Chiral Oxime Ethers in Asymmetric Synthesis. 3.[1] Asymmetric Synthesis of (*R*)-N-Protected α-Amino Acids by the Addition of Organometallic Reagents to the ROPHy Oxime of Cinnamaldehyde

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A new asymmetric synthesis of α-amino acids is described in which the key step is the diastereoselective addition of organometallic reagents to (*R*)-*O*-(1-phenylbutyl)cinnamaldoxime **5** to give hydroxylamines **6**. Subsequent reductive cleavage of the N−O bond in the hydroxylamine **6** followed by N-protection gave the carbamates **7**, which upon oxidation with ruthenium(III) chloride/periodate gave the N-protected amino acids **8**. The method was also adapted to the synthesis of a quaternary amino acid **15** from the ketoxime ether **9**.

Introduction

The development of new methodology for the asymmetric synthesis of α-amino acids, both natural and unnatural, continues to attract the attention of chemists worldwide.[2,3] Many of these methods involve stereoselective additions to C=N bonds,[4] and in this context we have recently reported the highly diastereoselective addition of organometallic reagents to the C=N bond of chiral oxime ethers to give chiral nonracemic hydroxylamines.[5,6] This subsequently resulted in the development of oxime ethers derived from (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamines (ROPHy and SOPHy) as useful reagents for asymmetric synthesis and their application in the asymmetric synthesis chiral amines (Scheme 1).[1,5,6] The methodology has been applied to the asymmetric synthesis of the hemlock piperidine alkaloids (−)-coniine and (+)-pseudoconhydrine[7] and of *β*-amino acids.[8] We now report the details of a new route to α-amino acids based on the highly diastereoselective addition of organolithium reagents to (*R*)-*O*-(1-phenylbutyl)cinnamaldoxime **5**.[9]

Results and Discussion

To adapt our asymmetric synthesis of protected amines (Scheme 1) into a route to N-protected amino acids, two strategies were considered (Scheme 2). The first involved the use of an oxime ether **1** that incorporates the carboxylic acid precursor R_A; addition of organometallic reagents, followed by cleavage of the N−O bond, and conversion of R_A into a carboxyl group would then give the required amino acid. Alternatively, the carboxyl synthon can be added as an organometallic reagent, R_AMet (Scheme 2b). Although we have investigated both approaches, it is the former method that is described in detail herein.

The group R_A that was initially chosen for study was the furan group; oxidation of the furan ring with a whole range of reagents has been reported to give the carboxylic acid,[10] and the strategy has been used, for example, in the synthesis of carbohydrate derivatives.[11] The synthesis

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(9) Some of the results have been described in preliminary form: Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *Synlett* **1997**, 659−660.

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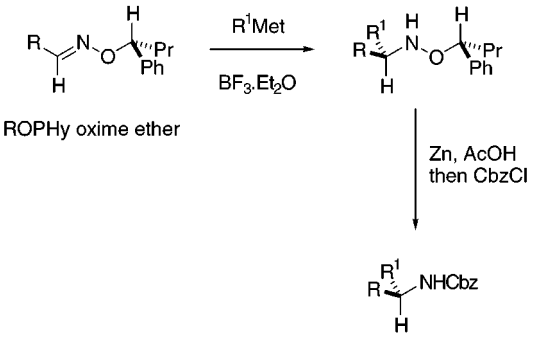
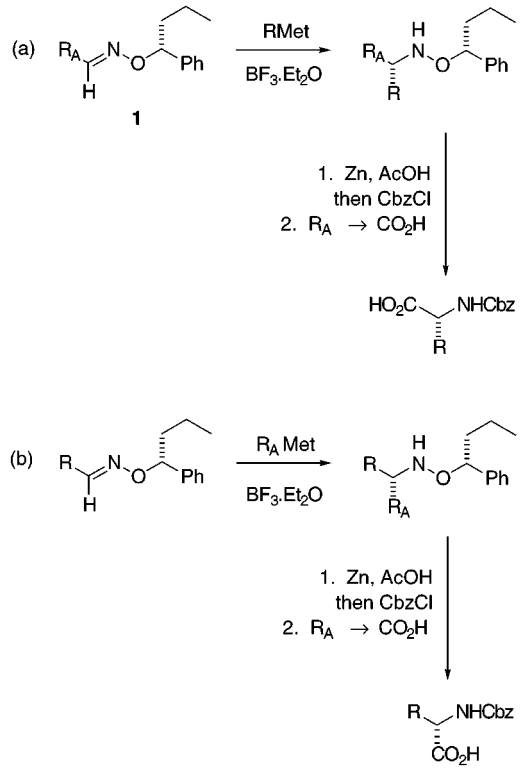
Scheme 1



Scheme 2



of furan-derived oximes proved straightforward. The one-pot procedure described previously[1] was used to convert the chiral alkoxyphthalimide **2** into the corresponding furan oxime ethers. However, the oxime derived from furfural itself proved unstable, and therefore, the 5-methylfurfural oxime ether **3**, obtained as the *E* isomer (83%) after chromatographic separation of the *Z* isomer, was used. The addition of organometallic reagents to the ROPHy oxime **3** was carried out under the usual conditions (excess organometallic in the presence of an excess of boron trifluoride etherate at −78 °C) and gave the corresponding hydroxylamines **4** in good yield (Scheme 3, Table 1). However, the diastereoselectivity of the addition (59−83%), as judged by ^{1}H NMR spectra of the crude hydroxylamine **4**, was considered too low for such a key step in the projected route to α-amino acids, and therefore, an alternative was investigated.

The alternative oxime precursor of the amino acids was the ROPHy oxime of cinnamaldehyde, in which the

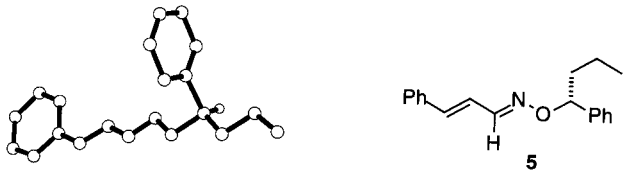
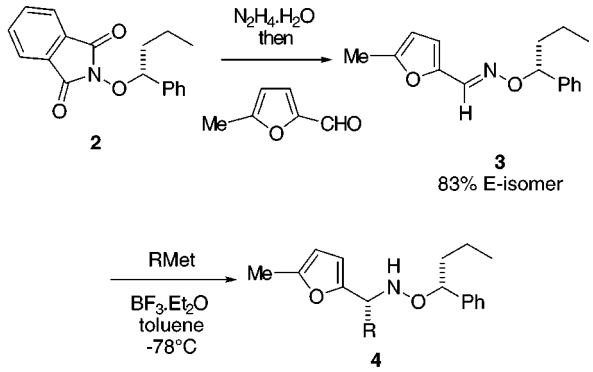


Figure 1. X-ray structure of (*R*)-(*O*)-(1-phenylbutyl)cinnamaldoxime **5**.

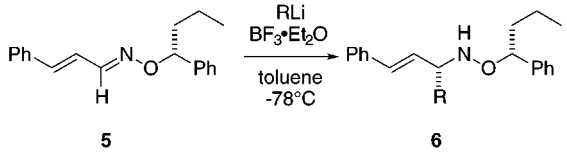
Table 1. Addition of Organometallic Reagents to the 5-methylfurfural Oxime Ether 3

RMet	hydroxylamine	yield/%	de/%
MeLi	**4a**	77	83
n-BuLi	**4b**	87	81
$H_2C{=}CHCH_2MgBr$	**4c**	56	59

Scheme 3



Scheme 4



alkene acts as precursor to the carboxylic acid group.[12] The oxime ether **5** was prepared from cinnamaldehyde and (*R*)-*O*-(1-phenylbutyl)hydroxylamine, obtained from cleavage of the corresponding phthalimide **2**, and was obtained in 76% yield as the crystalline *E* isomer after chromatographic separation of the *Z* isomer (23%). The oxime ether **5** gave crystals suitable for X-ray analysis (Figure 1), although the size of the crystals and low number of observed data precluded full anisotropic refinement of the structure.

The oxime **5** underwent addition of organometallic reagents in the presence of boron trifluoride etherate to give the hydroxylamines **6** in varying yields (Scheme 4, Table 2). The diastereoselectivity of the addition was readily measured from the ^{1}H NMR spectra of **6**; for example, the olefinic proton adjacent to the new stereocenter appeared as two clearly separated signals for the two diastereomers. Varying levels of asymmetric induction were observed (Table 2). The configuration of the new asymmetric center was assigned on the basis of our previous results, and this was confirmed in the case of **6a**−**d** by the subsequent conversion into amino acids **8** (see below). Generally, primary organolithium reagents

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Table 2. Addition of Organometallic Reagents to (*R*)-(*O*)-(1-Phenylbutyl)cinnamaldoxime 5

entry	organometallic	hydroxylamine	yield/%	de/%
1	MeLi	**6a**	95	92
2	*n*-BuLi	**6b**	92	93
3	*i*-BuLi	**6c**	93	92
4	PhLi	**6d**	76	90
5	MeMgBr	**6a**	41	73
6	EtMgBr	**6e**	91	71
7	*n*-BuMgBr	**6b**	89	78
8	$PhCH_2MgBr$	**6f**	34	72
9	PhMgBr	**6d**	69	80
10	*i*-PrMgBr	**6g**	<10	
11	*t*-BuMgBr	**6h**	<10	
12	*t*-BuLi	**6h**	<10	

gave better results than the corresponding Grignard reagents in terms of both yield and diastereomeric excess. It would thus appear that the counterion has an effect on the stereoselectivity of the reaction, although this has not been studied in detail. It is important to note that the lithium and the magnesium reagents both give the same major diastereomer. Organometallic reagents with branching at the α-position such as *t*-Bu and *i*-Pr gave complex reaction mixtures and a yield of the hydroxylamine of less than 10%. In these cases the counterion, lithium, or magnesium made little difference as exemplified by entries 11 and 12 (Table 2). *n*-Butyllithium gave the best result with a diastereomeric excess of 93% (entry 2), which is significantly better than that obtained for the addition to the 5-methylfuran derived oxime **3** (81% de). Also, methyllithium gave an excellent result (95% yield, 92% de, entry 1), which is again better than that gained from the furan oxime **3** (83% de). Phenyllithium previously has given poor yields but high diastereoselectivity in additions to the oxime ethers,[6] and this was also found to be true for the cinnamaldehyde oxime **5**. However, if the number of equivalents of phenyllithium is decreased from 3 to 1.5 then the yield of isolated hydroxylamine **6d** increased dramatically up to 76% with a good diastereomeric excess (90% de). Isobutyllithium, which was generated from the corresponding bromide, added to the cinnamaldehyde oxime **5** as smoothly as did commercially available organolithium reagents to give an excellent yield (93%) and de (92%) of the hydroxylamine **6c**.

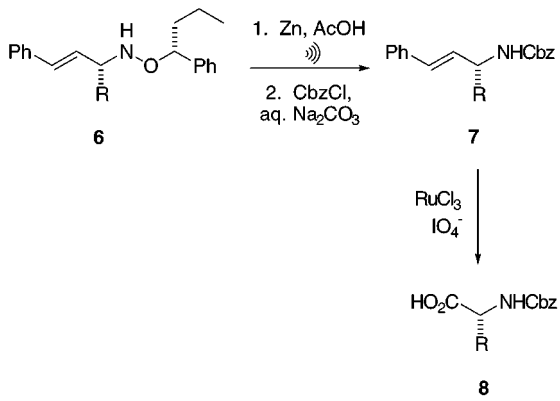
A range of commercially available Grignard reagents was also added to the cinnamaldehyde oxime **5**, but unfortunately, the results were not as good as the corresponding organolithium reagents in terms of yield and diastereoselectivity (Table 2, entries 5−11). For example, *n*-butyllithium gave 93% de and 92% yield, but the Grignard reagent, *n*-butylmagnesium bromide, gave only 78% de and 89% yield. The products from the Grignard additions were accompanied by side products that were not present in the organolithium reactions. Some results are worthy of note: the additions of phenyl-, ethyl-, and *n*-butylmagnesium bromides gave good yields of the hydroxylamines, 69, 91, and 89%, respectively, and reasonable diastereoselectivity (PhMgBr 80% de, Et 71% de, *n*-Bu 78% de). Methyl- and benzylmagnesium bromide both gave the addition products **6e** and **6f**; however, a substantial amount of starting material was recovered in each case.

The conversion of the hydroxylamines **6** into amino acids was achieved by initial cleavage of the N−O bond using the zinc/acetic acid/ultrasound method[13] and was exemplified using the methyl-, *n*-butyl-, isobutyl-, and phenyl-substituted derivatives **6a**−**d**, the hydroxylamines that were formed in the highest diastereomeric excess. The resulting amines were not isolated but were immediately converted into the benzyl carbamates **7** by reaction with benzyl chloroformate (Table 3). The chiral alcohol, (*R*)-1-phenylbutanol, was recovered from the reductive cleavage reactions essentially optically pure in about 80% yield. Finally, the double bond was cleaved using the $RuCl_3$/periodate method[14] to give the desired *N*-Cbz amino acids **8** in moderate yield (Scheme 5, Table 3). It is possible that the moderate yields in the oxidative cleavage are a result of competing oxidation of the Cbz-benzyl group, and while some benzyl groups are reported to survive ruthenium(VIII) oxidation,[11a] others do not.[11b] The configuration of the amino acid derivatives **8** was confirmed as *R* by comparison of their optical rotations with literature values.

Table 3. Conversion of Hydroxylamines 6 into *N*-Cbz-Protected Amino Acids 8

hydroxylamine **6**	R	*N*-Cbz-amine **7** yield/%	*N*-Cbz-amino acid **8** yield/%
a	Me	31	25
b	*n*-Bu	83	57
c	*i*-Bu	86	36
d	Ph	66	55

Scheme 5



Finally, we extended the method to the synthesis of quaternary amino acids[15] using ketoxime ethers as starting materials. The addition of organometallic reagents to ketoxime ethers is known,[16] although it is much rarer than the corresponding reactions of aldoxime ethers. Therefore, benzylideneacetone was converted into its oxime ether by reaction with ROPHy under the usual conditions; a mixture of oximes was obtained that was readily separable into the *E* and *Z* isomers **9** and **10** isolated in 54 and 31% yield, respectively (Scheme 6). Both oxime ethers underwent addition of *n*-butyllithium, although the reaction temperature had to be lowered to ca. −100 °C to obtain reasonable yields of the desired hydroxylamines. As expected, the *Z*-oxime **10** gave the

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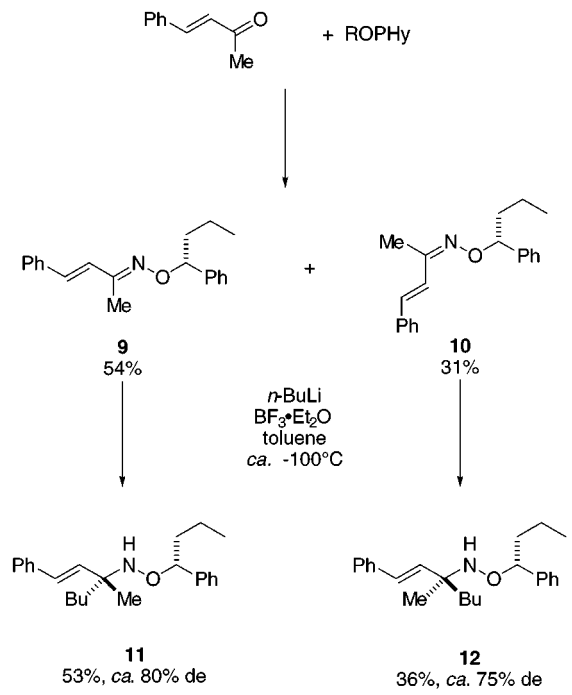
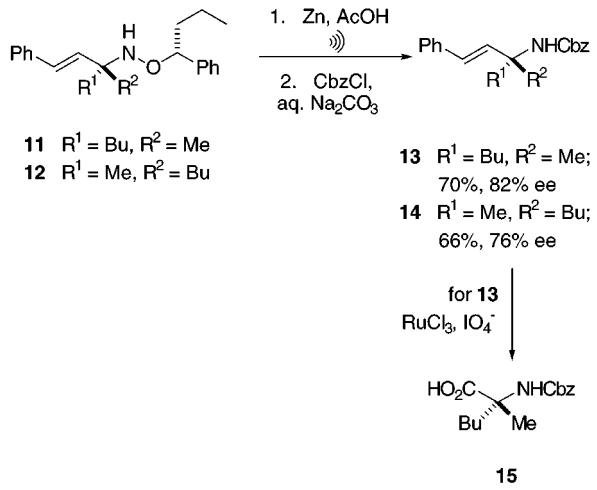
(16) Uno, H.; Terakawa, T.; Suzuki, H. *Synlett* **1991**, 559−560.

Scheme 6



Scheme 7



opposite major diastereomer to its E isomer (Scheme 6), although the exact diastereomeric ratio could not be obtained from the ^{1}H NMR spectra of the crude hydroxylamines **11** and **12**. The estimated de's were 80 and 75%, respectively, and these were confirmed by subsequent conversion into the carbamates **13** and **14** (see below). Hence, the ROPHy ketoxime ethers **9** and **10** would appear to exhibit lower diastereoselectivity in their addition reactions than their aldoxime counterparts.

The hydroxylamines **11** and **12** were subjected to the zinc in acetic acid/ultrasound reductive cleavage conditions, and the resulting amines were immediately protected as their benzyl carbamates **13** and **14** (Scheme 7). Analysis of the carbamates **13** and **14** by HPLC on a chiral stationary phase established their enantiomeric purity as 82 and 76% ee, respectively, in good agreement with the estimated diastereoselectivity of the original addition reaction (Scheme 6). Although the enantiomeric purity of the carbamates was disappointing, carbamate **13** was carried through to the corresponding quaternary amino acid by oxidative cleavage of the alkene (64%) (Scheme 7).

Experimental Section

For general experimental details, see refs 1 and 6. Coupling constants are reported in Hz. In reporting the NMR data for mixtures of diastereomers, signals arising from the major and minor isomers are reported separately if possible; the integration of signals is consistent within each isomer; e.g., a methyl group is reported as 3H for both isomers even though the peaks are unequal in area when the ratio of isomers is not 1:1. Compounds characterized by high-resolution mass spectrometry were chromatographically homogeneous.

General Method for the Preparation of Oxime Ethers. *N*-(1-Phenylbutoxy)phthalimide **2** (4.65 g, 15.8 mmol) and ethanol (100 mL) were added to a round-bottom flask, and the suspension was heated until the phthalimide dissolved. Hydrazine hydrate (0.77 mL, 15.8 mmol) was added at this elevated temperature, and the solution was allowed to cool to room temperature. Aldehyde or ketone (15.8 mmol) was added and the mixture stirred overnight. The solvent was evaporated, and carbon tetrachloride (30 mL) and magnesium sulfate were added to the residue. The resulting suspension was filtered and the filtrate evaporated; column chromatography of the residue on silica gel (diethyl ether−light petroleum 1:20) gave the oxime ether.

(*E*)-(*R*)-(+)-*O*-(1-Phenylbutyl)-5-methyl-2-furaldoxime 3. Obtained from 5-methyl-2-furaldehyde and separated from the *Z* isomer by column chromatography on silica gel (diethyl ether−light petroleum 1:20) as a colorless oil (83%): $[\alpha]^{20}_D$ +124.6 (*c* 1, CH_2Cl_2); IR (film) 2932, 1582 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (1H, s), 6.45 (1H, d, *J* 3.3), 6.03 (1H, d, *J* 3.3), 5.25 (1H, t, *J* 6.9), 2.33 (3H, s), 1.99 (1H, m), 1.78 (1H, m), 1.41 (2H, m), 0.96 (3H, t, *J* 7.3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.4, 145.9, 142.4, 139.2, 128.1, 127.3, 126.7, 114.3, 107.8, 85.4, 38.4, 18.8, 14.0, 13.8; MS (EI) *m*/*z* (relative intensity) 133 (37), 105 (39), 91 (100); HRMS calcd for $C_{16}H_{19}NO_2$ (M) 257.1416, found 257.1411.

(*E*)-(*R*)-(+)-*O*-(1-Phenylbutyl)cinnamaldoxime 5. Obtained from cinnamaldehyde as a colorless solid (80%), recrystallized from light petroleum: mp 65−67 °C; $[\alpha]^{20}_D$ +48.1 (*c* 1, CH_2Cl_2); IR (Nujol) 2931, 1625 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (1H, dd, *J* 1.6, 7.6), 7.32 (10H, m), 6.79 (2H, m), 5.14 (1H, dd, *J* 6.6, 7.1), 1.99 (1H, m), 1.78 (1H, m), 1.44 (2H, m), 0.98 (3H, t, *J* 7.3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 150.6, 142.4, 138.1, 136.5, 128.7, 128.5, 128.2, 127.4, 126.8, 126.6, 122.2, 85.4, 38.3, 18.8, 13.9; MS (EI) *m*/*z* (relative intensity) 279 (M^+, 14), 133 (58), 91 (100), 77 (20); HRMS calcd for $C_{19}H_{21}NO$ (M) 279.1623, found 279.1625. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.7; H, 7.6; N, 5.0. Found: C, 81.6; H, 7.5; N, 4.9.

(*R*)-(+)-*O*-(1-Phenylbutyl)benzylideneacetone Ketoximes 9 and 10. Obtained from benzylidene acetone and the isomers separated by column chromatography on silica gel (diethyl ether-light petroleum 1:20).

E isomer **9**: as a colorless solid (51%), recrystallized from light petroleum; mp 49−50 °C; $[\alpha]^{20}_D$ +91.6 (*c* 2, CH_2Cl_2); IR (CH_2Cl_2) 2959, 1583 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (10H, m), 6.83 (2H, s), 5.17 (1H, dd, *J* 6.3, 7.0), 2.18 (3H, s), 1.95 (1H, m), 1.83 (1H, m), 1.45 (2H, m), 0.98 (3H, t, *J* 7.3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.8, 143.1, 136.5, 132.4, 128.6, 128.2, 128.1, 127.2, 126.7, 126.4, 85.3, 38.7, 18.4, 14.0, 10.4; MS (EI) *m*/*z* (relative intensity) 133 (14), 105 (39), 91 (100), 77 (30); HRMS calcd for $C_{20}H_{23}NO$ (M) 293.1780, found 293.1780.

Z isomer **10**: as a colorless solid (34%), recrystallized from light petroleum; mp 78−79 °C; $[\alpha]^{20}_D$ −378.7 (*c* 0.75, CH_2Cl_2); IR (CH_2Cl_2) 2959, 1621 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* 16.6), 7.56 (2H, m), 7.33 (8H, m), 6.97 (1H, d, *J* 16.6), 5.17 (1H, dd, *J* 6.3, 6.8), 2.07 (3H, s), 1.97 (1H, m), 1.73 (1H, m), 1.45 (2H, m), 0.97 (3H, t, *J* 7.3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.2, 145.0, 138.5, 137.7, 130.8, 130.7, 130.1, 129.9, 129.4, 128.5, 119.9, 87.0, 40.7, 20.9, 18.9, 16.0; MS (EI) *m*/*z*

(relative intensity) 293 (M^+, 18), 105 (22), 91 (100), 77 (24); HRMS calcd for $C_{20}H_{23}NO$ (M) 293.1780, found 293.1780.

General Procedure for the Addition of Organometallic Reagents to the Oxime Ethers. The oxime ether (3.22 mmol) in toluene (16 mL) was cooled to −78 °C under nitrogen, and boron trifluoride etherate (1.2 mL, 9.7 mmol) was added. The solution was stirred for 15 min, after this time, the organometallic reagent (9.7 mmol) was added dropwise over 15 min. The resulting clear solution was stirred for a further 30 min when water (10 mL) was added. The solution was allowed to warm to room temperature, and ether (10 mL) was added. The two layers were separated, and the aqueous layer was washed with further portions of ether (2 × 15 mL). The combined organic portions were dried (K_2CO_3), filtered, and evaporated. Column chromatography (5% ether/light petroleum) afforded the hydroxylamine.

(1*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-5-(2-methylfuryl)-1-ethylamine 4a. Obtained from the addition of methyllithium to oxime **3** as a colorless oil (77%, 83% de): $[\alpha]^{20}_D$ +87.5° (*c* 1, CH_2Cl_2); IR (film) 3030, 2958, 1566 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.31 (5H, m), 6.05 (1H, d, *J* 3.1), 5.88 (1H, d, *J* 3.1), 5.43 (1H, br s), 4.58 (1H, dd, *J* 5.9, 7.3), 4.18 (1H, q, *J* 6.6), 2.25 (3H, s), 1.82 (1H, m), 1.62−1.27 (3H, m), 1.44 (3H, d, *J* 6.6), 0.93 (3H, t, *J* 7.4); minor diastereomer 6.15 (1H, d, *J* 3.1), 5.91 (1H, d, *J* 3.1), 4.42 (1H, dd, *J* 5.9, 7.3), 2.30 (3H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ major diastereomer 153.4, 151.2, 143.2, 128.2, 127.2, 126.5, 107.2, 105.9, 85.3, 76.5, 54.0, 38.7, 19.1, 16.9, 14.0, 13.5, minor diastereomer 126.6, 107.0, 85.4, 38.5, 16.9; MS (EI) *m*/*z* (relative intensity) 133 (16), 91 (100), 77 (17); HRMS calcd for $C_{17}H_{24}NO_2$ (MH) 274.1807, found 274.1807.

(1*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-(5-(2-methylfuryl)-1-pentylamine 4b. Obtained from the addition of *n*-butyllithium to oxime **3** as a colorless oil (87%, 81% de): $[\alpha]^{20}_D$ +90.3 (*c* 0.9, CH_2Cl_2); IR (film) 3030, 2957, 1565 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.27 (5H, m), 6.02 (1H, d, *J* 3.0), 5.84 (1H, d, *J* 3.0), 5.35 (1H, br s), 4.51 (1H, dd, *J* 5.7, 7.6), 3.92 (1H, dd, *J* 5.6, 8.6), 2.23 (3H, s), 1.79−1.21 (10H, m), 0.87 (6H, 2 × t), minor diastereomer 6.07 (1H, d, *J* 3.0), 4.48 (1H, dd, *J* 5.7, 7.6), 2.27 (3H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.3, 151.1, 143.8, 128.1, 127.1, 126.5, 107.9, 105.8, 85.0, 59.1, 38.6, 30.7, 28.3, 22.5, 19.1, 14.0, 13.9, 13.5; MS (EI) *m*/*z* (relative intensity) 166 (88), 151 (100), 133 (12); HRMS calcd for $C_{20}H_{30}NO_2$ (MH) 316.2276, found 316.2277.

(1*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-(5-(2-methylfuryl)-1-but-3-enylamine 4c. Obtained from the addition of allylmagnesium bromide to oxime **3** as a colorless oil (56%, 59% de): $[\alpha]^{20}_D$ +92.3 (*c* 1, CH_2Cl_2); IR (film) 3076, 2958, 1565 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.32 (5H, m), 6.07 (1H, d, *J* 3.0), 5.88 (1H, d, *J* 3.0), 5.75 (1H, m), 5.46 (1H, br s), 5.06 (2H, m), 4.53 (1H, t, *J* 7.3), 4.03 (1H, t, *J* 6.8), 2.66 (1H, m), 2.53 (1H, m), 2.25 (3H, s), 1.83−1.24 (4H, m), 0.90 (3H, t, *J* 7.2), minor diastereomer 6.11 (1H, d, *J* 3.0), 5.92 (1H, d, *J* 3.0), 2.29 (3H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ major diastereomer 152.2, 150.9, 143.1, 134.8, 128.1, 127.2, 126.5, 117.2, 108.2, 105.9, 85.2, 55.6, 38.5, 35.4, 19.1, 14.0, 13.5, minor diastereomer 153.3, 134.5, 117.4, 107.8, 85.3, 58.5, 19.0; MS (CI) *m*/*z* (relative intensity) 166 (80), 135 (100); HRMS calcd for $C_{19}H_{26}NO_2$ (MH) 300.1963, found 300.1964.

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1-phenyl-3-but-1-enylamine 6a. (a) Obtained by the addition of methyllithium to the cinnamaldoxime **5** as a colorless oil (95%, 92% de): $[\alpha]^{20}_D$ +87.4 (*c* 1, CH_2Cl_2); IR (film) 3252, 2959 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.27 (10H, m), 6.47 (1H, d, *J* 16.1), 6.03 (1H, dd, *J* 7.1, 16.1), 5.18 (1H, br s), 4.58 (1H, dd, *J* 5.8, 7.6), 3.75 (1H, m), 1.80 (1H, m), 1.63−1.27 (3H, m), 1.26 (3H, d, *J* 6.4), 0.91 (3H, t, *J* 7.2), minor diastereomer 6.51 (1H, d, *J* 15.1), 6.20 (1H, dd, *J* 7.1, 15.1), 1.15 (3H, d, *J* 6.4), 0.81 (3H, t, *J* 7.2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.6, 137.1, 131.2, 130.8, 128.4, 128.2, 127.4, 127.2, 126.6, 126.3, 85.4, 58.5, 38.7, 19.2, 18.6, 14.0; MS (EI) *m*/*z* (relative intensity) 163 (22), 131 (63), 91 (100), 77 (15); HRMS calcd for $C_{20}H_{25}NO$ (M) 295.1936, found 295.1933.

(b) Obtained by the addition of methylmagnesium bromide to the cinnamaldoxime **5** as a colorless solid (41%, 73% de): $[\alpha]^{20}_D$ +64.3 (*c* 1, CH_2Cl_2).

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1-phenyl-3-hept-1-enylamine 6b. (a) Obtained by the addition of *n*-butyllithium to the cinnamaldoxime **5**, as a colorless solid (95%, 92% de), recrystallized from light petroleum: mp 47−49 °C; $[\alpha]^{20}_D$ +57.3 (*c* 2, $CHCl_3$); IR (CH_2Cl_2) 3028, 2957 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.25 (10H, m), 6.46 (1H, d, *J* 15.9), 5.96 (1H, dd, *J* 8.4, 15.9), 4.57 (1H, dd, *J* 5.9, 7.6), 3.54 (1H, m), 1.93−1.28 (10H, m) 0.89 (6H, 2 x t), minor diastereomer 6.49 (1H, d, *J* 15.9), 6.12 (1H, dd, *J* 8.4, 15.9); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.5, 137.0, 132.2, 130.1, 128.4, 128.2, 127.3, 127.2, 126.6, 126.3, 85.3, 63.7, 38.6, 32.2, 28.0, 22.7, 19.2, 14.0, 13.9; MS (EI) *m*/*z* (relative intensity) 205 (23), 133 (38), 91 (100), 77 (10); HRMS calcd for $C_{23}H_{31}NO$ (M) 337.2405, found 337.2398. Anal. Calcd for $C_{23}H_{31}NO$: C, 81.8; H, 9.3; N, 4.15. Found: C, 81.6; H, 9.1; N, 4.0.

(b) Obtained by the addition of *n*-butylmagnesium bromide to the cinnamaldoxime **5** as a colorless oil (89%, 78% de): $[\alpha]^{20}_D$ +55.1 (*c* 1, CH_2Cl_2).

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-6-methyl-1-phenyl-3-hex-1-enylamine 6c. Obtained by the addition of isobutyllithium to the cinnamaldoxime **5** as a colorless solid (93%, 92% de): mp 61−63 °C, $[\alpha]^{20}_D$ +43.6 (*c* 1.42, CH_2Cl_2); IR (CH_2Cl_2) 3030, 2956 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.26 (10H, m), 6.49 (1H, d, *J* 16.0), 5.97 (1H, dd, *J* 8.3, 16.0), 5.15 (1H, br s), 4.57 (1H, t, *J* 7.4), 3.66 (1H, m), 1.81−1.12 (7H, m), 0.91 (9H, m), minor diastereomer 6.17 (1H, dd, *J* 8.3, 16.0); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.2, 137.0, 132.1, 130.5, 128.4, 128.2, 127.4, 127.2, 126.7, 126.3, 85.3, 62.0, 41.6, 38.5, 24.8, 23.5, 22.2, 19.2, 14.0; MS (CI) *m*/*z* (relative intensity) 338 (M^+, 12), 149 (100); HRMS calcd for $C_{23}H_{32}NO$ (MH) 338.2484, found 338.2484.

(3*S*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1,3-diphenyl-3-prop-1-enylamine 6d. (a) Obtained by the addition of phenyllithium to the cinnamaldoxime **5** as a colorless oil (76%, 90% de): $[\alpha]^{20}_D$ +43.0 (*c* 2.58, $CDCl_3$); IR (film) 2957, 1600 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.40 (15H, m), 6.49 (1H, d, *J* 15.9), 6.23 (1H, dd, *J* 8.3, 15.9), 5.48 (1H, br s), 4.81 (1H, d, *J* 8.4), 4.48 (1H, dd, *J* 5.9, 7.6), 1.74−0.81 (4H, m), 0.73 (3H, t, *J* 8.0), minor diastereomer 4.63 (1H, dd, *J* 8.3, 15.9); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.1, 141.5, 136.9, 132.2, 128.9, 128.4, 128.3, 128.3, 127.8, 127.6, 127.4, 127.3, 126.7, 126.4, 85.3, 68.0, 38.5, 18.8, 13.8; MS (EI) *m*/*z* (relative intensity) 357 (M^+, 4), 193 (100), 133 (74), 91 (86), 77 (32); HRMS calcd for $C_{25}H_{27}NO$ (M) 357.2093, found 357.2097.

(b) Obtained by the addition of phenylmagnesium bromide to the cinnamaldoxime **5** as a colorless oil (69%, 80% de): $[\alpha]^{20}_D$ +39.0 (*c* 1, CH_2Cl_2).

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1-phenyl-3-pent-1-enylamine 6e. Obtained by the addition of ethylmagnesium bromide to the cinnamaldoxime **5** as a colorless solid (91%, 71% de): mp 56−57 °C; $[\alpha]^{20}_D$ +42.6 (*c* 1.32, CH_2Cl_2); IR (CH_2Cl_2) 3250, 2960, 1599 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.31 (10H, m), 6.54 (1H, d, *J* 16.0), 6.00 (1H, dd, *J* 7.8, 16.0), 5.26 (1H, br s), 4.60 (1H, dd, *J* 6.0, 7.4), 3.50 (1H, m), 1.81 (2H, m), 1.63−1.29 (4H, m), 0.94 (6H, 2 × t, *J* 7.4), minor diastereomer 6.55 (1H, d, *J* 16.0), 6.17 (1H, dd, *J* 7.8, 16.0), 0.87 (3H, t, *J* 7.4); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ major diastereomer 143.0, 137.0, 132.5, 129.6, 128.4, 128.2, 127.4, 127.2, 126.6, 126.3, 85.5, 65.2, 38.6, 25.3, 19.2, 14.0, 10.2, minor diastereomer 132.0, 130.9, 85.5, 65.5, 38.7, 25.1, 19.1, 10.4; MS (CI) *m*/*z* (relative intensity) 280 (15), 149 (100); HRMS calcd for $C_{21}H_{28}NO$ (MH) 310.2171, found 310.2171.

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-1,4-diphenyl-3-but-1-enylamine 6f. Obtained by the addition of benzylmagnesium bromide to the cinnamaldoxime **5** as a colorless solid (34%, 72% de): mp 81−83 °C; $[\alpha]^{20}_D$ +45.7 (*c* 0.7, CH_2Cl_2); IR (CH_2Cl_2) 3028, 2958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ major diastereomer 7.33 (15H, m), 6.45 (1H, d, *J* 16.0), 6.12 (1H, dd, *J* 7.7, 16.0), 5.40 (1H, br s), 4.65 (1H, dd, *J* 6.3, 7.4), 3.81 (1H, m), 3.17 (1H, dd, *J* 6.6, 13.4), 2.85 (1H, dd, *J* 6.6, 13.4), 1.89 (1H, m), 1.64−1.32 (3H, m), 0.97 (3H, t, *J* 7.4), minor diastereomer 6.50 (1H, d, *J* 16.0), 6.21 (1H, dd, *J* 7.7, 16.0),

0.91 (3H, t, *J* 7.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ major diastereomer 143.3, 138.9, 137.4, 132.7, 130.0, 129.7, 128.8, 128.8, 128.7, 127.8, 127.0, 126.7, 126.6, 86.0, 65.1, 39.6, 39.0, 19.6, 14.4, minor diastereomer 132.4, 130.4, 65.1, 39.4, 14.5; MS (CI) *m*/*z* (relative intensity) 372 (MH^+, 9), 149 (100); HRMS calcd for $C_{26}H_{30}NO$ (MH) 372.2327, found 372.2327.

(3*R*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-3-methyl-1-phenyl-3-hept-1-enylamine 11. Obtained by the addition of *n*-butyllithium to (*E*)-benzylideneacetone oxime **9** as a colorless oil (53%, ~80% de): $[\alpha]^{20}_D$ +51.4 (*c* 1, CH_2Cl_2); IR (film) 3029, 2958 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.32 (10H, m), 6.44 (1H, d, *J* 16.4), 6.21 (1H, d, *J* 16.4), 5.00 (1H, br s), 4.59 (1H, dd, *J* 5.2, 7.6), 1.76 (1H, m), 1.56 (3H, m), 1.34 (2H, m), 1.30 (3H, s), 0.92 (3H, t, *J* 7.1), minor diastereomer 6.30 (1H, d, *J* 16.4); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ major diastereomer 143.5, 137.5, 135.4, 128.5, 128.4, 128.2, 127.1, 126.5, 126.2, 85.4, 61.0, 39.0, 37.8, 26.0, 23.3, 22.2, 19.2, 14.0, minor diastereomer 22.4; MS (CI) *m*/*z* (relative intensity) 352 (MH^+, 5), 202 (95), 150 (100); HRMS calcd for $C_{24}H_{34}NO$ (MH) 352.2640, found 352.2640.

(3*S*,1′*R*)-(+)-*N*-(1-Phenylbutoxy)-3-methyl-1-phenyl-3-hept-1-enylamine 12. Obtained by the addition of *n*-butyllithium to (*Z*)-benzylideneacetone oxime **10** as a colorless oil (36%, 77% de): $[\alpha]^{20}_D$ +52.3 (*c* 1.84, CH_2Cl_2); IR (film) 3029, 2958 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ major diastereomer 7.32 (10H, m), 6.44 (1H, d, *J* 16.4), 6.28 (1H, d, *J* 16.4), 5.00 (1H, br s), 4.59 (1H, dd, *J* 5.2, 7.6), 1.76 (1H, m), 1.56 (3H, m), 1.34 (2H, m), 1.30 (3H, s), 0.92 (3H, t, *J* 7.1), minor diastereomer 6.21 (1H, d, *J* 16.4); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.7, 137.7, 135.5, 128.5, 128.4, 128.3, 127.2, 126.6, 126.3, 85.6, 61.2, 39.2, 37.9, 26.2, 23.4, 22.5, 19.3, 14.2.

General Method for *N*-Cbz-Protected Amines 7 by N−O Bond Cleavage. Zinc dust (8 g, 122 mmol) was added to a solution of chiral hydroxylamine (3.1 mmol) in acetic acid and water (20 mL 1:1). The mixture was placed in a sonic bath at 40 °C for 2 h. The solution was filtered, ether (50 mL) and water (50 mL) were added, the layers were separated, and the aqueous layer was washed with further portions of ether and dichloromethane. The aqueous layer was basified with sodium hydroxide to pH 8 and further extracted with dichloromethane (2 × 30 mL). The combined organic extracts were evaporated, and THF/water (100 mL 1:1) was added to the residue. Sodium carbonate (1.27 g, 12 mmol) was added, the mixture was cooled to 0 °C, benzylchloroformate (0.6 mL, 4 mmol) was then added dropwise, and the mixture was allowed to warm to room temperature and was stirred for 12 h. The THF was removed in vacuo, ether (50 mL) was added, the layers were separated, and the aqueous layer was washed with further portions of ether. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Column chromatograpy of the residue on silica gel (ether−light petroleum 1:6) furnished the *title compound*.

(*R*)-(+)-*N*-(Benzyloxycarbonyl)-1-phenyl-3-but-1-enylamine 7a. Obtained from the cleavage of hydroxylamine **6a** and subsequent N-protection as a colorless solid (31%): mp 89−91 °C; $[\alpha]^{20}_D$ +48.8 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) 3309, 2974, 1681 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (10H, m), 6.53 (1H, d, *J* 15.8), 6.16 (1H, dd, *J* 15.8, 5.8), 5.15 (2H, s), 4.50 (1H, br s), 4.50 (1H, br m), 1.35 (3H, d, *J* 6.8); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 155.8, 136.6, 136.5, 131.1, 129.5, 128.5, 128.3, 128.0, 127.5, 126.6, 126.4, 66.7, 48.4, 21.0; MS (EI) *m*/*z* (relative intensity) 282 (MH^+, 19), 91 (100); HRMS calcd for $C_{18}H_{19}NO_2$ (M) 281.1416, found 281.1416.

(*R*)-(+)-*N*-(Benzyloxycarbonyl)-1-phenyl-3-hept-1-enylamine 7b. Obtained from the cleavage of hydroxylamine **6b** and subsequent N-protection as a colorless solid (82%): mp 80−83 °C; $[\alpha]^{20}_D$ +39.0 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) 3313, 2955, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (10H, m), 6.59 (1H, d, *J* 15.9), 6.13 (1H, dd, *J* 6.4, 15.9), 5.18 (2H, s), 4.85 (1H, br s), 4.38 (1H, br s), 1.67 (2H, m), 1.41 (4H, m), 0.95 (3H, t, *J* 6.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 137.2, 137.0, 130.7, 128.9, 128.5, 127.9, 126.8, 67.1, 53.6, 35.7, 28.3, 22.9, 14.4; MS (EI) *m*/*z* (relative intensity) 324 (MH^+, 4), 91 (100); HRMS calcd for $C_{21}H_{25}NO_2$ (M) 323.1885, found 323.1888.

(*R*)-(+)-*N*-(Benzyloxycarbonyl)-6-methyl-1-phenyl-3-hex-1-enylamine 7c. Obtained from the cleavage of hydroxylamine **6c** and subsequent N-protection as a colorless solid (86%): mp 54−56 °C; $[\alpha]^{20}_D$ +34.8 (*c* 2, CH_2Cl_2); IR (CH_2Cl_2) 3320, 2956, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (10H, m), 6.54 (1H, d, *J* 16.0), 6.09 (1H, dd, *J* 6.1, 16.0), 5.15 (2H, s), 4.83 (1H, br s), 4.42 (1H, m), 1.71 (1H, m), 1.48 (2H, m), 0.96 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 137.2, 131.0, 130.6, 129.5, 128.9, 1287, 128.5, 128.1, 127.1, 125.7, 67.1, 51.9, 45.2, 25.2, 23.1; MS (CI) *m*/*z* (relative intensity) 324 (MH^+, 12), 173 (100); HRMS calcd for $C_{21}H_{26}NO_2$ (MH) 324.1963, found 324.1964.

(*S*)-(+)-*N*-(Benzyloxycarbonyl)-1,3-diphenyl-3-prop-1-enylamine 7d. Obtained from the cleavage of hydroxylamine **6d** and subsequent N-protection as a colorless solid (66%): mp 110−111 °C; $[\alpha]^{20}_D$ +8.0 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) 3317, 2955, 1689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (15H, m), 6.64 (1H, d, *J* 15.9), 1H, dd, *J* 6.0, 15.9), 5.60 (1H, br s), 5.32 (1H, br s), 5.19 (2H, dd, *J* 12.2, 16.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 139.6, 135.0, 129.9, 127.8, 127.4, 127.2, 127.1, 127.0, 126.7, 126.4, 126.3, 125.6, 125.2, 65.6, 55.5; MS (CI) *m*/*z* (relative intensity) 344 (MH^+, 12), 193 (100), 91 (31); HRMS calcd for $C_{23}H_{22}NO_2$ (MH) 344.1650, found 344.1651.

(*R*)-(+)-*N*-(Benzyloxycarbonyl)-3-methyl-1-phenyl-3-hept-1-enylamine 13. Obtained from the cleavage of hydroxylamine **11** and subsequent N-protection as a colorless oil (70%): $[\alpha]^{20}_D$ +0.24 (*c* 6.6, CH_2Cl_2); IR (film) 3345, 2956, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (10H, m), 6.48 (1H, d, *J* 16.3), 6.36 (1H, d, *J* 16.3), 5.15 (2H, s), 4.96 (1H, br s), 1.86 (2H, m), 1.57 (3H, s), 1.36 (4H, m), 0.96 (3H, t, *J* 6.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 137.5, 137.2, 135.6, 129.2, 128.9. 128.5, 128.4, 128.1, 127.8, 126.9, 66.7, 56.8, 40.6, 26.5, 25.4, 23.4, 14.5; MS (CI) *m*/*z* (relative intensity) 338 (MH^+, 19), 187 (100); HRMS calcd for $C_{22}H_{28}NO_2$ (MH) 338.2120, found 338.2120.

(*S*)-(+)-*N*-(Benzyloxycarbonyl)-3-methyl-1-phenyl-3-hept-1-enylamine 14. Obtained from the cleavage of hydroxylamine **12** and subsequent N-protection as a colorless oil (66%).

General Procedure for the Synthesis of *N*-Cbz-amino Acids 8 by Oxidative Cleavage. The protected carbamate **7** (1.6 mmol) was stirred at room temperature in CCl_4 (2 mL), CH_3CN (2 mL), and water (3 mL) with periodic acid (6.6 mmol) for 10 min. $RuCl_3 \cdot 3H_2O$ (0.03 mmol) was added and the solution heated at 50 °C for 24 h. Water (20 mL) and dichloromethane (20 mL) were added, the layers were separated. The aqueous layer was exhaustively extracted with dichloromethane (4 × 20 mL) and the organic layers were combined, dried, filtered, and evapoared. The residue was passed through a short silica gel column (ether−light petroleum (1:1) as eluent) to yield a clear oil. The oil was dissolved in saturated aqueous sodium bicarbonate solution (15 mL) that was washed with ether (2 × 10 mL), the aqueous layer was acidified (pH 1) with concentrated hydrochloric acid and extracted with dichloromethane (3 × 20 mL), and the combined organic extracts were dried, filtered and evaporated to furnish the *title compound*.

(*R*)-(+)-*N*-Cbz-alanine 8a. Obtained from the double-bond cleavage of protected amine **7a** as a colorless solid (25%): mp 79−80 °C (lit.[17] mp 86−87 °C); $[\alpha]^{20}_D$ +12.8 (*c* 0.36, AcOH) (lit.[17] $[\alpha]^{25}_D$ +13.9 (*c* 2, AcOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (1H, br s), 7.31 (5H, m), 5.39 (1H, br d, *J* 6.7), 5.13 (2H, s), 4.42 (1H, m), 1.46 (3H, d, *J* 7.2).

(*R*)-(+)-*N*-Cbz-norleucine 8b. Obtained from the double-bond cleavage of protected amine **7b** as a colorless solid (57%): mp 51−52 °C (lit.[18] mp 56−58 °C); $[\alpha]^{20}_D$ +8.2 (*c* 1, MeOH) (lit.[17] $[\alpha]^{20}_D$ +5.6 (*c* 1, MeOH)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (5H, m), 5.25 (1H, br d, *J* 6.7), 5.13 (2H, s), 4.40 (1H, m), 1.87 (1H, m), 1.70 (1H, m), 1.35 (4H, m), 0.90 (3H, br t).

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(*R*)-(+)-*N*-Cbz-leucine 8c. Obtained from the double-bond cleavage of protected amine **7c** as a colorless oil (36%): $[\alpha]^{20}_D$ +12.5 (*c* 1, EtOH) (lit.[17] $[\alpha]^{20}_D$ +14.7 (*c* 1, EtOH)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.19 (1H, br d, *J* 6.7), 5.12 (2H, s), 4.42 (1H, m), 1.62 (3H, m), 0.95 (6H, 2d).

(*R*)-(−)-*N*-Cbz-phenylglycine 8d. Obtained from the double-bond cleavage of protected amine **7d** as a colorless solid (55%): mp 127−128 °C (lit.[19] 127.5−129.5 °C); $[\alpha]^{20}_D$ −110.0 (*c* 4, EtOH) (lit.[19] $[\alpha]^{24}_D$ −121.0 (*c* 0.48, EtOAc)); ^{1}H NMR (250 MHz, $CDCl_3$) δ rotamers 7.34 (10H, m), 5.86 (1H, br d, *J* 6.2), 5.40 (1H, br d, *J* 6.4), 5.10 (2H, s).

(*R*)-(−)-2-Benzyloxycarbonylamino-2-methylhexanoic Acid 15 (*N*-Cbz-α-methylnorleucine). Obtained from the double-bond cleavage of protected amine **13** as a colorless oil (64%): $[\alpha]^{20}_D$ −4.1 (*c* 1.6, EtOH); IR (film) 3346, 2959, 1713 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (5H, m), 5.63 (1H, br s), 5.10 (2H, d, *J* 7.1), 2.10 (1H, m), 1.84 (1H, m), 1.60 (3H, s), 1.25 (4H, m), 0.87 (3H, t, *J* 6.6); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 179.5, 179.1, 128.5, 128.4, 127.9, 67.2, 66.5, 36.6, 26.0, 23.2, 22.5, 13.8; MS (EI) *m*/*z* (relative intensity) 279 (M^+, 3), 91 (100); HRMS calcd for $C_{15}H_{21}NO_4$ (M) 279.1470, found 279.1476.

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Supporting Information Available: Crystallographic data for (*R*)-*O*-(1-phenylbutyl) cinnamaldoxime **5** and ^{13}C NMR spectra of **3**, **4**, **6**, **7**, **9**, **10**−**13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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