was thus apparent that other stereopure precursors of the chiral amine had to be considered, which led us to carbamate derivatives.

SCHEME 1. Synthesis of (*R*)-1 and (*S*)-1 from Racemic Alcohol 2



Readily available (1*R*)-menthyl chloroformate reacted with racemic **1** to generate the diastereomeric carbamates, which could easily be separated by simple silica gel chromatography (R_f 0.40 and 0.65, respectively, 1:4 ether−pentane).[11] Subsequent treatment of these derivatives with KOH in hot ethylene glycol[12] then yielded the enantiopure[13] amines (*R*)-**1** and (*S*)-**1**. Armed with these results, the sequence from the racemic alcohol to the enantiopure amines was optimized for scalability and yield. The optimized procedure that evolved requires only a single true chromatography and affords 8 g of each enantiomer from 30 g of racemic alcohol (Scheme 1).

The enantiopure amines were efficiently converted into the corrresponding *N*-hydroxylamines (*R*)-**7** and (*S*)-**7** by a three-step procedure (Scheme 2),[14] which was found to be superior to that reported by Wovkulich and Uskokovic[15] and proceeded without any erosion of the enantiopurity.[16]

Condensation of **7** with a variety of aldehydes in the presence of magnesium sulfate afforded nitrones **8a**−**g** in high yield (eq 4, Table 1).

The nitrones derived from this new chiral *N*-hydroxylamine were next subjected to samarium diiodide-induced reductive

(6) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265−2268.

(7) For reviews on the many applications in asymmetric synthesis of 1-phenylethylamine, see: Juaristi, E.; Escalante, J.; Leon-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715−740. Juaristi, E.; Leon-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441−2495.

(8) This transformation was achieved by treatment with $Zn(N_3)_2(Py)_2$, Ph_3P, and DIAD, followed by hydrogenation in EtOH over 10% Pd−C (69% overall yield).

(9) For a review on the synthesis of chiral (nonracemic) γ-amino acid derivatives, see: Trabocchi, A.; Guarna, F.; Guarna, A. *Curr. Org. Chem.* **2005**, *9*, 1127−1153. See also: Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, 82, 2365−2379. Friestad, G. K.; Marié, J.-C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249−3252 and references cited.

(10) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130−132. Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Org. Chem.* **2003**, *68*, 5826−5831. Ito, M.; Koyakumaru, K.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 377−378. Saito, A.; Saito, K.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 3955−3958. Reddy, G. V. S.; Rao, G. V.; Subramanyam, R. V. K.; Iyengar, D. S. *Synth. Commun.* **2000**, *30*, 2233−2237. Mizuno, M.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1997**, 2165−2166. Bolshan, Y.; Chen, C.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111−114. For a discussion of racemization under Mitsunobu conditions, see: Hiller, M. C.; Desrosiers, J.-N.; Marcoux, J.-F.; Grabowski, E. J. J. *Org. Lett.* **2004**, *6*, 573−576.

(11) For a similar study with 1-mesitylethylamine, see: Kohara, T.; Hashimoto, Y.; Shioya, R.; Saigo, K. *Tetrahedron: Asymmetry* **1999**, *10*, 4831−4840.

(12) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300−304. This was more effective than treatment with trichlorosilane (Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781−2782) or Dibal-H,[11] followed by hydrolysis.

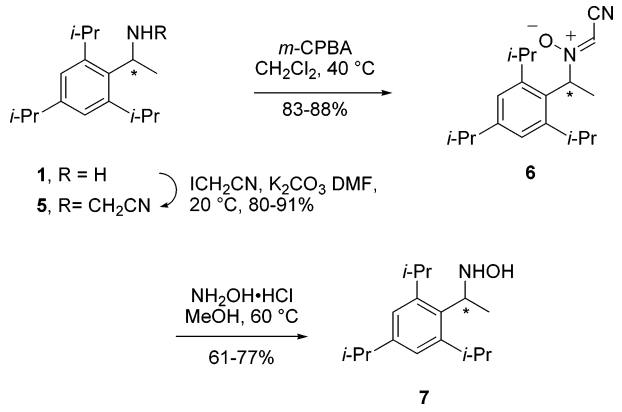
(13) By HPLC: Chiralpack AD-H, 5 μm, trifluoroacetic acid: 2-propanol: hexane = 0.1:4:96, 1.0 mL/min. t_R of (*R*)-(+) isomer = 4.23 min; t_R of (*S*)-(−) isomer = 5.83 min. Assignments were made through preparation of the (*S*)-(−) amine from the pure (*R*)-(+) alcohol[3] by Mitsunobu-type inversion, followed by hydrogenation[8] (92% ee).

(14) Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299−1304.

(15) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455−3462.

(16) By HPLC: Chiralpack AD-H, 5 μm, trifluoroacetic acid:2-propanol: hexane = 0.1:2:98, 0.5 mL/min. t_R of (*R*)-(+)-**7** = 10.43 min; t_R of (*S*)-(−)-**7** = 12.69 min.

SCHEME 2. Conversion of Enantiopure Amines to the Corresponding *N*-Hydroxylamines



coupling with ethyl acrylate to test the generality of the 1,3-stereoinduction shown in eq 3.[17] The reactions were performed

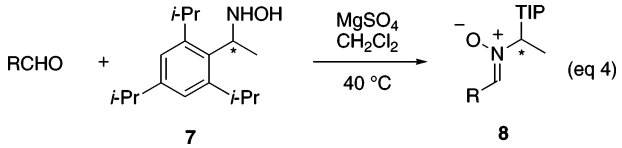


TABLE 1. Preparation of Nitrones 8a−g

entry	R	**7**	nitrone	time (h)	yield[a] (%)
1	Me	*R*	(*R*)-**8a**	4	84
2	Et	*R*	(*R*)-**8b**	6	84
3	*i*-Bu	*S*	(*S*)-**8c**	6.5	87
4	*i*-Pr	*S*	(*S*)-**8d**	24	92
5	*c*-Hex	*R*	(*R*)-**8e**	6	89
6	*t*-Bu	*rac*	*rac*-**8f**	48	91
7	Ph	*rac*	*rac*-**8g**	48	93

[a] After purification.

in the presence of 8 equiv of water to enhance the rates and the yields[6] (eq 5). The results are reported in Table 2.

Pleasingly, good yields and apparent total (NMR) diastereoselection again resulted when aliphatic nitrones were used (entries 1−5), except for that from pivalaldehyde (entry 6). The relative stereochemistry, previously determined in *rac*-**9c** through single-crystal X-ray structure analysis,[6,18] has been assigned in the other adducts by analogy.

The present study also brought to the forefront some apparent limitations in this asymmetric reductive coupling: with the hindered substrate **8f**, the expected γ-*N*-hydroxyamino ester **9f** did not result, but rather the conjugated imine resulting from dehydration of this adduct. Furthermore, the aromatic nitrone **8g** was merely reduced to the corresponding *N*-hydroxylamine

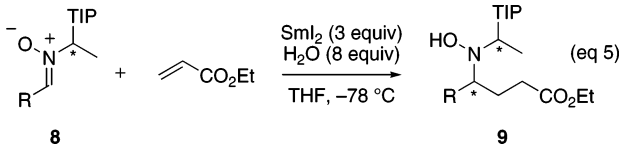


TABLE 2. SmI_2-Induced Reductive Coupling of Nitrones 8a−g with Ethyl Acrylate

entry	R	nitrone	product[a]	time (h)	yield[b] (%)	dr[c]
1	Me	(*R*)-**8a**	(*R*,*R*)-**9a**	2	78	> 95:5
2	Et	(*R*)-**8b**	(*R*,*R*)-**9b**	1.25	75	> 95:5
3	*i*-Bu	(*S*)-**8c**	(*S*,*R*)-**9c**	48	71	> 95:5
4	*i*-Pr	(*S*)-**8d**	(*S*,*R*)-**9d**	23	94	> 95:5
5	*c*-Hex	(*R*)-**8e**	(*R*,*S*)-**9e**	24	83	> 95:5
6	*t*-Bu	*rac*-**8f**	*rac*-**9f**	120	0[d]	
7	Ph	*rac*-**8g**	*rac*-**9g**	0.33	0[e]	

[a] The configuration of the new stereocenter follows that of the chiral auxiliary. [b] After purification by chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture (unique diastereomers observed). [d] The conjugated imine resulting from dehydration of the expected product was isolated (30%). [e] Only the hydroxylamine from nitrone reduction was isolated (70%).

under the reaction conditions.[19] Similar behavior has been previously noted with the nitrone derived from benzaldehyde and *N*-hydroxyvaline methyl ester.[6]

Significantly, the excellent diastereoselection observed in the SmI_2-induced reductive coupling of aliphatic nitrones with ethyl acrylate is also found with other unsaturated esters, such as methyl crotonate, methyl methacrylate, and ethyl propiolate, which broadens considerably the synthetic interest of this approach to γ-amino acid derivatives (Scheme 3).[20] The stereochemistry in adducts **10**, **11a**, and **12**, determined by X-ray analysis,[18,21,22] strongly supports the assignments made in **9a**,**b**,**d**,**e**.

γ-Amino acid derivatives are important building blocks for drug discovery, in particular for the preparation of diverse peptidomimetics with highly ordered structures.[9,23] Transformation of the reductive coupling adducts into potentially useful γ-amino and γ-*N*-hydroxyamino acid derivatives proved difficult;[24] however, it was finally found that *O*-acylation of the *N*-hydroxylamines **9a**−**e** serves to activate them toward acidic cleavage of the benzylic group. Thus, the γ-*N*-hydroxyamino esters **9a**−**e** were first treated with acetic anhydride to yield the corresponding acetates **13a**−**e**, which were then readily transformed into the γ-*N*-acetoxyamino esters **14a**−**e**[25] by treatment with 5% trifluoroacetic acid in dichloromethane (Scheme 4). These derivatives could be converted directly into the corresponding *N*-Boc-γ-amino esters **15a**−**e** by hydrogenation in the presence of Boc_2O.[26] These results are summarized in Table 3. While racemization in the transformations of **9a**−**e** into **15a**−**e** seemed highly unlikely, this possibility was nevertheless examined for **15d** and **15e** by HPLC of the corresponding benzyl esters: an ee >98% was found in each case.[27]

The γ-*N*-hydroxyamino esters **9** are also ready precursors of γ-lactams, which are found in numerous biologically active molecules.[28] Hydrogenation of **9c** and **9e** in acetic acid, followed by removal of the palladium catalyst and heating, effected

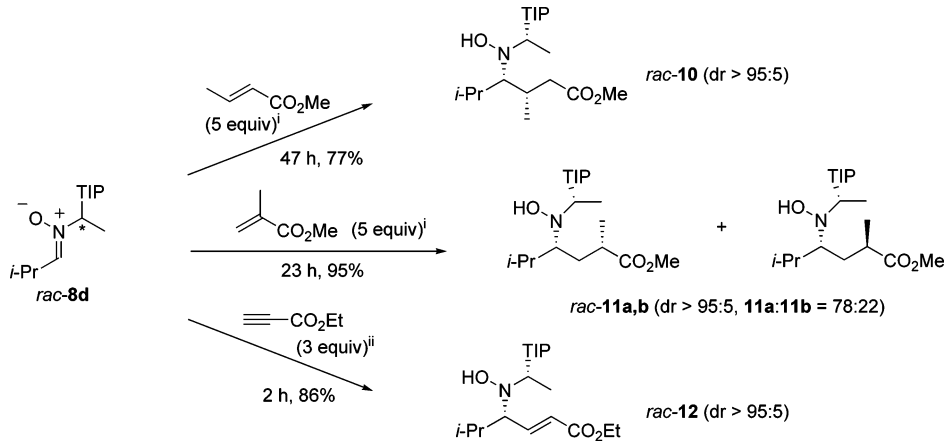
(17) A similar approach to enantiopure γ-*N*-hydroxyamino esters has been published: Johannesen, S. A.; Albu, S.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun.* **2004**, 1962−1963. The same group has reported that the use of chiral acrylates is less effective in terms of stereoinduction: Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229−231.

(18) Crystallographic information files (CIF) for compounds *rac*-**9c**, *rac*-**10**, *rac*-**11a**, and *rac*-**12** have been deposited as CCDC-201303, CCDC-601081, CCDC-611406, and CCDC-611364, respectively, at the Cambridge Crystallographic Data Centre and can be obtained online free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (+44) 1223−336033. E-mail: deposit@ccdc.cam.ac.uk).

(19) When the reaction was performed in the absence of water, a trace of the adduct **9g** was obtained, along with the *N*-hydroxylamine and unreacted nitrone.

(20) These reactions were performed on racemic material.

SCHEME 3. Diastereoselective Reductive Coupling of Nitrones with Crotonate, Methacrylate, and Propiolate Esters[a]



[a] Reagents and conditions: (i) SmI_2 (4 equiv), H_2O (8 equiv), THF, −78 °C; (ii) SmI_2 (6 equiv), H_2O (25 equiv), THF, −78 °C.

SCHEME 4. Conversion of *N*-Hydroxylamines 9a−e into γ-Amino Acid Derivatives 15a−e

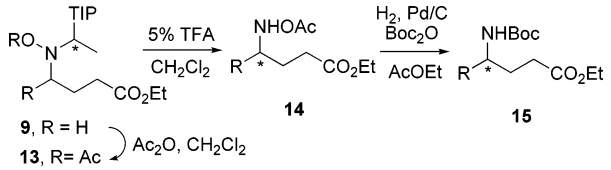


TABLE 3. Conversion of *N*-Hydroxylamines 9a−e into γ-Amino Acid Derivatives 15a−e

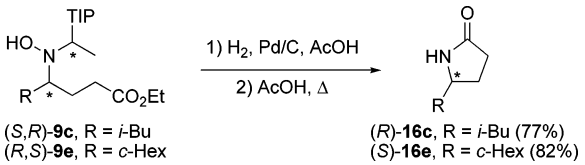
			yield[a] (%)		
entry	compd	R	acetylation[b]	acidic cleavage[c]	hydrogenation[d]
1	**9a**	Me	94	70	65
2	**9b**	Et	96	75	51
3	**9c**	*i*-Bu	92	83	78
4	**9d**	*i*-Pr	98	81	67
5	**9e**	*c*-Hex	93	66	59

[a] After purification. [b] Ac_2O (1.1 equiv), CH_2Cl_2, 40 °C, 0.75−2.25 h. [c] 5% TFA−CH_2Cl_2, 20 °C, 1.75−5.0 h. [d] H_2, Pd/C, Boc_2O, AcOEt, 20 °C, ca. 1 h.

reduction of the N−O bond, cyclization, and cleavage of the benzylic group to yield directly lactams **16c** and **16e**, respectively[29] (Scheme 5).

In summary, the enantiomers of 1-(2,4,6-triisopropylphenyl)-ethylamine have been prepared efficiently in >99% ee and used in a broad, highly diastereoselective nitrone-unsaturated ester reductive coupling for the preparation of a variety of enantiopure γ-amino acid derivatives. Other applications of this new auxiliary in asymmetric synthesis can readily be envisaged.[7]

SCHEME 5. Conversion of γ-*N*-hydroxyamino Esters 9c and 9e into Lactams 16c and 16e



Experimental Section

(*R*)- and (*S*)-1-(2,4,6-Triisopropylphenyl)ethylamine ((*R*)-1 and (*S*)-1). A stirred mixture of 30.0 g (121.0 mmol) of racemic 1-(2,4,6-triisopropylphenyl)ethanol (**2**), 63.0 g (240.2 mmol) of triphenylphosphine, and 27.6 g (89.7 mmol) of zinc azide bis-pyridine complex in 450 mL of dry toluene at 20 °C was treated dropwise over 10 min with 48.0 mL (49.3 g, 243.8 mmol) of diisopropyl azodicarboxylate. After 48 h, 7.5 mL of water was added, and stirring was continued for 30 min, whereupon 450 mL of cyclohexane was added. The resulting mixture was filtered over Celite, which was washed with 900 mL of 1:1 toluene/cyclohexane, and the filtrate was concentrated to provide the crude product.

(21) Crystal data for compound *rac*-**10**: $C_{26}NO_3H_{45}$, M = 419.65, monoclinic, a (Å) = 8.199(2), b (Å) = 16.132(3), c (Å) = 19.520(4), β (deg) = 91.19(2), V (Å^3) = 2581.2(8), D (g·cm^{-3}) = 1.080, T = 293 K, space group $P2_1/a$, Z = 4, λ (Å) = 1.54178, 2θ max (deg) = 150, μ (cm^{-1}) 5.358, 5675 reflections measured, 5597 unique (R_{int} = 0.04), 271 parameters, Reflections/parameters ratio: 10.0, R(F)[$I > 2\sigma(I)$] = 6.2%. R_w(F) [all data] = 7.8%. GOF = 1.99. Crystal data for compound *rac*-**11a**: $C_{26}NO_3H_{45}$, M = 419.65, monoclinic, a (Å) = 10.859(8), b (Å) = 24.85(2), c (Å) = 10.985-(3), β (deg) = 112.56(4), V (Å^3) = 2737(3), D (g·cm^{-3}) = 1.018, T = 293 K, space group $P2_1/n$, Z = 4, λ (Å) = 1.54178, 2θ max (deg) = 150, μ (cm^{-1}) 5.052, 6086 reflections measured, 6062 unique (R_{int} = 0.06), 271 parameters, reflections/parameters ratio: 10.6, R(F)[$I > 2\sigma(I)$] = 7.7%. R_w-(F) [all data] = 11.7%. GOF = 1.98. Crystal data for compound *rac*-**12**: $C_{26}NO_3H_{43}$, M = 417.63, monoclinic, a (Å) = 26.324(5), b (Å) = 11.919-(1), c (Å) = 17.271(3), β (deg) = 92.69(1), V (Å^3) = 5413(1), D (g·cm^{-3}) = 1.025, T = 293 K, space group $C2/c$, Z = 8, λ (Å) = 1.54178, 2θ max (deg) = 150, m (cm^{-1}) 5.108, 6039 reflections measured, 5855 unique (R_{int} = 0.02), 271 parameters, reflections/parameters ratio: 12.3, R(F)[$I > 2\sigma$-(I)] = 6.9%. R_w(F) [all data] = 11.6%. GOF = 1.98.

(22) The present work indicates an incorrect stereochemical assignment was made in reference 6 for the product analogous to **10** (benzyl replaces triisopropylphenylethyl): the anti configuration assigned to this compound in ref 6 (Scheme 1 and Table 1, entry 11) is erroneous and should be syn.

(23) "The structural diversity of γ-amino acids and γ-peptides has not been elucidated nearly as well as that of β-peptides: it is expected to be richer" (Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers* **2006**, *84*, 23−37). See also: Seebach, D.; Schaeffer, L.; Brenner, M.; Hoyer, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 776−778. Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573−584. Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem* **2001**, *2*, 445−455. Hanessian, S.; Luo, X.; Schaaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, 120, 8569−8570.

(24) As previously noted with 1-(2,4,6-triisopropylphenyl)ethoxy derivatives, the amine adducts were resistant to benzylic hydrogenolysis (only N−O bond reduction being observed). Benzylic oxidation of *N*-hydroxylamine **9c** using MnO_2 did afford an aryl-conjugated nitrone, but this could not be cleanly hydrolyzed. Similarly, dehydration of **9c** yielded an imine−enamine mixture, which resisted acid-catalyzed hydrolysis.

Partial purification of this material by filtration over dry silica gel (450 g) with 0−10% ether in pentane provided 40 g of azide, contaminated with the corresponding styrene (ca. 15%) and some toluene. A small sample of this material was further purified to provide a sample of pure azide **3**: mp 41−43 °C (MeOH−H_2O); ^{1}H NMR δ 1.23−1.27 (m, 18H), 1.51 (d, J = 7.1 Hz, 3H), 2.86 (sept, J = 6.9 Hz, 1H), 3.39 (br s, 2H), 5.37 (q, J = 7.1 Hz, 1H), 7.01 (s, 2H); ^{13}C NMR δ 21.6, 23.9, 24.8, 29.6, 34.0, 56.2, 120−124 (br s), 131.5, 148.1; MS (DCI) *m*/*z* 246 (17) $[M + H - N_2]^+$, 231 (100) $[M + H - HN_3]^+$; IR 3050, 2110, 1265, 1063 cm^{-1}. Anal. Calcd for $C_{17}H_{27}N_3$: C, 74.68; H, 9.95; N, 15.37. Found: C, 74.54; H, 9.94; N, 15.17.

A mixture of the above crude azide **3** and 1.50 g of 10% Pd/C in 1.50 L of 95% ethanol under hydrogen was stirred for 64 h, whereupon it was filtered over sand, which was then washed with ether. The filtrate was concentrated under vacuum to give 26 g of crude racemic amine **1**. This material in 180 mL of CH_2Cl_2 and 10.0 mL (123.6 mmol) of pyridine at 0 °C was treated dropwise with 26.0 mL (26.5 g, 121.2 mmol) of (−)-menthyl chloroformate. The resulting mixture was stirred at 20 °C for 13 h and then diluted with ether, which was washed with water, 10% aqueous HCl, and saturated sodium carbonate, dried over sodium sulfate, and filtered. Concentration of the filtrate left a brown solid, which was purified on 1.3 kg of dry silica gel with 4−25% ether in pentane to provide 16.03 g of pure less polar carbamate and 16.67 g of slightly impure more polar carbamate, which was recrystallized from MeOH−H_2O to give 15.30 g of pure material (60% combined overall yield, three steps). Less polar carbamate: white solid; mp 111−112 °C (MeOH−H_2O); $[\alpha]^{20}_D$ −82 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.60−2.20 (m, 39H), 2.86 (sept, J = 6.9 Hz, 1H), 3.33 (sept, J = 6.8 Hz, 2H), 4.51 (m, 1H), 4.93 (br s, 1H), 5.40 (br s, 1H), 7.00 (s, 2H); ^{13}C NMR δ 16.3, 20.8, 22.0, 22.5, 23.4, 23.90, 23.92, 24.4, 26.1, 31.4, 34.0, 34.4, 41.4, 45.6, 47.4, 74.5, 122.2 (br), 134.6, 146.3 (br), 147.4, 155.8; MS (−DCI) *m*/*z* 428 (100) $[M - H]^-$; IR 3456, 1721, 1380, 1228, 1055 cm^{-1}. Anal. Calcd for $C_{28}H_{47}NO_2$: C, 78.27; H, 11.03; N, 3.26. Found: C, 78.23; H, 11.32; N, 3.34. More polar carbamate: white solid; mp 122−123 °C (MeOH−H_2O); $[\alpha]^{20}_D$ −8.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.60−2.10 (m, 39H), 2.85 (sept, J = 6.9 Hz, 1H), 3.33 (m, 2H), 4.53 (dt, J = 4.3, 10.8 Hz, 1H), 4.96 (br s, 1H), 5.43 (br s, 1H), 6.99 (s, 2H); ^{13}C NMR δ 16.6, 20.8, 22.0, 22.6, 23.88, 23.92, 24.4, 24.6, 26.4, 29.8, 31.4, 34.0, 34.3, 41.5, 45.4, 47.4, 74.4, 122.5 (br), 134.6, 146.2 (br), 147.3, 155.8; MS (−DCI) *m*/*z* 428 (100) $[M - H]^-$; IR 3280, 1704, 1378, 1318, 1050 cm^{-1}. Anal. Calcd for $C_{28}H_{47}NO_2$: C, 78.27; H, 11.03; N, 3.26. Found: C, 78.51; H, 10.97; N, 3.26.

A mixture of 7.00 g (16.3 mmol) of the more polar carbamate and 28.0 g (499 mmol) of KOH in 140 mL of ethylene glycol was stirred in a closed system at 175−180 °C for 12 h. After being allowed to cool to room temperature, the reaction mixture was extracted with ether, which was washed with water, dried over sodium sulfate, filtered, and concentrated to provide the crude product. Purification of this material by chromatography on dry silica gel (400 g) with ether in pentane gave 3.55 g (88%) of the (*R*)-amine **1**: white solid; mp 83−84 °C; $[\alpha]^{20}_D$ +26.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.23−1.27 (m, 18H), 1.50 (d, J = 7.0 Hz, 3H), 1.54 (s, 2H), 2.85 (sept, J = 6.9 Hz, 1H), 3.70 (br m, 2H), 4.75 (q, J = 6.9 Hz, 1H), 6.99 (s, 2H); ^{13}C NMR δ 23.9, 23.9, 24.5, 24.6, 29.5, 34.0, 45.3, 120−124, 137.2, 146.8; MS (DCI) *m*/*z* 231 (100) $[M + H - NH_3]^+$; IR 3367, 3050, 2959, 2927, 2869, 1608 cm^{-1}. Anal. Calcd for $C_{17}H_{29}N$: C, 82.53; H, 11.81; N, 5.66. Found: C, 82.28; H, 11.68; N, 5.81. The less polar carbamate was treated in a similar manner to provide in 90% yield the (*S*)-amine **1**: $[\alpha]^{20}_D$ −26.9 (*c* 1.0, $CHCl_3$).

(*S*)-[1-(2,4,6-Triisopropylphenyl)ethylamino]acetonitrile ((*S*)-5). A stirred solution of (*S*)-amine **1** (5.11 g, 20.7 mmol) in 67 mL of dry DMF was treated with 7.15 g (51.7 mmol) of potassium carbonate, followed by 3.0 mL (6.92 g, 41.5 mmol) of iodoacetonitrile. The reaction mixture was stirred at 20 °C for 5 h, after which time 3 N aqueous NaOH was added and the mixture was extracted with ether, which was washed with 5% aqueous LiCl solution, dried over $MgSO_4$, and concentrated under vacuum to give the crude product. Purification of this material by column chromatography on silica gel with 5−10% ethyl acetate in pentane yielded 5.41 g (91%) of (*S*)-cyanomethylated amine **5** as a white solid: mp 127−129 °C; $[\alpha]^{20}_D$ −98.0 (*c* 1.6, $CHCl_3$); ^{1}H NMR δ 1.21−1.47 (m, 18H), 1.52 (d, J = 6.9 Hz, 3H), 2.85 (sept, J = 6.9 Hz, 1H), 3.35−3.45 (m, 2H), 3.41 (d, J = 17.5 Hz, 1H), 3.59 (d, J = 17.5 Hz, 1H), 3.97−4.09 (m, 1H), 4.71 (q, J = 6.8 Hz, 1H), 6.98 (s, 1H), 7.03 (s, 1H); ^{13}C NMR δ 21.4, 23.9, 24.2, 24.9, 28.5, 29.3, 34.0, 35.5, 50.8, 118.5, 121.0, 123.5, 132.7, 147.5; MS (DCI) *m*/*z* 287 (1) $[M + H]^+$, 231 (100) $[M + H - H_2NCH_2CN]^+$; IR 3334, 3056, 2959, 2927, 2868, 2313, 1608 cm^{-1}. Anal. Calcd for $C_{19}H_{30}N_2$: C, 79.66; H, 10.56; N, 9.78. Found: C, 79.59; H, 10.70; N, 9.61.

(*S*,*Z*)-*N*-(Cyanomethylene)-1-(2,4,6-triisopropylphenyl)ethanamine Oxide ((*S*)-6). A solution of 5.00 g (17.5 mmol) of (*S*)-cyanomethylated amine **5** in 430 mL of CH_2Cl_2 was treated with 4.96 g (20.1 mmol) of 70% *m*-chloroperbenzoic acid, and the resulting suspension was stirred at 40 °C. After 1 h, a second portion of 70% *m*-chloroperbenzoic acid (4.96 g, 20.1 mmol) was added to the reaction mixture, and stirring was continued for 18 h. After being allowed to cool to 20 °C, the reaction mixture was treated with a saturated aqueous solution of sodium thiosulfate, followed by a saturated solution of sodium bicarbonate. The aqueous phases were back-extracted with CH_2Cl_2, and the combined CH_2Cl_2 phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography with 5−10% ethyl acetate in pentane to yield (*S*)-nitrone **6** (4.63 g, 88%) as a white solid: mp 127−129 °C; $[\alpha]^{20}_D$ −2.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 1.26 (d, J = 6.9 Hz, 18H), 1.82 (d, J = 6.9 Hz, 3H), 2.75−3.20 (m, 2H), 2.89 (sept, J = 6.9 Hz, 1H), 5.63 (dq, J = 6.9, 1.5 Hz, 1H), 6.55 (d, J = 1.5 Hz, 1H), 7.06 (s, 2H); ^{13}C NMR (Tol-d_8, 80 °C) δ 17.8, 23.7, 23.8, 24.4, 29.8, 34.4, 70.1, 106.0, 112.6, 123.1, 131.0, 147.9, 150.3; MS (DCI) *m*/*z* 318 (3) $[M + NH_4]^+$, 285 (33) $[M + H - O]^+$, 231 (100) $[M + H -$

(25) These compounds, although not very stable to storage, represent potentially useful building blocks for the synthesis of *N*-hydroxy-γ-peptides. For studies related to *N*-hydroxypeptides, see, for example: Hara, Y.; Akiyama, M. *J. Am. Chem. Soc.* **2001**, 123, 7247−7256. (siderophores). Cartwright, R. J.; Dowell, R. I. (Zeneca Limited, UK; Zeneca-Pharma S.A), WO2000012467, 2000; *Chem. Abstr.* **2000**, *132*, 194665. Andrews, R. C.; Anderson, M. W.; Stanford, J. B.; Bubacz, D. G.; Chan, J. H.; Cowan, D. J.; Gaul, M. D.; McDougald, D. L.; Musso, D. L.; Rabinowitz, M. H.; Wiethe, R. W. (Glaxo Group Limited, UK), GB2348198, 2001; *Chem. Abstr.* **2001**, *134*, 42444 (metalloproteinase inhibition). Hin, S.; Zabel, C.; Bianco, A.; Jung, G.; Walden, P. *J. Immunol.* **1999**, 163, 2363−2367. Bianco, A.; Kaiser, D.; Jung, G. *J. Pept. Res.* **1999**, 54, 544−548. Bianco, A.; Zabel, C.; Walden, P.; Jung, G. *J. Pept. Sci.* **1998**, 4, 471−478. Hara, Y.; Akiyama, M. *Inorg. Chem.* **1996**, 35, 5173−5180. Dupont, V.; Aubry, A.; Marraud, M. *Pept. 1992, Proc. Eur. Pept. Symp., 22nd* **1993**, 603−604 (conformational studies). Lin, T. Y.; Kuo, D. W. *J. Enz. Inhib.* **1991**, *5*, 33−40 (collagenase inhibition).

(26) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(27) γ-Amino ethyl esters **15d** and **15e** were hydrolyzed using 2 N NaOH in dioxane/water (9:1), and the resulting carboxylic acids were treated with benzyl bromide (1.5 equiv) and cesium carbonate (1.5 equiv) in DMF to yield the corresponding benzyl esters. HPLC (Welk column, 5 μm): from **15d**, 2-propanol:hexane = 1:99 (1.0 mL/min), t_R of (*S*)-isomer = 16.7 min, t_R of (*R*)-isomer = 15.5 min; from **15e**, 2-propanol:hexane = 2:98 (1.0 mL/min), t_R of (*S*)-isomer = 9.6 min, t_R of (*R*)-isomer = 10.8 min.

(28) See, for example: Gouliaev, A. H.; Senning, A. *Brain Res. Rev.* **1994**, *19*, 180−222. Duan, J. J.-W.; Chen, L.; Wasserman, Z. R.; Lu, Z.; Liu, R. Q.; Covington, M. B.; Qian, M.; Hardman, K. D.; Magolda, R. L.; Newton, R. C.; Christ, D. D.; Wexler, R. R.; Decicco, C. P. *J. Med. Chem.* **2003**, *46*, 727−733. See also: Basavaiah, D.; Rao, S. *Tetrahedron Lett.* **2004**, *45*, 1621−1625 (ref 3).

(29) (a) Craven, A. P.; Dyke, H. J.; Thomas, E. J. *Tetrahedron* **1989**, *45*, 2417−2429. Burgess, L.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656−1662. Wei, Z.-Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439−4442. (b) Sinnreich, J.; Elad, D. *Tetrahedron* **1968**, *24*, 4509−4516 (racemic).

NCC(H)NOH]$^+$; IR 3121, 3056, 2307, 2223, 1718, 1615 cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 76.09; H, 9.44; N, 9.28.

(*S*)-*N*-[1-(2,4,6-Triisopropylphenyl)ethyl]hydroxylamine ((*S*)-7). A stirred solution of 4.54 g (15.1 mmol) of (*S*)-nitrone **6** in 100 mL of methanol was treated with 5.26 g (75.5 mmol) of hydroxylamine hydrochloride, and the resulting solution was heated at 60 °C for 18 h. After being allowed to cool to 20 °C, the mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and aqueous sodium bicarbonate (50 mL). The aqueous phase was separated and extracted with CH_2Cl_2, and the combined CH_2Cl_2 phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by silica gel chromatography with 1% ethyl acetate in pentane yielded 2.94 g (74%) of (*S*)-*N*-hydroxylamine **7** as a white solid: mp 135 °C; $[\alpha]^{20}_D$ −14.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 1.24 (d, J = 6.9 Hz, 18H), 1.50 (d, J = 6.9 Hz, 3H), 2.85 (sept, J = 6.9 Hz, 1H), 3.30 (m, 1H), 3.75 (m, 1H), 4.75 (q, J = 6.9 Hz, 1H), 5.27 (br s, 1H), 7.01 (s, 2H); ^{13}C NMR δ 19.1, 23.9, 24.5, 24.8, 25.3, 29.6, 34.0, 57.3, 110.4, 120.9, 123.1, 132.9, 147.5; MS (DCI) *m*/*z* 246 (100) [M + H − H_2O]$^+$, 231 (62) [M + H − NH_2OH]$^+$; IR 3578, 3271, 3050, 1608, 1571 cm^{-1}. Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.15; H, 11.19; N, 5.70.

General Procedure for the Preparation of Nitrones 8a−g. To a well-stirred solution of 1.0 mmol of *N*-hydroxylamine **7** in 10 mL of CH_2Cl_2 were added 1.0 mmol of the aldehyde and 2 g (excess) of anhydrous $MgSO_4$. The reaction mixture was refluxed with vigorous stirring until the disappearance of starting materials (TLC, 4−48 h). After being allowed to cool, the mixture was filtered and the filtrate concentrated. The crude product was triturated with either pentane or cyclohexane or chromatographed on silica gel to afford the pure nitrone (**8a**−**g**, 84−93% yield).

(*R*,*Z*)-*N*-Ethylidene-1-(2,4,6-triisopropylphenyl)ethanamine Oxide ((*R*)-8a): white solid; mp 81−82 °C; $[\alpha]^{20}_D$ +59.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 1.25 (d, J = 6.8 Hz, 6H), 1.26 (d, J = 7.0 Hz, 12H), 1.84 (d, J = 7.3 Hz, 3H), 1.96 (dd, J = 5.9, 2.2 Hz, 3H), 2.88 (sept, J = 6.9 Hz, 1H), 3.08 (br s, 2H), 5.49−5.60 (m, 1H), 6.61 (dq, J = 5.9, 1.8 Hz, 1H), 7.03 (s, 2H); ^{13}C NMR δ 12.8, 18.3, 23.8, 23.9, 24.4, 29.4, 29.6, 34.0, 65.7, 120−125 (br s), 131.4, 133.1, 148.9; MS (DCI) *m*/*z* 274 (96) [M + H − O]$^+$, 231 (100) [M + H − CH_3CHNOH]$^+$; IR 3045, 1599 cm^{-1}. Anal. Calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.59; H, 10.94; N, 4.85.

(*R*,*Z*)-*N*-Propylidene-1-(2,4,6-triisopropylphenyl)ethanamine Oxide ((*R*)-8b): colorless oil; $[\alpha]^{20}_D$ +79.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.02 (t, J = 7.7, 0.9 Hz, 3H), 1.25 (br d, J = 6.7 Hz, 6H), 1.26 (dd, J = 6.9, 0.9 Hz, 12H), 1.83 (dd, J = 7.2, 0.9 Hz, 3H), 2.45−2.52 (m, 2H), 2.88 (sept, J = 6.9 Hz, 1H), 3.08 (br s, 2H), 5.47−5.58 (m, 1H), 6.49 (dt, J = 5.7, 1.7 Hz, 1H), 7.03 (s, 2H); ^{13}C NMR δ 9.9, 14.1, 18.4, 20.4, 23.8, 24.0, 24.3, 29.6, 34.0, 65.7, 120−125 (br s), 131.1, 139.0, 148.9; MS (DCI) *m*/*z* 304 (9) [M + H]$^+$, 288 (13) [M + H − O]$^+$, 231 (100) [M + H − C_2H_5-CHNOH]$^+$; IR 3431, 3045, 1602 cm^{-1}. Anal. Calcd for $C_{20}H_{33}$-NO: C, 79.15; H, 10.96; N, 4.62. Found: C, 79.45; H, 10.94; N, 4.60.

(*S*,*Z*)-*N*-(3-Methylbutylidene)-1-(2,4,6-triisopropylphenyl)-ethanamine Oxide ((*S*)-8c): white solid; mp 77−78 °C; $[\alpha]^{20}_D$ −64.5 (*c* 2.4, $CHCl_3$); ^{1}H NMR δ 0.87 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.8 Hz, 6H), 1.26 (d, J = 6.7 Hz, 12H), 1.81 (sept, J = 6.7 Hz, 1H), 1.84 (d, J = 7.0 Hz, 3H), 2.16−2.27 (m, 1H), 2.48−2.57 (m, 1H), 2.89 (sept, J = 6.9 Hz, 1H), 3.00−3.20 (m, 2H), 5.55 (qd, J = 7.2, 2.1 Hz, 1H), 6.53 (ddd, J = 7.0, 5.3, 1.8 Hz, 1H), 7.03 (s, 2H); ^{13}C NMR δ 18.4, 22.7, 22.8, 23.9, 24.1, 24.5, 24.7, 25.9, 29.7, 30.6, 34.1, 35.9, 66.0, 120.9, 131.1, 137.9, 146.5, 149.0; MS (DCI) *m*/*z* 332 (28) [M + H]$^+$, 231 (100) [M + H − C_3H_7CHNOH]$^+$; IR 3059, 1613, 1566 cm^{-1}; HRMS(ESI) Calcd for $C_{22}H_{38}NO$ 332.2948, found 332.2955.

(*S*,*Z*)-*N*-(2-Methylpropylidene)-1-(2,4,6-triisopropylphenyl)-ethanamine Oxide ((*S*)-8d): white solid; mp 77−78 °C; $[\alpha]^{20}_D$ −89.9 (*c* 1.9, $CHCl_3$); ^{1}H NMR δ 1.03 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.10−1.30 (br s, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.27 (d, J = 6.9 Hz, 12H), 1.83 (d, J = 7.1 Hz, 3H), 2.90 (sept, J = 6.9 Hz, 1H), 3.09 (br s, 2H), 3.18 (sept, J = 7.0 Hz, 1H), 5.51 (q, J = 7.0 Hz, 1H), 6.36 (dd, J = 7.1, 1.9 Hz, 1H), 7.03 (s, 2H); ^{13}C NMR δ 18.4, 18.8, 19.1, 23.8, 24.0, 26.4, 29.3, 29.7, 30.0, 34.0, 66.0, 121.4, 123.6, 130.7, 142.8, 148.9; MS (DCI) *m*/*z* 318 (17) [M + H]$^+$, 302 (22) [M + H − O]$^+$, 231 (100) [M + H − C_3H_7CHNOH]$^+$; IR 3431, 1609, 1570 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.60; H, 11.11; N, 4.42.

(*R*,*Z*)-*N*-(Cyclohexylmethylene)-1-(2,4,6-triisopropylphenyl)-ethanamine Oxide ((*R*)-8e): white solid; mp 108 °C; $[\alpha]^{20}_D$ + 83.0 (*c* 2.6, $CHCl_3$); ^{1}H NMR δ 1.03−2.41 (m, 5H), 1.21 (d, J = 7.0 Hz, 9H), 1.23 (d, J = 7.0 Hz, 9H), 1.63 (m, 3H), 1.80 (d, J = 7.2 Hz, 3H), 1.81 (m, 2H), 2.86 (sept, J = 6.9 Hz, 1H), 2.94−3.06 (m, 3H), 5.48 (q, J = 7.2 Hz, 1H), 6.30 (dd, J = 7.3, 1.8 Hz, 1H), 7.00 (s, 2H); ^{13}C NMR δ 18.3, 23.7, 23.9, 25.3, 25.8, 28.5, 29.0, 33.9, 35.5, 66.0, 121.2, 123.1, 130.6, 141.3, 148.8; MS (DCI) *m*/*z* 358 (43) [M + H]$^+$, 342 (100) [M + H − O]$^+$, 231 (65) [M + H − $C_6H_{11}CHNOH$]$^+$; IR 3050, 1609, 1570 cm^{-1}. Anal. Calcd for $C_{24}H_{39}NO$: C, 80.61; H, 10.99; N, 3.92. Found: C, 80.35; H, 11.06; N, 3.80.

(*Z*)-*N*-(2,2-Dimethylpropylidene)-1-(2,4,6-triisopropylphenyl)-ethanamine Oxide (*rac*-8f): white solid; mp 121 °C; ^{1}H NMR δ 1.08−1.27 (m, 27H), 1.80 (d, J = 7.2 Hz, 3H), 2.88 (sept, J = 7.0 Hz, 1H), 3.07 (m, 2H), 5.21 (qd, J = 7.2, 1.7 Hz, 1H), 6.30 (d, J = 1.7 Hz, 1H), 7.02 (s, 2H); ^{13}C NMR δ 18.4, 23.8, 24.1, 26.1, 32.9, 34.0, 67.0, 120−123 (br s), 131.1, 143.1, 148.9; MS (DCI) *m*/*z* 332 (6) [M + H]$^+$, 316 (100) [M + H − O]$^+$, 231 (76) [M + H − C_4H_9CHNOH]$^+$; IR 3049, 1609, 1576 cm^{-1}. Anal. Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.22. Found: C, 79.52; H, 11.01; N, 4.10.

(*Z*)-*N*-Benzylidene-1-(2,4,6-triisopropylphenyl)ethanamine Oxide (*rac*-8g): white solid; mp 143−144 °C; ^{1}H NMR δ 0.90−1.32 (m, 3H), 1.28 (d, J = 7.2 Hz, 15H), 1.90 (d, J = 7.2 Hz, 3H), 2.90 (sept, J = 6.9 Hz, 1H), 3.16−3.20 (m, 2H), 5.76 (q, J = 7.2 Hz, 1H), 7.06 (s, 2H), 7.23 (br s, 1H), 7.35−7.37 (m, 3H), 8.13−8.17 (m, 2H); ^{13}C NMR δ 18.3, 23.9, 24.1, 24.4, 34.1, 67.7, 128.4, 128.5, 129.9, 130.8, 131.6, 133.4, 149.0; MS (DCI) *m*/*z* 352 (100) [M + H]$^+$, 336 (32) [M + H − O]$^+$; IR 3050, 1606, 1575, 1558 cm^{-1}. Anal. Calcd for $C_{24}H_{33}NO$: C, 82.00; H, 9.46; N, 3.98. Found: C, 82.11; H, 9.53; N, 4.00.

General Procedure for the Preparation of γ-*N*-Hydroxyamino Esters 9a−e. A stirred and carefully deoxygenated solution of 0.5 mmol of nitrone **8** in 10 mL of THF was cooled to −78 °C under argon. Ethyl acrylate (70 mg, 0.7 mmol), degassed water (72 mg, 4 mmol), and a solution of SmI_2 in THF (ca. 0.1 M, 15 mL, 1.5 mmol) were then added. The temperature was kept at −78 °C until the reaction was judged complete by TLC, whereupon a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) was added. The yellow mixture was extracted with ethyl acetate, and the combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography with ethyl acetate in pentane to furnish the γ-*N*-hydroxyamino ester (**9a**−**e**, 71−94% yield).

(*R*)-Ethyl 4-(hydroxy-((*R*)-1-(2,4,6-triisopropylphenyl)ethyl)-amino)pentanoate ((*R*,*R*)-9a): colorless oil; $[\alpha]^{20}_D$ −5.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR δ 1.12 (d, J = 6.3 Hz, 3H), 1.19−1.26 (m, 21H), 1.34 (d, J = 7.0 Hz, 3H), 1.68−1.78 (m, 1H), 1.80−2.00 (m, 1H), 2.32−2.53 (m, 2H), 2.78−2.90 (sept, J = 6.9 Hz, 1H), 3.07−3.18 (m, 1H), 3.34−3.43 (m, 1H), 4.01−4.08 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 4.67 (q, J = 6.9 Hz, 1H), 6.98 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 14.2, 19.3, 23.6, 23.9, 23.9, 24.6, 24.8, 25.2, 28.3, 29.4, 31.2, 33.8, 55.0, 57.1, 60.1, 120.7, 123.0, 134.6, 146.3, 146.6, 148.2, 174.3; MS (DCI) *m*/*z* 392 (53) [M + H]$^+$, 376 (100) [M + H −

O]$^+$, 374 (58) [M + H − H_2O]$^+$; IR 3577, 3052, 1724 cm^{-1}. Anal. Calcd for $C_{24}H_{41}NO_3$: C, 73.61; H, 10.55; N, 3.58. Found: C, 73.93; H, 10.62; N, 3.52.

(*R*)-Ethyl 4-(hydroxy-((*R*)-1-(2,4,6-triisopropylphenyl)ethyl)-amino)hexanoate ((*R*,*R*)-9b): yellow oil; $[\alpha]^{20}_D$ −14.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.20−1.29 (m, 21H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.34−1.55 (m, 1H), 1.81−1.95 (m, 3H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.78−2.87 (m, 2H), 3.41 (sept, *J* = 7.2 Hz, 1H), 4.00 (s, 1H), 3.98−4.05 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.78 (q, *J* = 6.9 Hz, 1H), 6.95 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 11.6, 14.3, 18.6, 19.4, 23.6, 23.9, 23.9, 24.6, 24.9, 25.3, 25.6, 28.3, 29.4, 31.2, 33.9, 56.7, 60.1, 61.3, 120.7, 123.0, 134.7, 146.5, 146.6, 148.3, 174.5; MS (DCI) *m*/*z* 406 (44) [M + H]$^+$, 388 (100) [M + H − H_2O]$^+$; IR 3580, 3056, 1725 cm^{-1}. Anal. Calcd for $C_{25}H_{43}NO_3$: C, 74.03; H, 10.69; N, 3.45. Found: C, 73.95; H, 10.65; N, 3.46.

(*R*)-Ethyl 4-(hydroxy-((*S*)-1-(2,4,6-triisopropylphenyl)ethyl)-amino)-6-methylheptanoate ((*S*,*R*)-9c): white solid; mp 55−56 °C; $[\alpha]^{20}_D$ +25.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 0.95 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 1.19−1.34 (m, 24H), 1.43−1.57 (m, 2H), 1.60−1.77 (m, 1H), 1.78−2.03 (m, 2H), 2.38−2.60 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.99−3.09 (m, 1H), 3.43 (sept, *J* = 6.8 Hz, 1H), 3.91 (br s, 1H), 4.06 (sept, *J* = 6.8 Hz, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.77 (q, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 1.9 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR δ 14.3, 19.2, 21.7, 23.7, 23.9, 23.9, 24.3, 24.5, 24.9, 25.4, 25.4, 26.5, 28.2, 29.4, 31.0, 33.9, 34.2, 56.3, 57.4, 60.1, 120.7, 123.0, 134.8, 146.5, 146.6, 148.3, 174.5; MS (DCI) *m*/*z* 434 (100) [M + H]$^+$; IR 3494, 3030, 1731, 1600, 1461 cm^{-1}. Anal. Calcd for $C_{27}H_{47}NO_3$: C, 74.78; H, 10.92; N, 3.23. Found: C, 74.47; H, 10.73; N, 3.08.

(*R*)-Ethyl 4-(hydroxy-((*S*)-1-(2,4,6-triisopropylphenyl)ethyl)-amino)-5-methylhexanoate ((*S*,*R*)-9d): colorless oil; $[\alpha]^{20}_D$ +12.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 0.99 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.21−1.32 (m, 24H), 1.74−1.80 (m, 1H), 1.94−2.03 (m, 1H), 2.32−2.42 (m, 1H), 2.47 (dd, *J* = 7.2, 6.7 Hz, 2H), 2.74 (dt, *J* = 10.2, 2.9 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.35−3.48 (m, 1H), 3.92 (br s, 1H), 3.93−4.07 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.87 (q, *J* = 6.9 Hz, 1H), 6.96 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 14.3, 19.1, 19.6, 20.9, 22.2, 23.7, 23.8, 23.9, 24.5, 25.0, 25.1, 25.4, 28.1, 29.4, 31.5, 33.8, 56.9, 60.0, 63.7, 120.7, 123.0, 134.6, 146.4, 146.6, 148.3, 174.5; MS (DCI) *m*/*z* 420 (49) [M + H]$^+$, 402 (100) [M + H − H_2O]$^+$; IR 3489, 3030, 1731, 1609, 1466 cm^{-1}. Anal. Calcd for $C_{26}H_{45}NO_3$: C, 74.42; H, 10.81; N, 3.34. Found: C, 74.08; H, 10.73; N, 3.19.

(*S*)-Ethyl 4-cyclohexyl-4-(hydroxy((*R*)-1-(2,4,6-triisopropylphenyl)ethyl)amino)butanoate ((*R*,*S*)-9e): colorless oil; $[\alpha]^{20}_D$ −8.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 1.03−1.42 (m, 28H), 1.56−1.83 (m, 6H), 1.94−2.09 (m, 3H), 2.45 (t, *J* = 6.9 Hz, 2H), 2.63−2.68 (m, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 3.35−3.48 (m, 1H), 3.91 (br s, 1H), 3.98−4.11 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.88 (q, *J* = 6.9 Hz, 1H), 6.96 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 14.1, 19.5, 22.0, 23.5, 23.7, 23.8, 24.3, 25.0, 25.2, 26.4, 26.6, 27.1, 28.0, 29.4, 29.8, 31.6, 32.1, 33.7, 36.1, 56.8, 59.9, 64.1, 120.6, 122.8, 134.5, 146.2, 146.5, 148.1, 174.3; MS (DCI) *m*/*z* 460 (100) [M + H]$^+$, 442 (64) [M + H − H_2O]$^+$; IR 3567, 3056, 1731, 1608, 1466 cm^{-1}; HRMS(ESI) calcd for $C_{29}H_{50}NO_3$ 460.3785, found 460.3786.

(3*S,4*S**)-Methyl 4-(hydroxy-((*S**)-1-(2,4,6-triisopropylphenyl)ethyl)amino)-3,5-dimethylhexanoate (*rac*-10)** (for experimental conditions, see Scheme 3): white crystals; mp 133−135 °C (MeOH); ^{1}H NMR δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.15−1.31 (m, 21H), 1.36 (d, *J* = 6.8 Hz, 3H), 2.22−2.45 (m, 3H), 2.62−2.70 (m, 2H), 2.82−2.87 (m, 1H), 3.42−3.47 (m, 1H), 3.64 (s, 3H), 3.67−3.76 (m, 1H), 4.07−4.12 (m, 1H), 4.97 (q, *J* = 6.8 Hz, 1H), 6.96 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 17.6, 19.9, 21.1, 23.0, 23.4, 23.6, 23.7, 24.6, 24.9, 25.2, 26.0, 27.9, 29.2, 30.3, 33.6, 40.1, 51.1, 57.9, 67.0, 120.6, 122.6, 134.4, 146.4, 147.8, 173.8, 190.4; MS (DCI) *m*/*z* 420 (18) [M + H]$^+$, 402 (100) [M + H − H_2O]$^+$; IR 3501, 3030, 1745, 1610, 1573, 1460 cm^{-1}. Anal. Calcd for $C_{26}H_{45}NO_3$: C, 74.42; H, 10.81; N, 3.34. Found: C, 74.31; H, 10.94; N, 3.29.

(2*S,4*R**)-Methyl 4-(hydroxy-((*S**)-1-(2,4,6-triisopropylphenyl)ethyl)amino)-2,5-dimethylhexanoate (*rac*-11a)** (for experimental conditions, see Scheme 3): white crystals; mp 133−135 °C (MeOH); ^{1}H NMR δ 0.96 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.18−1.30 (m, 24H), 1.66−1.84 (m, 2H), 2.31−2.47 (m, 1H), 2.72−2.98 (m, 3H), 3.31−3.48 (m, 1H), 3.69 (s, 3H), 4.02−4.18 (m, 1H), 4.07−4.12 (m, 1H), 4.88 (q, *J* = 6.9 Hz, 1H), 6.95 (s, 1H), 7.03 (s, 1H); ^{13}C NMR δ 18.5, 18.7, 19.0, 22.0, 23.6, 23.7, 24.0, 24.1, 24.6, 25.3, 27.8, 29.2, 30.2, 33.7, 36.1, 51.0, 56.6, 62.0, 120.5, 122.8, 134.5, 146.3, 146.4, 148.1, 177.6; MS (DCI) *m*/*z* 420 (100) [M + H]$^+$, 402 (34) [M + H − H_2O]$^+$; IR 3579, 3053, 1731, 1606, 1455 cm^{-1}. Anal. Calcd for $C_{26}H_{45}NO_3$: C, 74.42; H, 10.81; N, 3.34. Found: C, 74.38; H, 10.90; N, 3.36.

(2*R,4*R**)-Methyl 4-(hydroxy ((*S**)-1-(2,4,6-triisopropylphenyl)ethyl)amino)-2,5-dimethylhexanoate (*rac*-11b)** (for experimental conditions, see Scheme 3): white solid; mp 78−80 °C; ^{1}H NMR δ 0.96 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.24 (d, *J* = 7.0 Hz, 12H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H), 2.14−2.27 (m, 1H), 2.38−2.49 (m, 1H), 2.77−2.91 (m, 3H), 3.31−3.48 (m, 1H), 3.69 (s, 3H), 3.90 (br s, 1H), 3.95−4.04 (m, 1H), 4.90 (q, *J* = 7.0 Hz, 1H), 6.96 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 15.4, 18.9, 19.3, 22.3, 23.7, 23.8, 23.9, 24.3, 24.9, 25.3, 28.3, 29.2, 29.4, 33.9, 35.4, 51.5, 56.7, 61.2, 120.7, 122.9, 134.7, 146.5, 146.6, 148.2, 178.2; MS (DCI) *m*/*z* 420 (22) [M + H]$^+$, 419 (100) [M + NH_4 − H_2O]$^+$; IR 3492, 3050, 1739, 1608, 1550, 1456 cm^{-1}.

(*S,*E*)-Ethyl 4-(hydroxy((*S**)-1-(2,4,6-triisopropylphenyl)-ethyl)amino)-5-methylhex-2-enoate (*rac*-12)** (for experimental conditions, see Scheme 3): white crystals; mp 127−129 °C (MeOH); ^{1}H NMR δ 0.69 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.82−1.95 (m, 1H), 2.66 (t, *J* = 9.0 Hz, 1H), 2.77 (sept, *J* = 6.9 Hz, 1H), 3.10−3.22 (m, 1H), 3.88−4.02 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.39 (q, *J* = 6.5 Hz, 1H), 4.57 (br s, 1H), 5.34 (d, *J* = 16.1 Hz, 1H), 6.84 (s, 1H), 6.91 (s, 1H), 7.21 (dd, *J* = 16.1, 9.3 Hz, 1H); ^{13}C NMR δ 14.2, 20.0, 20.1, 21.6, 22.4, 23.8, 23.9, 25.0, 25.8, 26.0, 28.3, 29.5, 30.3, 33.8, 59.8, 60.1, 70.1, 121.0, 122.7, 124.8, 132.8, 146.0, 146.2, 147.1, 148.4, 165.9; MS (DCI) *m*/*z* 418 (23) [M + H]$^+$, 400 (100) [M + H − H_2O]$^+$; IR 3579, 3479, 3054, 1710, 1645, 1606, 1568, 1467 cm^{-1}. Anal. Calcd for $C_{26}H_{43}NO_3$: C, 74.77; H, 10.38; N, 3.35. Found: C, 74.76; H, 10.62; N, 3.16.

General Procedure for the Preparation of γ-*N*-Acetoxyamino Esters 14a−e. A stirred solution of 0.5 mmol of the γ-*N*-hydroxyamino ester **9** in 10 mL of dry CH_2Cl_2 under argon was treated with 0.052 mL (56 mg, 0.55 mmol) of freshly distilled acetic anhydride. The solution was stirred at 40 °C until completion (TLC), and then concentrated under vacuum. The residue was filtered through a plug of silica gel with 10% ethyl acetate in pentane to afford the acetylated product (**13a**−**e**, 92−98% yield).

This material was stirred at 20 °C with 2.0 mL of a 5% solution of TFA in dichloromethane until complete transformation of the starting material (TLC), and then a saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with dichloromethane, which was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by chromatography on silica gel with 5−50% ethyl acetate in pentane afforded the γ-*N*-acetoxyamino ester (**14a**−**e**, 66−83% yield).

(*R*)-Ethyl 4-(ethanoyloxyamino)pentanoate ((*R*)-14a): colorless oil; $[\alpha]^{20}_D$ +11.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 1.04 (d, *J* = 6.4 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.56−1.63 (m, 2H), 2.03 (s, 3H), 2.35 (ddd, *J* = 6.9, 6.8, 3.7 Hz, 2H), 3.05 (sext, *J* = 6.4 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 14.1, 17.6, 19.1, 28.9, 30.5, 55.6, 60.4, 170.9, 173.3; MS (DCI) *m*/*z* 204 (69) [M + H]$^+$; IR 3244, 1736 cm^{-1}.

(*R*)-Ethyl 4-(ethanoyloxyamino)hexanoate ((*R*)-14b): colorless oil; $[\alpha]^{20}_D$ +7.9 (*c* 1.5, $CHCl_3$); ^1H NMR δ 0.96 (t, J = 7.6 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.43−1.54 (m, 2H), 1.76−1.86 (m, 2H), 2.09 (s, 3H), 2.44 (t, J = 7.8 Hz, 2H), 2.88 (quint., J = 6.3 Hz, 1H), 4.13 (q, J = 7.2 Hz, 1H), 7.56 (br s, 1H); ^{13}C NMR δ 10.1, 14.2, 19.2, 24.5, 26.8, 30.6, 60.4, 61.5, 170.9, 173.5; MS (DCI) *m*/*z* 218 (100) $[M + H]^+$, 160 (94) $[M + H - C_2H_2O_2]^+$; IR 3247, 1737 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.60; H, 8.91; N, 5.97.

(*R*)-Ethyl 4-(ethanoyloxyamino)-6-methylheptanoate ((*R*)-14c): colorless oil; $[\alpha]^{20}_D$ −29.3 (*c* 1.1, $CHCl_3$); ^1H NMR δ 0.89 (d, J = 6.5 Hz, 6H), 1.24 (t, J = 6.5 Hz, 3H), 1.13−1.38 (m, 2H), 1.52−1.84 (m, 3H), 2.07 (s, 3H), 2.38−2.47 (m, 2H), 2.98−3.04 (m, 1H), 4.11 (q, J = 7.2 Hz, 1H), 7.51 (br s, 1H); ^{13}C NMR δ 14.2, 19.2, 22.5, 22.9, 24.9, 27.7, 30.4, 41.0, 58.0, 60.4, 170.9, 173.5; MS (DCI) *m*/*z* 246 (100) $[M + H]^+$, 188 (77) $[M + H - i\text{-Bu}]^+$, 186 (73) $[M + H - AcOH]^+$, 142 (66) $[M + H - i\text{-Bu} - EtOH]^+$, 140 (22) $[M + H - AcOH - EtOH]^+$; IR 3244, 1777, 1738 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.38; H, 9.35; N, 5.28.

(*R*)-Ethyl 4-(ethanoyloxyamino)-5-methylhexanoate ((*R*)-14d): colorless oil; $[\alpha]^{20}_D$ −1.6 (*c* 1.7, $CHCl_3$); ^1H NMR δ 0.95 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H), 1.63−1.73 (m, 1H), 1.81−1.93 (m, 2H), 2.08 (s, 3H), 2.43−2.49 (m, 2H), 2.71−2.77 (m, 1H), 4.14 (q, J = 7.2 Hz, 1H), 7.66 (br s, 1H); ^{13}C NMR δ 14.1, 18.0, 18.6, 19.0, 23.7, 29.1, 31.1, 60.2, 65.2, 170.6, 173.3; MS (DCI) *m*/*z* 232 (37) $[M + H]^+$, 174 (76) $[M + H - C_2H_2O_2]^+$, 128 (100) $[M + H - C_2H_2O_2 - EtOH]^+$; IR 3247, 1737 cm^{-1}; HRMS(ESI) calcd for $C_{11}H_{21}NO_4Na$ 254.1368, found 254.1367.

(*S*)-Ethyl 4-cyclohexyl-4-(ethanoyloxyamino)butanoate ((*S*)-14e): colorless oil; $[\alpha]^{20}_D$ +4.2 (*c* 1.2, $CHCl_3$); ^1H NMR δ 0.96−1.26 (m, 5H), 1.25 (t, J = 7.1 Hz, 3H), 1.68−1.78 (m, 1H), 1.34−1.51 (m, 1H), 1.57−1.77 (m, 6H), 1.79−1.93 (m, 1H), 2.07 (s, 3H), 2.44 (t, J = 7.4 Hz, 2H), 2.63−2.76 (m, 1H), 4.12 (q, J = 7.1 Hz, 1H), 7.63 (br s, 1H); ^{13}C NMR δ 14.2, 19.3, 24.3, 26.3, 26.4, 28.9, 29.2, 31.2, 39.4, 60.3, 64.9, 170.7, 173.5; MS (DCI) *m*/*z* 272 (28) $[M + H]^+$, 214 (100) $[M + H - C_2H_2O_2]^+$, 168 (78) $[M + H - C_2H_2O_2 - EtOH]^+$; IR 3251, 1734 cm^{-1}; HRMS(ESI) calcd for $C_{14}H_{25}NO_4Na$ 294.1681, found 294.1681.

General Procedure for the Preparation of *N*-Boc-γ-amino Esters 15a-e. To a vigorously stirred suspension of 10% palladium on charcoal in 0.5 mL of dry ethyl acetate under 1 atm of hydrogen was added a solution of the γ-*N*-acetoxyamino ester **14** (0.055 mmol) and di-*tert*-butyl dicarbonate (0.066 mmol) in 1.0 mL of ethyl acetate, and the resulting suspension was stirred at room temperature until completion (TLC, ca. 1 h). Celite was added to the reaction mixture, which was then filtered through a pad of Celite. The filtrate was concentrated under vacuum and the residue was purified on silica gel with 1−10% ethyl acetate in pentane to afford the *N*-protected γ-amino acid (**15a**−**e**, 59−78% yield).

(*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)pentanoate ((*R*)-15a): colorless oil; $[\alpha]^{20}_D$ +1.4 (*c* 1.2, $CHCl_3$); ^1H NMR δ 1.14 (d, J = 6.7 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.70−1.80 (m, 2H), 2.35 (t, J = 7.1 Hz, 2H), 3.60−3.77 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.28−4.51 (br d, 1H); ^{13}C NMR δ 14.2, 21.4, 28.4, 31.2, 32.1, 46.3, 60.4, 79.1, 155.4, 173.5; MS (DCI) *m*/*z* 246 (26) $[M + H]^+$, 207 (42) $[M + NH_4 - C_4H_8]^+$, 190 (91) $[M + H - C_4H_8]^+$, 146 (100) $[M + H - C_4H_8 - CO_2]^+$; IR 3434, 1714, 1506 cm^{-1}. Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.99; H, 9.60; N, 5.31.

(*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)hexanoate ((*R*)-15b): colorless oil; $[\alpha]^{20}_D$ +8.3 (*c* 1.3, $CHCl_3$); ^1H NMR δ 0.92 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.25−1.65 (m, 3H), 1.43 (s, 9H), 1.78−1.92 (m, 1H), 2.36 (t, J = 7.6 Hz, 2H), 3.53−3.63 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.23 (br d, 1H); ^{13}C NMR δ 10.2, 14.2, 28.4, 30.0, 31.1, 51.8, 60.4, 79.0, 155.8, 173.7; MS (DCI) *m*/*z* 260 (37) $[M + H]^+$, 221 (30) $[M + NH_4 - C_4H_8]^+$, 204 (95) $[M + H - C_4H_8]^+$, 160 (100) $[M + H - C_4H_8 - CO_2]^+$; IR 3438, 1708, 1505 cm^{-1}; HRMS(ESI) calcd for $C_{13}H_{26}NO_4$ 260.1856, found 260.1861.

(*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-6-methylheptanoate ((*R*)-15c): colorless oil; $[\alpha]^{20}_D$ −11.3 (*c* 1.2, $CHCl_3$); ^1H NMR δ 0.91 (d, J = 6.5 Hz, 6H), 1.24−1.32 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.60−1.89 (m, 3H), 2.36 (t, J = 7.7 Hz, 2H), 3.53−3.72 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.24 (br d, 1H); ^{13}C NMR δ 14.2, 22.3, 23.0, 24.9, 28.4, 31.0, 45.2, 48.5, 60.3, 78.9, 155.6, 173.7; MS (DCI) *m*/*z* 288 (18) $[M + H]^+$, 232 (44) $[M + H - C_4H_8]^+$, 188 (100) $[M + H - C_4H_8 - CO_2]^+$; IR 3431, 3360, 1712, 1505 cm^{-1}. Anal. Calcd for $C_{15}H_{29}NO_4$: C, 62.69; H, 10.17; N, 4.87. Found: C, 62.98; H, 10.39; N, 4.81.

(*R*)-Ethyl 4-(*tert*-butoxycarbonylamino)-5-methylhexanoate ((*R*)-15d): white solid; mp 55−56 °C; $[\alpha]^{20}_D$ −1.5 (*c* 1.0, $CHCl_3$); ^1H NMR δ 0.88 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.43 (s, 9H), 1.46−1.89 (m, 3H), 2.36 (t, J = 7.4 Hz, 2H), 3.38−3.46 (m, 1H), 4.13 (q, J = 7.2 Hz, 2H), 4.30 (br d, 1H); ^{13}C NMR δ 14.2, 17.8, 19.0, 27.5, 28.4, 31.5, 32.6, 55.4, 60.4, 79.0, 156.0, 173.8; MS (DCI) *m*/*z* 274 (59) $[M + H]^+$, 218 (98) $[M + H - C_4H_8]^+$, 174 (100) $[M + H - C_4H_8 - CO_2]^+$; IR 3438, 1719, 1509 cm^{-1}. Anal. Calcd for $C_{14}H_{27}NO_4$: C, 61.52; H, 9.96; N, 5.13. Found: C, 61.58; H, 10.10; N, 4.84.

(*S*)-Ethyl 4-(*tert*-butoxycarbonylamino)-4-cyclohexylbutanoate ((*S*)-15e): white solid; mp 64−65 °C; $[\alpha]^{20}_D$ −7.0 (*c* 1.1, $CHCl_3$); ^1H NMR δ 0.81−1.38 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 1.50−1.93 (m, 7H), 2.35 (t, J = 7.5 Hz, 2H), 3.34−3.48 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.30 (br d, 1H); ^{13}C NMR δ 14.2, 26.2, 26.4, 27.4, 27.6, 28.4, 29.5, 31.4, 42.7, 54.9, 60.4, 78.9, 155.9, 173.8; MS (DCI) *m*/*z* 314 (73) $[M + H]^+$, 258 (94) $[M + H - C_4H_8]^+$, 214 (100) $[M + H - C_4H_8 - CO_2]^+$; IR 3434, 1718, 1506 cm^{-1}. Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.04; H, 10.18; N, 4.34.

Lactamizations. (*R*)-5-Isobutylpyrrolidin-2-one ((*R*)-16c). A mixture of 108 mg (0.25 mmol) of γ-*N*-hydroxyamino ester (*S*,*R*)-**9c** and 15 mg of 10% Pd−C in 3.0 mL of glacial acetic acid was stirred under hydrogen for 5 h. The catalyst was removed by filtration with the aid of acetic acid, and the filtrate (6.0 mL) was heated in a pressure vessel at 220 °C for 5 h. After being allowed to cool to 20 °C, the solution was concentrated and the crude product was purified by dry silica gel chromatography with 50−100% ethyl acetate in pentane and then 5−10% methanol in ethyl acetate to give 27 mg (77%) of (*R*)-**16c**.[28a] The analytical sample was secured by evaporative distillation (10^{-2} Torr): white solid; mp 63−65 °C; $[\alpha]^{20}_D$ −13.0 (*c* 0.8, $CHCl_3$); ^1H NMR δ 0.93 (d, J = 6.5 Hz, 6H), 1.25−1.50 (m, 2H), 1.55−1.80 (m, 2H), 2.20−2.40 (m, 3H), 3.71 (m, 1H), 6.03 (br s, 1H); MS (DCI) *m*/*z* 159 (7) $[M + NH_4]^+$, 142 (100) $[M + H]^+$; IR 3183, 1699, 1368, 1319, 1270 cm^{-1}. Anal. Calcd for $C_8H_{15}NO$: C, 68.05; H, 10.71; N, 9.92. Found: C, 68.10; H, 10.89; N, 9.96.

(*S*)-5-Cyclohexylpyrrolidin-2-one ((*S*)-16e). A mixture of 50 mg (0.11 mmol) of γ-*N*-hydroxyamino ester (*R*,*S*)-**9e** and 8 mg of 10% Pd−C in 1.0 mL of glacial acetic acid was stirred under hydrogen for 4 h. The catalyst was removed by filtration with the aid of acetic acid, and the filtrate (6.0 mL) was heated in a pressure vessel at 220 °C for 5 h. After being allowed to cool to 20 °C, the solution was concentrated and the crude product was purified by dry silica gel chromatography with 0−100% ethyl acetate in pentane and then 10% methanol in ethyl acetate to give 15 mg (82%) of (*S*)-**16e**.[28b] The analytical sample was secured by evaporative distillation (10^{-2} Torr): white solid; mp 71−73 °C; $[\alpha]^{20}_D$ −5.6 (*c* 1.0, $CHCl_3$); ^1H NMR δ 0.80−1.00 (m, 2H), 1.10−1.30 (m, 4H), 1.60−1.80 (m, 6H), 2.10−2.30 (m, 3H), 3.36 (ps q, J = 6.9 Hz, 1H), 6.00 (br s,1H); MS (DCI) *m*/*z* 185 (4) $[M + NH_4]^+$, 168 (100) $[M + H]^+$; IR 3208, 1681, 1357, 1276 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.82; H, 10.25; N, 8.38. Found: C, 71.94; H, 10.44; N, 8.51.

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Supporting Information Available: Copies of spectra for compounds **9e**, **11b**, **12**, **14a**,**d**,**e**, and **15b**, as well as crystallographic data (CIF) for compounds *rac*-**9c**, *rac*-**10**, *rac*-**11a**, and *rac*-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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