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A General, Highly Enantioselective Method for the Synthesis of D and L α-Amino Acids and Allylic Amines

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Abstract: Catalytic and enantioselective synthesis of amino acids is a subject of intense interest in the field of asymmetric catalysis. Traditionally, researchers have concentrated their efforts largely on the design and discovery of enantiopure catalysts for the Strecker reaction, alkylation of *tert*-butyl gylcinate-benzophenone, electrophilic amination of carbonyl compounds, and hydrogenation of *N*-acyl-aminoacrylic acid; however, the scope of these reactions is limited. In this paper, we report on a different approach to amino acids based on an expeditious route to enantiopure allylic amines. A highly enantioselective and catalytic vinylation of aldehydes leads to allylic alcohols that are then transformed to the allylic amines via Overman's [3,3]-sigmatropic rearrangement of imidates. Oxidative cleavage of the allylic amines furnishes the amino acids in good yields and excellent ee's. The scope and utility of this method are demonstrated by the synthesis of challenging allylic amines and their subsequent transformation to valuable nonproteinogenic amino acids, including both D and L configured (1-adamantyl)glycine.

Introduction

The development of enantio- and regioselective syntheses of nonproteinogenic amino acids and their derivatives remains an important goal.[1−5] In particular, processes that are catalytic and highly enantioselective[6,7] toward both enantiomers of substituted α-amino acids remain scarce. One of the most popular methods for the catalytic asymmetric synthesis of α-amino acids was introduced by O'Donnell et al.[8,9] This process involves the alkylation of a *tert*-butyl glycinate-benzophenone Schiff base under phase-transfer catalysis using *N*-benzylcinchoninium cations. Modification of the phase-transfer catalyst by Corey and Noe[10] resulted in a highly enantioselective method for alkylation of *tert*-butyl glycinate derivatives. This method relies on an S_N2 substitution reaction and is, therefore, most suitable for the synthesis of unhindered α-amino acids. It is not applicable to the synthesis of α-amino acids bearing bulky substituents on the α-carbon.

An excellent route that has been used to prepare α-amino acids with high ee's is catalytic asymmetric hydrogenation of *N*-acylaminoacrylic acids and related compounds.[7,11−16] This methodology has been used very successfully in the synthesis of α-amino acids that possess a primary alkyl group directly bonded to the α-carbon.

The electrophilic amination of carbonyl compounds also represents an efficient method to generate precursors to amino acids.[17] This method usually involves attack of a nucleophilic α-carbon on a diazo compound.[18−21] This method has been done asymmetrically with chiral metal catalysts[22−24] and with organic catalysts.[25]

Another approach that holds great promise is the catalytic asymmetric Strecker reaction.[26−37] In this chemistry, *N*-alkyl or *N*-aryl imines are treated with HCN, or another cyanide

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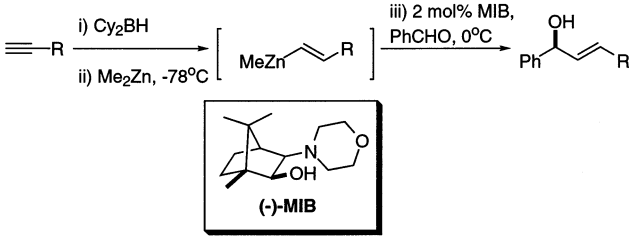
Scheme 1. Enantioselective Synthesis of Allylic Alcohols



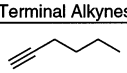
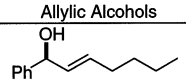
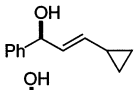
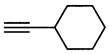
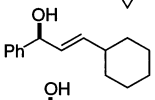
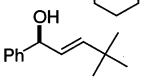
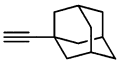
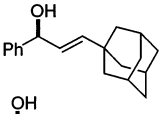
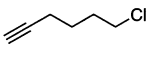
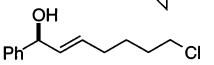
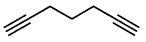
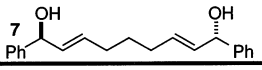
source, in the presence of an asymmetric catalyst to furnish amino nitriles. Several Lewis acids and organic catalysts have been developed that give excellent enantioselectivities with a range of imine substrates.[26,37] The resulting amino nitriles are converted to α-amino acids by deprotection of the amino group and hydrolysis of the nitrile to the acid. Two drawbacks to this approach to amino acid synthesis are the harsh conditions necessary to hydrolyze the nitrile and the extreme toxicity of HCN.

In this report, we outline an efficient and highly enantioselective synthesis of protected D and L α-amino acids from terminal alkynes. The key steps in our synthesis are a catalytic asymmetric vinylation of an aldehyde, followed by an Overman imidate rearrangement to install the nitrogen.[38,39] An attractive feature of this methodology is that it provides entry into sterically hindered allylic amines that are difficult to access using conventional methods.[40] The protected allylic amines are versatile intermediates that can be transformed directly into a series of functionalized building blocks such as α-amino acids, aldehydes, esters, and alcohols through oxidative cleavage of the double bond. To highlight this methodology, we have synthesized a series of α-amino acids, including the synthetically challenging (1-adamantyl)glycine (>99% ee).[41−43]

Results and Discussion

Synthesis of Allylic Alcohols. The synthesis begins with an enantioselective one-pot preparation of an allylic alcohol using a modified Oppolzer protocol (Scheme 1).[44] Hydroboration of a terminal alkyne with dicyclohexylborane proceeds regioselectively to afford the vinylborane.[45] Transmetalation of this vinylborane with Me_2Zn or Et_2Zn generates the reactive vinylzinc reagent in situ (Scheme 1).

Table 1. Yields and ee's of Allylic Alcohols (Scheme 1)

Entry	Terminal Alkynes	Allylic Alcohols	Yield (%ee)
1			85 (95)
2			94 (95)
3			85 (95)
4			86 (96)
5			75 (97)
6			76 (93)
7			65 (88)

The transmetalation reactions were typically performed at −78 °C;[44,46−48] however, we found that this step could be performed at 0 °C, as outlined below. To perform the asymmetric addition reaction, we chose Nugent's isoborneol-based amino alcohol ligand, MIB.[49−51] Both enantiomers of MIB can be easily synthesized from commercially available (*R*)- and (*S*)-camphor in only three steps and one purification.[49,52−54] Addition of Nugent's (−)-MIB ligand (2 mol %) to the vinylzinc reagent, followed by benzaldehyde, leads to asymmetric C−C bond formation to afford the *E*-allylic alcohols with excellent ee's and in good yields (Table 1). The reactions were carried out on a 1.0−20.0 mmol scale, and the operational simplicity of the methodology makes it amenable to larger scale synthesis. It is noteworthy that highly enantioselective catalytic vinylations of aldehydes are rare, and only a few ligands have been shown to successfully promote this addition.[46−48,55−59] Furthermore, the existing ligands require greater synthetic effort than MIB.

One of the strengths of this asymmetric vinylation reaction is its compatibility with a wide range of terminal alkynes. We found that the substituents on the propargylic position had very little effect on the enantioselectivity of the reaction. For example, 1-hexyne gave the corresponding allylic alcohol **1** (Table 1) in 95% ee, and the bulky 1-adamantyl acetylene gave allylic alcohol **5** in 97% ee. In fact, all substrates tested gave ee's in the mid-90's, except for the commercially available diyne, which gave the diol **7** in 88% ee. In this case, the allylic alkoxide generated upon reaction of the first equivalent of aldehyde may

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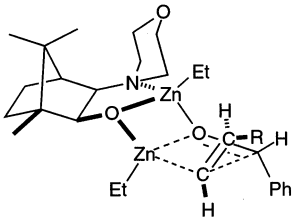


Figure 1. Possible transition state for the vinylation of benzaldehyde.

influence the vinylation of the second equivalent and lower the ee. To our knowledge, catalytic asymmetric vinylation of aldehydes to provide such C_2-symmetric bis(allylic) alcohols was previously unknown. Our initial attempts at generating the bis(allylic) alcohol from 1,6-heptadiyne gave unsatisfying results, largely due to the insolubility of the bis(vinylzinc) species at low temperature. To solve this problem, we used an inverse-addition procedure to keep the concentration of the bis(vinylzinc) intermediate low and to take advantage of the greater reactivity of the vinylzinc group over Me_2Zn. The bis(vinylborane) was added slowly to a solution of Me_2Zn, MIB, and benzaldehyde at 0 °C. At that temperature, the reaction of Me_2Zn with benzaldehyde in the presence MIB is negligible, while the vinylzinc species generated in situ reacts rapidly. By this method, we were able to obtain the desired bis(allylic) alcohol **7** in 65% yield (Table 1, entry 7).

A transition state for the asymmetric vinylation of aldehydes is illustrated in Figure 1 using the Noyori model.[11] Other transition states have also been proposed for this reaction.[60]

Nonlinear Effects in Vinyl Addition Reactions. Positive nonlinear effects in asymmetric catalysis, or "asymmetric amplification", can provide important information about reaction mechanisms.[61−64] They can also be useful in synthesis because ligands that are far from enantiopure can be employed to generate product of high ee.[65] We have previously demonstrated the substrate dependence of nonlinear effects in the asymmetric addition of alkyl groups to aldehydes.[51] Examination of nonlinear effects in the vinyl addition to benzaldehyde was performed by variation of the ee of (−)-MIB and determination of the ee of the allylic alcohol product (Scheme 1). As can be seen in Figure 2, the vinylation reaction does exhibit a strong positive nonlinear effect. Thus, use of MIB of 50% ee gives product of 91% ee, whereas use of enantiopure (−)-MIB generates product of 96% ee. A comparison with the diethylzinc addition to benzaldehyde using MIB is also shown in Figure 2. These results indicate that the vinylation of benzaldehyde does not exhibit as strong a nonlinear effect as the addition of ethyl groups to this substrate.[59]

Synthesis of Allylic Amines. By making use of the high ee's achieved in the vinylation step, we transformed the allylic alcohols **1**−**7** into valuable allylic amines[40] via Overman's [3,3]-sigmatropic rearrangement of trichloroacetimidates (Scheme 2).[38,39] Chirality is conserved in the rearrangement, and, as a result, the stereochemistry set in the initial vinylation is transferred to the allylic amine. Following Overman's procedure,[38,39] the allylic alcohols were treated with catalytic potassium hydride and trichloroacetonitrile to afford the corresponding allylic trichloroacetimidates (Scheme 2). In general, thermal rearrangement of these imidates to the trichloroacetamides took place smoothly in 1−2 h in refluxing toluene (Table 2, TAc = $COCCl_3$).

The ee's were maintained in all cases except for that of the cyclopropyl derivative **9**, where a small decrease in ee (95% to 89%) was observed. The cyclopropyl substituent significantly lowers the barrier for the [3,3]-sigmatropic rearrangement, and, as a result, the [3,3]-sigmatropic shift occurs readily at ambient temperature. The reactions to generate the allylic imidate from **2** with catalytic KH did not go to completion. We found,

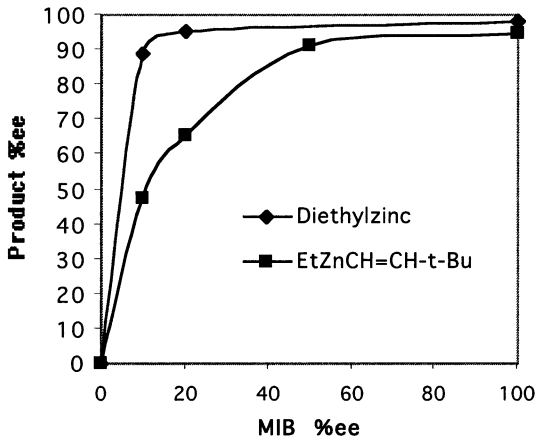


Figure 2. Nonlinear effects in the addition of vinyl ethyl zinc and diethylzinc to benzaldehyde with (−)-MIB.

Scheme 2. Synthesis of Allylic Amine Derivatives

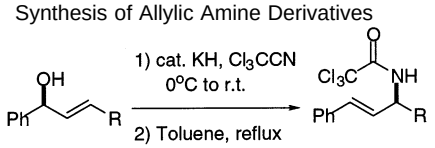
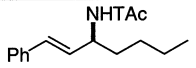
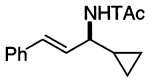
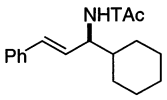
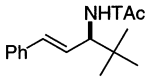
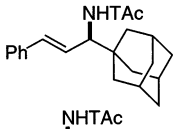
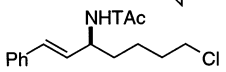
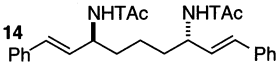


Table 2. Yields and ee's of Allylic Amines (Scheme 2)

Entry	N-Protected Allylic Amines[a]	Yield (%ee)
1	**8** 	64 (95-**99**[b])
2	**9** 	93 (89)[c]
3	**10** 	96 (95-**99**[b])
4	**11** 	90 (96-**99**[b])
5	**12** 	83 (97-**99**[b])
6	**13** 	66 (**93**)
7	**14** 	65[d] (**88**)

[a] NHTAc = $NHCOCCl_3$. [b] %ee after one recrystallization listed in bold; determined by HPLC Chiralcel OD-H. [c] The Boc derivative can be recrystallized to 99% ee. [d] Combined yield; see Scheme 3.

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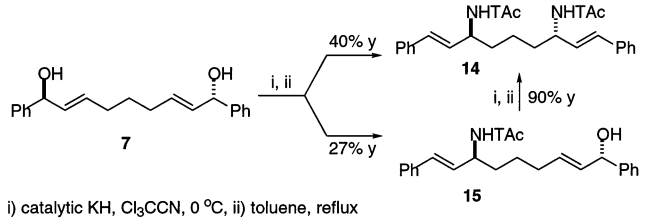
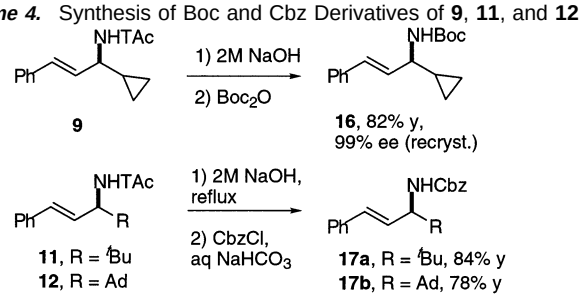
Scheme 3. Conversion of **7** to **14**



Scheme 4. Synthesis of Boc and Cbz Derivatives of **9**, **11**, and **12**



however, that by switching to DBU (15 mol %),[66] we could successfully convert the allylic alcohol directly to the trichloroacetamide **9** in one pot, at ambient temperature and in 93% yield.

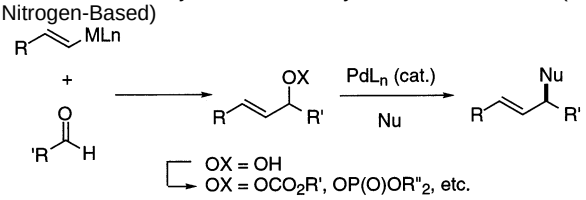
Under normal rearrangement conditions, the bis(allylic) alcohol gave a mixture of two products. The major product (40%) was the desired bis(allylic) trichloroacetamide protected amine **14**, and the minor product **15** (27%) was a result of the rearrangement of only one allylic imidate and hydrolysis of the other (Scheme 3).

Products **14** and **15** were easily separated by column chromatography. The minor product **15** was subsequently recycled to give the desired product **14** in 90% yield (Table 2) by treatment under the same reaction conditions (Scheme 3).

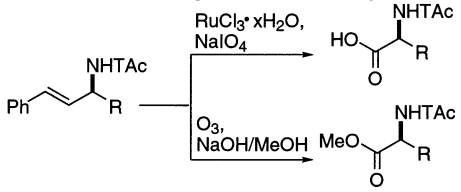
It is noteworthy that, in most cases, the resultant trichloroacetamides are highly crystalline, and, upon a single recrystallization, they are enriched to greater than 99% ee (Table 2). Recrystallization of the cyclopropyl derivative **9** proved difficult. Therefore, hydrolysis of the trichloroacetamide moiety was performed in the presence of excess 2 M NaOH in ethanol. In the same reaction flask, the free amine was converted directly to the Boc derivative **16** in 82% yield and 99% ee after recrystallization. Additionally, the *tert*-butyl and adamantyl trichloroacetamides **11** and **12** were converted to the Cbz protected **17a** and **17b** in 84% and 78% yield, respectively (Scheme 4).

The two-step method for the asymmetric synthesis of allylic amines outlined here features excellent control over regio- and enantioselectivity. This is an advantage over the well-established method of transition metal catalyzed allylic substitution reactions with amine-based nucleophiles (Scheme 5).[40,67,68] Substrates for these reactions are typically allylic acetates, carbonates, and phosphates, the most studied of which is the allylic alcohol derivative where R = R′ = Ph (Scheme 5).[69] Several catalysts will promote the efficient and highly enantioselective amination of this substrate; however, when R ≠ R′, or when R and R′ are similar in size or electronic properties, most catalysts give mixtures of regioisomers[70] or low enantioselectivities[71] due to the formation of diastereomeric metal-allyl intermediates.[40,67,68]

Scheme 5. Pd-Catalyzed Route to Allylic Amine Derivatives (Nu Is Nitrogen-Based)



Scheme 6. Oxidative Cleavage of Protected Allylic Amines



Oxidative Cleavage of Protected Allylic Amines. All of the *N*-protected allylic amines prepared here were successfully cleaved with catalytic $RuCl_3 \cdot 3H_2O$, using $NaIO_4$ as the stoichiometric oxidant,[75] to afford the corresponding *N*-protected amino acids in good yields (Table 3). This procedure worked well with the trichloroacetamide, Boc, and Cbz protected amines. In addition, the *N*-protected allylic amines were ozonized in 2.5 M methanolic NaOH, according to Marshall's procedure,[76] to give the orthogonally protected methyl esters **27**−**30** (Table 4). HPLC analysis of the Cbz-protected amino ester **30** indicated that no racemization occurred under the ozonolysis conditions (>99% ee).

We have also applied our methodology to the synthesis of α,α′-diamino diacids. Certain α,α′-diamino diacids such as (*S*,*S*)-diaminopimelic acid (DAP) play a crucial role in bacterial biosynthesis of α-amino acids.[77−79] (*S*,*S*)-DAP, epimerized by L,L-DAP epimerase, forms *meso*-DAP, which confers structural rigidity to Gram positive and many Gram negative bacteria by cross-linking the polysaccharides of the peptidoglycan in their cell walls.[80] *meso*-DAP is also converted to L-lysine by *meso*-DAP decarboxylase.[77] There is a significant interest in the use of α,α′-diamino diacids as potential antibiotics because peptidoglycans and lysine biosynthesis are foreign to mammalian biochemistry.[78] Additionally, several naturally occurring and synthetic derivatives of DAP peptides such as RP 56124[81] have

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Table 3. Oxidative Cleavage Products from Scheme 6

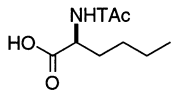
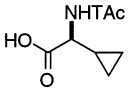
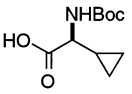
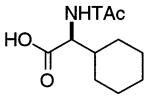
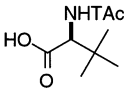
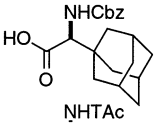
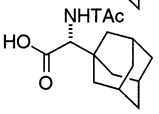
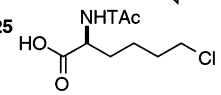
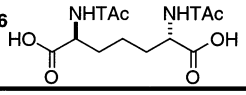
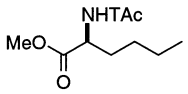
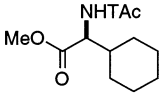
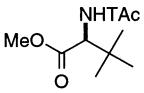
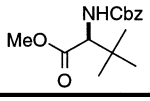
Entry	Amino Acid Derivatives	Yield (%)
1	**18** 	72
2	**19** 	85
3	**20** 	68
4	**21** 	83
5	**22** 	92
6	**23** 	80
7	**24** 	57
8	**25** 	67
9	**26** 	89

Table 4. Oxidative Cleavage to Form Esters from Scheme 6

Entry	Amino Acid Derivatives	Yield (%)
1	**27** 	84
2	**28** 	78
3	**29** 	75
4	**30** 	94

been used as immunostimulants.[81] Use of DAP derivatives as cross-linking agents can increase the activity and stability of biologically active peptides.[82−84]

Several routes to homochiral α,α′-diamino diacids have been published.[85−106] Some of these employ separation and resolution of the (*S*,*S*), (*R*,*R*), and *meso* forms.[42,107−109] Others employ diastereoselective syntheses based on chiral auxiliaries such as Schöllkopf's auxiliary.[95,96,102,103,110,111] Application of Schöllkopf's auxiliary, however, results in low diastereoselectivity (60% de).

Employing the methodology outlined above, we have synthesized the *N*,*N*-protected DAP **26** (Table 3) in just three steps. More importantly, this sequence of reactions can be applied to structural variants of DAP, and we are currently pursuing this objective.

Conclusions

We have successfully synthesized highly substituted nonproteinogenic α-amino acids such as *tert*-leucine, (cyclopropyl)glycine, (cyclohexyl)glycine, and (1-adamantyl)glycine that are important in peptidomimetics and are components in pharmaceutical agents. In the past, these amino acids have been synthesized in enantiopure form by classical resolving agents, use of chiral auxiliaries, and enzymatic kinetic resolutions; however, there are few catalytic asymmetric methods for generating this class of amino acids.[36] Access into the unnatural D-configured α-substituted amino acids using conventional methods is even more challenging. Our approach constitutes an efficient and general method toward both the L and the D configuration of this class of α-substituted glycines, as demonstrated by our synthesis of *N*-protected L and D (1-adamantyl)glycines.

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We are currently applying the methodology outlined here to the synthesis of other amino acids and their derivatives.

Experimental Section

General Methods. All reactions, except oxidative cleavage, 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 dimethylzinc were carried out using an inert atmosphere in a Vacuum Atmosphere drybox with an attached MO-40 Dritrain or by using standard Schlenk or vacuum line techniques. Dichloromethane, diethyl ether, toluene, THF, and hexanes were dried through alumina columns. Benzaldehyde and trichloroacetonitrile were distilled prior to use and stored under N_2 in glass vessels sealed with Teflon stoppers. Unless otherwise specified, all chemicals were obtained from Acros, Aldrich, or GFS Chemicals, and all solvents were purchased from Fischer Scientific. All terminal alkynes are commercially available, except for (1-adamantyl)acetylene[112] and (1-cyclohexyl)acetylene,[113] which were prepared by literature methods. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained on a Brüker 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 ultra-violet 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. All new compounds were assigned correspondingly.

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

(*S*)-3-Cyclopropyl-1-phenyl-prop-2-en-1-ol (2). General Procedure A. To a stirred solution of Cy_2BH (22.0 mmol) in hexanes (40 mL) prepared according to Oppolzer's procedure was added cyclopropylacetylene (1.87 mL, 22.0 mmol) dropwise (Caution: exothermic!).[44] The homogeneous reaction mixture was stirred for 15 min at room temperature, then cooled to −78 °C. Et_2Zn (3.08 g, 25.0 mmol) in hexanes (10 mL) or Me_2Zn in toluene (12.5 mL, 2.0 M) was added followed by (−)-MIB (96 mg, 2.0 mol %, 0.4 mmol). The reaction was transferred into a 0 °C bath, and benzaldehyde (2.03 mL, 20 mmol) was added over 30 min. The reaction was stirred at 0 °C for 2 h and quenched with 5 mL of H_2O. After stirring for 1 h, $MgSO_4$ was added, and the content of the flask was filtered and thoroughly rinsed with diethyl ether. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (5% ethyl acetate in hexanes) to afford **2** in 94% yield (3.27 g, 18.8 mmol) as a colorless oil. $[\alpha]^{25}_D = +58.8$ ($c = 0.98$, $CHCl_3$, 94.5% ee). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.38−0.41 (m, 2H), 0.70−0.74 (m, 2H), 1.39−1.42 (m, 1H), 1.83 (s, 1H), 5.15 (d, 1H, $J = 6.8$ Hz), 5.29 (dd, 1H, $J = 15.3$, 8.8 Hz), 5.74 (dd, 1H, $J = 15.3$, 7.0 Hz), 7.25−7.38 (m, 5H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 7.29 ($-(CH_2)_2-$ are overlapped), 13.90, 75.53, 126.57, 127.91, 128.89, 130.28, 136.98, 143.90 ppm. IR (neat): 3450, 1605, 1550, 1495, 1450. HRMS-CI *m*/*z* 174.1052 [M^+; calcd for $C_{12}H_{14}O$: 174.1044].

(*S,S*)-1,9-Diphenyl-nona-2,7-diene-1,9-diol (7). Inverse-Addition Procedure. To a stirred solution of Cy_2BH (10.0 mmol) in toluene (10 mL), prepared according to Oppolzer's procedure (flask A),[44] was added 1.14 mL (5.0 mmol) of 1,7-heptadiyne dropwise at ambient temperature. In a separate flask (B) charged with 48 mg (2.0 mol %, 0.2 mmol) of (−)-MIB was added Me_2Zn (7 mL, 14.0 mmol, 2.0 M in toluene), and it was all diluted with 20 mL of toluene. The reaction was cooled to 0 °C, and 1.01 mL (10 mmol) of benzaldehyde was added. The contents of the flask (A) were taken up in a syringe and added to the flask (B), with the aid of a syringe pump, over 1 h. The reaction was stirred at 0 °C for 2 h and quenched with 2.0 mL of H_2O. After the reaction was stirred for 1 h, $MgSO_4$ was added, and the content of the flask was filtered and thoroughly rinsed with ether. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (10−20% ethyl acetate in hexanes) to afford **7** as a viscous oil in 65% yield (1.02 g, 3.25 mmol). $[\alpha]^{25}_D = -90$ ($c = 0.48$, $CHCl_3$, 88% ee). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.53−1.56 (m, 2H), 2.0 (s, 2H), 2.10 (m, 4H), 5.19 (d, 2H, $J = 6.6$ Hz), 5.66−5.78 (m, 4H, overlapping vinyl H's), 7.29−7.39 (m, 10H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 28.72, 32.08, 75.55, 126.57, 127.95, 128.91, 132.53, 133.11, 143.75 ppm. IR (neat): 3392, 1704, 1666, 1614, 1492, 1450 cm^{-1}. HRMS-ESI *m*/*z* 331.1665 [$(M + Na)^+$; calcd for $C_{21}H_{24}O_2$-Na: 331.1675].

(*S*)-*N*-(1-Cyclopropyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide (9). A 25 mL round-bottom flask under N_2 atmosphere was charged with (*S*)-3-cyclopropyl-1-phenyl-2-en-1-ol, **2** (174 mg, 1.0 mmol), and Cl_3-CCN (120 μL, 1.2 mmol) followed by 10 mL of dry CH_2Cl_2. The reaction mixture was cooled to 0 °C with an ice bath. DBU (22.4 μL, 0.15 mmol) was added dropwise to the reaction mixture via a microsyringe. The reaction was allowed to stir at this temperature for 30 min, then warmed to room temperature and stirred for an additional 3.5 h. The solvent was removed in vacuo, and the residue was chromatographed on silica (5% ethyl acetate in hexanes) to afford 296 mg (93% yield) of **9** as a viscous oil that solidified on standing over several days. mp 66−68 °C. $[\alpha]^{25}_D = -32.2$ ($c = 0.64$, $CHCl_3$, 89% ee). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.46−0.47 (m, 1H), 0.53−0.57 (m, 1H), 0.65−0.72 (m, 2H), 1.4−1.6 (m, 1H), 4.08 (m, 1H), 6.22 (dd, 1H, $J = 14.7$, 5.76 Hz), 6.68 (d, 1H, $J = 15.8$ Hz), 6.83 (d, 1H, $J = 6.7$ Hz), 7.29−7.42 (m, 5H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 3.56, 3.71, 15.77, 57.80, 81.5, 126.99, 127.18, 128.4, 129.03, 132.17, 136.68, 161.6 ppm. IR (film): 3333, 1709, 1691.6, 1512, 1492, 1485 cm^{-1}. HRMS-CI *m*/*z* 317.0125 [M^+; calcd for $C_{14}H_{14}Cl_3NO$: 317.0140].

(*S*)-*N*-(1-Adamantyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide (12). General Procedure B. To a stirred solution of (*S*)-3-adamantyl-1-phenyl-prop-2-en-1-ol, **5** (1.5 g, 5.3 mmol), in 150 mL of dry ether was added KH (60 mg, 1.5 mmol) in one portion under a stream of N_2. The reaction was stirred for 15 min until H_2 gas evolution ceased and a yellow to orange appearance was observed. The mixture was transferred via cannula to a flask containing Cl_3CCN (795 μL, 7.95 mmol) in 100 mL of dry ether at 0 °C over 10 min. After being stirred for 1 h at ambient temperature, the reaction was quenched with 61 μL of MeOH, filtered, and thoroughly rinsed with ether. The filtrate was concentrated in vacuo, and 50 mL of dry toluene was added. The reaction was refluxed for 1−2 h under N_2 atmosphere. The toluene was removed in vacuo to afford 1.81 g of **12** (4.4 mmol, 83% yield) after a single recrystallization from hexanes−ethyl acetate. mp 164−165 °C. $[\alpha]^{25}_D = -38.6$ ($c = 0.50$, $CHCl_3$, 99% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.6−1.79 (m, 12H), 2.07 (s, 3H), 4.27 (t, 1H), 6.21 (dd, 1H, $J = 15.8$, 7.7 Hz), 6.6 (d, 1H, $J = 15.8$ Hz), 6.79 (d, 1H, $J = 9.2$ Hz), 7.25−7.42 (m, 5H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 28.6, 37.24, 37.53, 39.19, 62.69, 81.6, 124.50, 126.94, 128.32, 129.02, 133.94, 136.85, 161.6 ppm. IR (KBr): 3423, 1706, 1509, 1449 cm^{-1}. HRMS-CI *m*/*z* 411.1010 [M^+; calcd for $C_{21}H_{24}Cl_3NO$: 411.0922].

(*S*)-(1-Cyclopropyl-3-phenyl-allyl)-carbamic Acid *tert*-Butyl Ester (16). To a 100 mL round-bottom flask charged with (*S*)-*N*-(1-cyclopropyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide, **9** (318 mg, 1.0 mmol), were added absolute ethanol (20 mL) and 2 N NaOH (10 mL). The reaction was stirred for 14 h at ambient temperature. Excess

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$(Boc)_2O$ (436.5 mg, 2.0 mmol) was added directly into the reaction mixture. Disappearance of baseline material deemed the reaction complete. The reaction mixture was concentrated in vacuo, and the residue was taken up in CH_2Cl_2 (30 mL) and washed with H_2O (30 mL). The aqueous layer was back extracted twice with CH_2Cl_2 (10 mL × 2). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was recrystallized with hexanes with a minimum amount of ethyl acetate to afford 223 mg (0.816 mmol, 81.6% yield) of **16** as white needles. $[\alpha]^{25}_D = -3.38$ (*c* = 0.33, $CHCl_3$, 99% ee). ^1H NMR (C_6D_6, 500 MHz, at 343 K): δ 0.09−0.18 (m, 1H), 0.27−0.34 (m, 3H), 0.63−0.72 (m, 1H), 1.47 (s, 9H), 3.87 (br, 1H), 4.37 (br, 1H), 6.01 (dd, 1H, *J* = 15.9, 5.8 Hz), 6.49 (d, 1H, *J* = 16.0 Hz), 7.02−7.21 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (C_6D_6, 500 MHz, at 343 K to detect missing carbons because of restricted bond rotation): δ 2.99, 3.01, 16.36, 28.58, 56.48, 78.85, 126.85, 127.56, 128.70, 130.30, 130.51, 137.73, 155.32 ppm. IR (KBr): 3367, 1679, 1525, 1444 cm^{-1}. HRMS-ESI *m*/*z* 273.1724 [M^+; calcd for $C_{17}H_{23}NO_2$: 273.1729].

(*S*)-(1-Adamantyl-3-phenyl-allyl)-carbamic Acid Benzyl Ester (17b). To a 50 mL round-bottom flask charged with (*S*)-*N*-(1-adamantyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide, **12** (210 mg, 0.5 mmol), were added absolute ethanol (30 mL) and 2 N NaOH (10 mL). The reaction was refluxed for 4 h and monitored by TLC for the disappearance of starting material. The reaction mixture was concentrated in vacuo, and the residue was taken up in CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (10 mL). The biphasic mixture was cooled to 0 °C, and 107 μL of Cbz-Cl (0.75 mmol) was added dropwise. After 14 h of stirring at room temperature, the organic layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL × 2). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (5% ethyl acetate in hexanes) on silica to afford 157 mg (0.39 mmol, 78% yield) of **17b** as white foam. $[\alpha]^{25}_D = -5.15$ (*c* = 0.86, $CHCl_3$, 99% ee). ^1H NMR (500 MHz, $CDCl_3$): δ 1.57−1.75 (m, 12H), 2.03 (s, 3H), 4.02 (br, 1H), 4.91 (br, 1H), 5.15 (s, 2H), 6.18 (dd, 1H, *J* = 15.8, 7.5 Hz), 6.53 (d, 1H, *J* = 15.7 Hz), 7.26−7.40 (m, 10H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 28.75, 37.02, 37.37, 39.21, 62.77, 67.27, 126.53, 127.91, 128.55, 128.84, 132.45, 137.01, 137.33, 156.3 ppm (two 4° carbons were not detected). IR (KBr): 3330, 1697, 1530, 1448 cm^{-1}. HRMS-ESI *m*/*z* 424.2244 [$(M + Na)^+$; calcd for $C_{27}H_{31}NaNO_2$: 424.2255].

(*S*)-2-(2,2,2-Trichloro-acetylamino)-hexanoic Acid (18). General Procedure C. To a stirred solution of 100 mg (0.3 mmol) of (*S*)-*N*-(1-butyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide, **8**, in 1.0 mL of carbon tetrachloride, 1.0 mL of acetonitrile, and 1.5 mL of water was added 260 mg (1.2 mmol) of sodium periodate. Once all of the sodium periodate had dissolved, 1.7 mg (0.008 mmol) of ruthenium trichloride hydrate was added, and the reaction mixture was stirred vigorously overnight at room temperature. It was then extracted with dichloromethane; the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give a deep purple oil. The crude product was then redissolved in dichloromethane and stirred for 30 min with 28 μL (50 equiv with respect to the ruthenium catalyst) of dimethyl sulfoxide and 2 g of silica gel. The solvent was removed in vacuo, and the product, now preadsorbed to silica, was purified by column chromatography (0.25% acetic acid and 20−50% ethyl acetate in hexanes) to give **18** as a white solid in 75% yield (62 mg, 0.22 mmol). mp 60−63 °C. $[\alpha]^{29}_D = +35.2$ (*c* = 0.27, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 0.93 (t, *J* = 7.0 Hz, 3H), 1.34−1.43 (m, 4H), 1.81−1.89 (m, 1H), 2.01−2.08 (m, 1H), 4.63 (dt, *J* = 7.3, 5.4 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 13.5, 21.9, 26.8, 31.2, 53.5, 91.8, 161.4, 176.1 ppm. IR (KBr): 3420, 2930, 2371, 1707, 1519, 1384, 1246, 828 cm^{-1}. HRMS-ESI *m*/*z* 297.9819 [$(M + Na)^+$; calcd for $C_8H_{12}Cl_3NO_3Na$: 297.9780].

(*S*)-6-Chloro-2-(2,2,2-trichloro-acetylamino)-hexanoic Acid (25). The product was prepared according to procedure C using (*S*)-*N*-(5-chloro-1-styryl-pentyl)-2,2,2-trichloro-acetamide, **13** (369 mg, 1.0 mmol), $NaIO_4$ (941 mg, 4.4 mmol), and $RuCl_3 \cdot 3H_2O$ (4.1 mg, 0.02 mmol). After column chromatography on silica (15−50% ethyl acetate in hexanes and 0.25% glacial acetic acid), the reaction afforded 252 mg (0.81 mmol, 81% yield) of **25** as a viscous oil. $[\alpha]^{25}_D = +36.8$ (*c* = 0.50, $CHCl_3$, 93.3% ee). ^1H NMR ($CDCl_3$, 500 MHz): δ 1.58−1.62 (m, 2H), 1.84−1.91 (m, 3H), 2.0−2.10 (m, 1H), 3.55−3.58 (t, *J* = 6.3 Hz, 2H), 4.63−4.67 (dt, 1H, *J* = 7.2 Hz), 6.8−7.3 (br, 1H, $-CO_2H$), 7.25 (d, 1H, *J* = 7.3 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 22.67, 31.38, 32.09, 44.70, 53.97, 92.42, 162.19, 175.96 ppm. IR (KBr): 3330, 1702, 1515, 1420 cm^{-1}. HRMS-CI *m*/*z* 309.9556 [MH^+; calcd for $C_8H_{12}Cl_4NO_3$: 309.9569].

(*S*)-2-(2,2,2-Trichloro-acetylamino)-hexanoic Acid Methyl Ester (27). General Procedure D. Ozone was passed through a stirred solution of 100 mg (0.3 mmol) of (*S*)-*N*-(1-butyl-3-phenyl-allyl)-2,2,2-trichloro-acetamide, **8**, in 10 mL of dichloromethane and 1.0 mL of 2.5 M methanolic sodium hydroxide at −78 °C. After 1 h, the characteristic blue color of ozone persisted in the reaction mixture. At this point, oxygen was bubbled through the reaction mixture for 15 min. It was then diluted with dichloromethane and water, allowed to warm slowly to room temperature, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by column chromatography (20% ethyl acetate in hexanes) to give **27** as a colorless oil in 84% yield (73 mg, 0.25 mmol). $[\alpha]^{23}_D = -35.7$ (*c* = 1.63, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 0.84 (t, *J* = 7.0 Hz, 3H), 1.19−1.31 (m, 4H), 1.69−1.74 (m, 1H), 1.88−1.93 (m, 1H), 3.74 (s, 3H), 4.51 (dt, *J* = 7.2, 5.4 Hz, 1H), 7.16 (d, *J* = 5.7 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 13.8, 22.2, 27.0, 31.7, 52.8, 53.9, 92.0, 161.4, 171.8 ppm. IR (neat): 3345, 2958, 1711, 1519, 1218, 827 cm^{-1}. HRMS-ESI *m*/*z* 311.9930 [$(M + Na)^+$; calcd for $C_9H_{14}Cl_3NO_3Na$: 311.9937].

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