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Hydrogen-Mediated Coupling of Conjugated Enynes and Diynes with Ethyl (*N*-Sulfinyl)iminoacetates:

Synthesis of Unnatural α -Amino Acids *via* Rhodium Catalyzed C-C Bond Forming

Hydrogenation

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Abstract

Rhodium catalyzed hydrogenation of 1,3-enynes **1a-8a** and 1,3-diynes **9a-13a** at ambient temperature and pressure in the presence of ethyl (*N-tert*-butanesulfinyl)iminoacetate and ethyl (*N*-2,4,6-triisopropylbenzenesulfinyl)iminoacetates, respectively, results in reductive coupling to afford unsaturated α -amino acid esters **1b-13b** in good to excellent yields with exceptional levels of regio- and stereocontrol. Further hydrogenation of the diene containing α -amino acid esters **1b-8b** using Wilkinson's catalyst at ambient temperature and pressure results in regioselective reduction to afford the β,γ -unsaturated α -amino acid esters **1c-8c** in good to excellent yields. Exhaustive hydrogenation of the unsaturated side chains of the Boc- and Fmoc-protected derivatives of enyne and diyne coupling products **14b-16b** occurs in excellent yield using Crabtree's catalyst at ambient temperature and pressure to afford the α -amino acid esters **14d-16d**, which possess saturated side chains. Finally, cross-metathesis of the Boc-protected reductive coupling product **14b** with *cis*-1,4-diacetoxy-2-butene proceeds readily to afford the allylic acetate **14e**. Isotopic labeling studies that involve reductive coupling of enyne **1a** and diyne **9a** under an atmosphere of elemental deuterium corroborate a catalytic mechanism in which oxidative coupling of the alkyne and imine residues is followed by hydrogenolytic cleavage of the resulting metallacycle. A stereochemical model accounting for the observed sense of asymmetric induction is provided. These studies represent the first use of imines as electrophilic partners in hydrogen-mediated reductive carbon-carbon bond formation.

Introduction

Reductive methods for catalytic C-C bond formation have emerged as the subject of intensive investigation.¹⁻⁷ The direct catalytic reductive coupling of alkenes,¹ alkynes,² allenes,³ enones,^{4,6a-d} 1,3-dienes,^{2,6e} 1,3-enynes^{5,6f} and 1,3-diynes^{6g} to carbonyl partners have been reported. Inspired by the prospect of developing completely atom economical variants of such transformations, hydrogen-mediated C-C bond formation has become the focus of research in our lab.^{6,7} Hydrogen-mediated reductive couplings to carbonyl partners using conjugated enones,^{6a-d} dienes,^{6e} enynes^{6f} and diynes^{6g} have been achieved, as well as hydrogen-mediated reductive cyclizations of 1,6-diynes and 1,6-enynes.^{6h,i} These studies are among the first examples of hydrogen-mediated C-C bond formation that proceed in absence of carbon monoxide.^{8,9}

To further broaden this emergent class of reductive couplings, the use of imines as electrophilic partners in hydrogen-mediated C-C bond formation was explored. Whereas three component

couplings of alkynes, organoboranes and imines are reported,¹⁰ simple hydrometallative variants are unknown. Here, we disclose that hydrogenation of 1,3-enynes or 1,3-diynes in the presence of ethyl (*N*-sulfinyl)iminoacetates^{11,12} enables highly regio- and stereoselective reductive coupling to afford unnatural diene- and enyne containing α -amino acid esters.¹³

Results and Discussion

Reductive Coupling of Conjugated Alkynes and *N*-Sulfinyl Iminoacetates

Initial efforts focused on the hydrogen-mediated coupling of 1,3-enyne **1a** (200 mol%) to assorted (*N*-sulfinyl)iminoacetates (100 mol%) at ambient pressure and temperature in dichloromethane (0.1 M). The rhodium precatalyst was generated *in situ* from Rh(COD)₂OTf (5 mol%) and BIPHEP (5 mol%). It was found that hydrogenation of **1a** in the presence of ethyl (*N*-*para*-toluenesulfinyl)iminoacetate (100 mol%) provides the desired reductive coupling product in 95% yield, but with poor control of diastereoselectivity. A further decrease in stereoselection is observed in conjunction with the use of the corresponding mesityl derivative. However, hydrogenation of 1,3-enyne **1a** in presence of ethyl (*N*-*tert*-butanesulfinyl)iminoacetate furnishes reductive coupling product **1b** in 55% yield as a single regio- and stereoisomer. When the reaction is conducted at higher concentration (0.3 M), the yield is increased to 92% without loss of selectivity. Finally, at slightly elevated temperature (35° C), **1b** is obtained in 99% yield as a single diastereomer (Scheme 1).

The use of ethyl (*N*-*tert*-butanesulfinyl)iminoacetate under these conditions proved to be general across a range of structurally diverse enynes **1a-8a**. In all cases examined, >95:5 regio- and diastereoselectivity is observed (Table 1). The chemoselectivity of the hydrogen-mediated coupling is underscored by the fact that over-reduction of the diene-containing products **1b-8b** is not observed. The regio- and stereochemical assignment of reductive coupling products **1b-8b** is described in the supporting information, and is based upon crystallographic analysis of a derivative of **4b**.

The hydrogen-mediated reductive coupling of 1,3-diynes to (*N*-sulfinyl)iminoacetates was explored next. For the purpose of optimization, the rhodium catalyzed hydrogenation of 1-phenyl-1,3-pentadiyne **9a** (200 mol%) in the presence of assorted (*N*-sulfinyl)iminoacetates (100 mol%) at ambient pressure and temperature in dichloromethane (0.1 M) was studied. Interestingly, under conditions established for the reductive coupling of enynes **1a-8a**, coupling of diyne **9a** to ethyl (*N*-*tert*-butanesulfinyl)iminoacetate is not observed, presumably due to the diminished electrophilicity of the alkyl substituted sulfinyl imine. In contrast, hydrogenation of diyne **9a** in the presence of (*N*-*para*-toluenesulfinyl)iminoacetate delivers a 94% yield of the desired coupling product **9b** as a 1.2:1 mixture of diastereomers. Remarkably, **9b** appears as a single regioisomer, as coupling occurs exclusively at the aromatic terminus of the conjugated diyne **9a**. Upon use of the corresponding mesityl derivative, coupling product **9b** is obtained 96% yield with >95:5 regio- and diastereocontrol. Comparable results were

obtained in conjunction with the use of ethyl *N*-(2,4,6-triisopropyl)benzenesulfinyl iminoacetate, which was adopted as the standard coupling partner due to its enhanced chromatographic stability and, hence, ease of purification (Scheme 2).

The coupling of 1,3-diynes **9a-13a** to ethyl *N*-(2,4,6-triisopropyl)benzenesulfinyl iminoacetate under the aforementioned conditions provides the enyne-containing α -amino acid esters **9b-13b** as single regio- and stereoisomers in good to excellent yield. The regioisomeric products **9c-12c** are not observed. The stereochemical assignment of **9b-13b** is made in analogy to that established *via* single crystal x-ray diffraction analysis for a derivative of **4b**, as described in the supporting information.

Elaboration of Reductive Coupling Products

In a preliminary effort to explore further manipulation of the coupling products, compound **1a** was exposed to Wilkinson's catalyst at ambient pressure and temperature.^{5,14} In the event, regioselective hydrogenation of the terminal alkene occurs cleanly to afford the β,γ -unsaturated α -amino esters **1c** in 74% yield, without over-reduction to the fully saturated derivative **1d**. These regioselective hydrogenation conditions were applied to all enyne coupling products **1b-8b**. The β,γ -unsaturated α -amino esters **1c-8c** were obtained in 70-93% yield (Table 1). Exhaustive hydrogenation of the diene side chain using Crabtree's catalyst was explored next.¹⁵ Here, the *N-tert*-butanesulfinyl residue must be exchanged for a carbamate protecting group, as in **14b** and **15b**. Hydrogenation of **14b** using Crabtree's catalyst at ambient pressure and temperature provides the fully saturated Boc-protected amino acid ester **14d** in 99% as a 2:1 mixture of diastereomers. Under identical conditions, the saturated Fmoc-protected amino acid ester **14d** is obtained in 95% as a 2.4:1 mixture of diastereomers. Conversion of **9b** to the corresponding Boc-derivative **16b** followed by exhaustive hydrogenation of the enyne side chain using Crabtree's catalyst provides the saturated amino acid ester **16d** in excellent yield. The relative stereochemistry of **14d-16d** was not assigned (Scheme 3).

Whereas enynes possessing vinylic substitution couple readily to glyoxal partners under hydrogenation conditions,^{6f} the present enyne-iminoacetate couplings do not tolerate vinylic substitution. Hence, functionalization of the diene terminus *via* cross-metathesis was explored. Gratifyingly, exposure of the Boc-protected reductive coupling product **14b** to *cis*-1,4-diacetoxy-2-butene in the presence of substoichiometric quantities of the second generation Grubb's catalyst provides the allylic acetate **14e** in 80% yield as a 10:1 mixture of alkene stereoisomers (Scheme 4).¹⁶

Catalytic Mechanism and Model for Stereoinduction

Under an atmosphere of elemental deuterium, rhodium catalyzed reductive coupling of **1a** and ethyl (*N-tert*-butanesulfinyl)iminoacetate provides *mono*-deuterio-**1b**. Similarly, the reductive coupling of **9a** to ethyl *N*-(2,4,6-triisopropyl)benzenesulfinyl iminoacetate under a deuterium atmosphere provides *mono*-deuterio-**9b**. These results are consistent with a catalytic mechanism involving alkyne-imine oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle. An analogous mechanism for related hydrogen-mediated carbocyclizations catalyzed by rhodium has been inferred on the basis of more detailed mechanistic studies.⁶ⁱ The hydrogenolytic cleavage of the metallacyclic intermediate likely involves hydrogen activation *via* σ -bond metathesis. An increasing body of evidence supports participation of organorhodium(III) intermediates in σ -bond metathesis pathways,¹⁷ including reactions with hydrogen.^{17c} Factors dictating the regiochemistry of C-C bond formation remain uncertain. However, previously disclosed competition experiments^{6f} suggest back-bonding from low valent rhodium to the bound alkyne, which enables generation of a nucleophilic metallacyclopentene, may play a decisive role.¹⁸ Nucleophilic activation of alkynes through complexation by low valent early transition metals is well established.¹⁹ For

low valent late transition metals, this pattern of reactivity may represent a driving force that assists the oxidative coupling of alkynes to C=O π -bonds, as in the Ni(0) catalyzed reductive coupling of alkynes and aldehydes.^{2,3} The modest nucleophilic character of a Rh(I)-alkyne complex may account for the requirement of highly activated electrophilic partners such as iminoacetates and, as previously reported, glyoxals (Scheme 5).^{6f,6g}

Given the observed sense of stereoinduction, two stereochemical models **A** and **B** are proposed. In each case, the iminoacetate is bound to rhodium(I) in a 5-membered chelate. This mode of coordination has been established for late transition metal complexes of α -iminoketones and α -iminoesters.²⁰ Upon oxidative coupling, the alkyne is delivered to the less encumbered π -face of the imine, as dictated by the anticipated conformational preference of the *N*-sulfinyl imine.²¹ The resulting metallacycle **C** possesses an unoccupied coordinate site **L**, which should facilitate subsequent hydrogen activation (Scheme 6).

Summary

In this account, the reductive coupling of conjugated alkynes and iminoacetates is achieved through catalytic hydrogenation, representing the first use of imines as electrophilic partners in simple hydrometallative reductive coupling. Good to excellent yields and exceptional levels of regiocontrol are observed. Moreover, the high levels of relative stereocontrol with respect to the *N*-sulfinyl moiety allow the absolute stereochemical course of the reductive coupling to be directed.

Initial studies on the elaboration of the reductive coupling products reveal that the unsaturated side chain of the diene-containing products **1b-8b** may be partially hydrogenated to afford the corresponding β,γ -unsaturated α -amino acid esters **1c-8c**. Exhaustive hydrogenation of both diene and enyne containing reductive couplings is possible, as demonstrated by the hydrogenation of compounds **14b-16b** to furnish **14d-16d**, which possess completely saturated side chains. Finally, as demonstrated by the conversion of **14b-14e**, cross-metathesis of the diene containing α -amino acid esters occurs in good yield.

The outcome of isotopic labeling studies, which involve the reductive coupling of enyne **1a** and diyne **9a** to iminoacetates under an atmosphere of elemental deuterium, are consistent with a catalytic mechanism involving oxidative coupling of the alkyne and imine residues followed by hydrogenolytic cleavage of the resulting metallacyclic intermediate. The requirement of π -unsaturated reactants in the form of activated imines and conjugated alkynes suggest alkyne coordination by low valent rhodium to form a weakly nucleophilic metalocyclopropene. For low valent late transition metals, this pattern of reactivity may represent a driving force that assists the oxidative coupling of alkynes to C=O π -bonds.

Experimental Section

General

Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. Dichloromethane (DCM) was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F₂₅₄). Preparative column chromatography employing silica gel was performed according to the method of Still. ¹H-NMR spectra were recorded with a Varian Gemini (400 MHz or 300 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (¹³C-NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical

shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Representative Procedure for the Reductive Coupling of 1,3-Enynes and *N*-(*tert*-Butanesulfinyl)iminoacetate

To a solution of *N*-(*tert*-Butanesulfinyl)iminoacetate (41 mg, 0.2 mmol, 100 mol%) and 3-buten-1-ynyl-benzene **1a** (50.9 mg, 0.4 mmol, 200 mol%) in DCM (0.67 mL, 0.3M) at 35 °C was added Rh(COD)₂OTf (4.7 mg, 0.01 mmol, 5 mol%) and BIPHEP (5.3 mg, 0.01 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at 35 °C under 1 atm of hydrogen until complete consumption of substrate, at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography.

2-(2-methyl-propane-2-sulfinylamino)-3-phenyl-hexa - 3,5-dienoic acid ethyl ester (**1b**)

^1H NMR (400 MHz, CDCl_3): 7.34-7.26 (m, 3H), 7.19-7.16 (m, 2H), 6.42 (d, J = 10.8 Hz, 1H), 6.30 (dt, J = 16.8, 10.4 Hz, 1H), 5.15 (dd, J = 10.0, 1.6 Hz, 1H), 5.14 (dd, J = 10.0, 1.6 Hz, 1H), 4.80 (d, J = 4.0 Hz, 1H), 4.34 (d, J = 4.0, 1H), 4.17 (q, J = 7.2 Hz, 2H), 1.19 (s, 9H), 1.18 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 171.0, 137.9, 137.0, 133.3, 132.6, 129.3, 128.0, 127.6, 120.1, 62.8, 62.0, 55.9, 22.5, 13.9. HRMS: Calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_1\text{O}_3\text{S}_1$ [$\text{M}+1$] 336.1633, found 336.1632. FTIR (neat): 3285, 3072, 2980, 1738, 1602, 1494, 1474, 1444, 1366, 1296, 1256, 1219, 1184, 1076, 914, 851, 776 cm^{-1} .

2-(2-methyl-propane-2-sulfinylamino)-3-naphthalen-2-yl-hexa-3,5-dienoic acid ethyl ester (**2b**)

^1H NMR (400 MHz, CDCl_3): 7.84-7.78 (m, 3H), 7.66 (s, 1H), 7.51-7.46 (m, 2H), 7.30 (dd, J = 8.4, 1.6 Hz, 1H), 6.51 (d, J = 11.2 Hz, 2H), 6.35 (t, J = 10.4 Hz, 1H), 6.51 (d, J = 11.2 Hz, 1H), 6.30 (dt, J = 17.2, 10.4 Hz, 1H), 5.40 (dd, J = 16.8, 1.4 Hz, 1H), 5.16 (dd, J = 10.2, 1.4 Hz, 1H), 4.90 (d, J = 4.4 Hz, 1H), 4.41 (d, J = 4.0, 1H), 4.20-4.15 (m, 2H), 1.19 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 171.0, 137.9, 134.5, 133.3, 133.0, 132.9, 132.6, 128.5, 127.9, 127.6, 127.2, 126.2, 126.2, 120.3, 62.8, 62.1, 56.0, 22.5, 14.0. HRMS: Calcd. for $\text{C}_{22}\text{H}_{28}\text{N}_1\text{O}_3\text{S}_1$ [$\text{M}+1$] 386.1790, found 386.1786. FTIR (neat): 3283, 2979, 1733, 1473, 1366, 1258, 1219, 1184, 1075, 914, 859, 824, 751 cm^{-1} .

2-(2-methyl-propane-2-sulfinylamino)-3-furan-2-yl-hexa-3,5-dienoic acid ethyl ester (**3b**)

^1H NMR (400 MHz, CDCl_3): 7.42 (d, J = 1.2, 1H), 7.12 (dt, J = 17.6, 10.7, 1H), 6.42 (d, J = 3.2 Hz, 1H), 6.40-6.38 (m, 1H), 6.30 (d, J = 11.2 Hz, 1H), 5.46 (d, J = 8.4 Hz, 1H), 5.36 (dd, J = 10.0, 1.2 Hz, 1H), 4.80 (d, J = 3.2 Hz, 1H), 4.44 (d, J = 2.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): 171.0, 150.8, 142.2, 133.4, 132.4, 125.9, 111.0, 110.8, 62.2, 61.4, 55.7, 22.4, 13.9. HRMS: Calcd. for $\text{C}_{16}\text{H}_{24}\text{N}_1\text{O}_4\text{S}_1$ [$\text{M}+1$] 326.1426, found 326.1426. FTIR (neat): 3287, 2980, 1737, 1467, 1366, 1260, 1224, 1114, 1072, 1021 cm^{-1} .

3-(1*H*-Indol-2-yl)-2-(2-methyl-propane-2-sulfinyl amino)-hexa-3,5-dienoic acid ethyl ester (**4b**)

^1H NMR (400 MHz, CDCl_3): 8.90 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.16 (td, J = 7.6, 1.1 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.90 (dt, J = 17.2, 10.6 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.48 (d, J = 10.8, 1H), 5.50 (d, J = 16.0 Hz, 1H), 5.33 (d, J = 10.0 Hz, 1H), 4.85 (d, J = 3.6, 1H), 4.46 (d, J = 3.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.20 (s, 9H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): 172.2, 136.0, 134.8, 133.4, 133.2, 127.9, 127.8, 122.5, 122.0, 120.5, 120.0, 110.9, 105.2, 62.4, 61.8, 56.0, 22.5, 13.7. HRMS: Calcd. for $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_3\text{S}_1$ [$\text{M}+1$] 375.1742, found 375.1747. FTIR (neat): 3274, 2978, 1731, 1455, 1404, 1366, 1224, 1056, 913, 850, 795, 783 cm^{-1} . MP: 50 - 52 °C.

3-Allylidene-2-(2-methyl-propane-2-sulfinylamino)-octanoic acid ethyl ester (5b)

¹H NMR (400 MHz, CDCl₃): 6.58 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.11 (d, *J* = 11.2 Hz, 1H), 5.27 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.19 (dd, *J* = 9.8, 1.4 Hz, 1H), 4.45 (d, *J* = 4.0, 1H), 4.32 (d, *J* = 4.0 Hz, 1H), 4.27-4.17 (m, 2H), 2.19 (t, *J* = 8.0, 2H), 1.44-1.36 (m, 2H), 1.29-1.26 (m, 7H), 1.26 (s, 9H), 0.88 (t, *J* = 2.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.6, 138.0, 132.1, 130.6, 118.9, 62.0, 62.0, 55.8, 31.9, 28.6, 28.6, 22.6, 22.4, 14.0, 14.0. HRMS: Calcd. for C₁₇H₃₂N₁O₃S₁ [M+1] 330.2103, found 330.2090. FTIR (neat): 3452, 2956, 2869, 1734, 1465, 1365, 1255, 1182, 1078, 908, 851 cm⁻¹.

3-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl ester (6b)

¹H NMR (400 MHz, CDCl₃): 6.62 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.13 (d, *J* = 10.8 Hz, 1H), 5.32 (dd, *J* = 15.2, 1.4 Hz, 1H), 5.24 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.59 (d, *J* = 4.4 Hz, 1H), 4.44-4.38 (m, 2H), 4.32-4.23 (m, 2H), 4.17-4.41 (m, 1H), 1.27 (t, *J* = 1.2, 3H), 1.25 (s, 9H), 0.09 (s, 9H), 0.062 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): 171.4, 136.4, 131.2, 131.1, 120.3, 61.8, 60.1, 58.6, 55.8, 25.8, 22.6, 18.3, 14.0, -5.52. HRMS: Calcd. for C₁₉H₃₈N₁O₄Si₁S₁ [M+1] 404.2291, found 404.2299. FTIR (neat): 3418, 2956, 2925, 2857, 1735, 1472, 1365, 1255, 1212, 1077, 838, 778, 736 cm⁻¹.

3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl (7b)

¹H NMR (400 MHz, CDCl₃): 6.55 (dt, *J* = 16.8, 10.6 Hz, 1H), 6.12 (d, *J* = 10.8, 2H), 5.24 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 1H), 4.32 (d, *J* = 4.4, 1H), 4.25-4.11 (m, 2H), 3.63-3.53 (m, 2H), 2.48-2.34 (m, 2H), 1.24 (t, *J* = 6.4 Hz, 3H), 1.21 (s, 9H), 0.84 (s, 9H), 0.018 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): 171.4, 134.1, 132.3, 132.1, 119.5, 62.4, 62.1, 62.0, 55.9, 32.2, 25.9, 22.6, 18.2, 14.0, -5.37. HRMS: Calcd. for C₂₀H₄₀N₁O₄Si₁S₁ [M+1] 418.2447, found 418.2447. FTIR (neat): 3447, 3283, 2956, 2929, 2857, 1734, 1646, 1472, 1388, 1365, 1255, 1181, 1086, 989, 912, 836, 776 cm⁻¹.

3-(tert-Butoxycarbonylamino-methyl)-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl ester (8b)

¹H NMR (400 MHz, CDCl₃): 6.67 (dt, *J* = 16.4, 10.4 Hz, 1H), 6.26 (d, *J* = 11.2 Hz, 1H), 5.39 (d, *J* = 16.4 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 4.58 (s, 1H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.45 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.94 (d, *J* = 5.2 Hz, 1H), 1.43 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): 170.9, 155.3, 134.5, 132.9, 131.1, 121.4, 79.4, 62.2, 61.2, 55.8, 37.3, 28.2, 22.5, 14.0. HRMS: Calcd. for C₁₈H₃₃N₂O₅S₁ [M+1] 389.2110, found 389.2108. FTIR (neat): 3384, 2978, 1734, 1707, 1507, 1457, 1391, 1366, 1251, 1170, 1064, 917, 734 cm⁻¹.

deuterio-2-(2-methyl-propane-2-sulfinylamino)-3-phenyl-hexa-3,5-dienoic acid ethyl ester (deuterio-1b)

¹H NMR (400 MHz, CDCl₃): 7.34-7.25 (m, 3H), 7.18-7.15 (m, 2H), 6.29 (dd, *J* = 16.8, 10.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.79 (d, *J* = 4.8 Hz, 1H), 4.34 (d, *J* = 4.4, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.17 (s, 9H), 1.17 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.0, 137.8, 137.0, 133.2, 129.3, 128.0, 127.6, 120.1, 62.8, 62.1, 55.9, 22.5, 13.9. HRMS: Calcd. for C₁₈H₂₅D₁N₁O₃S₁ [M+1] 337.1696, found 337.1692. FTIR (neat): 3285, 3056, 2980, 2870, 1732, 1601, 1493, 1473, 1444, 1412, 1391, 1366, 1253, 1220, 1074, 911, 852, 735, 703, cm⁻¹.

Representative Procedure for the Regioselective Hydrogenation of Dienes

To a solution of diene **1b** (33.5 mg, 0.1 mmol, 100 mol%) in toluene (1 mL, 0.1M) at ambient temperature was added RhCl(PPh₃)₃ (9.3 mg, 0.01 mmol, 10 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen until complete consumption of substrate, at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography.

2-(2-Methyl-propane-2-sulfinylamino)-3-phenyl-hex-3-enoic acid ethyl ester (**1c**)

¹H NMR (400 MHz, CDCl₃): 7.32-7.23 (m, 3H), 7.13-7.10(m, 2H), 5.83 (t, *J* = 7.4 Hz, 1H), 4.72 (d, *J* = 4.4 Hz, 2H), 4.23 (d, *J* = 4.0 Hz, 1H), 4.20-4.12 (m, 2H), 1.99 (qt, *J* = 7.4 Hz, 2H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.19 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.4, 137.3, 136.0, 135.6, 129.1, 127.9, 127.2, 63.1, 61.8, 55.8, 22.5, 22.3, 14.0, 13.9. HRMS: Calcd. for C₁₈H₂₈N₁O₃S₁ [M+1] 338.1790, found 338.1792. FTIR (neat): 3279, 2964, 2930, 2871, 1735, 1458, 1365, 1295, 1254, 1214, 1183, 1076, 1022, 884, 847, 760, 702 cm⁻¹.

2-(2-Methyl-propane-2-sulfinylamino)-3-naphthalen-2-yl-hex-3-enoic acid ethyl ester (**2c**)

¹H NMR (400 MHz, CDCl₃): 7.83-7.76 (m, 3H), 7.60 (s, 1H), 7.49-7.45 (m, 2H), 7.25 (d, *J* = 8.6, 1H), 5.90 (t, *J* = 7.6 Hz, 1H), 4.81 (s, 1H), 4.33 (s, 1H), 4.21-4.13 (m, 2H), 2.02 (qt, *J* = 7.5 Hz, 2H), 1.20 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.3, 136.5, 135.6, 134.9, 133.0, 132.4, 128.0, 127.5, 127.5, 127.4, 126.0, 125.9, 63.1, 61.9, 29.6, 22.7, 22.6, 22.4, 14.0. HRMS: Calcd. for C₂₂H₃₀N₁O₃S₁ [M+1] 388.1946, found 388.1953. FTIR (neat): 3285, 3054, 2961, 2870, 1734, 1597, 1503, 1458, 1365, 1181, 1075, 1019, 859, 749 cm⁻¹.

3-Furan-2-yl-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (**3c**)

¹H NMR (400 MHz, CDCl₃): 7.36 (t, *J* = 2.0 Hz, 1H), 6.37-6.36 (m, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 5.77 (t, *J* = 7.2 Hz, 1H), 4.75 (s, 1H), 4.41 (s, 1H), 4.23-4.15 (m, 2H), 2.42 (qt, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.14 (s, 9H), 1.09 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.3, 150.7, 141.3, 137.4, 125.6, 110.7, 109.6, 62.0, 61.8, 29.7, 22.8, 22.4, 14.0, 13.9. HRMS: Calcd. for C₁₆H₂₆N₁O₄S₁ [M+1] 328.1583, found 328.1573. FTIR (neat): 3288, 2966, 2921, 2850, 1735, 1458, 1366, 1261, 1221, 1071, 1025 cm⁻¹.

3-(1*H*-Indol-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (**4c**)

¹H NMR (400 MHz, CDCl₃): 8.84 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.1 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 1.2, 1H), 5.94 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 3.2 Hz, 2H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.14 (qd, *J* = 7.2, 1.2 Hz, 2H), 2.45-2.37 (m, 2H), 1.21 (s, 9H), 1.10 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.5, 140.1, 136.6, 133.4, 127.9, 126.1, 122.1, 120.3, 119.8, 110.9, 103.9, 62.3, 62.1, 55.9, 22.1, 22.6, 22.5, 14.0, 13.9. HRMS: Calcd. for C₂₀H₂₉N₂O₃S₁ [M+1] 377.1900, found 377.1900. FTIR (neat): 3403, 3276, 2965, 2861, 1732, 1653, 1456, 1366, 1301, 1225, 1054 cm⁻¹. MP: 36 -38 °C.

2-(2-Methyl-propane-2-sulfinylamino)-3-propylidene - octanoic acid ethyl ester (**5c**)

¹H NMR (400 MHz, CDCl₃): 5.47 (t, *J* = 7.2 Hz, 1H), 4.38 (d, *J* = 4.4 Hz, 1H), 4.25 - 4.16 (m, 1H + 2H), 2.22-2.01 (m, 4H), 1.37-1.25 (m, 6H), 1.25 (s, 9H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 172.2, 134.6, 133.7, 62.3, 61.7, 55.7, 32.0, 28.3, 30.0, 22.6, 22.5, 21.3, 14.1, 14.0, 13.9. HRMS: Calcd. for C₁₇H₃₄N₁O₃S₁ [M+1] 332.2259, found 332.2251. FTIR (neat): 3422, 2959, 2862, 1734, 1638, 1465, 1255, 1077 cm⁻¹.

3-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(2-methyl - propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (6c)

¹H NMR (400 MHz, CDCl₃): 5.55 (t, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 4.27 (d, *J* = 4.4 Hz, 1H), 4.29-4.09 (m, 2H + 2H), 2.11 (qd, *J* = 7.5, 2.4 Hz, 2H), 2.78 (t, *J* = 4.4 Hz, 3H), 1.25 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): 171.8, 134.4, 134.2, 61.5, 60.4, 58.2, 55.6, 25.9, 22.6, 21.0, 18.3, 14.0, -5.5. HRMS: Calcd. for C₁₉H₄₀N₁O₄Si₁S₁ [M+1] 406.2447, found 406.2448. FTIR (neat): 2957, 2930, 2857, 1736, 1472, 1389, 1364, 1253, 1204, 1082, 849, 777 cm⁻¹.

3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-2-(2-methy-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (7c)

¹H NMR (400 MHz, CDCl₃): 5.51 (t, *J* = 7.2 Hz, 1H), 4.38 (d, *J* = 5.2 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 4.22-4.11 (m, 2H), 3.60-3.48 (m, 2H), 2.36-2.21 (m, 2H), 2.07 (qt, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.22 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): 171.9, 135.6, 130.9, 62.6, 61.9, 61.8, 55.7, 31.7, 25.9, 22.6, 21.4, 18.3, 14.0, 13.9, -5.3. HRMS: Calcd. for C₂₀H₄₀N₁O₄Si₁S₁ [M+1] 418.2447, found 418.2447. FTIR (neat): 2958, 2857, 1736, 1472, 1364, 1255, 1188, 1084, 836, 776 cm⁻¹.

3-(tert-Butoxycarbonylamino-methyl)-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (8c)

¹H NMR (400 MHz, CDCl₃): 5.71 (t, *J* = 7.2 Hz, 1H), 4.55 (s, 1H), 4.46 (d, *J* = 2.8 Hz, 1H), 4.38 (s, 1H), 4.22 (q, *J* = 7.1, 2H), 3.81 (d, *J* = 5.2, 2H), 2.19 (qt, *J* = 7.6, 2H), 1.42 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H), 1.02 (t, *J* = 7.6, 3H). ¹³C NMR (100 MHz, CDCl₃): 171.5, 155.4, 138.5, 130.8, 79.3, 62.2, 61.6, 55.7, 37.2, 29.7, 28.4, 22.6, 21.3, 14.0, 13.9. HRMS: Calcd. for C₁₈H₃₅N₂O₅S₁ [M+1] 391.2267, found 391.2278. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm⁻¹.

Representative Procedure: the Reductive Coupling of 1,3-Diynes and *N*-(2,4,6-triisopropyl) benzenesulfinyl iminoacetate

To a solution of *N*-(2,4,6-triisopropyl) benzenesulfinyl iminoacetate (70.3 mg, 0.2 mmol, 100 mol%) and 1,3-diyne **9a** (56.1 mg, 0.4 mmol, 200 mol%) in DCM (2 mL, 0.1M) at ambient temperature was added Rh(COD)₂OTf (4.7 mg, 0.01 mmol, 5 mol%) and BIPHEP (5.3 mg, 0.01 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen until complete consumption of substrate, at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography.

3-Phenyl-2-(2,4,6-triisopropyl-benzenesulfinylamino) - hept-3-en-5-ynoic acid ethyl ester (9b)

¹H NMR (400 MHz, CDCl₃): 7.44-7.41 (m, 2H), 7.33-7.27 (m, 3H), 7.02 (s, 2H), 5.88 (qd, *J* = 2.4, 0.4 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 4.80 (d, *J* = 8.4 Hz, 1H), 4.19-4.08 (m, 2H), 3.92 (s, 2H), 2.84 (qt, *J* = 6.9 Hz, 1H), 1.82 (d, *J* = 2.4, 3H), 1.20 (d, *J* = 6.8, 6H), 1.18 (d, *J* = 6.8 Hz, 12H), 1.63 (t, *J* = 7.2, 3H). ¹³C NMR (100 MHz, CDCl₃): 170.8, 152.1, 148.0, 146.3, 137.4, 136.5, 128.6, 128.1, 128.0, 122.9, 111.9, 91.9, 62.8, 61.8, 34.3, 28.1, 24.3, 24.1, 23.7, 23.7, 13.9, 4.5. HRMS: Calcd. for C₃₀H₄₀N₁O₃S₁ [M+1] 494. 2729, found 494.2736. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm⁻¹.

7-(tert-Butyl-dimethyl-silanyloxy)-3-phenyl-2-(2,4,6 - triisopropyl-benzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (10b)

¹H NMR (400 MHz, CDCl₃): 7.40-7.37 (m, 2H), 7.32-7.26 (m, 3H), 7.02 (s, 2H), 5.94 (t, *J* = 1.0 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.28 (d, *J* = 2.0 Hz, 2H), 4.16-4.10

(m, 2H), 3.91 (s, 2H), 2.84 (qt, $J = 7.0$ Hz, 1H), 1.20 (d, $J = 7.2$, 6H), 1.17 (d, $J = 6.8$ Hz, 12H), 1.16 (t, $J = 7.2$, 3H), 0.83 (s, 9H), -0.017 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): 170.6, 152.1, 148.1, 148.0, 137.3, 136.2, 128.6, 128.3, 128.1, 123.0, 111.0, 93.2, 81.6, 62.8, 61.9, 52.1, 34.3, 28.1, 25.7, 24.3, 24.1, 23.7, 18.2, 13.9, -5.31. HRMS: Calcd. for $\text{C}_{36}\text{H}_{54}\text{N}_1\text{O}_4\text{Si}_1\text{S}_1$ [$M+1$] 624.3543, found 624.3534. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm^{-1} .

7-tert-Butoxycarbonylamino-3-phenyl-2-(2,4,6-triisopropyl-benzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (11b)

^1H NMR (400 MHz, CDCl_3): 7.40-7.37 (m, 2H), 7.38-7.27 (m, 3H), 7.02 (s, 2H), 5.90 (d, $J = 0.8$ Hz, 1H), 4.94 (d, $J = 8.4$ Hz, 1H), 4.82 (d, $J = 8.4$ Hz, 1H), 4.49 (s, 1H), 4.19-4.07 (m, 2H), 3.90 - 3.88 (m, 4H), 2.84 (qt, $J = 6.9$ Hz, 1H), 1.40 (s, 9H), 1.21 (d, $J = 7.2$, 6H), 1.17 (dd, $J = 6.8$, 2.0 Hz, 12H), 1.15 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, CDCl_3): 170.5, 155.1, 152.1, 148.4, 148.1, 137.3, 136.2, 128.5, 128.4, 128.1, 123.0, 110.8, 90.9, 80.2, 79.8, 62.9, 62.0, 34.3, 31.2, 28.3, 28.2, 24.3, 24.1, 23.7, 23.7, 13.9. HRMS: Calcd. for $\text{C}_{35}\text{H}_{48}\text{N}_2\text{O}_5\text{S}_1$ [$M+1$] 608.3284, found 608.3283. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm^{-1} .

3-Furan-2-yl-2-(2,4,6-triisopropyl-benzenesulfinyl amino)-hept-3-en-5-ynoic acid ethyl ester (12b)

^1H NMR (400 MHz, CDCl_3): 7.29 (d, $J = 2.0$, 1H), 7.21 (d, $J = 3.2$, 1H), 7.05 (s, 2H), 6.44 (q, $J = 1.7$, 1H), 5.68 (q, $J = 2.7$, 1H), 5.21 (d, $J = 9.2$ Hz, 1H), 4.93 (d, $J = 9.2$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 2H), 2.87 (qt, $J = 6.9$ Hz, 1H), 2.09 (d, $J = 2.8$, 3H), 1.24 - 1.19 (m, 18H), 1.14 (t, $J = 7.0$, 3H). ^{13}C NMR (100 MHz, CDCl_3): 170.6, 151.9, 150.8, 147.9, 141.4, 137.9, 135.4, 122.9, 111.7, 111.3, 107.9, 96.4, 78.1, 61.9, 61.8, 34.3, 28.2, 24.3, 24.1, 23.8, 23.7, 13.9, 4.94. HRMS: Calcd. for $\text{C}_{28}\text{H}_{38}\text{N}_1\text{O}_4\text{S}_1$ [$M+1$] 484.2522, found 484.2504. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm^{-1} .

7-Hydroxy-3-hydroxymethyl-2-(2,4,6-triisopropyl-benzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (13b)

^1H NMR (400 MHz, CDCl_3): 7.06 (s, 2H), 5.72 (s, 1H), 5.32 (d, $J = 8.4$ Hz, 1H), 4.75 (d, $J = 8.4$ Hz, 1H), 4.59 (d, $J = 14.4$ Hz, 1H), 4.45 (d, $J = 14.0$ Hz, 1H), 4.41 (d, $J = 0.8$ Hz, 2H), 4.23-4.15 (m, 2H), 3.94 (s, 2H), 3.50 (s, 1H), 2.89 - 2.82 (m, 1H), 2.31 (s, 1H), 1.31 (d, $J = 6.8$, 6H), 1.24 (t, $J = 7.2$, 3H), 1.22 (d, $J = 6.8$ Hz, 12H). ^{13}C NMR (100 MHz, CDCl_3): 170.3, 152.4, 149.1, 147.7, 137.1, 123.1, 111.5, 95.5, 80.6, 62.3, 61.8, 60.4, 51.3, 34.3, 28.5, 24.4, 24.1, 23.7, 14.0. HRMS: Calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_1\text{O}_5\text{S}_1$ [$M+1$] 464.2471, found: 464.2472. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm^{-1} .

deuterio-3-Phenyl-2-(2,4,6-triisopropylbenzene sulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (deuterio -9b)

^1H NMR (400 MHz, CDCl_3): 7.45 - 7.43 (m, 2H), 7.34-7.28 (m, 3H), 7.03 (s, 2H), 4.96 (d, $J = 8.0$ Hz, 1H), 4.81 (d, $J = 8.0$ Hz, 1H), 4.19-4.09 (m, 2H), 3.92 (br, 2H), 2.89-2.82 (m, 1H), 1.83 (s, 3H), 1.25-1.16 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): 170.8, 152.0, 148.0, 146.1, 137.3, 136.4, 128.5, 128.1, 128.0, 122.9, 91.8, 62.7, 61.8, 34.2, 28.1, 24.2, 24.1, 23.7, 13.9, 4.5. HRMS: Calcd. for $\text{C}_{30}\text{H}_{39}\text{D}_1\text{N}_1\text{O}_3\text{S}_1$ [$M+1$] 495.2792, found 495.2785. FTIR (neat): 2960, 2868, 1739, 1597, 1462, 1363, 1257, 1189, 1094, 1027, 879, 697 cm^{-1} .

Representative Procedure for the Exhaustive Hydrogenation of Dienes and Enynes

To a solution of diene **14b** (198.9 mg, 0.6 mmol, 100 mol%) in DCM (6 mL, 0.1M) at ambient temperature was added $\text{Ir}(\text{COD})(\text{Pyr})[\text{P}(c\text{-Hex})_3]\text{PF}_6$ (24.2 mg, 0.03 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir

at ambient temperature under 1 atm of hydrogen until complete consumption of substrate, at which point the reaction mixture was evaporated onto silica gel and the product purified by silica gel chromatography.

2-*tert*-Butoxycarbonylamino-3-phenyl-hexa-3,5-dienoic acid ethyl ester (14b)

¹H NMR (400 MHz, CDCl₃): 7.17-7.26 (m, 3H), 7.17 (s, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 11.2 Hz, 1H), 6.23 (dt, *J* = 16.8, 10.5 Hz, 1H), 5.34 (d, *J* = 1.6 Hz, 1H), 5.30 (d, *J* = 1.6 Hz, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.14 (m, 2H), 1.43 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 170.5, 154.7, 138.3, 137.0, 133.3, 131.0, 129.2, 128.2, 127.7, 119.6, 79.9, 61.6, 59.7, 28.2, 13.7. HRMS: Calcd. for C₁₉H₂₆N₁O₄ [M+1] 332.1862, found 332.1862. FTIR (neat): 3439, 2978, 2933, 1740, 1717, 1492, 1367, 1323, 1248, 1162, 1058, 1026, 912, 865, 777, 704 cm⁻¹.

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-phenyl - hexa-3,5-dienoic acid ethyl ester (15b)

¹H NMR (400 MHz, CDCl₃): 7.77 (d, *J* = 7.6 Hz, 2H), 7.60-7.55 (m, 2H), 7.42-7.29 (m, 7H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.44 (d, *J* = 10.8 Hz, 1H), 6.23 (dt, *J* = 17.2, 10.5 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.44 (dd, *J* = 10.2, 7.0 Hz, 1H), 4.26 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.25 - 4.17 (m, 3H), 1.21 (t, *J* = 7.2, 3H). ¹³C NMR (100 MHz, CDCl₃): 170.2, 155.2, 143.7, 143.6, 141.2, 138.0, 136.9, 133.2, 131.2, 129.2, 128.2, 127.8, 127.6, 127.0, 125.1, 125.0, 120.0, 119.9, 67.0, 61.8, 60.0, 47.1, 14.0. HRMS: Calcd. for C₂₉H₂₈N₁O₄ [M+1] 454.2018, found 454.2015. FTIR (neat): 3344, 2979, 1720, 1498, 1449, 1321, 1194, 1047, 912, 758, 740, 703 cm⁻¹.

2-*tert*-Butoxycarbonylamino-3-phenyl-hept-3-en-5-ynoic acid ethyl ester (16b)

¹H NMR (400 MHz, CDCl₃): 7.47-7.36 (m, 2H), 7.37-7.27 (m, 3H), 5.85 (d, *J* = 2.0 Hz, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 7.6 Hz, 1H), 4.19-4.07 (m, 2H), 1.84 (d, *J* = 2.4, 3H), 1.42 (s, 9H), 1.15 (t, *J* = 6.8, 3H). ¹³C NMR (100 MHz, CDCl₃): 170.4, 154.6, 146.1, 136.9, 128.3, 127.9, 110.9, 91.4, 80.0, 61.7, 58.7, 28.2, 13.9, 4.5. HRMS: Calcd. for C₂₀H₂₆N₁O₄ [M+1] 344.1862, found 344.1861. FTIR (neat): 3375, 2978, 2932, 1740, 1717, 1495, 1367, 1325, 1247, 1164, 1054, 1026, 913, 865, 744, 699 cm⁻¹.

2-*tert*-Butoxycarbonylamino-3-phenyl-hexanoic acid ethyl ester (14d)

¹H NMR (300MHz, CDCl₃) Major: 7.33-7.24 (m, 3H), 7.18-7.15 (m, 2H), 5.06 (d, *J* = 9.3 Hz, 1H), 4.47 (t, *J* = 8.1 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.93 (q, *J* = 7.4 Hz, 1H), 1.78 (q, *J* = 7.5 Hz, 2H), 1.45 (s, 9H), 1.27-1.12 (m, 2H), 1.05 (t, *J* = 7.0, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). Minor: 7.30 -7.11 (m, 3H), 7.11 - 7.09 (m, 2H), 4.77 (d, *J* = 8.7 Hz, 1H), 4.55 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.16 (dd, *J* = 16.2, 7.5 Hz, 1H), 1.72 (q, *J* = 7.9 Hz, 2H), 1.39 (s, 9H), 1.24 - 1.19 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100MHz, CDCl₃) Major: 171.8, 155.2, 139.9, 128.4, 128.3, 127.0, 79.8, 60.9, 58.4, 49.1, 33.3, 28.3, 20.5, 13.9, 13.8. HRMS: Calcd. for C₁₉H₃₀N₁O₄ [M+1] 336.2175, found 336.2175. FTIR (mixture, neat): 3442, 3558, 2960, 2932, 2871, 1718, 1496, 1454, 1391, 1367, 1340, 1253, 1171, 1048, 1026, 863, 776, 757, 701 cm⁻¹.

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-phenyl - hexanoic acid ethyl ester (15d)

¹H NMR (400MHz, CDCl₃) Major: 7.78 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.35-7.24 (m, 5H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.33 (d, *J* = 9.2 Hz, 1H), 4.55 (t, *J* = 8.2 Hz, 1H), 4.47 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.36 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.23 (t, *J* = 6.8 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.96 (q, *J* = 7.3 Hz, 1H), 1.80 (q, *J* = 7.6 Hz, 2H), 1.24-1.15 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). Minor: 7.77 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 8.4 Hz, 2H), 7.41 (td, *J* = 7.3, 1.9 Hz, 2H), 7.34-7.24 (m, 5H), 7.10 (d, *J* = 6.8 Hz, 2H), 5.04 (d, *J* = 9.6 Hz, 1H), 4.66 (q, *J* = 4.7 Hz, 1H), 4.45 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.34 (dd, *J*

= 10.8, 6.8 Hz, 1H), 4.22 (t, J = 7.0 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 9.8 Hz, 1H), 1.73 (q, J = 11.4 Hz, 2H), 1.30-1.22 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100MHz, CDCl_3) Major: 171.4, 155.7, 143.9, 143.7, 141.3, 139.5, 128.4, 128.3, 127.7, 127.1, 127.0, 125.1, 125.0, 119.9, 66.9, 61.1, 58.8, 49.1, 47.2, 33.2, 20.5, 13.9, 13.8. HRMS: Calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_1\text{O}_4$ $[\text{M}+1]$ 458.2331, found 458.2336. FTIR (neat): 3442, 3558, 2960, 2932, 2871, 1718, 1496, 1454, 1391, 1367, 1340, 1253, 1171, 1048, 1026, 863, 776, 757, 701 cm^{-1} .

2-*tert*-Butoxycarbonylamino-3-phenyl-heptanoic acid ethyl ester (16d)

^1H NMR (400 MHz, CDCl_3): 7.31-7.11 (m, 5H), 5.04 and 4.78 (major: d, J = 9.2 Hz, minor: d, J = 8.8 Hz, 1H), 4.57 and 4.45 (minor: dd, J = 9.6, 5.2 Hz, major: t, J = 8.0 Hz, 1H), 4.12 and 3.97 (minor: q, J = 7.2 Hz, major: q, J = 7.2 Hz, 2H), 3.18-3.15 and 2.91-2.86 (minor: m, major: m, 1H), 1.82-1.74 (m, 2H), 1.42 and 1.41 (major: s, minor: s, 9H), 1.38-1.01 (m, 7H), 0.85-0.80 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) Major: 171.7, 155.1, 139.9, 128.4, 128.2, 126.9, 79.7, 60.8, 58.4, 49.3, 30.7, 29.5, 28.2, 22.5, 13.8. Minor: 171.7, 155.6, 139.4, 128.4, 128.2, 127.1, 79.7, 61.0, 57.6, 47.8, 31.1, 29.4, 28.2, 22.5, 14.1. HRMS: Calcd. for $\text{C}_{20}\text{H}_{32}\text{N}_1\text{O}_4$ $[\text{M}+1]$ 350.2331, found 350.2329. FTIR (neat): 3359, 2958, 2932, 2870, 1718, 1496, 1454, 1367, 1250, 1171, 1055, 1027, 864, 700 cm^{-1} .

Procedure for Cross-Metathesis Reaction with Diene 14b and 1,4-Diacetoxy-*cis*-2-butene. 7-Acetoxy-2-*tert*-butoxycarbonylamino-3-phenyl-hepta-3,5-dienoic acid ethyl ester (14e)

To a solution of Grubbs' catalyst (17.6 mg, 0.021 mmol, 5 mol%) in DCM (2.1 mL, 0.2 M) was added diene **14b** (139.4 mg, 0.42 mmol, 100 mol%) and 1,4-diacetoxy-*cis*-2-butene (215 mg, 1.25 mmol, 300 mol%), and the solution stirred for 12 h at 40 °C. The volatiles were removed by rotary evaporation, and the residue was purified by silica flash chromatography to provide the title compounds as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 7.35-7.30 (m, 3H), 7.15 (d, J = 6.8 Hz, 2H), 6.63 and 6.37 (minor: d, J = 11.6 Hz, major: d, J = 10.8 Hz, 1H), 6.12 and 6.01 (major: t, J = 13.0 Hz, minor: t, J = 11.6 Hz, 1H), 5.85 and 5.53-5.47 (major: dt, J = 15.2, 6.4 Hz, minor: m, 1H), 5.33 and 5.13 (major: d, J = 7.2 Hz, minor: m, 1H), 5.03 and 4.89 (major: d, J = 7.6 Hz, minor: m, 1H), 4.77 and 4.48 (minor: d, J = 6.8 Hz, major: d, J = 6.0 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.06 and 1.99 (minor: s, major: s, 3H), 1.41 (s, 9H), 1.16 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) Major: 190.6, 154.6, 139.4, 136.7, 130.4, 129.3, 129.2, 129.1, 129.0, 128.2, 127.8, 79.9, 64.6, 61.7, 59.7, 28.2, 20.8, 13.9. HRMS: Calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_1\text{O}_6$ $[\text{M}+1]$ 404.2073, found 404.2069. FTIR (neat): 3375, 3374, 2978, 2923, 1741, 1715, 1493, 1368, 1325, 1230, 1161, 1056, 1025, 976, 865, 777, 704.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Optimization of the hydrogen-mediated reductive coupling of 1,3-enyne **1a** to various ethyl (*N*-sulfinyl)iminoacetates.

Scheme 2.

Optimization of the hydrogen-mediated reductive coupling of 1,3-diyne **9a** to various ethyl (*N*-sulfinyl)iminoacetates.

Scheme 3.

Exhaustive hydrogenation of the diene and enyne side chains of coupling product **1b**, **14b** and **15b** and exhaustive hydrogenation of the enyne side chain of **16b**.

Scheme 4.
Cross-metathesis of **14b** to afford allylic acetate **14e**.

Scheme 5.

Proposed catalytic mechanism as corroborated by deuterium labeling.

Scheme 6.
Proposed models for asymmetric induction.

Table 1

Hydrogen-mediated reductive coupling of 1,3-enynes **1a-8a** and ethyl (*N-tert*-Butanesulfinyl)iminoacetates and regioselective hydrogenation of coupling products **1b-8b** to provide β,γ -unsaturated α -amino acid esters **1c-8c**^a

Entry	Substrate	Coupling Product	mono-Reduction Product
1		1b , 99% (>95:5 d.r.)	1c , 74%
2		2b , 96% (>95:5 d.r.)	2c , 70%
3		3b , 81% (>95:5 d.r.)	3c , 79%
4		4b , 76% (>95:5 d.r.)	4c , 81%
5		5b , 66% (>95:5 d.r.)	5c , 93%
6		6b , 68% (>95:5 d.r.) 7b , 70% (>95:5 d.r.)	6c , 80% 7c , 87%
7		8b , 94% (>95:5 d.r.)	8c , 81%

^aThe reductive coupling of **1a-8a** was performed at ambient temperature, in accordance with the reaction conditions cited in Scheme 1 at 0.3 M and at 35 °C under otherwise identical conditions. The reductive couplings were complete in less than 8 hours. The partial hydrogenation of **1b-8b** to provide β,γ -unsaturated amino acid esters **1c-8c** was performed at ambient pressure and temperature using Wilkinson's catalyst in toluene solvent. See experimental section for detailed reaction conditions.

Table 2

Hydrogen-mediated reductive coupling of 1,3-diynes **9a-13a** and ethyl *N*-(2,4,6-triisopropylbenzenesulfinyl) iminoacetate^a

Entry	Substrate	Regioisomeric Coupling Products	
1
2
3
4
5			N/A

^aThe reductive coupling of **9a-12a** was performed at ambient temperature, in accordance with the reaction conditions cited in Scheme 2. The reductive coupling of **13a** was performed at 35 °C in DCM-THF (2:1). The reductive couplings were complete in less than 2 hours. See experimental section for detailed reaction conditions.