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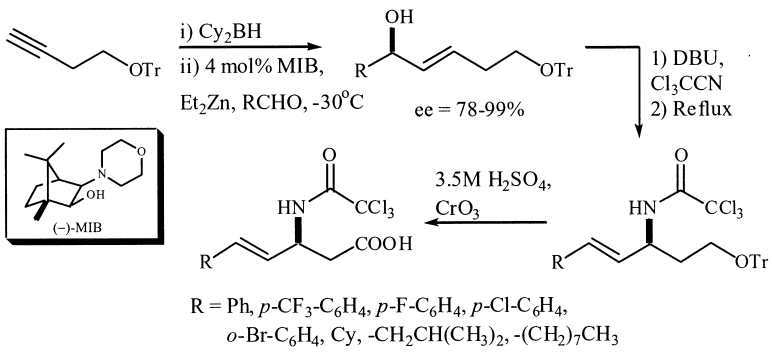

R = Ph, *p*-CF_3-C_6H_4, *p*-F-C_6H_4, *p*-Cl-C_6H_4, *o*-Br-C_6H_4, Cy, -$CH_2CH(CH_3)_2$, -$(CH_2)_7CH_3$

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A Catalytic Asymmetric Method for the Synthesis of γ-Unsaturated β-Amino Acid Derivatives

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Abstract: Catalytic enantioselective synthesis of β-amino acid derivatives is an area of intense interest, due to the importance of these compounds as components in pharmaceutical agents and peptidomimetics. In this report, we present the first catalytic enantioselective method for the synthesis of γ-unsaturated β-amino acids and their corresponding 1,3-amino alcohol derivatives. This methodology takes advantage of a highly enantioselective vinylzinc addition to an aldehyde to set chirality. The resulting allylic alcohols are then transformed into the corresponding allylic amines via Overman's [3,3]-sigmatropic imidate rearrangement, and subsequent one-pot deprotection−oxidation of a pendant oxygen leads to the γ-unsaturated β-amino acid derivatives of high enantiopurity.

Introduction

The development of synthetically useful methodology for the preparation of enantioenriched β-amino acids and their derivatives has gained increasing attention due to the importance of these compounds as building blocks in a variety of biologically active natural products and peptidomimetics.[1−5] In addition to serving as synthetic precursors to β-lactams, a class of compounds well-known for its antibiotic properties,[6−8] β-amino acids are the monomers that make up β-peptides. Such β-peptides have emerged as promising tools for probing the structure−activity relationships of biologically active molecules. They exhibit increased resistance to peptidases and proteases, an important property in the development of pharmaceuticals, and have been shown to fold into helices, sheets, and turns, the same kind of structural motifs found in peptides derived from α-amino acids.[9−11] γ-Unsaturated β-amino acids represent an interesting subclass of compounds, the enantioselective synthesis of which has been largely unaddressed. One naturally occurring unsaturated β-amino acid that has generated significant synthetic interest is (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda, Figure 1).[12−15] This amino acid

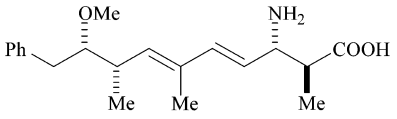

Figure 1. The Adda residue.

residue appears in the hepatotoxins cyanovirifin RR, nodularin, motuporin, and the microcystins.[15−21]

While various diastereoselective methods for the synthesis of β-amino acids, based on chiral substrates or chiral auxiliaries, have been developed, there exist relatively few catalytic enantioselective methods.[1−5] The most common of these employ conjugate addition of aminonucleophiles to acrylate derivatives,[22−29] hydrogenation of aminoacrylates,[30−39] aminohydroxylation of

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α,β-unsaturated esters,[40−50] and Mannich-type reactions of imine derivatives with silyl enolates.[51−60]

Both Sibi[25,26,28] and Jørgensen[23,27] have utilized bis(oxazoline)-derived chiral Lewis acid catalysts in the conjugate addition of hydroxylamines or aromatic amines as nitrogen nucleophiles to α,β-unsaturated carboxylic acid derivatives. Jacobsen[24] has demonstrated the conjugate addition of hydrazoic acid to α,β-unsaturated imides catalyzed by a chiral (salen)Al(III) complex, and Miller and co-workers[22,61] have developed conditions for the enantioselective conjugate addition of azide ion using a 3.8:1 mixture of $TMSN_3$ and $^tBuCO_2H$ and a simple peptide catalyst. In all cases, moderate to good yields and high ee's are obtained for substrates with alkyl substitution at the β-position. In the case of aryl substituents, only Sibi's system is successful, using 30 mol % of catalyst. In general, the conjugate addition strategy requires that substrates not commercially available must be synthesized via Horner−Emmons chemistry.

A different strategy for the synthesis of β-amino acid derivatives is the asymmetric hydrogenation of aminoacrylates, and Zhang and co-workers[32−34] have recently made significant progress in this area. Their Ru−BINAPO catalyst system is the first to give excellent enantioselectivities for β-aryl-substituted β-(acylamino)acrylates. Unlike previous systems, which gave only moderate levels of enantioselectivity, the Ru−BINAPO system can tolerate an *E*/*Z* mixture of substrates.

Sharpless asymmetric aminohydroxylation[42,43,49] of α,β-unsaturated esters provides entry into *syn*-α-hydroxy-β-amino acid derivatives, generally with a high degree of enantioselectivity. The reactions are typically carried out in an alcohol/water solvent mixture using catalytic $K_2OsO_2(OH)_4$, an alkaloid-derived ligand, and the lithium or sodium salt of an *N*-halogenated sulfonamide,[40,50] alkyl carbamate,[47] amide,[41] or an amino-substituted heterocycle.[46] Enantioselectivity and regioselectivity, which has a direct impact on reaction yield, can vary significantly, depending upon the ligand and the nitrogen source used with a given substrate. One of the earliest and most outstanding applications of this methodology to the synthesis of α-hydroxy-β-amino acid derivatives was Sharpless' large-scale synthesis of the taxol side chain.[44] Starting from isopropyl cinnamate, the target molecule was obtained in two steps with 68% yield and 99% ee.

Another approach that has attracted particular interest lately is the Mannich-type reaction of aldimines with silyl enolates to synthesize β-amino esters. Chiral zirconium-based catalysts for the asymmetric version of this reaction were developed by Kobayashi[53,54,57,58] and Wulff.[56] These systems require an *N*-aryl substituent with a pendant chelating group for bidentate binding to the catalyst which must subsequently be removed under strong oxidizing or reducing conditions. Nonetheless, good yields and enantioselectivities are obtained with aromatic imines. More recently, Jacobsen[55] has developed a urea-derived catalyst that allows for the use of Boc-protected aryl imines, and Kobayashi[54,59] has introduced a chiral copper catalyst that shows good enantioselectivity for the addition of silyl enol ethers derived from thioesters to *N*-acylamino esters. A drawback of the Mannich-type chemistry is the need to preform the silyl enolate, and Barbas and co-workers[51] recently addressed this issue by developing a system catalyzed by proline in which an aliphatic aldehyde adds to α-amino ethyl glyoxylate. This reaction gives very good diastereoselectivity with aldehydes having a chain length of 5 carbons or more.

To our knowledge, only one method has been developed for the synthesis of enantioenriched γ-unsaturated β-amino acids. Davies and co-workers[15] have applied the diastereoselective conjugate addition of lithium (*S*)-(α-methylbenzyl)allylamide to (*E*,*E*)-*tert*-butyl hex-2,4-dienoate to give the corresponding γ-unsaturated β-amino acid derivative (Scheme 1). A lengthy protecting group exchange under somewhat harsh conditions is required, however, to remove the *N*-α-methylbenzyl group and the *N*-allyl group and to replace them with the more synthetically useful Boc group. This methodology was utilized by Gani and co-workers in their synthesis of an abbreviated Adda residue, which they used to study the effects of structural changes on the biological activity of nodularin.[17]

In this report, we outline the first enantioselective catalytic method for the synthesis of γ-unsaturated β-amino acids. This methodology, illustrated in Scheme 2, utilizes the highly enantioselective addition of a vinylzinc species to an aldehyde,[62−64] which has previously been reported by our group en route to the synthesis of α-amino acids.[65] The allylic alcohol product

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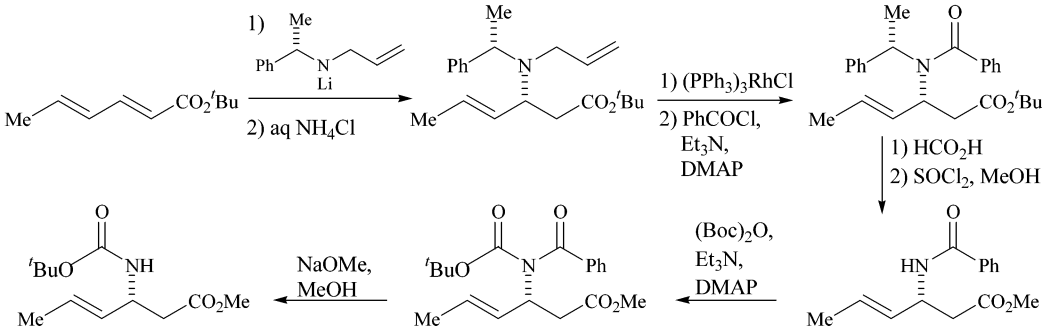
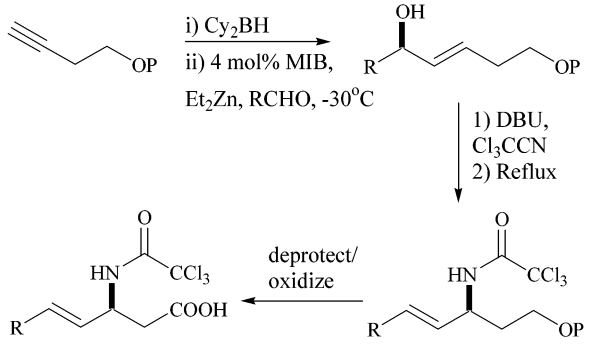
Scheme 1. Davies' Synthesis of (3*R*)-(*E*)-(*N*-*tert*-Butyloxycarbonyl)aminohex-4-enoate



of this addition is then subjected to Overman imidate rearrangement conditions[66,67] to install the nitrogen, and the chirality established in the vinylation step is transferred to the resultant allylic amine. One-pot deprotection and oxidation of a pendant oxygen leads to the γ-unsaturated β-amino acid derivatives. It should be noted that both the D and L configurations of the amino acids are accessible via this methodology.

Scheme 2. Synthesis of γ-Unsaturated β-Amino Acid Derivatives



Results and Discussion

Vinylzinc Additions to Aldehydes. We have previously demonstrated the highly enantioselective addition of a series of vinylzinc species to benzaldehyde[65] catalyzed by Nugent's MIB ligand.[68−70] The vinylzinc reagents were generated in situ via hydroboration of a terminal alkyne with dicyclohexylborane and transmetalation of the resulting vinylborane with Et_2Zn.[62,71,72] While a range of alkyne starting materials was found to be compatible with this system, the scope of the reaction for different aldehydes was not explored initially. In the present study, the terminal alkyne, 1-butyn-3-ol, was protected as the trityl ether[73] (**1**, Scheme 3) and underwent hydroboration regioselectively to give the corresponding vinylborane. Initial attempts to perform the addition reaction under conditions used in our previous study[65] by transmetalating at −78 °C, warming to 0 °C, and adding the aldehyde slowly to the vinylzinc species in the presence of MIB resulted in low yields of the allylic alcohol products. It was found, however, that slow addition of the vinylborane over the course of 1 h to a stirred solution of the aldehyde, Et_2Zn, and (−)-MIB (4 mol %) at −30 °C afforded the product allylic alcohols in high ee and moderate to good yields for a range of aliphatic and aromatic aldehydes (Scheme 3, Table 1).

Scheme 3. Asymmetric Vinylzinc Addition to Aldehydes

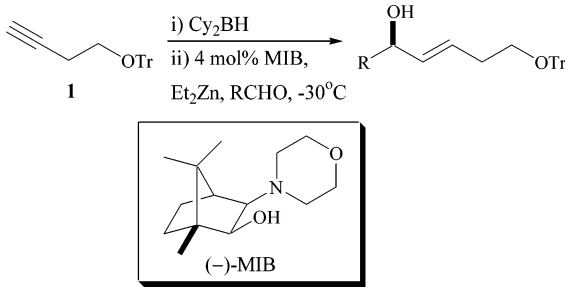
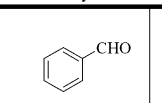
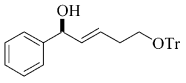
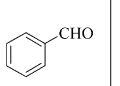
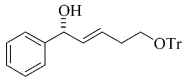
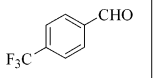
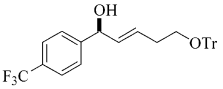
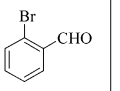
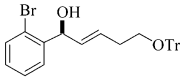
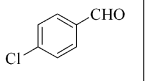
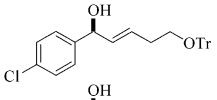
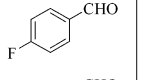
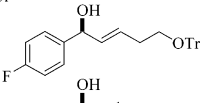
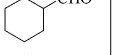
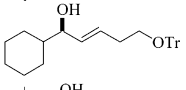
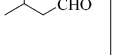
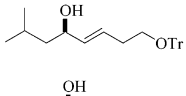
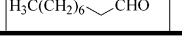
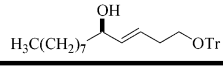


Table 1. Ee's and Yields for Allylic Alcohol Products from Scheme 3

Entry	Aldehydes	Allylic Alcohols		% ee[a] (Yield)
1			**2**	90[b] (75)
2			**3**	90[c] (74)
3			**4**	97[b] (67)
4			**5**	99[b] (83)
5			**6**	94[b] (76)
6			**7**	94[b] (71)
7			**8**	93[b] (66)
8			**9**	99[b] (54)
9			**10**	78[b] (68)

[a] Ee's determined by HPLC Chiralcel OD-H. [b] Product from reaction with (−)-MIB. [c] Product from reaction with (+)-MIB.

The choice of oxygen protecting groups on the alkyne turned out to be important. Low yields were obtained with a variety

(66) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224.
(67) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901−2910.
(68) Chen, Y. K.; Costa, A. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 5378−5379.
(69) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369−1370.
(70) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511−2513.
(71) Dahmen, S.; Bräse, S. *Org. Lett.* **2001**, *3*, 4119−4122.
(72) Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589−1590.
(73) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 95−98.

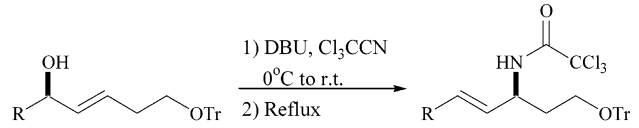
of silyl protecting groups, and attempts to use the oxidized alkyne protected as the TIPS ester resulted in none of the desired vinyl addition product. Fortuitously, not only did the trityl group (Tr = CPh_3) give improved yields in the vinylation reaction, it also had the advantage of allowing a one-pot deprotection−oxidation under acidic conditions to unveil the carboxylic acid functionality and furnish the β-amino acids, as outlined below.[74]

The vinylation was carried out successfully with both aromatic aldehydes bearing ortho and para substitution and aliphatic aldehydes. In all cases, except with nonyl aldehyde, ee's in the 90's were obtained. The best substrate was *ortho*-bromobenzaldehyde, which gave the corresponding allylic alcohol product in 99% ee and 83% yield (**5**, Table 1). Such a substrate is particularly attractive, because the aryl bromide provides a handle for further elaboration via coupling reactions with the enantioenriched product. *Para*-substituted benzaldehyde derivatives *p*-(trifluoromethyl)benzaldehyde and *p*-chlorobenzaldehyde also resulted in products of high ee (97% and 94% respectively; **4** and **6**, Table 1) as did the aliphatic aldehydes cyclohexanecarboxaldehyde and isovaleraldehyde (93% and 99%; **8** and **9**, Table 1), although yields for these substrates were slightly lower.

It should be noted that both enantiomers of the MIB ligand can be easily synthesized from commercially available (*R*)- and (*S*)-camphor in only three steps and one purification.[68−70] This allows easy access to both enantiomers of the allylic alcohol products and, thus, to both the D and L configurations of the β-amino acid derivatives.

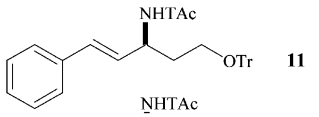
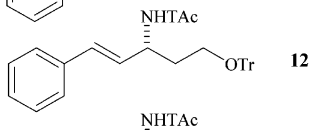
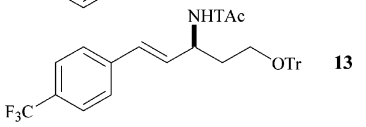
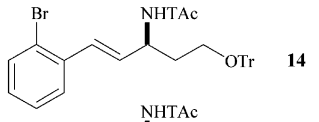
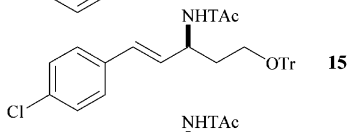
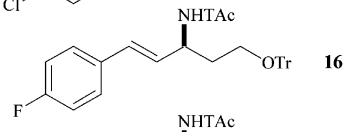
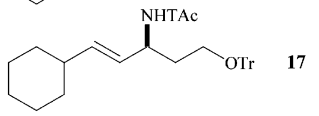
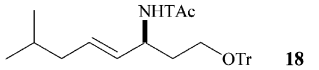
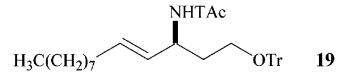
[3,3]-Sigmatropic Rearrangement. Taking advantage of the high enantioselectivities achieved in the vinyl addition step, we utilized Overman's [3,3]-sigmatropic trichloroacetimidate rearrangement[66,67] (Scheme 4) to convert allylic alcohols **2**−**10** (Table 1) into allylic amines **11**−**19** (Table 2).

Scheme 4. [3,3]-Sigmatropic Rearrangement to Allylic Amine Derivatives



Chirality is conserved in the rearrangement, and as a result, the stereochemistry set in the initial vinylation reaction is transferred to the allylic amine. Overman's procedure calls for treating an allylic alcohol with catalytic potassium hydride and trichloroacetonitrile to afford the corresponding allylic trichloroacetimide, which then undergoes thermal rearrangement to the allylic amine in refluxing toluene.[66,67] It was found that using a modified procedure[75,76] with DBU (20 mol %) as the catalytic base, instead of potassium hydride, led to improved yields for substrates with an aromatic R group (**11**−**16**, Table 2). For aliphatic substrates (**17**−**19**, Table 2), 120 mol % of DBU was used to form the trichloroacetimidates, and the rearrangement was carried out under basic conditions in refluxing *p*-xylene with potassium carbonate.[77] Filtration of the crude products and recrystallization from hexanes led to clean allylic amine products in moderate to good yields (Table 2).

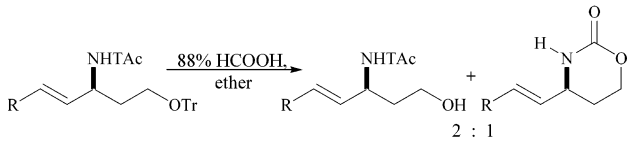
Table 2. Allylic Amine Products from Scheme 4

Entry	*N*-Protected Allylic Amines[a]		% Yield
1[b]		**11**	70
2[b]		**12**	72
3[b]		**13**	69
4[b]		**14**	71
5[b]		**15**	68
6[b]		**16**	81
7[c]		**17**	66
8[c]		**18**	74
9[c]		**19**	68

[a] NHTAc = $NHCOCCl_3$. [b] 20 mol% DBU, refluxed in toluene. [c] 120 mol% DBU, refluxed in *p*-xylene and K_2CO_3.

Deprotection and Oxidation to γ-Unsaturated β-Amino Acid Derivatives. The trityl ether group on the allylic amines in Table 2 could be deprotected under acidic conditions to give the corresponding unsaturated *N*-protected 1,3-amino alcohols. Initial attempts to remove the trityl group with 88% formic acid solution gave a 2:1 mixture of the desired deprotected product and a cyclic carbamate that resulted from attack of the free hydroxyl group on the trichloroacetamide (Scheme 5).

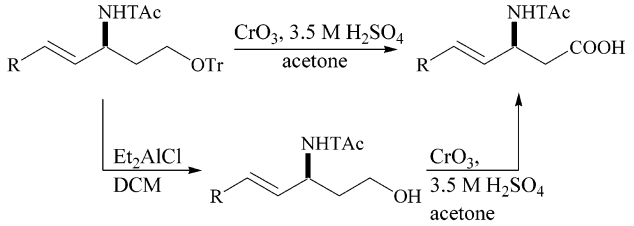
Scheme 5. Mixture of Products from Deprotection with Formic Acid



It was found, however, that cyclization could be successfully avoided and the free alcohol obtained in high yield by using the Lewis acid Et_2AlCl (Scheme 6, Table 3).[78] The amino alcohols could then be oxidized to the corresponding acid derivatives with Jones reagent (Scheme 6).[79] In addition, we

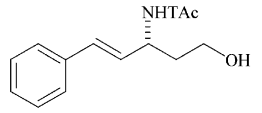
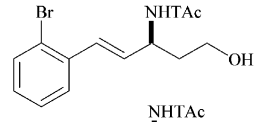
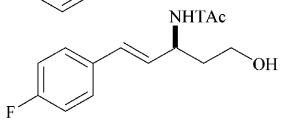
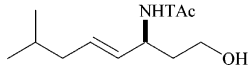
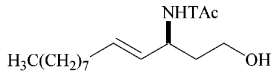
(74) Medgyes, A.; Farkas, E.; Liptak, A.; Pozsgay, V. *Tetrahedron* **1997**, *53*, 4159−4178.
(75) Schmidt, U.; Respondek, M.; Lieferknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256−261.
(76) Mehmandoust, M.; Yves, P.; Larcheveque, M. *Tetrahedron Lett.* **1992**, *33*, 4313−4316.
(77) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188−192.
(78) Koster, H.; Sinha, N. D. *Tetrahedron Lett.* **1982**, *23*, 2641−2644.
(79) Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 604−607.

Scheme 6. Deprotection and Oxidation to *N*-Protected γ-Unsaturated β-Amino Acids



were pleased to discover that this deprotection−oxidation sequence could be carried out in one pot. Subjecting the trityl ether derivatives to 3.5 M sulfuric acid and chromium trioxide in acetone and dichloromethane solution at 0 °C and gradually warming to room temperature led to the *N*-protected γ-unsaturated β-amino acids in good yield (Scheme 6, Table 4).[80]

Table 3. *N*-Protected Amino Alcohols from Scheme 6

Entry	*N*-Protected Amino Alcohols[a]		% Yield
1		**20**	88
2		**21**	91
3		**22**	95
4		**23**	92
5		**24**	89

[a] NHTAc = $NHCOCCl_3$.

Conclusions

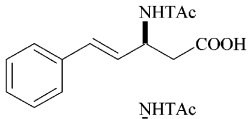
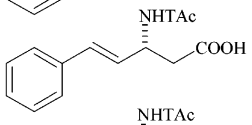
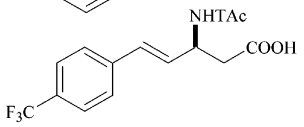
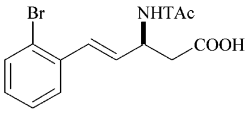
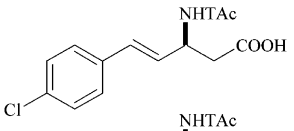
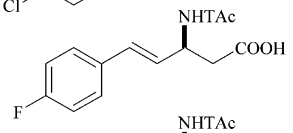
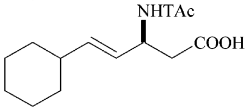
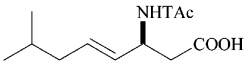
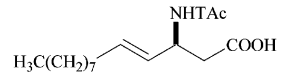
We have successfully developed a catalytic asymmetric method for the synthesis of γ-unsaturated β-amino acid derivatives, which are important building blocks in peptidomimetics and pharmaceutical agents. Utilizing a highly enantioselective vinylzinc addition to an aldehyde to set chirality, followed by a [3,3]-sigmatropic trichloroacetimidate rearrangement and one-pot deprotection−oxidation of a pendant oxygen, we have demonstrated a general approach to the synthesis of both the D and L configuration of this important class of β-amino acid derivatives.

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere with oven-dried glassware. The progress of all reactions was monitored by thin-layer chromatography to ensure the reactions had reached completion. All manipulations involving dicyclohexylborane and dialkylzinc reagents were carried out using an inert atmosphere

(80) Wulff, W. D.; McCallum, J. S.; Kunng, F.-A. *J. Am. Chem. Soc.* **1988**, *110*, 7419−7434.

Table 4. *N*-Protected γ-Unsaturated β-Amino Acids from Scheme 6

Entry	β-Amino Acid Derivatives		% Yield
1		**25**	94[a]
2		**26**	95[b]
3		**27**	97[b]
4		**28**	100[a]
5		**29**	93[a]
6		**30**	98[a]
7		**31**	97[b]
8		**32**	95[a]
9		**33**	96[a]

[a] Yield for oxidation from amino alcohol. [b] Yield for one-pot deprotection-oxidation from trityl ether.

in a Vacuum Atmosphere drybox with an attached MO-40 Dritrain or by using the standard Schlenk or vacuum line techniques. Dichloromethane, diethyl ether, toluene, and hexanes were dried through alumina columns. All aldehydes and trichloroacetonitrile were distilled or recrystallized and sublimed prior to use and stored under N_2. Unless otherwise specified, all chemicals were obtained from Acros, Aldrich, or GFS Chemicals, and all solvents were purchased from Fischer Scientific. All aldehydes and terminal alkynes are commercially available. The ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were obtained on a Bruker AM-500 Fourier transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in Hertz. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with cerric ammonium molybdate stain. Silica gel (230−400 mesh, Silicycle) was used for air-flashed chromatography. Analysis of enantiomeric excess was performed using a Hewlett-Packard 1050 Series HPLC and a Chiralcel OD-H column. Absolute configuration was determined by comparison of optical rotation to literature data for known compounds.

General procedures are presented below. Synthesis and full characterization of all compounds are provided in the Supporting Information.

(*S*)-1-Phenyl-5-(trityloxy)pent-2-en-1-ol (2). General Procedure A. To a stirred solution of Cy_2BH (0.75 mmol) in toluene (1 mL),

prepared according to Oppolzer's procedure[62] (flask A), was added a solution of trityl-protected 3-butyn-1-ol (234 mg, 0.75 mM in toluene) dropwise. The homogeneous reaction mixture was stirred for 30 min at room temperature. To a separate flask (B) at −30 °C was added 0.5 mL of toluene and (−)-MIB (4.8 mg, 0.02 mmol), followed by benzaldehyde (51 μL, 0.5 mmol) and then Et_2Zn (1.0 mL, 1.0 M) or Me_2Zn (0.5 mL, 2.0 M) in toluene. The contents of flask A were then transferred dropwise to flask B over 1 h with a syringe pump. The reaction was stirred at −30 °C for 3.5 h and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with H_2O and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (10% ethyl acetate in hexanes) to afford the title compound in 75% yield (158 mg, 0.38 mmol) as a colorless oil: $[\alpha]^{20}_D = +14.8$ ($c = 1.05$, $CHCl_3$, 90% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.85 (s, 1H), 2.36 (dt, 2H, $J = 6.4$, 6.3 Hz), 3.13 (t, 2H, $J = 6.6$ Hz), 5.15 (d, 1H, $J = 6.0$ Hz), 5.70−5.81 (m, 2H), and 7.19−7.42 (m, 20H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 32.7, 62.7, 74.8, 86.2, 125.9, 126.6, 127.3, 127.5, 128.2, 128.4, 129.0, 133.8, 142.9, and 144.0 ppm; IR (neat) 3372, 3060, 2922, 1597, 1491, 1448, 1220 cm^{-1}; HRMS-CI(*m*/*z*) found 443.2007 [$(M + Na)^+$], calcd for $C_{30}H_{28}O_2Na$ 443.1987.

(*S*)-2,2,2-Trichloro-*N*-[3-phenyl-1-(2-(trityloxy)ethyl)allyl]acetamide (11). General Procedure B. DBU (2.4 μL, 0.016 mmol) was added to a stirred solution of (*S*)-1-phenyl-5-(trityloxy)pent-2-en-1-ol (**2**) (33.5 mg, 0.08 mmol) in 2 mL of dry diethyl ether. The reaction flask was cooled to −5 °C, and Cl_3CCN (12.0 μL, 0.12 mmol) was added dropwise. After being stirred for 1 h with gradual warming from −5 °C to rt (room temperature), the reaction was filtered quickly through a plug of silica gel, rinsing thoroughly with diethyl ether. The filtrate was concentrated in vacuo, and 5 mL of dry toluene was added. The reaction was refluxed 17 h under a N_2 atmosphere, and then the toluene was removed in vacuo to afford 32 mg of the title compound (0.06 mmol, 70% yield) as a white solid after recrystallization from hexanes: mp 82−86 °C; $[\alpha]^{20}_D = -15.1$ ($c = 0.35$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.85−1.89 (m, 1H), 2.04−2.08 (m, 1H), 3.26−3.30 (m, 2H), 4.68−4.71 (m, 1H), 5.89 (dd, 1H, $J = 15.9$, 6.3 Hz), 6.41 (d, 1H, $J = 16.0$ Hz), and 7.14−7.37 (m, 21H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 33.7, 51.7, 60.0, 87.4, 126.3, 126.7, 126.9, 127.5, 127.7, 128.2, 128.4, 131.4, 136.0, 143.3, and 161.0 ppm; IR (KBr) 3423, 3063, 3031, 2924, 2367, 2344, 1690, 1654, 1508, 1448 cm^{-1}; HRMS-ESI (*m*/*z*) 586.1109 [$(M + Na)^+$], calcd for $C_{32}H_{28}Cl_3NO_2Na$ 586.1083.

2,2,2-Trichloro-*N*-[3-cyclohexyl-1-(2-(trityloxy)ethyl)allyl]acetamide (17). General Procedure C. DBU (62 μL, 0.41 mmol) was added to a stirred solution of 1-cyclohexyl-5-(trityloxy)pent-2-en-1-ol (**8**) (146 mg, 0.34 mmol) in 2.0 mL of dry dichloromethane. The reaction flask was cooled to 0 °C, and Cl_3CCN (51 μL, 0.51 mmol) was added dropwise. After being stirred for 1 h with gradual warming from 0 °C to rt, the reaction was quenched with about 0.5 mL of saturated NH_4Cl. The reaction mixture was then filtered quickly through a plug of silica gel and $NaSO_4$, rinsing thoroughly with dichloromethane. The filtrate was concentrated in vacuo and dissolved in 5.0 mL of *p*-xylene, and K_2CO_3 (10 mg) was added. The reaction was refluxed 20 h under a N_2 atmosphere and then filtered. The solvent was removed in vacuo to afford 128 mg of the title compound (0.22 mmol, 66% yield) after recrystallization from hexanes: mp: 80−82 °C; $[\alpha]^{20}_D = -19.6$ ($c = 0.69$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88−0.92 (m, 2H), 1.04−1.09 (m, 1H), 1.11−1.20 (m, 2H), 1.51−1.57 (m, 3H), 1.60−1.63 (m, 2H), 1.73−1.82 (m, 2H), 1.90−1.97 (m, 1H), 3.17−3.22 (m, 2H), 4.45−4.49 (m, 1H), 5.11 (dd, 1H, $J = 15.6$, 6.2 Hz), 5.44 (dd, 1H, $J = 15.6$, 6.5 Hz), 7.10 (br d, 1H), 7.11−7.17 (m, 3H), 7.22 (t, 6H, $J = 7.9$ Hz), and 7.35 (d, 6H, $J = 7.2$ Hz) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 26.2, 26.3, 32.9, 33.0, 34.4, 40.4, 51.9, 60.5, 87.7, 125.1, 127.3, 128.1, 128.9, 138.9, 143.9, and 161.1 ppm; IR (KBr) 3451, 3058, 2917, 2843, 2354, 2339, 1694, 1605, 1553, 1501, 1442, 1375, 1323, 1271, 1227 cm^{-1}; HRMS-CI (*m*/*z*) 592.1535 [$(M + Na)^+$], calcd for $C_{32}H_{34}Cl_3NO_2Na$ 592.1553.

(*S*)-2,2,2-Trichloro-*N*-[3-(4-fluorophenyl)-1-(2-hydroxyethyl)allyl]acetamide (22). General Procedure D. Et_2AlCl (920 μL, 1.8 M in toluene) was added dropwise to a stirred solution of (*S*)-2,2,2-trichloro-*N*-[3-(4-fluorophenyl)-1-(2-(trityloxy)ethyl)allyl]acetamide (**16**) (64.0 mg, 0.11 mmol) in 3.0 mL of dry dichloromethane. After being stirred for 20 min at room temperature, the reaction was quenched with saturated $NaHCO_3$. The organic layer was extracted with dichloromethane, washed with H_2O, and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (20−30% EtOAc in hexanes) to afford the title compound as a colorless oil in 95% yield (35 mg, 0.10 mmol): $[\alpha]^{20}_D = -60.6$ ($c = 0.52$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.85−1.90 (m, 1H), 2.05 (br s, 1H), 2.11−2.16 (m, 1H), 3.84−3.92 (m, 2H), 4.80−4.82 (m, 1H), 6.10 (dd, 1H, $J = 15.9$, 6.0 Hz), 6.58 (d, 1H, $J = 15.9$ Hz), 7.01 (t, 2H, $J = 8.6$ Hz), 7.26−7.36 (m, 2H), and 7.71 (br d, 1H, $J = 6.6$ Hz) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 36.0, 51.5, 59.4, 80.8, 115.5, 115.7, 126.7, 128.08, 128.14, 130.8, 132.31, 132.34, 161.6, 161.8, and 163.5 ppm; IR (neat) 3314, 3036, 2953, 2921, 1694, 1602, 1506, 1229, 1158 cm^{-1}; HRMS-CI (*m*/*z*) 338.9991 (M^+), calcd for $C_{13}H_{13}Cl_3FNO_2$ 338.9996.

7-Methyl-3-((2,2,2-trichloroacetyl)amino)oct-4-enoic acid (32). General Procedure E. A solution of 2,2,2-trichloro-*N*-[5-methyl-1-(2-hydroxyethyl)hex-2-enyl]acetamide (**23**) (33.6 mg, 0.11 mmol) in 1 mL of acetone and 1 mL of dichloromethane was cooled to 0 °C, and 94 μL of Jones' reagent was added dropwise. After being stirred at 0 °C for 3 min, the reaction was warmed to rt. The reaction was stirred at rt for 20 min and filtered through Celite, and the acetone was removed in vacuo. The remaining aqueous solution was extracted with dichloromethane, and the organic layer was washed with sat. $NaHCO_3$. This aqueous layer was then acidified to pH 2 with 2 M HCl. The resulting aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over $MgSO_4$. The crude product was purified by column chromotagraphy (1% MeOH in dichloromethane to 1% MeOH and 0.5% AcOH in dichloromethane) to afford the title compound in 95% yield (33.2 mg, 0.105 mmol) as a white solid: $[\alpha]^{20}_D = -7.4$ ($c = 0.57$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.2$ Hz), 1.58−1.67 (m, 1H), 1.94 (t, 2H, $J = 6.7$ Hz), 2.79 (br d, 2H, $J = 7.2$ Hz), 4.75 (m, 1H), 5.49 (dd, 1H, $J = 15.3$, 6.1 Hz), 5.73 (dt, 1H, $J = 15.2$, 6.9 Hz), and 7.59 (br d, 1H, $J = 8.3$ Hz) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 22.1, 22.2, 28.0, 37.8, 41.4, 49.2, 127.0, 133.5, 161.1, and 176.1 ppm; IR (neat) 3336, 3025, 2955, 2919, 2861, 1710, 1517, 1466, 1408, 1367, 1290, 1261 cm^{-1}; HRMS-CI (*m*/*z*) 316.0269 [$(M + H)^+$], calcd for $C_{11}H_{17}Cl_3NO_3$ 316.0274.

3-((2,2,2-Trichloroacetyl)amino)-5-(4-(trifluoromethyl)phenyl)-pent-4-enoic Acid (27). General Procedure F. A solution of 2,2,2-trichloro-*N*-[3-(4-(trifluoromethyl)phenyl)-1-(2-(trityloxy)ethyl)allyl]-acetamide (**27**) (35.5 mg, 0.056 mmol) in 1.0 mL of acetone and 1.0 mL of dichloromethane was cooled to 0 °C, and 50 μL of Jones' reagent was added dropwise. After being stirred at 0 °C for 3 min, the reaction was warmed to rt. The reaction was stirred at rt for 4 h and filtered through Celite, and then the organic solvent was removed in vacuo. The remaining aqueous solution was extracted with dichloromethane. After washing of the organic layer with saturated $NaHCO_3$, the resulting aqueous layer was acidified to pH 2 with 2 M HCl and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, and the crude product was purified by column chromotagraphy (1% MeOH in dichloromethane to 1% MeOH and 0.5% AcOH in dichloromethane) to afford the title compound in 97% yield (22.0 mg, 0.054 mmol) as a white solid: $[\alpha]^{20}_D = -34.1$ ($c = 0.17$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.80−2.89 (m, 2H), 4.89−4.92 (m, 1H), 6.26 (dd, 1H, $J = 15.9$, 6.4 Hz), 6.61 (d, 1H, $J = 15.9$ Hz), 7.39 (d, 2H, $J = 8.1$ Hz), 7.50 (d, 2H, $J = 8.1$ Hz), and 7.72 (br d, 1H, $J = 8.5$ Hz)

ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 29.7, 49.3, 92.7, 125.6, 125.7, 126.9, 128.2, 128.9, 131.6, 161.4, and 173.9 ppm; IR (neat) 3331, 2921, 2849, 1709, 1614, 1514, 1408, 1320, 1261, 1161 cm^{-1}; HRMS-CI (*m*/*z*) 402.9742 (M^+), calcd for $C_{14}H_{11}Cl_3F_3NO_2$ 402.9757.

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Supporting Information Available: Synthesis and full characterization of all compounds and conditions for the resolution of racemates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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