JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

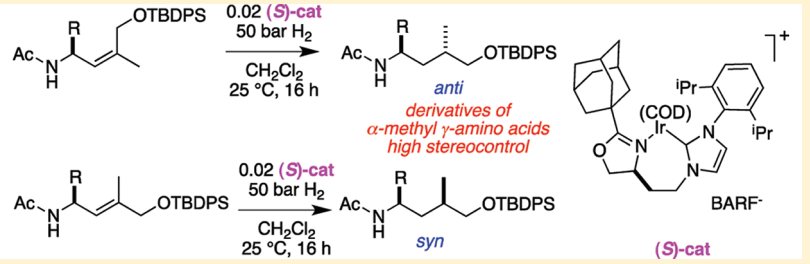
Asymmetric Syntheses of α-Methyl γ-Amino Acid Derivatives

Ye Zhu, Sakunchai Khumsubdee, Amber Schaefer, and Kevin Burgess*

Department of Chemistry, Texas A & M University, Box 30012, College Station, Texas 77841, United States

Supporting Information

ABSTRACT: This project was undertaken to demonstrate the potential of asymmetric hydrogenations mediated by the chiral, carbene-oxazoline analogue of Crabtree's catalyst "**cat**" in asymmetric hydrogenations of allylic amine derivatives of amino acids. Peripheral features of the substrates (protecting groups, functional groups related by redox processes, and alkene geometries) were varied to optimize the stereochemical vectors exerted by the substrate and align them with the catalyst vector. *N*-Acetyl-protected, *O*-TBDPS-protected allylic substrates **9a**−**e** emerged as the best for this reaction; *syn*-products were formed from the *E*-alkenes, while the *Z*-isomers gave *anti*-target materials, both with high diastereoselectivities. This study featured asymmetric catalysis to elaborate optically active substrates into more stereochemically complex chirons; we suggest that the approach used, optimization of stereocontrol by varying peripheral aspects of the *substrate*, tends to be easier than *de novo* catalyst design for each substrate type. In other words, optimization of the substrate vector is likely to be more facile than enhancement of the catalyst vector via ligand modifications.



INTRODUCTION

γ-Amino acids are important in medicinal chemistry. For instance, γ-aminobutyric acid (GABA) has pivotal neurological functions as a modulator of synaptic responses; these relate to its interactions with various types of receptors, even ones in different catagories, including ligand-gated ion channels[1−3] and some G-coupled protein receptors.[4] Several neurological diseases can be attributed to imbalances of GABA levels in the central nervous system, and hence analogues of GABA have therapeutic potential.[5,6] *Lipophilic* analogues of GABA have better bioavailabilities, particularly with repect to permeation of the blood−brain barrier, than GABA itself.[7−9] *Chiral* derivatives of GABA with side-chains appropriate for interactions with protein surfaces can *selectively* interact with some of the receptors modulated by GABA and thus have useful pharmacological properties.[10] Consequently, lipophilic, chiral analogues of GABA have emerged as important pharmaceuticals such as (*R*)-baclofen,[11−13] (*S*)-pregabalin,[14−16] and (*S*)-vigabatrin.[10,17,18]

This paper is specifically about α-substituted γ-amino acids. Consistent with the discussion above, these fragments are found in some experimental therapeutics, including those shown in Figure 1. α-Substituted γ-amino acids are also found in natural products in the tubulysin series. Baclofen,[19−21] pregabalin,[22] vigabatrin,[10] the experimental therapeutics in Figure 1, and the tubulysins *all* feature one particular enantiomeric form. Consequently, asymmetric syntheses of these fragments are potentially important for design of CNS pharmaceuticals and in natural product syntheses. Literature preparations of these materials tend to feature somewhat classical and dated approaches like resolutions and diastereoselective reactions involving chiral auxiliaries.[23−25]

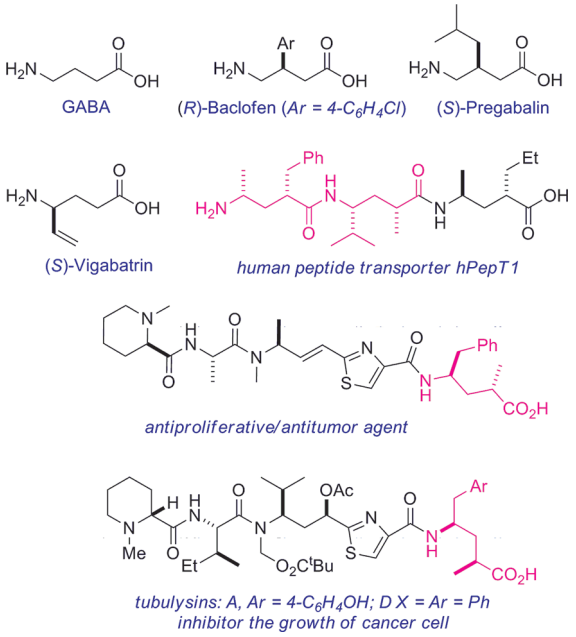


Figure 1. Important compounds containing optically active γ-amino acids.

Received: June 10, 2011
Published: August 18, 2011

Here we describe how chiral analogues of Crabtree's catalyst[26,27] can be used to prepare compounds **1** in this series. Chiral analogues of Crabtree's catalyst are special insofar as they can mediate hydrogenations of alkenes without an obvious coordinating functional group.[26] Interactions of chiral Crabtree's catalysts analogues with the requisite substrates have never been studied before, so there are two ways to approach this type of situation. The first is to *modify the catalyst* so that it gives high stereoselectivities for each substrate. Catalyst development is slow and ideal ligand structures and conditions cannot be predicted with certainty, so this is a poor strategy. We hypothesized that a more effective approach would be to *modify the substrate* (alkene geometries and protecting/functional groups) so that stereoselectivities obtained from a good catalyst become better. Thus our objective in this research was to modify optically pure amino acid derivatives into alkenes that could be hydrogenated with high stereoselectivities by matching the influence of our chiral catalyst **cat**[28,29] with the stereochemical vectors exerted by the substrate (Figure 2).

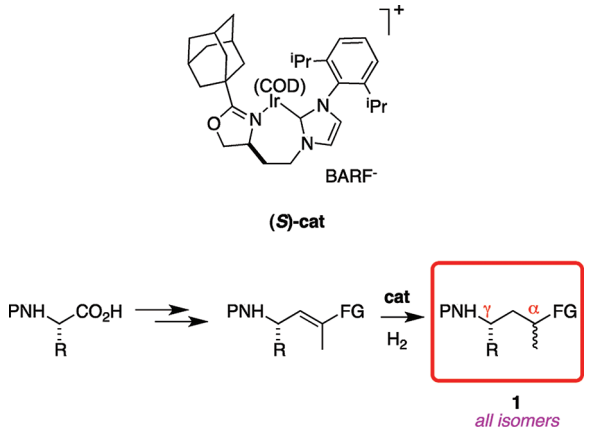


Figure 2. Proposed asymmetric hydrogenation of optically pure allyl amines from amino acids.

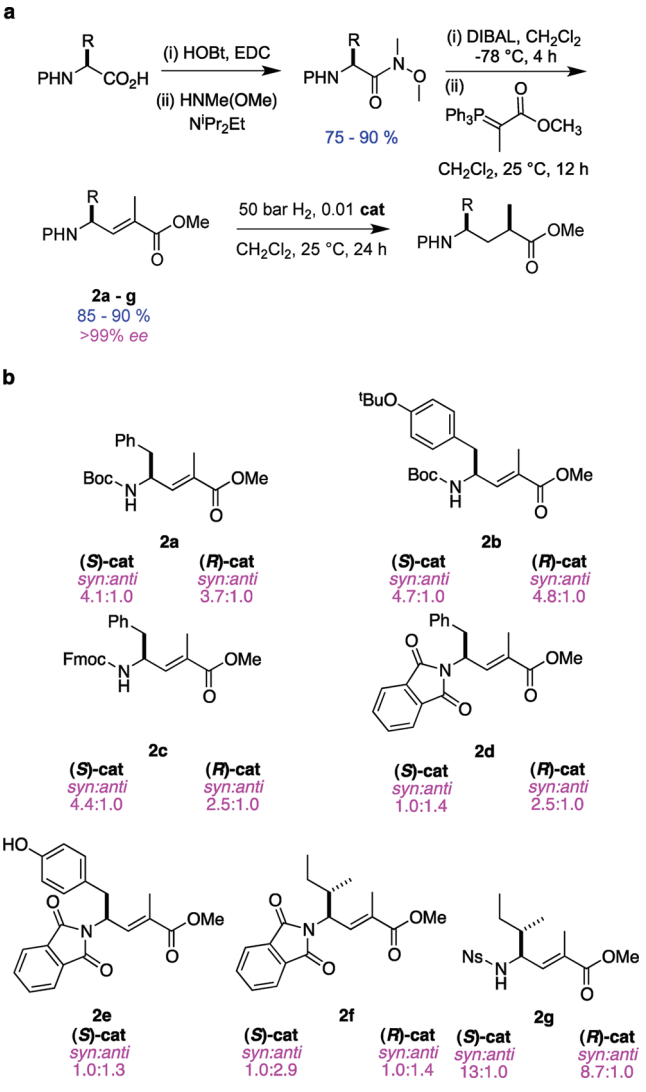
RESULTS AND DISCUSSION

To begin this project, amino acids with *tert*-butyloxycarbonyl, phthalyl, or nosyl (here 2-nitrophenylsulfonyl, Ns) *N*-protecting groups were converted to known[30] Weinreb amide[31] derivatives and then reduced to aldehydes.[30] These stereochemically delicate intermediates were not isolated, but instead they were immediately converted to the allyl amines **2**. These alkenes were then subjected to hydrogenations mediated by **cat**; the best stereoselectivity obtained in this series was good (13:1.0; Scheme 1), but there were possibilities for further improvements, and these were explored next.

One of our previous studies on acyclic stereocontrol using **cat** featured chiral allylic alcohol substrates derived from lactic acid.[32] That research showed **cat** delivered hydrogen to the ester **A** with only moderate diastereofacial selectivity, but the allylic *diol* substrates **B** and **C** were reduced with much higher selectivities. Extrapolating those observations suggested substrates **D**, having similar structural modifications, would give better stereoselectivies in the hydrogenation reactions (Figure 3).

Scheme 2 shows how the concept outlined in Figure 3 was tested. Ester **2a** (R = Bn) was reduced to the allylic alcohol **3a**, and then several substrates with different *N*- and *O*-protection modalities were prepared and hydrogenated using **cat**. These experiments showed a modest stereoselectivity for the *N*-Boc substrate **3a**, while the free amine **5a** gave no significant conversion.

Scheme 1. (a) Preparation and (b) Asymmetric Hydrogenation of γ-Aminobutenoate Esters



However, an excellent stereoselectivity was obtained for **6a**, a substrate that has a bulky *N*-silyl protecting group and a free hydroxyl; the only drawback with this reaction was that the catalyst loading, 5 mol %, was a little high. Consequently, several more substrates were prepared and tested. Those experiments showed that the potentially coordinating formamide group of **10a** correlated with poor conversion and selectivity. Interestingly, the *N*-Boc and silyl alcohol **7a** gave a good selectivity in favor of the *anti*-product; this is opposite to all the other substrates discussed so far. The best stereoselectivity in the series was eventually obtained from the acetamido silyl ether (*E*)-**9a**. Hydrogenation of this compound was highly *syn*-selective, and only 2 mol % of **cat** was required. High *syn*-selectivity was also observed for the corresponding *N*-trifluoroacetate, but slightly more catalyst was necessary to obtain 100% conversion. In summary, hydrogenation of the acetamido silyl ether (*E*)-**9a** provided the answer to the challenge of obtaining the *syn*-isomer in the phenylalanine series, and hence we turned our attention to the *anti*-isomers.

Review of the data accumulated so far indicated *substrate control* for most, though not all, of the alkenes hydrogenated using **cat**.

dx.doi.org/10.1021/jo201215c |J. Org. Chem. 2011, 76, 7449–7457

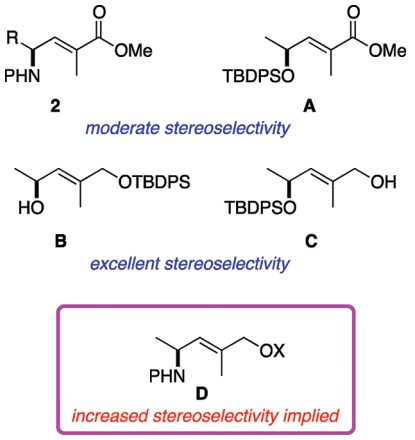


Figure 3. Proposed substrate modifications for enhancing the stereoselectivities in asymmetric hydrogenations.

This was *not* predicted on the basis of most of our previous studies,[32−36] but it is not surprising either. Most of the allylic amines used in these experiments have substituents that are very large, capable of coordination, or both. As a guide, it seemed that 1,3-allylic strain effects[37] in the substrate were dominant in most of these reactions (Figure 4a and b). Influences of 1,3-allylic strain are enhanced for *Z*-alkenes relative to their *E*-isomers, so we saw hydrogenation of the *cis*-alkenes as a gateway to *anti*-isomers (Figure 4c).

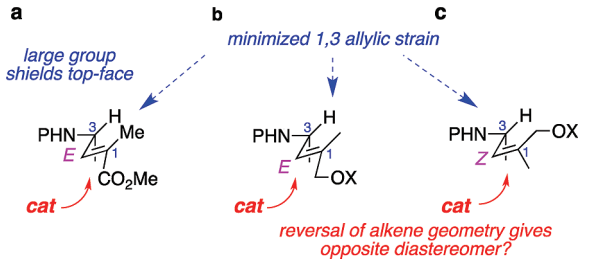


Figure 4. Hypothesis for obtaining the *anti*-skeletons of α-methyl γ-amino acid derivatives.

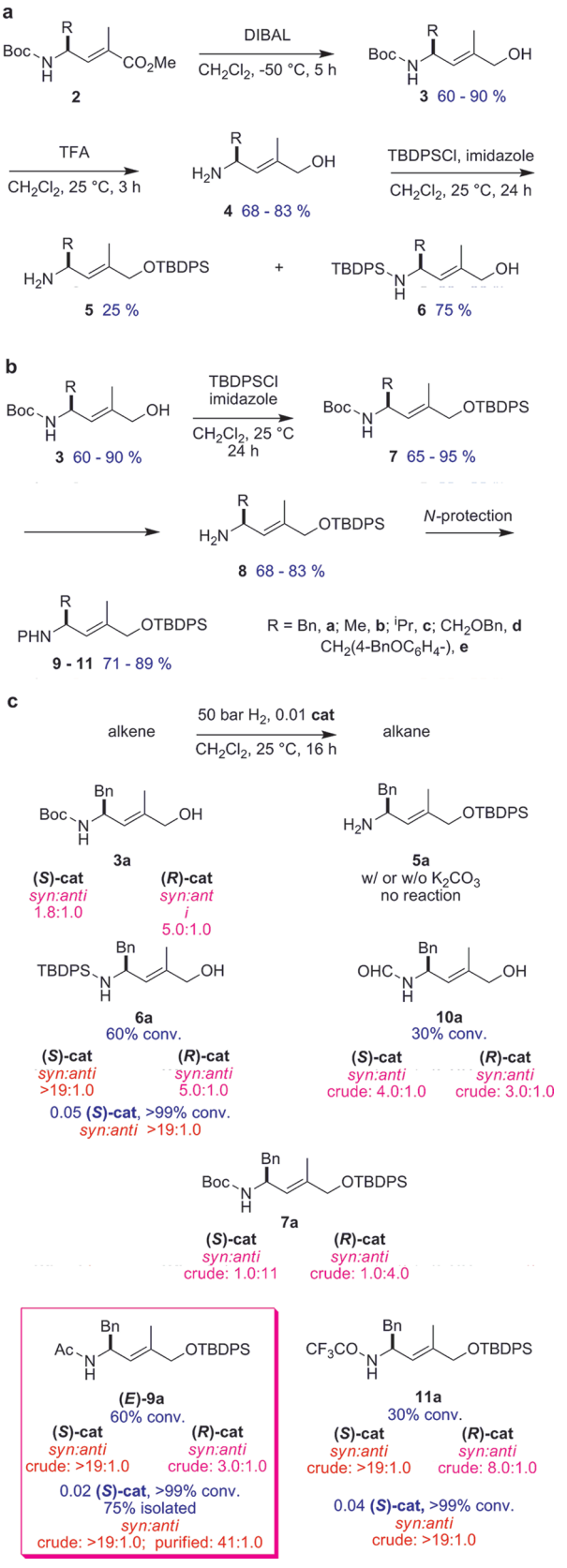
Scheme 3 shows the syntheses and hydrogenations of the *Z*-allylic alcohol derivative **9a**, formed via the Still−Gennari reaction,[38] to test the thesis presented in Figure 4. Gratifyingly, a high stereoselectivity was obtained without modification of the substrate and using only 2 mol % catalyst. Thus the *anti*-skeleton of the target materials was obtained for the phenylalanine derivative (series **a**).

Other substrates were prepared in the final phase of this project to test if syntheses of the *syn*- and *anti*isomers of the phenylalanine derivatives **1a** (Schemes 2 and 3) could be extrapolated to the allylic amines from other amino acids. Preparations of the substrates follow the sequences already outlined here, and full details are given in the Supporting Information. Table 1 shows the results obtained for eight more substrates, specifically the *E*- and *Z*-forms of **9b**−**e**. Throughout excellent stereoselectivities were obtained, the conversions were complete, and only 2 mol % of catalyst was used.

CONCLUSIONS

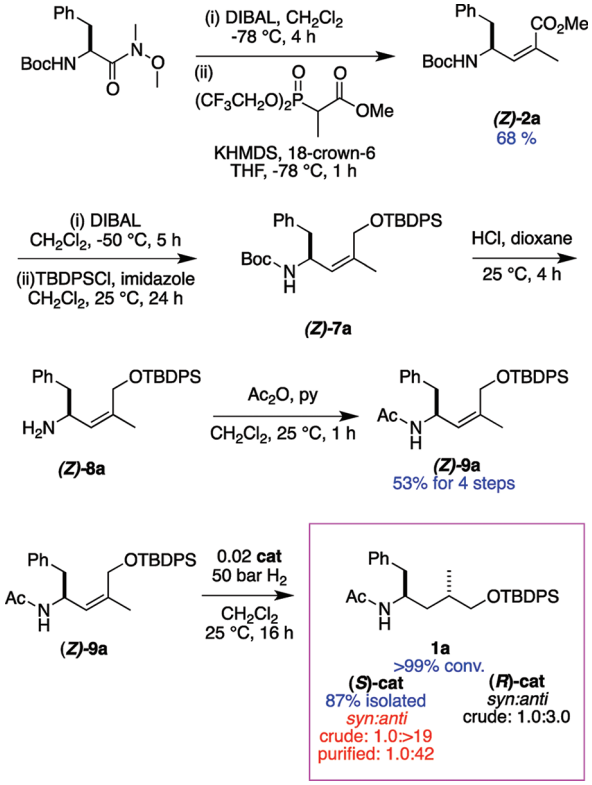
Review of the products indicated in Table 1 shows that we have made carbon frameworks corresponding to appropriate chirons for all of the significant molecules shown in Figure 1 and an epimer of each. Perhaps more importantly, however, is a

Scheme 2. (a, b) Synthesis and (c) Asymmetric Hydrogenation of *N*- or *O*-Protected Amino Alcohol Derivatives



dx.doi.org/10.1021/jo201215c |J. Org. Chem. 2011, 76, 7449–7457

Scheme 3. Synthesis and Hydrogenation of (*Z*)-9a

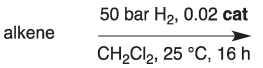


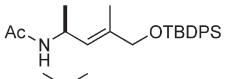
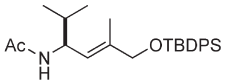
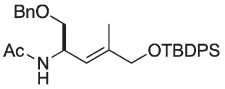
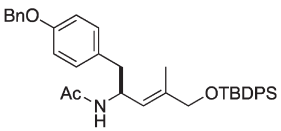
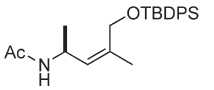
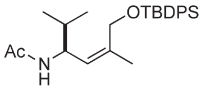
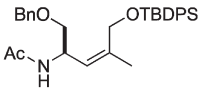
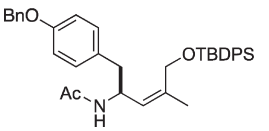
philosophical conclusion about the *tactics* used to reach this goal. Many organic methodology papers emphasize how a particular catalyst can transform a variety of substrate types with high stereoselectivities. This approach is fine for *enantioselective* reactions, and it is wholly justifiable if the products have intrinsic value. However, researchers wishing to apply new catalysts for *stereocontrolled reactions of chiral substrates* will usually find it easier to modify peripheral features of a new *substrate* (e.g., protecting groups, functional groups related via oxidation levels, alkene geometries) than the *catalyst*. That strategy was used here, and our experience indicates that in the process of elaborating structures of stereochemically complex molecules, substrate modifications are more rewarding than the somewhat arbitrary process of catalyst discovery and optimization.[28,39,40] In other words, it is easier to optimize substrate vectors than catalyst vectors. Several established concepts (protecting group size, 1,3-allylic strain, etc.) can be used to understand and predict the effects of changes in the substrate, whereas similar perturbations to the catalyst are harder to make and have effects that are less predictable. This should not be taken to mean that substrate modifications and the substrate vector *always* correlate in readily understable ways, as examples in this work demonstrate. However, substrate vectors tend to be the ones to optimize first because they are easier to make, and sometimes they *do* correlate in rational ways with substrate structures. It follows that accounts such as this, showing the strengths *and* limitations of the catalyst with respect to a range of substrates, are most useful to potential practioners of the method.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out under an inert atmosphere (nitrogen or argon where stated) with dry solvents under anhydrous conditions. Glassware for anhydrous reactions was dried in an oven at 140 °C for a minimum of 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at a high commercial quality (typically 97% or higher) and used without further purification, unless otherwise stated. High field NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts of ^{1}H and ^{13}C spectra were referenced to the NMR solvents. Flash chromatography was performed using silica gel (230−600 mesh). Thin layer chromatography was performed using glass plates coated with silica gel 60 F254. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dq = double quartet m = multiplet, br = broad.

Table 1. Hydrogenation of Varying α-Substituted Alkene Substrates Using (*S*)-cat



9	R	syn:anti[a,b] crude	syn:anti[a,b] purified	isolated yield (%)
(*E*)-b		19:1.0	39:1.0	90
(*E*)-c		49:1.0	49:1.0	91
(*E*)-d		12:1.0	40:1.0	75
(*E*)-e		24:1.0	43:1.0	89
(*Z*)-b		1.0:9.0	1.0:40	72
(*Z*)-c		1.0:19	1.0:43	83
(*Z*)-d		1.0:11	1.0:38	73
(*Z*)-e		1.0:18	1.0:49	83

[a] Determined via HPLC on an unbonded silica 300 Å. [b] Stereochemistry was determined by comparison with known compound (see Supporting Information).

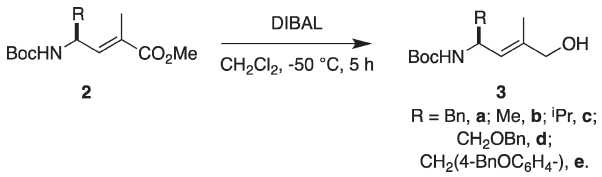
Synthesis of α-Methyl γ-Amino Acid Derivatives 2. α-Methyl γ-amino acid alkene derivatives (*E*)-**2** and (*Z*)-**2** were synthesized via a known procedure.[1−6]

(*S*)-*E*-Methyl 4-((*tert*-Butoxycarbonyl)amino)-2-methyl-5-phenylpent-2-enoate (*E*-2a). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.08 (5H, m), 6.56 (1H, d, *J* = 12 Hz), 4.72−4.54 (2H, br), 3.75 (3H, s), 2.98 (1H, dd, *J* = 6.0, 14 Hz), 2.79 (1H, dd, *J* = 12, 18 Hz), 1.71 (3H, d, *J* = 1.1 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.0, 137.9, 129.9, 128.5, 126.6, 125.0, 79.9, 52.2, 50.4, 41.4,

dx.doi.org/10.1021/jo201215c |*J. Org. Chem.* 2011, 76, 7449–7457

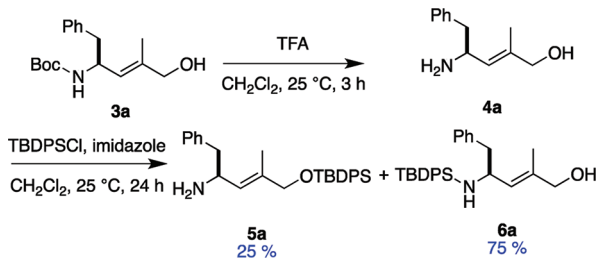
28.6, 12.9. HRMS (ESI): exact mass calcd for $C_{18}H_{25}LiNO_4$ $[M + Li]^+$ 326.1944, found 326.2052.

General Procedure for Syntheses of Compounds (*E*)-3, Illustrated for 3a.



The phenylalanine derivative **2a** (0.9 g, 2.7 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to −50 °C. A DIBAL solution (1 M in hexane) (8.1 mL, 8.1 mmol) was added slowly, and then the reaction was stirred at −50 °C for 5 h and then quenched by addition of EtOAc (0.5 mL). Saturated potassium sodium tartrate solution (20 mL) was added, and the mixture was warmed to 25 °C and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 30% EtOAc/hexanes as eluent giving (*S*)-*E*-*tert*-butyl (5-hydroxy-4-methyl-1-phenylpent-3-en-2-yl)carbamate (**3a**) as a colorless oil (0.7 g, 2.4 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (5H, m), 5.31 (1H, dq, J = 1.5, 9.0 Hz), 4.55 (2H, br), 3.97 (2H, s), 2.94 (1H, dd, J = 6.0, 13 Hz), 2.73 (1H, dd, J = 7.2, 13 Hz), 1.51 (3H, d, J = 1.5 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.0, 137.9, 129.9, 128.5, 126.6, 125.0, 79.6, 76.9, 68.1, 50.0, 42.3, 28.7, 14.2. HRMS (ESI): exact mass calcd for $C_{17}H_{25}NNaO_3$ $[M + Na]^+$ 314.1732, found 314.1768.

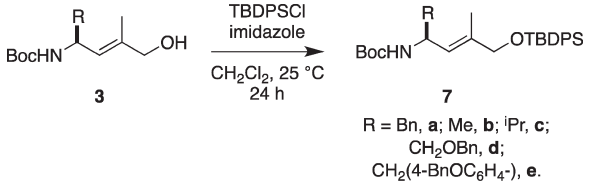
Synthesis of Phenylalanine Derivative (*E*)-5a.



The Boc-protected allylamine **3a** (1.4 g, 4.9 mmol) was dissolved in 30 mL of CH_2Cl_2 and cooled to 0 °C. Trifluoroacetic acid (25 mL) was added in one portion, and then the mixture was warmed to 25 °C and stirred for 3 h. Solvent was evaporated under a stream of nitrogen, and the residue was dissolved in 20 mL of CH_2Cl_2 and washed with 20 mL of saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, and solvent was removed *in vacuo*. The residue **4a** was used without further purification.

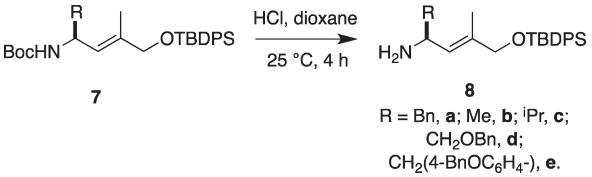
Allylic amine **4a** was dissolved in CH_2Cl_2 (20 mL), and imidazole (1.2 equiv) was then added. *tert*-Butyldiphenylsilyl chloride (1.1 equiv) was then added slowly, and the resulting mixture was stirred for 1 h at 25 °C. The reaction was quenched with 20 mL of saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 5% MeOH/CH_2Cl_2 to give 25% of compound **5a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (4H, m), 7.43−7.34 (5H, m), 7.30−7.18 (6H, m), 5.43 (1H, dd, J = 1.2, 8.8 Hz), 5.30 (1H, s), 4.01 (2H, s), 3.06 (1H, m), 2.69 (2H, t, J = 6.3 Hz), 1.48 (3H, d, J = 0.9 Hz), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 135.8, 135.2, 134.0, 129.9, 129.8, 128.6, 128.3, 127.9, 126.4, 68.6, 50.8, 44.8, 27.1, 19.6, 14.0. HRMS (ESI): exact mass calcd for $C_{28}H_{36}NOSi$ $[M + H]^+$ 430.2566, found 430.2502.

General Procedure for Syntheses of Compounds (*E*)-7, Illustrated for 7a.



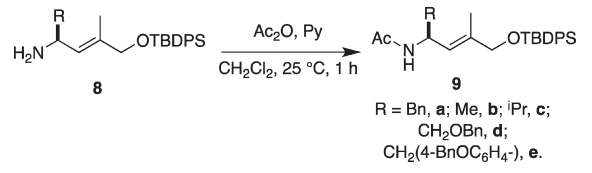
Imidazole (0.7 g, 10 mmol) was added to a stirred solution of Boc-protected allylic amine **3a** (2.7 g, 9.4 mmol) in CH_2Cl_2 (20 mL). *tert*-Butyldiphenylsilyl chloride (2.5 mL, 9.9 mmol) was then added slowly, and the resulting mixture was stirred for 24 h. Water (30 mL) was added to the reaction, and the layers were separated. The aqueous layer was extracted using CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 10% EtOAc/hexanes as eluent giving (*S*)-*E*-*tert*-butyl (5-((*tert*-butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)carbamate (**7a**) (4.1 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.66 (4H, m), 7.48−7.37 (6H, m), 7.29−7.19 (5H, m), 5.41 (1H, d, J = 9.3 Hz), 4.72−4.50 (1H, br), 4.50−4.39 (1H, br), 4.01 (2H, s), 3.05−2.90 (1H, m), 2.75 (1H, dd, J = 7.5, 13 Hz), 1.47 (9H, s), 1.44 (3H, s), 1.09 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 137.8, 137.2, 135.6, 135.5, 133.6 (2 peaks), 129.8, 129.7, 128.2, 127.7, 126.2, 123.0, 79.2, 67.8, 49.6, 42.2, 28.5, 26.9, 19.3, 13.8. HRMS (ESI): exact mass calcd for $C_{33}H_{43}LiNO_3Si$ $[M + Li]^+$ 536.3172, found 536.3175.

General Procedure for Syntheses of Compounds (*E*)-8, Illustrated for 8a.



A dioxane solution of 4 M HCl (3.0 mL, 12 mmol) was added to the Boc-protected amine **7a** (0.5 g, 1.0 mmol) in Et_2O 30 mL, and the mixture was stirred at 25 °C for 4 h. The mixture was made basic by addition of a 10% NaOH solution, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The product **8a** was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (4H, m), 7.43−7.34 (6H, m), 7.30−7.18 (5H, m), 5.43 (1H, dd, J = 1.2, 8.8 Hz), 5.30 (1H, s), 4.01 (2H, s), 3.87 (1H, q), 2.69 (2H, t, J = 6.3 Hz), 1.52−1.31 (1H, br), 1.48 (3H, d, J = 0.9 Hz), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 136.6, 135.8, 135.7, 133.7, 133.6, 130.1, 129.9, 128.8, 128.0, 127.1, 120.4, 68.6, 50.8, 44.8, 27.1, 19.6, 14.0. HRMS (ESI): exact mass calcd for $C_{28}H_{36}NOSi$ $[M + H]^+$ 430.2566, found 430.2502.

General Procedure for Syntheses of Allylic Acetates (*E*)-9.

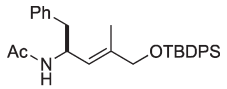


Allylic amine **8** was dissolved in CH_2Cl_2 (0.1M), and pyridine (1.5 equiv) was added to the solution. Acetic anhydride (1.1 equiv)

dx.doi.org/10.1021/jo201215c |*J. Org. Chem.* 2011, 76, 7449–7457

was added and the mixture was stirred at 25 °C for 1 h. The solution was washed with 1 M HCl(aq) (10 mL), saturated $NaHCO_3$(aq) (10 mL), and water (10 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using 50% EtOAc/hexanes as eluent.

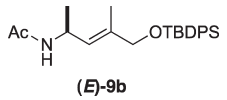
(*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)acetamide (*E*)-9a.



(*E*)-9a

Product was obtained as a colorless oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.48−7.36 (6H, m), 7.30−7.17 (5H, m), 5.44 (1H, dd, J = 1.5, 9.0 Hz), 5.26 (1H, d), 5.01−4.90 (1H, m), 4.01 (2H, s), 2.96 (1H, dd, J = 4.8, 13 Hz), 2.79 (1H, dd, J = 7.5, 13 Hz), 1.97 (3H, s), 1.28 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 138.3, 137.8, 135.7, 133.9, 133.7, 130.1, 129.9, 128.5, 127.9, 126.5, 122.2, 67.8, 48.2, 41.7, 27.1, 23.7, 19.5, 14.1. HRMS (ESI): exact mass calcd for $C_{30}H_{38}NO_2Si$ $[M + H]^+$ 472.2672, found 472.2666.

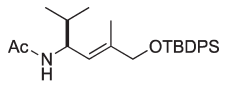
(*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*)-9b.



(*E*)-9b

Product was obtained as a colorless oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.68 (4H, m), 7.47−7.39 (6H, m), 5.40−5.38 (2H, m), 4.82−4.72 (1H, m), 4.08 (2H, s), 1.97 (3H, s), 1.66 (3H, s), 1.22 (3H, d, J = 6.6 Hz), 1.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 136.9, 135.6, 133.7, 133.6, 129.7, 127.7, 125.1, 68.0, 43.1, 26.9, 23.6, 21.9, 19.3, 13.9. HRMS (ESI): exact mass calcd for $C_{24}H_{34}NO_2Si$ $[M + H]^+$ 396.2359, found 396.2570.

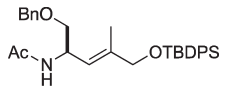
(*S*)-*E*-*N*-(6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhex-4-en-3-yl)acetamide (*E*)-9c.



(*E*)-9c

Product was obtained as a colorless oil (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.63 (4H, m), 7.42−7.28 (6H, m), 5.42 (1H, d, J = 6.0 Hz), 5.22 (1H, d, J = 6.0 Hz), 4.59−4.45 (1H, m), 4.07 (2H, s), 1.97 (3H, s), 1.83−1.70 (1H, m), 1.63 (3H, s), 1.07 (9H, s) 0.89 (6H, dd, J = 6.3, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 138.3, 135.5 (2 peaks), 133.7, 133.6, 129.7, 127.7, 121.5, 67.9, 51.9, 32.9, 26.8, 23.6, 19.3, 18.7, 18.1, 14.2. HRMS (ESI): exact mass calcd for $C_{26}H_{38}NO_2Si$ $[M + H]^+$ 424.2672, found 424.2682.

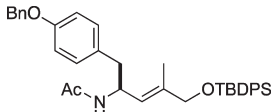
(*R*)-*E*-*N*-(1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*)-9d.



(*E*)-9d

Product was obtained as a colorless oil (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.70 (4H, m), 7.44−7.36 (11H, m), 5.82 (1H, d, J = 7.5 Hz), 5.69 (1H, dd, J = 3.0, 15 Hz), 5.05−4.92 (1H, m), 4.58 (2H, d, J = 2.7 Hz), 4.11 (2H, s), 3.60 (1H, dd, J = 5.0, 7.5 Hz), 3.52 (1H, dd, J = 5.0, 8.4 Hz), 2.00 (3H, s), 1.70 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 138.4, 138.1, 135.6, 133.7, 133.6, 129.7, 128.5, 128.2, 127.7, 73.3, 72.5, 68.0, 46.9, 26.9, 23.5, 19.3, 14.0. HRMS (ESI): exact mass calcd for $C_{31}H_{40}NO_3Si$ $[M + H]^+$ 502.2777, found 502.2801.

(*S*)-*E*-*N*-(1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*E*)-9e.

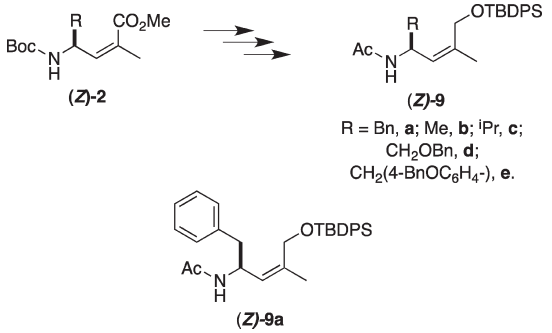


(*E*)-9e

Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (4H, m), 7.48−7.40 (11H, m), 7.12 (2H, dd, J = 13 Hz), 6.92 (2H, d, J = 8.0 Hz), 5.47 (1H, d, J = 0.9 Hz), 5.39 (1H, d, J = 6.0 Hz), 5.07 (2H, s), 5.01−4.89 (1H, m), 4.05 (2H, s), 2.92 (1H, dd, J = 3.0, 12 Hz), 2.85 (1H, dd, J = 0.9, 9.0 Hz), 2.00 (3H, s), 1.49 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 157.4, 138.0, 137.2, 135.6, 133.7, 133.5, 130.8, 130.0, 129.7, 128.6, 128.0, 127.7, 127.5, 122.2, 114.7, 70.0, 67.7, 48.2, 40.7, 26.9, 23.5, 19.3, 14.0. HRMS (ESI): exact mass calcd for $C_{37}H_{44}NO_3Si$ $[M + H]^+$ 578.3090, found 578.3075.

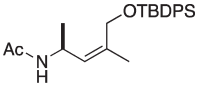
Synthesis of (*Z*)-9. (*Z*)-**9** was synthesized from (*Z*)-**2** by using the same procedure as for synthesis of compounds (*E*)-**9**.

(*S*)-*Z*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)acetamide (*Z*)-9a.



Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.45−7.37 (6H, m), 7.25−7.17 (3H, m), 7.08−7.05 (2H, m), 5.23 (1H, d, J = 6.0 Hz), 5.08 (1H, d, J = 15 Hz), 4.74−4.62 (1H, m), 4.14 (1H, d, J = 7.2 Hz), 3.97 (1H, d, J = 13 Hz), 2.82 (1H, dd, J = 0.6, 3.0 Hz), 2.69 (1H, dd, J = 6.9, 13 Hz), 1.87 (3H, s), 1.80 (3H, s), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 138.4, 137.4, 135.6, 135.6, 133.5, 129.7, 129.6, 128.2, 127.8, 127.7, 126.3, 125.1, 62.5, 48.2, 41.4, 26.8, 23.4, 21.1, 19.3. HRMS (ESI): exact mass calcd for $C_{30}H_{38}NO_2Si$ $[M + H]^+$ 472.2672, found 472.2723.

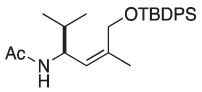
(*S*)-*Z*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*)-9b.



(*Z*)-9b

Product was obtained as a colorless oil (70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.69 (4H, m), 7.46−7.41 (6H, m), 5.28−5.26 (1H, m), 5.12−5.09 (1H, m), 4.59−4.50 (1H, m), 4.30 (2H, dd, J = 12, 39 Hz), 1.88 (3H, s), 1.83 (3H, s), 1.08 (9H, s), 0.90 (3H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 135.6, 135.5, 134.8, 133.9, 129.6, 127.7, 63.2, 53.9, 43.6, 29.2, 26.8, 22.5, 21.8. HRMS (ESI): exact mass calcd for $C_{24}H_{34}NO_2Si$ $[M + H]^+$ 396.2359, found 396.2570.

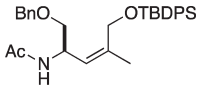
(*S*)-*Z*-*N*-(6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhex-4-en-3-yl)acetamide (*Z*)-9c.



(*Z*)-9c

Product was obtained as a colorless oil (71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (4H, m), 7.48−7.38 (6H, m), 5.28 (1H, d, J = 8.7 Hz), 5.09 (1H, dd, J = 1.2, 9.4 Hz), 4.39−4.36 (1H, m), 4.34 (1H, s), 4.28 (1H, d, J = 12 Hz), 1.91 (3H, s), 1.86 (3H, d, J = 1.2 Hz), 1.79−1.69 (1H, m), 1.09 (9H, s), 0.85 (3H, d, J = 3.9 Hz), 0.83 (3H, d, J = 3.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 138.7, 135.7, 133.7 (2 peaks), 129.6, 127.7, 124.6, 62.8, 52.0, 32.7, 26.9, 23.5, 21.4, 19.4, 18.6, 18.3. HRMS (ESI): exact mass calcd for $C_{26}H_{38}NO_2Si$ $[M + H]^+$ 424.2672, found 424.2689.

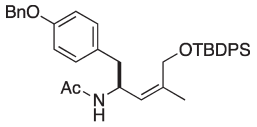
(*R*)-*Z*-*N*-(1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*)-9d.



(*Z*)-9d

Product was obtained as a colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.68 (4H, m), 7.47−7.30 (11H, m), 5.69 (1H, d, J = 6.9 Hz), 5.30 (1H, dd, J = 1.5, 9 Hz), 4.71−4.66 (1H, m), 4.48 (2H, d, J = 2.1 Hz), 4.39 (1H, dd, J = 0.9, 12 Hz), 4.24 (1H, d, J = 13 Hz), 3.48−3.35 (2H, m), 1.89 (3H, s), 1.85 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.8, 138.0, 135.6, 133.6 (2 peaks), 129.7, 128.5, 127.8, 127.7, 123.8, 73.2, 72.4, 62.8, 46.9, 26.9, 23.4, 21.4, 19.3. HRMS (ESI): exact mass calcd for $C_{31}H_{40}NO_3Si$ $[M + H]^+$ 502.2777, found 502.2758.

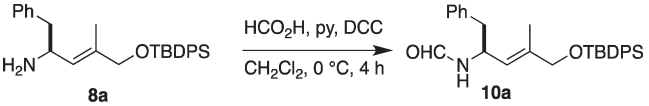
(*S*)-*Z*-*N*-(1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)-oxy)-4-methylpent-3-en-2-yl)acetamide (*Z*)-9e.



(*Z*)-9e

Product was obtained as a colorless oil (75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (4H, m), 7.48−7.40 (11H, m), 7.12 (2H, d, J = 13 Hz), 6.92 (2H, d, J = 8.0 Hz), 5.47 (1H, d, J = 0.9 Hz), 5.39 (1H, d, J = 6.0 Hz), 5.07 (2H, s), 5.01−4.89 (1H, m), 4.05 (2H, s), 2.92 (1H, dd, J = 3.0, 12 Hz), 2.85 (1H, dd, J = 0.9, 9.0 Hz), 2.00 (3H, s), 1.49 (3H, s), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 157.6, 138.1, 135.2 (2 peaks), 134.2, 134.0, 131.4, 129.7, 128.4, 127.4, 126.9, 126.3, 114.2, 70.1, 62.3, 48.7, 40.6, 26.2, 23.3, 20.9, 19.2. HRMS (ESI): exact mass calcd for $C_{37}H_{44}NO_3Si$ $[M + H]^+$ 578.3090, found 578.3077.

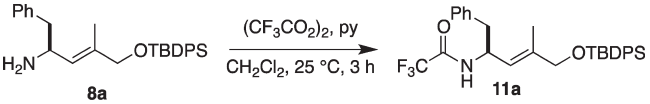
Synthesis of (*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)formamide (10a).



8a **10a**

Formic acid (0.2 g, 5 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise to a solution of DCC (0.5 g, 2.5 mmol) in 3 mL of CH_2Cl_2 at 0 °C. The mixture was stirred for 5 min and then added to an ice bath cooled solution of *O*-TBDPS-allylic amine **8a** (0.4 g, 1 mmol) in 3 mL of pyridine. The mixture was then stirred in ice bath for 4 h. The solid was removed via filtration and washed with Et_2O (10 mL). The combined extracts were evaporated and purified by flash chromatography using 40% EtOAc/hexanes giving formamide **10a** as a colorless oil (0.4 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.63 (4H, m), 7.48−7.31 (6H, m), 7.29−7.19 (5H, m), 5.45 (1H, dd, J = 1.2, 9.1 Hz), 5.31 (1H, d, J = 6.0 Hz), 5.10−5.00 (1H, m), 4.02 (1H, s), 2.98 (1H, dd, J = 5.4, 13 Hz), 2.82 (1H, dd, J = 7.5, 13 Hz), 1.59 (2H, s), 1.47 (3H, d, J = 0.6 Hz), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 160.0, 138.4, 138.0, 137.2, 136.5, 135.5 (2 peaks), 133.6, 133.5, 129.8, 129.7 (2 peaks), 126.9, 126.5, 122.3, 121.7, 67.5 (2 peaks), 61.3, 46.8, 43.4, 41.5, 26.8, 19.3, 13.8 (2 peaks). HRMS (ESI): exact mass calcd for $C_{29}H_{36}NO_2Si$ $[M + H]^+$ 458.2515, found 458.2577.

Synthesis of (*S*)-*E*-*N*-(5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpent-3-en-2-yl)-2,2,2-trifluoroacetamide (11a).

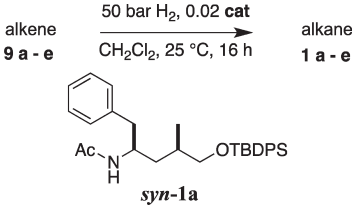


8a **11a**

O-TBDPS-allylic amine **8a** (0.2 g, 0.5 mmol) was dissolved in 2 mL of CH_2Cl_2 and cooled to 0 °C. Trifluoroacetic anhydride (76 μL, 0.6 mmol) was added dropwise to this solution followed by pyridine (61 μL, 0.8 mmol). The mixture was stirred for 2 h at 25 °C, and then additional aliquots of trifluoroacetic anhydride (38 μL, 0.3 mmol) and pyridine (30 μL, 0.4 mmol) were added to this solution, which was stirred for an additional 1 h. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography using 10% EtOAc/hexanes giving acetamide **11a** as a colorless oil (0.3 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.65 (4H, m), 7.49−7.37 (6H, m), 7.34−7.18 (5H, m), 6.30 (1H, d, J = 8.0 Hz), 5.56−5.52 (1H, m), 5.02−4.97 (1H, m), 4.05 (2H, s), 3.01 (1H, dd, J = 5.4, 13 Hz), 2.88 (1H, dd, J = 7.8, 13 Hz), 1.48 (3H, d, J = 1.2 Hz), 1.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 155.9, 140.1, 136.4, 135.5 (2 peaks), 133.5, 133.4, 129.8, 129.7, 128.6, 128.1, 127.8, 126.8, 120.2, 117.8, 114.0, 67.4, 48.9, 41.0, 26.9, 19.3, 13.9. HRMS (ESI): exact mass calcd for $C_{30}H_{34}F_3LiNO_2Si$ $[M + H]^+$ 532.2471, found 532.2474.

General Catalytic Hydrogenation Conditions. The corresponding alkenes (0.1 mmol) and (*S*)-**1** (2 mol %) were dissolved in CH_2Cl_2 (0.5 M). The resulting mixture was degassed by three cycles of freeze−pump−thaw and then transferred to a Parr bomb. The bomb was pressurized to 50 bar with hydrogen, and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented, and solvent was evaporated. The crude product was passed through a short silica plug using 50% EtOAc/hexanes as the eluent. The diastereomeric ratio was then measured by HPLC analysis using an unbonded silica 300 Å column.

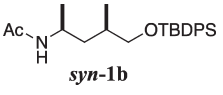
***N*-((2*R*,4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpentan-2-yl)acetamide (*syn*-1a).**



syn-1a

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.62 (4H, m), 7.46−7.35 (6H, m), 7.33−7.17 (5H, m), 5.17 (1H, d, J = 9.0 Hz), 4.39−4.21 (1H, m), 3.52−3.40 (2H, m), 2.83−2.80 (2H, m), 1.89 (3H, s), 1.78−1.64 (1H, m), 1.55 (1H, s), 1.30−1.21 (1H, s), 1.07 (9H, s), 0.89 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 137.8, 135.6, 135.5, 133.9, 133.7, 129.6, 128.3, 127.8, 126.4, 69.2, 47.8, 41.4, 37.4, 32.7, 26.9, 23.4, 19.3, 16.4. HRMS (ESI): exact mass calcd for $C_{30}H_{40}NO_2Si$ $[M + H]^+$ 474.2828, found 474.2832.

***N*-(2*S*,4*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-1b).**



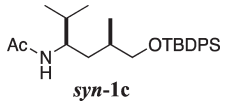
syn-1b

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.43−7.36 (6H, m), 5.12 (1H, d, J = 8.7 Hz), 4.13−3.97 (1H, m), 4.06−4.01 (1H, m), 1.88 (3H, s), 1.79−1.60 (1H, m), 1.62 (1H, s), 1.25−1.13 (2H, m), 1.11

dx.doi.org/10.1021/jo201215c |*J. Org. Chem.* 2011, 76, 7449–7457

(3H, d, J = 3.3 Hz), 1.08 (9H, s), 0.91 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.8, 129.6 (2 peaks), 127.7 (2 peaks), 68.1, 28.5, 26.9, 26.6, 22.0, 19.3, 13.7. HRMS (ESI): exact mass calcd for $C_{24}H_{36}NO_2Si$ $[M + H]^+$ 398.2515, found 398.2552.

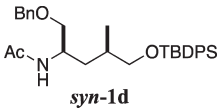
***N*-((3*R*,5*R*)-6-((tert-Butyldiphenylsilyl)oxy)-2,5-dimethylhexan-3-yl)acetamide (*syn*-1c).**



***syn*-1c**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.41−7.38 (6H, m), 5.00 (1H, d, J = 9.9 Hz), 3.91−3.88 (1H, m), 3.53−3.39 (2H, m), 1.91 (3H, s), 1.78−1.55 (1H, m), 1.56 (1H, s), 1.52−1.45 (1H, m), 1.19−1.10 (1H, m), 1.06 (9H, s), 0.91−0.84 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (2 peaks), 129.6, 127.6 (2 peaks), 69.8, 51.9, 37.4, 33.1, 33.0, 26.9, 23.7, 19.8, 19.3, 19.1, 16.2. HRMS (ESI): exact mass calcd for $C_{26}H_{40}NO_2Si$ $[M + H]^+$ 426.2828, found 426.2851.

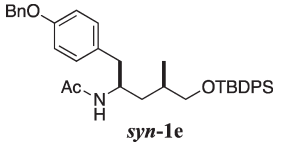
***N*-((2*R*,4*R*)-1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-1d).**



***syn*-1d**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.40−7.32 (11H, m), 5.47 (1H, d, J = 9.0 Hz), 4.50 (2H, dd, J = 12, 17 Hz), 4.24−4.12 (1H, m), 3.50−3.43 (4H, m), 1.89 (3H, s), 1.80−1.76 (1H, m), 1.73−1.59 (1H, m), 1.27−1.20 (1H, m), 1.16 (9H, s), 0.93 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 129.6, 128.4, 127.6 (2 peaks), 73.5, 72.8, 69.9, 47.0, 36.1, 33.2, 27.0, 23.8, 19.2, 18.0. HRMS (ESI): exact mass calcd for $C_{31}H_{42}NO_3Si$ $[M + H]^+$ 504.2934, found 504.2952.

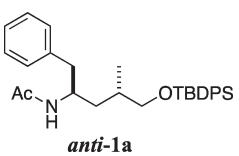
***N*-((2*R*,4*R*)-1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*syn*-1e).**



***syn*-1e**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.62 (4H, m), 7.45−7.37 (11H, m), 7.09 (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.4 Hz), 5.07 (2H, s), 4.32−4.19 (1H, m), 3.53−3.40 (2H, m), 2.76 (1H, s), 2.74 (1H, d, J = 2.1 Hz), 1.89 (3H, s), 1.78−1.60 (1H, m), 1.62 (1H, s), 1.59−1.46 (1H, m), 1.30−1.19 (1H, m), 1.06 (9H, s), 0.89 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 157.5, 137.1, 135.6 (2 peaks), 130.6, 130.2, 129.7, 128.6, 128.0, 127.7, 127.5, 114.7, 70.0, 69.2, 47.9, 40.0, 37.4, 32.7, 26.9, 23.5, 19.3, 16.5. HRMS (ESI): exact mass calcd for $C_{37}H_{46}NO_3Si$ $[M + H]^+$ 580.3247, found 580.3253.

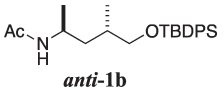
***N*-((2*R*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-1-phenylpentan-2-yl)acetamide (*anti*-1a).**



***anti*-1a**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.65 (4H, m), 7.48−7.38 (6H, m), 7.33−7.11 (5H, m), 5.40 (1H, d, J = 8.7 Hz), 4.38−4.22 (1H, m), 3.59 (1H, dd, J = 5.4, 10 Hz), 3.49 (1H, dd, J = 5.6, 10 Hz), 2.85−2.75 (2H, m), 1.90 (3H, s), 1.88−1.70 (2H, m), 1.29−1.24 (1H, m), 1.08 (9H, s), 0.96 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 137.9, 137.8, 136.3, 135.6, 135.4, 135.3, 133.8, 133.7, 130.0 (2 peaks), 129.6, 129.5, 128.3 (2 peaks), 127.9, 127.8, 127.7, 127.6, 126.4, 126.3, 113.7, 68.2, 48.0 (2 peaks), 40.2, 41.0, 38.0, 37.1, 32.8, 26.9, 26.5, 23.5, 23.4, 19.3, 19.2, 17.2, 12.9. HRMS (ESI): exact mass calcd for $C_{30}H_{40}NO_2Si$ $[M + H]^+$ 474.2828, found 474.2833.

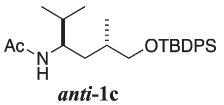
***N*-((2*S*,4*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-1b).**



***anti*-1b**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.63 (4H, m), 7.53−7.13 (6H, m), 4.10−3.95 (1H, m), 3.49−3.44 (2H, m), 2.60−2.51 (1H, m), 2.35 (3H, s), 1.97−1.62 (1H, m), 1.53 (3H, d, J = 6.0 Hz), 1.21 (3H, d, J = 9.0 Hz), 1.08 (9H, s), 0.97−0.79 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.8, 129.7, 129.0, 128.2, 124.6, 95.4, 29.7, 26.8, 17.8. HRMS (ESI): exact mass calcd for $C_{24}H_{36}NO_2Si$ $[M + H]^+$ 398.2515 Found 398.2571.

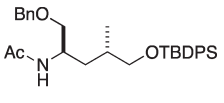
***N*-((3*R*,5*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,5-dimethylhexan-3-yl)acetamide (*anti*-1c).**



***anti*-1c**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (4H, m), 7.48−7.38 (6H, m), 4.92 (1H, d, J = 9.0 Hz), 3.98−3.91 (2H, m), 3.62−3.49 (2H, m), 1.96 (3H, s), 1.80−1.53 (2H, m), 1.40−1.20 (1H, m), 1.09 (9H, s), 0.96−0.81 (9H, m);^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.8, 133.6, 132.3, 129.9, 127.8, 122.0, 67.9, 51.7, 35.2, 32.1, 26.3, 24.5, 21.8, 20.7, 19.8, 18.0. HRMS (ESI): exact mass calcd for $C_{26}H_{40}NO_2Si$ $[M + H]^+$ 426.2828, found 426.2842.

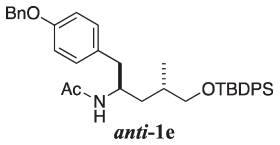
***N*-((2*R*,4*S*)-1-(Benzyloxy)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-1d).**



***anti*-1d**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.63 (4H, m), 7.47−7.30 (11H, m), 5.73 (1H, d, J = 8.1 Hz), 4.52 (2H, s), 4.17−4.14 (1H, m), 3.60−3.44 (4H, m), 1.94 (3H, s), 1.89−1.55 (2H, m), 1.37−1.32 (1H, m), 1.08 (9H, s), 0.97 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 137.2, 135.1, 134.5, 132.7, 128.5, 127.7, 127.3, 71.3, 68.1, 42.7, 34.7, 32.8, 26.0, 22.5, 19.8, 17.2. HRMS (ESI): exact mass calcd for $C_{31}H_{42}NO_3Si$ $[M + H]^+$ 504.2934, found 504.2971.

***N*-((2*R*,4*S*)-1-(4-(Benzyloxy)phenyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpentan-2-yl)acetamide (*anti*-1e).**



***anti*-1e**

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.66 (4H, m), 7.65−7.36 (11H, m), 7.08 (2H, dd, J = 9.0 Hz), 6.91 (2H, d, J = 8.7 Hz), 5.05 (2H, s), 4.25−4.18 (1H, m), 3.58−3.45 (1H, m), 2.78−2.72 (2H, m), 2.28 (2H, br), 1.89 (3H, s), 1.68−1.59 (1H, br), 1.11 (9H, s), 1.10 (2H, s), 0.95 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 137.1, 135.6, 135.3, 135.2, 134.8, 133.7, 130.0, 129.7, 128.6, 127.9, 127.8, 127.5, 121.1, 116.5, 114.7, 68.2, 53.5, 48.1, 39.2, 37.0, 32.8, 26.6, 23.5, 19.4, 17.2. HRMS (ESI): exact mass calcd for $C_{37}H_{46}NO_3Si$ $[M + H]^+$ 580.3247, found 580.3272.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for compounds **2** and **5**−**11** and discussion of assignments of absolute configuration of compounds **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: burgess@tamu.edu.

■ ACKNOWLEDGMENT

We thank The National Science Foundation (CHE-0750193) and The Robert A. Welch Foundation (A-1121) for financial support for this work.

■ REFERENCES

(1) Johnston, G. A. R. *Curr. Top. Med. Chem.* **2002**, *2*, 903–913.
(2) Chebib, M.; Johnston, G. A. R. *J. Med. Chem.* **2000**, *43*, 1427–1447.
(3) Johnston, G. A. R. *Phrmacol. Ther.* **1996**, *69*, 173–198.
(4) Bowery *Eur. J. Pharmacol.* **1981**, *71*, 53.
(5) Hardman, J. G.; Limbird, L. E.; Goodman, G. A. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed.; McGraw-Hill: New York, 2001.
(6) McGeer, P. L.; McGeer, E. G. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*;, 4th ed.; Raven: New York, 1989.
(7) Pardridge, W. M. *Annu. Rep. Med. Chem.* **1985**, *20*, 305–313.
(8) Shashoua, V. E.; Jacob, J. N.; Ridge, R.; Campbell, A.; Baldessarini, R. J. *J. Med. Chem.* **1984**, *27*, 659–664.
(9) Meldrum, B. S.; Horton, R. W. In *Epilepsy, Proceedings of the Hans Berger Centenary Symposium*; Churchill Livingstone: London1974, 55−64.
(10) Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441–445.
(11) Sachais, B. A.; Logue, J. N.; Carey, M. S. *Arch. Neurol.* **1977**, *34*, 422–428.
(12) Fromm, G. H.; Terrence, C. F.; Chattha, A. S.; Glass, J. D. *Arch. Neurol.* **1980**, *37*, 768–771.
(13) Costantino, G.; Macchiarulo, A.; Guadix, A. E.; Pellicciari, R. *J. Med. Chem.* **2001**, *44*, 1827–1832.
(14) Yuen, P. W.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823–826.
(15) Lauria-Horner Bianca, A.; Pohl Robert, B. *Exp. Opin. Invest. Drugs* **2003**, *12*, 663–672.
(16) Sills, G. J. *Curr. Opin. Pharmacol.* **2006**, *6*, 108–113.
(17) Silverman, R. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3500–3504.
(18) Jung, M. J.; Palfreyman, M. G. Vigabatarin. In *Antiepileptic Drugs*, 4th ed.; Cambridge University Press: New York, 1995.
(19) Olpe, H. R.; Demieville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133–136.
(20) Allan, R. D.; Bates, M. C.; Drew, C. A.; Duke, R. K.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Spence, I. *Tetrahedron* **1990**, *46*, 2511–2524.
(21) Ong, J.; Kerr, D. I. S.; Doolette, D. J.; Duke, R. K.; Mewett, K. N.; Allen, R. D.; Johnston, G. A. R. *Eur. J. Pharmacol.* **1993**, *233*, 169–172.
(22) Hoekstra, M. S. S.; D., M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Process Res. Dev.* **1997**, *1*, 26–38.
(23) Ordonez, M.; Cativiela, C. *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.
(24) Friestad, G. K.; Banerjee, K. *Org. Lett.* **2009**, *11*, 1095–1098.
(25) Friestad, G. K.; Marie, J.-C.; Deveau, A. M. *Org. Lett.* **2004**, *6*, 3249–3252.
(26) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.
(27) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.
(28) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113–123.
(29) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879.
(30) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676–678.
(31) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(32) Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 8894–8895.
(33) Zhao, J.; Burgess, K. *J. Am. Chem. Soc.* **2009**, *131*, 13236–13237.
(34) Zhao, J.; Burgess, K. *Org. Lett.* **2008**, *11*, 2053–2056.
(35) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.—Eur. J.* **2007**, *13*, 7162–7170.
(36) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131.
(37) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
(38) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
(39) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **1996**, *35*, 220–222.
(40) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180–9187.