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Synthesis of *E*-vinylogous (*R*)-amino acid derivatives via metal-catalyzed allylic substitutions on enzyme-derived substrates

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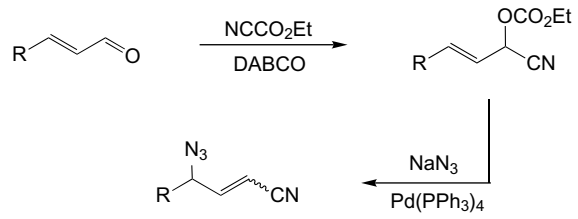
Abstract—Oxynitrilase-derived allylic (*R*)-cyanohydrin carbonates **3** and allylic (*R*)-α-hydroxy ester carbonates **6** were examined as substrates for a palladium(0)-catalyzed allylic azidation reaction. The enantioselectivities and *cis*/*trans* diastereoselectivities of the concomitant 1,3-chirality transposition step were studied. The cyano carbonates **3a**–**c** were found to be unimpressive substrates producing γ-azido-α,β-unsaturated nitriles **4a**–**c** with *cis*/*trans* ratios that approached unity and gave enantiomeric excesses that ranged from 57% to 85%. In contrast, ester carbonates **6a** and **b** were excellent substrates for the reaction exclusively affording *trans* substitution products **7a** and **b** in identical enantiomeric excesses of 95% ee.

1. Introduction

The enantioselective preparation of natural and unnatural amino acids has been the subject of intense fundamental research.[1] Our own interest in this area grew from the notion that γ-azido-α,β-unsaturated nitriles ought to provide straightforward access to γ-amino-α,β-unsaturated carboxylic acids,[2,3] an intriguing family of conformationally restricted amino acids. The incorporation of vinylogous amino acids into peptides,[4] with special attention toward conformational analysis and structure,[5] has been described. Recently, we reported[6] an efficient, two-step route to a racemic series of γ-azido-α,β-unsaturated nitriles (Scheme 1). The methodology involves the concomitant cyanation—ethoxycarbonylation of an α,β-unsaturated aldehyde followed by a regiospecific palladium(0)-catalyzed allylic azidation of the intermediate cyanohydrin carbonate. The resulting γ-azido substitution products were isolated as *cis*/*trans* mixtures with the *E*-isomer in predominance. Overall yields for the sequence exceeded 80%. Herein we report our findings on an asymmetric variant of this reaction series.



Scheme 1. Racemic preparation of γ-azido-α,β-unsaturated nitriles.

2. Results and discussion

2.1. Synthesis of (*E*)(*R*)-γ-azido-α,β-unsaturated nitriles

Our overarching strategy for the enantioselective preparation of (*R*)-γ-azido-α,β-unsaturated nitriles **4** blends the natural enantioselectivity of enzymes with the rich chemistry of π-allylpalladium.[7] The enantioselective pathway is outlined in Scheme 2. Although chirality is initially induced at the aldehydic carbon using the almond enzyme (*R*)-oxynitrilase,[8] a subsequent palladium-catalyzed allylic substitution step with an azide ion repositions the stereocenter to the γ-carbon.[9] Table 1 lists the chemical yields and enantiomeric excesses as well as other pertinent data for the intermediates and products associated with the three-step sequence.

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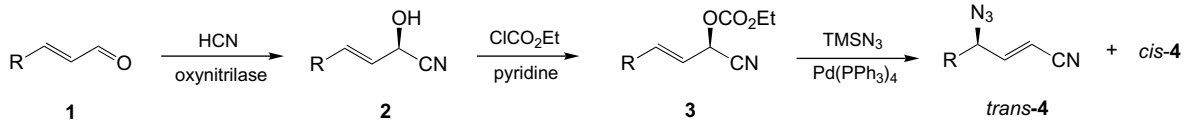
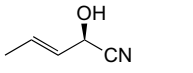
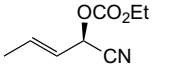
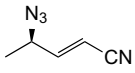
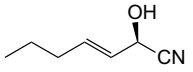
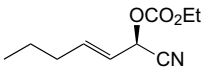
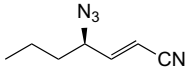
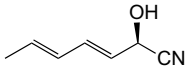
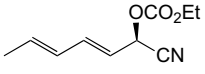
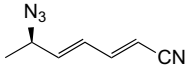
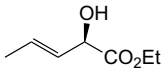
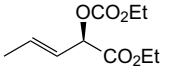
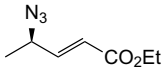
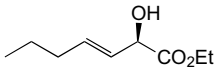
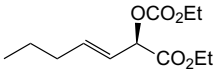
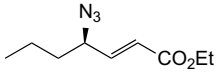


Scheme 2. Enantioselective preparation of (*R*)-γ-azido-α,β-unsaturated nitriles **4**.

Table 1. Two-step conversion of α,β-unsaturated (*R*)-cyanohydrins **2** and (*R*)-α-hydroxy ethyl esters **5** into (*R*)-γ-azido-α,β-unsaturated nitriles **4** and esters **7** via a palladium(0)-catalyzed azidation of intermediate allylic carbonates **3** and **6**, respectively

Cyanohydrin[a]	% Ee (yield[b]/%)	Carbonate[a]	% Ee (yield[b]/%)	γ-Azide[a,c]	% Ee[d] (yield[e]/%)
 **2a**	>95 (91)	 **3a**	>95 (95)	 *trans*-**4a**	81 (87)
 **2b**	>95 (77)	 **3b**	>95 (87)	 *trans*-**4b**	85 (85)
 **2c**	>95 (77)	 **3c**	>95 (89)	 *trans, trans*-**4c**	57 (86)
 **5a**	>95 (88)	 **6a**	>95 (91)	 **7a**	95 (85)
 **5b**	>95 (85)	 **6b**	>95 (91)	 **7b**	95 (84)

[a] Compounds **2**, **3**, and **4** are known compounds. Experimentally determined optical rotations for the nitrile products are: **2a**: $[\alpha]_D^{25} = -27.8$ (*c* 1.345, $CHCl_3$); **2b**: $[\alpha]_D^{25} = -22.05$ (*c* 1.680, $CHCl_3$); **2c**: $[\alpha]_D^{25} = -29.2$ (*c* 1.275, $CHCl_3$); **3a**: $[\alpha]_D^{25} = -7.0$ (*c* 1.465, $CHCl_3$); **3b**: $[\alpha]_D^{25} = -12.8$ (*c* 1.370, $CHCl_3$); **3c**: $[\alpha]_D^{25} = -46.0$ (*c* 1.155, $CHCl_3$); **4a**: $[\alpha]_D^{25} = -38.7$ (*c* 1.870, $CHCl_3$); **4b**: $[\alpha]_D^{25} = +16.0$ (*c* 1.735, $CHCl_3$); **4c**: $[\alpha]_D^{22} = -6.9$ (*c* 0.57, $CHCl_3$). For the specific rotations of ester products **5**, **6**, and **7** see Experimental.

[b] Isolated yields.

[c] Nitrile products are a mixture of *E*–*Z* isomers. Only the major *E*-isomer displayed.

[d] Enantiomeric excess data for *E*-isomer only.

[e] Yield data for nitrile products based upon combined mass of *E*–*Z* isomers.

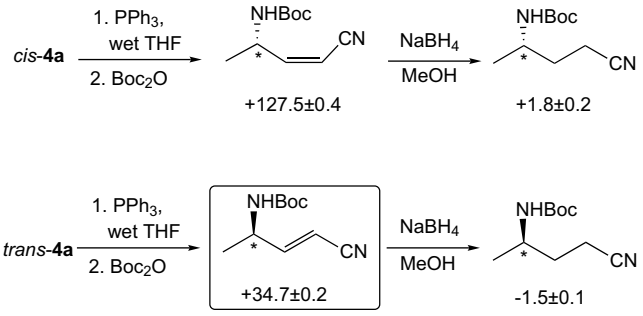
Oxynitrilase [EC 4.1.2.10][10] is well suited for our needs since it is convenient, robust, and accepts a wide range of substrates in organic solvents.[11] Although the purified enzyme is an article of commerce, we found it more prudent to prepare fresh, active oxynitrilase from defatted almond meal. This in-house enzyme preparation efficiently catalyzed[12] the asymmetric hydrocyanation of unsaturated aldehydes **1** with HCN and oxynitrilase in diisopropyl ether. (*R*)-Cyanohydrins **2** were isolated in chemical yields that range from 77% to 91% and enantiomeric excesses that exceed 95% in all cases (vide infra).

Conversion of **2** into the corresponding cyanohydrin carbonate **3** was executed in high yield without noticeable loss of enantiopurity using ethyl chloroformate in pyridine at 0 °C. This observation was confirmed by 400 MHz NMR experiments on **3** complexed with an Eu-derived chiral shift reagent.[13] Previously, we reported that these unsaturated carbonates **3** are excellent substrates for palladium(0)-catalyzed allylic substitutions.[14] Azidations performed with NaN_3 in THF–H_2O (1:1) under these catalytic conditions[15] are completely regioselective as reorganized γ-azido-α,β-unsaturated nitriles **4** are the only substitution products isolated. The thermodynamic forces that favor conjugative overlap are apparently responsible for the observed regiochemistry.[16] In the current study, however, the aqueous azidation procedure has been abandoned in favor of the operationally more practical anhydrous conditions of $TMSN_3$ in CH_2Cl_2.[17]

2.2. Stereochemical investigations

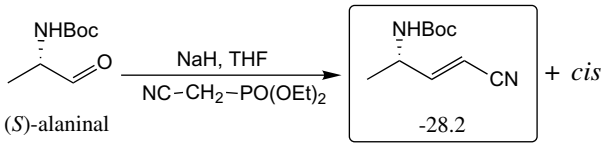
The metal-catalyzed allylic substitution with an azide ion is the linchpin reaction for the three-step sequence. Due to the success of this methodology depending heavily on the enantiofidelity of the 1,3-transposition machinery, a clear understanding of this mechanism was warranted. We decided to first examine the relative configurations of transposed *cis*- and *trans*-γ-azido isomers **4a** following the synthetic strategy outlined in Scheme 3. The reaction sequence of the Staudinger reduction,[18] Boc protection, and conjugated double-bond reduction[19] yielded both

saturated nitriles uneventfully. With opposite but arguably identical rotations within the margins of standard deviation, we concluded that the Boc-protected 4-aminopentanenitrile products were enantiomeric. Although no assumptions could be drawn regarding their absolute configurations based upon these experiments, there is evidence in the literature that palladium-catalyzed azidations reactions occur with retention of configuration.[9]



Scheme 3. Determination of relative configurations for *cis*- and *trans*-**4a**.

The absolute configurations of *cis*-**4a** and *trans*-**4a** were unequivocally established with the stereochemical correlation study illustrated in Scheme 4. Commercially available Boc-protected (*S*)-alaninal was reacted with the Wittig reagent derived from the cyanomethyl phosphonate[20] to afford predominantly the *E*-isomer of (*S*)-4-(*tert*-butoxycarbonylamino)pent-2-enenitrile. Direct comparison of this nitrile with the other bracketed nitrile in Scheme 3 revealed that these two compounds also had opposite rotations. This outcome denoted the (*R*)-configuration for *trans*-**4a**, the rearranged azido product. Accordingly, the minor product, *cis*-**4a**, was assigned the (*S*)-configuration by inference. Therefore, the substitutive 1,3-chirality transfer proceeds with retention of configuration for the *trans* product—relative to the displaced carbonate moiety—and with inversion of configuration for the cis product. Incidentally, we attribute the slightly lower specific rotation for the (*S*)-enantiomer in Scheme 4 to the known isomerization mechanisms that can plague *N*-protected α-amino aldehydes.[21]

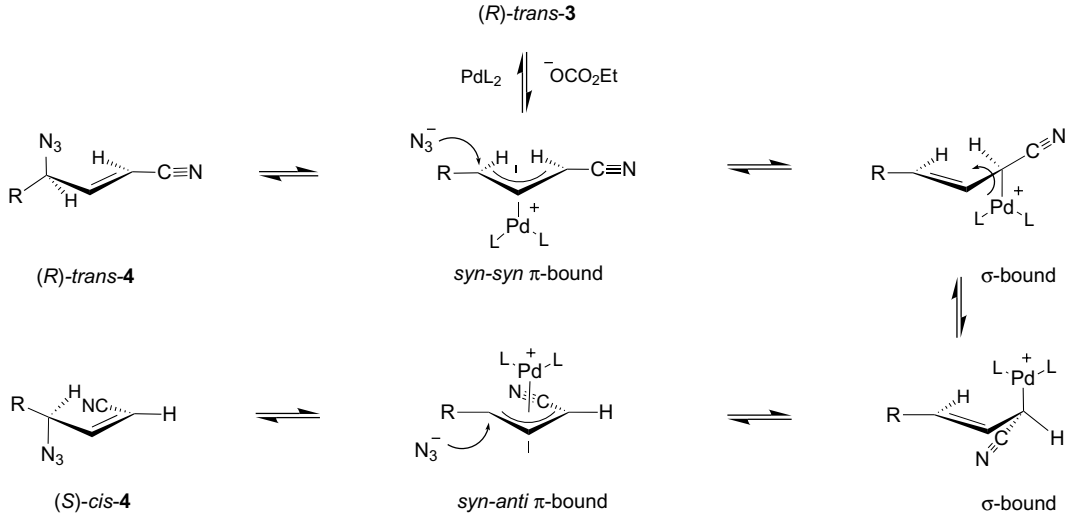


Scheme 4. Stereochemical correlation study.

2.3. Proposed palladium(0)-catalyzed 1,3-chirality transfer mechanism

The preponderance of experimental evidence supports a mechanism[22] of dynamic π–σ–π-isomerization between two competing π-allylpalladium complexes as represented in Scheme 5. The process begins with the stereoselective oxidative addition of a reactive palladium(0) catalyst to the (*R*)-*trans*-**3** carbonate, which necessarily leads to the corresponding *syn–syn* metal π-allyl complex. The *syn–syn* nomenclature refers to the relationship between the π-allyl's two terminal substituents and its methinyl hydrogen (not shown) on the middle carbon.[23] With the ejection of the carbonate anion, a separate sequence of cascading events is set into motion: First, the carbonate moiety decomposes into CO_2 and ethoxide rendering the step irreversible; second, the liberated ethoxide attacks $TMSN_3$ on silicon displacing the azide ion; and lastly, the nucleophilic azide is trapped by the cationic *syn–syn* π-allylpalladium complex affording the (*R*)-*trans*-**4** product. Since nucleophilic attack selectively occurs at the distal end of the π-allyl system on the face opposite the metal, only the γ-substituted product of the (*R*)-configuration is obtainable via this route.

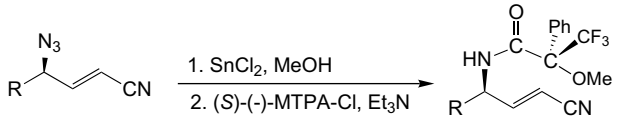
The (*S*)-*cis*-**4** product is accessible via the opposing pathway that involves a π–σ–π-interconversion mechanism of equilibrating π-allylpalladium complexes. The



Scheme 5. Proposed palladium(0)-catalyzed 1,3-chirality transfer mechanism.

π-bound *syn–syn* complex is also in dynamic equilibrium with its σ-bound counterpart. A subsequent 180° rotation about the single bond followed by regeneration of the planar π-allyl species leads to the *syn–anti* orientation for the metal complex. In general, *syn–anti* structures are considered higher in energy than the corresponding *syn–syn* versions due to increased steric congestion in the bay region of the π-allyl. As a result, *E*-products tend to dominate over the thermodynamically less-favorable *Z*-products in palladium-catalyzed allylic substitutions. In this case, however, the *anti*-substituent is a sleek, sp-hybridized cyano group that points away from the other *anti* group—hydrogen—minimizing the steric interaction between the atoms. Since nucleophilic attack upon the *syn–anti* complex leads inescapably to the (*S*)-*cis*-**4** isomer, we believe this structural anomaly accounts for the unexpectedly high percentage of the *cis*-isomer isolated from the reaction mixture. We have omitted from our analysis any discussion of the *anti–anti* π allyl since it would seem highly unlikely that an appreciable population of this complex would ever form.

The enantiomeric compositions of (*R*)-*trans*-**4a–c** were unequivocally determined by the GC analysis of the corresponding Mosher-derived amides[24] on an HP-101 capillary column. The diastereomers were obtained via a one-pot reductive amination-derivation sequence using the protocol of Evans et al.[25] as described in Scheme 6. Table 1 lists the enantiomeric excesses for (*R*)-*trans*-**4a–c**, which ranged from a low of 57 to a high of only 85%. Clearly, the combination of disappointing enantiomeric excesses and poor control over double-bond stereochemistry compromises the usefulness of this methodology. This prompted us to retreat from our original strategy and seek an alternative tactic.

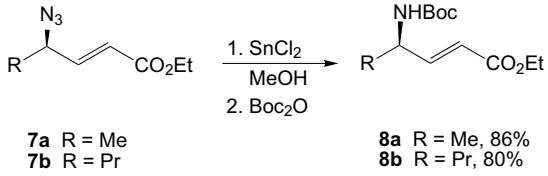


Scheme 6. One-pot reductive amidation of (*R*)-*trans*-**4** with (−)-Mosher's acid chloride.

2.4. Synthesis of (*E*)(*R*)-γ-azido-α,β-unsaturated ethyl esters

We were confident that the putative *syn–anti* π-complex was at the root of our problems. We surmised that a more bulky group, such as an sp^2-hybridized alkoxycarbonyl moiety, in place of the linear cyano function would raise the energy of the π-allyl complex disfavoring the *cis* pathway. A synthetic plan was devised and implemented according to Scheme 7. The conversion of (*R*)-*trans*-cyanohydrins **2a** and **b** into α-hydroxy esters **5a** and **b** with ethanolic HCl was accomplished[26] in >80% yield without observable racemization. Subsequent ethoxycarbonylation of the α-hydroxy functions on **5a** and **b** once more configured the alkenes for the allylic substitution step. To our delight, the palladium-catalyzed azidation of **6a** and **b** afforded the unsaturated γ-azido esters **7a** and **b** with exclusive *trans*-diastereoselectivity. This exciting result suggested that the problematic π–σ–π-isomerization mechanism had been controlled, which lent support to our hypothesis.

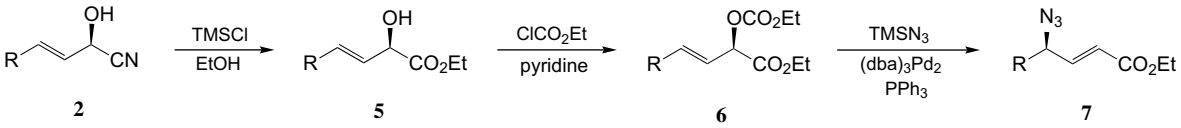
The enantiopurities of the azido esters **7** were quantified with the same reductive-amidation procedure used for the azido nitriles **4**. Excellent levels of enantiomeric enrichment were achieved for esters **7a** and **b** as corroborated by the identical values of 95% ee (see Table 1). We believe that these outcomes provide consummate proof-of-concept for this novel methodology. Moreover, the simple one-pot transformation of azido esters **7** into Boc-protected amino esters **8** (Scheme 8) ultimately validates our contention that *E*-vinylogous (*R*)-amino acids are accessible from α,β-unsaturated (*R*)-cyanohydrins.



Scheme 8. Preparation of Boc-protected (*E*)-vinylogous (*R*)-amino acid ethyl esters **8**.

3. Conclusions

We have investigated the enantiofidelity of palladium-catalyzed allylic substitution/azidation reactions that involve the transfer of chirality across the π-allyl systems of conjugated nitriles and esters. Oxynitrilase-derived allylic (*R*)-cyanohydrin carbonates **3** and allylic (*R*)-α-hydroxy ester carbonates **6** were found to be efficient progenitors of asymmetry to chiral π-allylpalladium complexes. Although allylic carbonates **3** and **6** afforded γ-azido products **4** and **7** in high chemical yields, the enantioselectivities and *cis*/*trans* diastereoselectivities of these compounds varied greatly. The nitrile substrates **3a–c** accrued some disappointing results in both categories. On the other hand, ester substrates **6a** and **b** gave superior results as underscored by the duplicate values of 95% ee and exclusively *trans* double bond



Scheme 7. Enantioselective preparation of (*E*)(*R*)-γ-azido-α,β-unsaturated ethyl esters **7**.

geometries. Moreover, stereochemical correlation experiments clearly showed that the (*R*)-configurational asymmetry initially induced by oxynitrilase in the aldehydic carbon was faithfully transmitted to the γ-azido position of *trans* products. Finally, through the judicious replacement of a linear cyano function with a trigonal ester moiety, we ostensibly shifted the equilibrium of the π–σ–π isomerization mechanism to a point where only *trans* products were realized. The broader significance of this new methodology and its application to natural products synthesis are currently under investigation.

4. Experimental

4.1. General methods

All reactions were carried out under nitrogen or argon unless otherwise indicated. Aldehydes were purchased from commercial sources, distilled, and stored under nitrogen. Reagent grade solvents were further purified by simple distillation under nitrogen as follows: MeOH and EtOH were distilled from magnesium turnings and iodine, pyridine and CH_2Cl_2 were refluxed and distilled from CaH_2, and THF was distilled from a deep blue solution of sodium benzophenone ketyl. TMSCl was distilled as needed and ethyl chloroformate was used as received. NMR spectra were acquired at 300 or 400 MHz on Bruker Avance spectrometers with $CDCl_3$ as the solvent. Optical rotations were measured in $CHCl_3$ on a JASCO 360-DIP polarimeter in water-jacketed microcells and FTIR spectra were collected on a model 8300 Shimadzu spectrophotometer. Diastereomeric ratios of the Mosher-derived amides were determined on a Hewlett-Packard Series II 5890 gas chromatograph equipped with a 25 m × 0.2 mm o.d. HP-101 capillary column. TLC analyses were done on glass-backed silica plates coated with a 0.25 mm thickness of silica gel 60 F_{254} from J. T. Baker. Chromatographic separations were performed on silica gel-coated glass rotors (1, 2, or 4 mm layers) via radial chromatography on a Harrison Research Chromatotron. Elemental analyses were obtained at Desert Analytics and HRMS spectra were recorded at the University of California, Riverside Mass Spectrometry Facility.

CAUTION: Azido compounds may represent an explosion hazard when concentrated under vacuum or stored neat. A safety shield and appropriate handling procedures are recommended.

4.2. General procedure for the preparation of cyanohydrins 2 via asymmetric hydrocyanation of unsaturated aldehydes 1 with HCN and oxynitrilase

4.2.1. (*E*)(*R*)-Crotonaldehyde cyanohydrin 2a. An ice-cold solution of KCN (6 g, 107.1 mmol) in water (45 mL) was acidified with HCl (6 M, 6 mL) to a pH of 1. The solution was extracted (3 × 15 mL) with isopropyl ether, and the organic layers collected. In a separate Erlenmeyer flask, almond meal (6 g, ground to a fine powder and defatted with three washes with EtOAc) was wetted with 0.02 M pH 5.5 citrate buffer (6 mL). The resulting thick paste was pressed against the side of the flask and crotonaldehyde (1.5 mL, 1.25 g, 17.8 mmol) then added dropwise to the paste. The isopropyl ether/HCN solution was carefully poured into the flask containing the almond mixture to initiate the reaction. The flask was partially submerged in a 2 °C constant-temperature bath and monitored via TLC (3:1 hexanes/EtOAc; R_f 0.33). After approximately 12 h, the reaction mixture was diluted by the addition of ethyl ether (15 mL) and passed through a short plug of SiO_2 layered with $MgSO_4$ (1:4 $MgSO_4/SiO_2$). The filtrate was concentrated in vacuo via rotary evaporation and the crude oil purified via radial chromatography (4 mm SiO_2 plate; 4:1 hexanes/EtOAc) to afford 1.25 g (72%) of colorless, clear oil.

Unsaturated cyanohydrins **2a**, **2b**, and **2c** have been previously prepared with oxynitrilase.[27,28]

4.3. Representative example for the preparation of unsaturated ethyl carbonates 3 and 6 from cyanohydrins 2 and α-hydroxyesters 5, respectively

4.3.1. Ethyl (*E*)(*R*)-2-hydroxypent-3-enoate ethyl carbonate 6a. To an ice-cold, stirred solution (1 M) of α-hydroxyester **5a** (1.25 g, 8.66 mmol) in freshly distilled pyridine was added dropwise (~4 drops/min) ethyl chloroformate (0.50 mL, 1.89 g, 17.3 mmol). The temperature was maintained at 0 °C and the reaction's progress monitored via TLC (6:1 hexanes/EtOAc) until judged complete after 45 min. The reaction mixture was quenched by dilution with ether (50 mL). The organic layer was washed with saturated solutions of NH_4Cl (3 × 15 mL), 0.1 M HCl (3 × 15 mL), and NaCl (1 × 15 mL). The organic phase was dried over $MgSO_4$, concentrated in vacuo, and the crude oil purified via radial chromatography (4 mm SiO_2 plate, 7:1 hexanes/EtOAc) to afford 1.7 g (91%) of colorless, clear oil. R_f 0.39 (SiO_2; 6:1 hexanes/EtOAc); bp (bulb-to-bulb) 70 °C at 0.50 Torr; $[\alpha]_D^{25.0} = -52.1$ (*c* 1.428, $CHCl_3$); ^{1}H NMR δ 6.00 (ddq, *J* = 0.9, 6.6, 15.3 Hz, 1H), 5.57 (ddq, *J* = 1.5, 7.2, 15.3 Hz, 1H), 5.29 (ddq, *J* = 0.9, 0.9, 7.2, 1H), 4.29–4.19 (m, 4H), 1.76 (ddd, *J* = 0.9, 1.5, 6.6 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 168.7, 154.2, 133.4, 122.6, 75.9, 64.5, 61.6, 17.8, 14.1, 14.0; IR (film) 2985, 1755, 1683, 1278, 1195 cm^{-1}; Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.27; H, 7.46.

4.3.2. Ethyl (*E*)(*R*)-2-hydroxyhept-3-enoate ethyl carbonate 6b. R_f 0.35 (SiO_2; 6:1 hexanes/EtOAc); bp (bulb-to-bulb) 90 °C at 0.65 Torr; $[\alpha]_D^{25.0} = -55.4$ (*c* 1.705, $CHCl_3$); ^{1}H NMR δ 5.90 (dt, *J* = 7.2, 15.2 Hz, 1H), 5.48 (dd, *J* = 7.2, 15.2 Hz, 1H), 5.21 (d, *J* = 7.2 Hz, 1H), 4.20–4.11 (m, 4H), 2.00 (dt, *J* = 7.2, 7.6 Hz, 2H), 1.4–1.3 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H) 1.20 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 170.0, 155.3, 139.2, 122.4, 76.5, 65.0, 62.1, 34.6, 21.9, 14.3, 14.2, 13.7; IR (film) 2941, 1751, 1373, 1028 cm^{-1}; Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.88; H, 8.25.

4.4. General procedure for the preparation of γ-azido compounds 4 and 7 via a palladium(0)-catalyzed allylic azidation of carbonates 3 and 6 with $TMSN_3$ in CH_2Cl_2

4.4.1. Ethyl (*E*)(*R*)-4-azidopent-2-enoate 7a. To an ice-cold, stirred 0.3 M solution of allylic carbonate **6a** (107 mg, 0.535 mmol), $TMSN_3$ (0.11 mL, 92.4 mg, 0.80 mmol), and PPh_3 (8.4 mg, 0.032 mmol) in freshly distilled CH_2Cl_2 was added catalytic DBA_3Pd_2 (7.4 mg, 0.008 mmol) in a single portion. The reaction was maintained at 0 °C and monitored via TLC (SiO_2, 1:1 CH_2Cl_2/hexanes). After 1.5 h, the reaction was diluted by the addition of ether and the resulting slurry passed through a short plug of SiO_2 layered with $MgSO_4$ ($MgSO_4/SiO_2$, 1:4) with additional ether. The filtrate was concentrated in vacuo via rotary evaporation, and the crude oil was purified via radial chromatography (2 mm SiO_2 plate; 1:1 CH_2Cl_2/hexanes) to afford 70 mg (84%) of colorless clear oil. R_f 0.35 (SiO_2; 1:1 hexanes/CH_2Cl_2); bp (bulb-to-bulb) 47 °C at 0.50 Torr; $[\alpha]_D^{25.5} = -13.0$ (*c* 0.89, $CHCl_3$); ^{1}H NMR δ 6.78 (dd, J = 6.0, 15.6 Hz, 1H), 5.98 (dd, J = 1.6, 15.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.11–4.20 (m, 1H), 1.33 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 165.8, 145.4, 122.2, 60.7, 57.4, 19.1, 14.2; IR (film) 2984, 2112, 1720, 1661, 1271 cm^{-1}.

4.4.2. Ethyl (*E*)(*R*)-4-azidohept-2-enoate 7b. R_f 0.40 (SiO_2; 1:1 hexanes/CH_2Cl_2); bp (bulb-to-bulb) 50 °C at 0.50 Torr; $[\alpha]_D^{25.2} = 20.0$ (*c* 1.56, $CHCl_3$); ^{1}H NMR δ 6.79 (dd, J = 6.8, 15.6 Hz, 1H), 6.02 (dd, J = 1.2, 15.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.05–3.98 (m, 1H), 1.63–1.56 (m, 2H), 1.50–1.35 (m, 2H), 1.31 (t, J = 6.8 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 166.9, 145.6, 123.8, 62.9, 61.2, 36.3, 19.1, 14.4, 13.8; IR (film) 2963, 2104, 1724, 1659, 1271, 1178, 1040 cm^{-1}.

4.5. Representative example for the preparation of β,γ-unsaturated α-hydroxy ethyl esters 5a and 5b from α,β-unsaturated cyanohydrins 2

4.5.1. Ethyl (*E*)(*R*)-2-hydroxypent-3-enoate 5a. To an ice-cold, stirred 2 M solution of cyanohydrin **2a** (255 mg, 2.62 mmol) in freshly distilled EtOH was added TMSCl (0.565 mL, 478 mg, 3.94 mmol) dropwise. The reaction was maintained at 0 °C and monitored via TLC (6:1 hexanes/EtOAc) for the disappearance of starting material. After the reaction was deemed complete (~21 h), the mixture was diluted with the addition of ether (15 mL) and the insoluble imine salt hydrolyzed by the addition of water (0.25 mL). The aqueous phase was extracted with ether (3 × 15 mL) and the combined extracts washed with brine (1 × 10 mL) and then dried over $MgSO_4$. The organic phase was passed through a short plug of SiO_2 layered with $MgSO_4$ ($MgSO_4/SiO_2$, 1:4) with additional ether, and the filtrate concentrated in vacuo via rotary evaporation. The crude oil was purified via radial chromatography (2 mm SiO_2 plate; 4:1 hexanes/EtOAc) to afford 325 mg (88%) of colorless, clear oil. R_f 0.19 (SiO_2; 6:1 hexanes/EtOAc); bp (bulb-to-bulb) 47 °C at 0.55 Torr; $[\alpha]_D^{25.6} = -70.4$ (*c* 1.50, $CHCl_3$); ^{1}H NMR δ 5.92 (ddq, J = 1.6, 6.4, 15.2 Hz, 1H), 5.38 (ddq, J = 1.6, 6.0, 15.2 Hz, 1H), 4.59 (t, J = 6.0 Hz, 1H), 4.3–4.22 (m, 2H), 2.88 (d, J = 6.0 Hz, 1H), 1.75 (dt, J = 1.6, 6.4 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 175.1, 130.5, 128.3, 72.0, 62.5, 18.0, 14.4; IR (film) 3477, 2983, 1726, 1683, 1449, 1208, 1141 cm^{-1}; HRMS (DCI/NH_3) calcd for $C_7H_{16}NO_3$ (MNH_4^+) 162.1126, found 162.1130.

4.5.2. Ethyl (*E*)(*R*)-2-hydroxyhept-3-enoate 5b. R_f 0.20 (SiO_2; 6:1 hexanes/EtOAc); bp (bulb-to-bulb) 65 °C at 0.70 Torr; $[\alpha]_D^{25.4} = -60.75$ (*c* 1.515, $CHCl_3$); ^{1}H NMR δ 5.89 (ddt, J = 1.2, 6.8, 15.2 Hz, 1H), 5.51 (ddt, J = 1.2, 6.0, 15.2 Hz, 1H), 4.59 (d, J = 5.2 Hz, 1H), 4.23–4.29 (m, 2H), 2.91 (br s, 1H), 2.08–2.02 (m, 2H), 1.42 (tq, J = 7.2, 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 175.0, 135.3, 127.2, 71.9, 62.3, 34.5, 22.2, 14.3, 13.7; IR (film) 3470, 2961, 2874, 1737, 1684, 1209, 1109 cm^{-1}; HRMS (DCI/NH_3) calcd for $C_9H_{20}NO_3$ (MNH_4^+) 190.1448, found 190.1443.

4.6. General procedure for the preparation of Boc-carbamates 8a and 8b via a one-pot azido reduction-derivation sequence on γ-azido-α,β-unsaturated ethyl esters 7a and 7b

4.6.1. Ethyl (*E*)(*R*)-4-(*tert*-butoxycarbonylamino)hept-2-enoate 8b. To a stirred solution (0.1 M) of γ-azido ester **7b** (200 mg, 1.02 mmol) in freshly distilled methanol was added $SnCl_2$ (385 mg, 2.03 mmol). The reaction was monitored via TLC (6:1 hexanes/EtOAc) for the disappearance of the starting material. After 3 h, the reduction was deemed complete and the slurry concentrated in vacuo via rotary evaporation until a foamy oil appeared. When this crude material had dissolved in freshly distilled 1,4-dioxane (9.2 mL, 0.11 M), an aqueous solution (1 mL, 1 M) of $NaHCO_3$ (342 mg, 4.06 mmol, 4 equiv) was added in a single portion. After stirring for several minutes, 1.5 equiv of di-*tert*-butyldicarbonate (332 mg, 1.52 mmol) were added and the reaction again monitored via TLC (6:1 hexanes/EtOAc). The reaction was judged complete after 22 h and quenched by dilution with EtOAc and water. The stirred mixture was acidified to pH 1 with 2 M $NaHSO_4$, and the aqueous phase extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated solutions of $NaHCO_3$ (1 × 15 mL) and NaCl (1 × 15 mL). Concentration under reduced pressure, followed by radial chromatography (2 mm SiO_2 plate, 7:1 hexanes/EtOAc) afforded 216 mg (80%) of colorless oil that crystallized at 0 °C. R_f 0.30 (SiO_2; 5:1 hexanes/EtOAc); bp (bulb-to-bulb) 90 °C at 0.45 Torr; $[\alpha]_D^{25} = +15.5$ (*c* 1.36, $CHCl_3$); ^{1}H NMR δ 6.83 (dd, J = 5.2, 15.6 Hz, 1H), 5.89 (dd, J = 1.6, 15.6 Hz, 1H), 4.57 (d, J = 8.0 Hz, 1H), 4.28 (s, 1H), 4.21–4.13 (m, 2H), 1.43 (s, 9H), 1.6–1.3 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 166.6, 155.3, 148.8, 120.7, 79.8, 60.6, 51.4, 36.9, 28.5, 19.1, 14.4, 13.9; IR (neat) 3350, 2978, 2875, 1726, 1653, 1281, 1170 cm^{-1}; HRMS (DCI/NH_3) calcd for $C_{14}H_{29}N_2O_4$ (MNH_4^+) 289.2137, found 289.2127.

4.6.2. Ethyl (*E*)(*R*)-4-(*tert*-butoxycarbonylamino)pent-2-enoate 8a.[29] R_f 0.30 (SiO_2; 5:1 hexanes/EtOAc); $[\alpha]_D^{25} = +20.7$ (*c* 1.78, $CHCl_3$); ^{1}H NMR δ 6.85 (dd,

J = 4.8, 15.6 Hz, 1H), 5.87 (dd, J = 1.6, 15.6 Hz, 1H), 4.49 (br s, 1H), 4.38 (br s, 1H), 4.7 (q, J = 6.8 Hz, 2H), 1.42 (s, 9H), 1.26 (t, J = 6.8 Hz, 3H), 1.24 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 167.3, 155.8, 150.3, 120.7, 80.1, 60.7, 47.2, 28.4, 20.3, 14.2; IR (neat) 3353, 2979, 2935, 1725, 1653, 1277, 1173, 1047 cm^{-1}.

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