HHS Public Access

Author manuscript

Tetrahedron. Author manuscript; available in PMC 2016 September 16.

Published in final edited form as:

Tetrahedron. 2015 September 16; 71(37): 6349–6353. doi:10.1016/j.tet.2015.05.092.

Construction of Tertiary Chiral Centers by Pd-catalyzed Asymmetric Allylic Alkylation of Prochiral Enolate Equivalents

Yusuke Kita[a], **Yoshitaka Numajiri**[a], **Noriko Okamoto**[a], and **Brian M. Stoltz**[a]

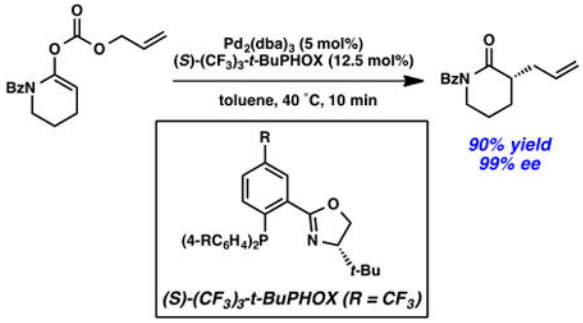
Brian M. Stoltz: stoltz@caltech.edu

[a]The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

Abstract

The palladium-catalyzed decarboxylative allylic alkylation of enol carbonates derived from lactams and ketones is described. Employing these substrates with an electronically tuned Pd catalyst system trisubstituted chiral centers are produced. These stereocenters have been previously challenging to achieve using Pd complex/chiral P–N ligand systems.

Graphical abstract



Keywords

palladium; alkylation; catalysis; enantioselective

1. Introduction

Development of straightforward and selective synthetic methods for enantioselective C-C bond formation is a fundamental goal in the area of synthetic organic chemistry.[1]

Correspondence to: Brian M. Stoltz, stoltz@caltech.edu.

Dedicated to Professor Jiro Tsuji on the occasion of his receipt of the 2014 Tetrahedron Prize for Creativity in Organic Chemistry.

Supplementary Information: Supplementary data associated with this article can be found in the online version, at www.xxxxxxx.

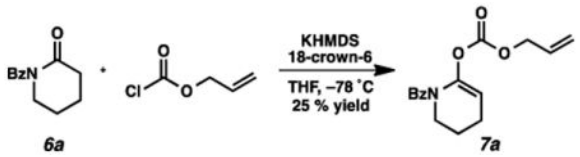
Asymmetric allylic alkylation of prochiral or racemic substrates is one of the most effective synthetic methods to construct stereochemically defined chiral centers.[2] The well-established nucleophilic substitution of activated allylic fragments is among the most useful and direct stereoselective methods for the functionalization of a variety of carbon-nucleophiles.[3] Over the last decade, our laboratory has reported Pd-catalyzed decarboxylative allylic alkylation reactions (Scheme 1). Since our initial efforts in this area, leading to the formation of α-quaternary ketones **2** from racemic β-ketoesters **1** in good yields and enantioselectivities using (*S*)-4-(*tert*-butyl)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole [(*S*)-*t*-BuPHOX][4] as a chiral ligand,[5] we have expanded the scope[6] and demonstrated the use of these methods in a number of applications.[7] We recently developed the asymmetric allylic alkylation, giving α-quaternary lactams **4** from racemic β-amidoesters **3** using (*S*)-2-(2-(bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-(*tert*-butyl)-4,5-dihydrooxazole [(*S*)-$(CF_3)_3$-*t*-BuPHOX][8] as a chiral ligand.[9] In the context of preparing trisubstituted tertiary stereocenters (i.e., Scheme 2, **3a**), this methodology encountered problems; (1) allylic alkylation of β-amidoester **3a** gave a mixture of mono-, di-allylated and unallylated lactams, and (2) the ee value of **4a** produced was low (Scheme 2a). This low mono-allylation selectivity is attributed to the fact that a deprotonated β-carboxyamides can serve as a nucleophile to form α-allyl-β-carboxyamides, eventually leading to di-allylated products. Rare exceptions are found in recent work wherein we achieved the synthesis of α-secondary ketopiperazines,[9b] and some other groups developed asymmetric alkylation constructing trisubstituted chiral centers at the α-position of amides.[10]

Since enol carbonates cannot undergo the unwanted background deprotonation and allylic alkylation reaction, catalyst controlled decarboxylative allylic alkylation of enol carbonates should generally proceed with high mono-allylic alkylation selectivity. As expected, alkylation using enol carbonate **7a** with $Pd_2(dba)_3$ and (*S*)-(CF_3)-*t*-BuPHOX at 40 °C proceeded smoothly to give **4a** in 90% yield with 99% ee (Scheme 2b). This high enantioselectivity and yield is probably due to easy kinetic access to an enolate allyl Pd complex, which was proposed by a DFT study in our previous report.[11] Herein, we report the palladium-catalyzed decarboxylative allylic alkylation of enol carbonates derived from lactams and ketones constructing trisubstituted chiral centers at the α-position of various carbonyl groups.

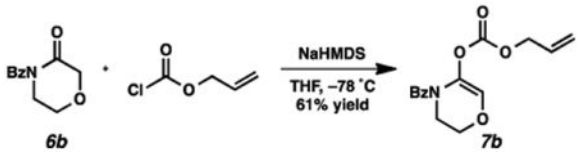
2. Results and Discussion

The synthesis of enol carbonates **7a-f** was difficult due to challenges associated with the formation of *C*-acylated compounds along with the desired *O*-acylated structures. In order to selectively *O*-acylate the corresponding enolate, we screened bases, solvents and additives using methods previously employed for synthesizing enol carbonates.[10b] Fortunately, **7a** could be prepared from *N*-benzoylpiperidin-2-one by using potassium hexamethyldisilazide (KHMDS) with 18-crown-6 as an additive in THF (eq 1). *O*-acylation of 4-benzoylmorpholin-3-one (**6b**) proceeded without any additive, presumably due to a stabilization effect of the endocyclic oxygen atom to favor the enolate form (eq 2). For thiomorpholine (**6c**), ε-caprolactam (**6d**), and azocan-2-one (**6e**), we used NaHMDS as a base and tetramethylethylenediamine (TMEDA) as an activator (eq 3). The 2-chloroallyl

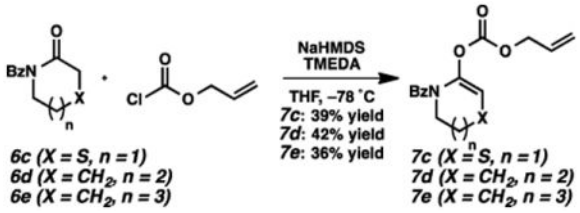
group was introduced by using allyloxycarbonyl imidazole as an acylating reagent and BF_3•OEt_2 as an activator (eq 4).



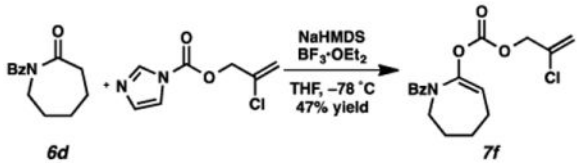
(1)



(2)



(3)

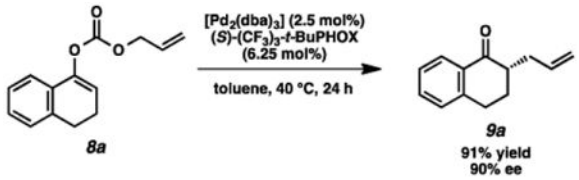


(4)

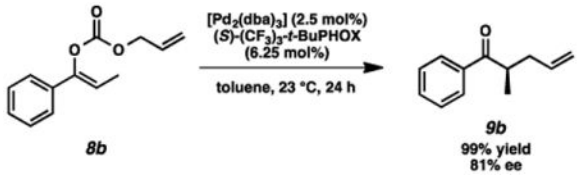
With the enol carbonate substrates in hand, we performed allylic alkylation reactions of lactam-derived enol carbonates **7b-7f** with $Pd_2(dba)_3$ (2.5 mol%) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (6.25 mol%) in toluene at 23 °C for 24 h (Scheme 3). Reaction of carbonate **7b** afforded morpholinone **4b** in 73% yield and 94% ee. Replacement of oxygen with sulfur gave thiomorpholinone **4c** in 82% yield but only 65% ee along with the formation of unallylated product **6b** in 10% yield. Caprolactam **7d** was also reactive with this catalytic system by using tris(4,4′-methoxydibenzylideneacetone)dipalladium(0) $[Pd_2(pmdba)_3]$[12] as the palladium(0) source, furnishing lactam **4d** in 83% yield and 85% ee. Chloride substitution at

the 2-position of the allyl group in **7d** increased the enantioselectivity, furnishing caprolactam **4f** in 91% ee. Ring size of the lactam significantly affected enantioselectivity, as the reaction of the 8-membered ring substrate **7e** proceeded to give the amide **4e** in 84% yield and 59% ee.

Next, we explored the scope of the allylation of ketones, forming α-tertiary alkyl(cyclo)alkanone derivatives. We were pleased to discover that use of enol carbonate **8a**, derived from the corresponding tetralone, resulted in a smooth reaction and delivered allylated tetralone **9a** in high yield and enantioselectivity (eq 5). It is noteworthy that the more challenging acyclic substrate **8b** was reactive with this catalytic system as well, affording the corresponding ketone **9b** in 99% yield and 81% ee (eq 6).[13]



(5)



(6)

3. Conclusions

Asymmetric allylic alkylation of enol carbonates is an effective method to construct trisubstituted chiral centers, which have been difficult to introduce using previously developed systems in our laboratory. Herein, we report that a palladium/P–N catalyst system displays activity for enol carbonates derived from lactams. In addition, this system could be applied to the allylation of ketones in both cyclic and acyclic systems.

4. Experimental section

Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[14] Reaction progress was monitored by thin-layer chromatography (TLC) which was performed using E. Merck silica gel 60 F254 precoated glass plated (0.25 mm) and visualized by UV fluorescence quenching, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40-63 nm) was used

for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and d 77.16, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet, and br s = broad singlet. IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiracel (OD-H, OJ-H or OB-H) columns (4.6 mm × 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+), or a Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (ESI/APCI).

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem or Alfa Aesar and used as received unless otherwise stated. Et_3N and tetramethylethylenediamine (TMEDA) were distilled from calcium hydride prior to use. (*S*)-2-(2-(bis(4-(trifluoromethyl)phenyl)phosphino)-5-(trifluoromethyl)phenyl)-4-(*tert*-butyl)-4,5-dihydrooxazole [(*S*)-$(CF_3)_3$-*t*-BuPHOX][15] and tris(4,4′-methoxydibenzylideneacetone)dipalladium(0) [$Pd_2(pmdba)_3$][16] were prepared by known methods.

4.1. General Procedure for Asymmetric Allylic Alkylation Reactions

In a nitrogen-filled glove box, [$Pd_2(dba)_3$] (4.6 mg, 0.005 mmol, 0.025 equiv.) and (*S*)-$(CF_3)_3$-*t*-BuPHOX (7.4 mg, 0.0125 mmol, 0.0625 equiv.) were added to a 20 mL scintillation vial equipped with a magnetic stirring bar. The vial was then charged with toluene (4.0 mL) and stirred at 25 °C for 30 min. To the preformed catalyst solution was added a solution of enol carbonate (0.2 mmol, 1 equiv.) in toluene (2.1 mL). The vial was sealed and stirred at 23 °C for 24 h. The reaction mixture was concentrated *in vacuo*. Flash column chromatography (SiO_2) afforded α-allylated carbonyl compounds.

4.1.1. 3-Allylpiperidin-2-one (4a)—Reaction performed in toluene at 40 °C. Compound **4a** was isolated by flash chromatography (SiO_2, 7 to 10% EtOAc in hexanes) as a white solid. 90% yield. R_f = 0.31 (17% EtOAc in hexanes). M.p. 66.5-67.2 °C; 99% ee, $[\alpha]_D^{25}$ -77.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.50 (m, 2H), 7.47 (m, 1H), 7.42–7.35 (m, 2H), 5.77 (m, 1H), 5.13–5.05 (m, 2H), 3.89–3.74 (m, 2H), 2.67–2.54 (m, 2H), 2.28 (m, 1H), 2.14–2.02 (m, 2H), 1.96 (m, 1H), 1.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 174.8, 136.5, 135.6, 131.5, 128.3, 127.9, 117.5, 46.2, 43.8, 35.3, 26.8, 22.1. IR (Neat Film, NaCl) 3073, 2947, 2870, 1699, 1679, 1641, 1478, 1367, 1288, 1167, 1153, 1076, 1056, 1025, 1001 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1332,

found 244.1372. SFC conditions: 5% MeOH, 2.5 mL/min, Chiralpak AD-H column, λ = 254 nm, t_R (min): major = 9.10, minor = 6.18.

4.1.2. 2-Allylmorpholin-3-one (4b)—Reaction performed in toluene at 50 °C. Compound **4b** was isolated by flash chromatography (SiO_2, 7 to 10% EtOAc in hexanes) as a white solid. 73% yield. R_f = 0.52 (33% EtOAc in hexanes). 94% ee, $[\alpha]_D^{25}$ -127.5 (*c* 0.80, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.48 (m, 3H), 7.42–7.38 (m, 2H), 5.91 (m, 1H), 5.23–5.16 (m, 2H), 4.23 (m, 2H), 4.04 (m, 1H), 3.93–3.82 (m, 2H), 2.73 (m, 1H), 2.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 171.3, 135.7, 133.4, 132.0, 128.3, 128.2, 118.5, 78.5, 63.4, 45.3, 36.3. IR (Neat Film, NaCl) 3358, 3076, 2977, 2898, 2867, 1686, 1642, 1601, 1583, 1463, 1449, 1432, 1398, 1374, 1301, 1282, 1228, 1178, 1165, 1138, 1124, 1104 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found 246.1124. SFC conditions: 5% MeOH, 3.0 mL/min, Chiralpak OD-H column, λ = 254 nm, t_R (min): major = 6.74, minor = 5.99.

4.1.3. 2-Allyl-4-benzoylthiomorpholin-3-one (4c)—Reaction performed in toluene at 40 °C. Compound **4c** was isolated by flash chromatography (SiO_2, 15% EtOAc in hexanes) as a white solid. 82% yield. R_f = 0.51 (33% EtOAc in hexanes). 65% ee, $[\alpha]_D^{25}$ -31.1 (*c* 0.36, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.57 (m, 2H), 7.51 (m, 1H), 7.45–7.38 (m, 2H), 5.85 (m, 1H), 5.20–5.10 (m, 2H), 4.78 (ddd, *J* = 14.2, 4.8, 3.4 Hz, 1H), 3.79 (dd, *J* = 7.7, 5.7 Hz, 1H), 3.73 (ddd, *J* = 14.2, 11.7, 4.2 Hz, 1H), 3.16 (m, 1H), 3.10 (td, *J* = 11.7, 4.8 Hz, 1H), 2.76 (m, 1H), 2.35 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 171.6, 135.6, 134.1, 132.0, 128.2, 128.1, 118.1, 43.6, 42.2, 33.3, 26.9. IR (Neat Film, NaCl) 3362, 3065, 2933, 1687, 1600, 1580, 1534, 1450, 1378, 1326, 1281, 1177, 1132, 1071, 1026 cm^{-1}. HRMS (FAB+) m/z calc'd for $C_{14}H_{16}NO_2S$ $[M+H]^+$: 262.0902, found 262.0895. SFC conditions: 5% MeOH, 3.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 9.26, minor = 8.79.

4.1.4. 3-Allyl-1-benzoylazepan-2-one (4d)—Reaction performed in toluene at 40 °C. Compound **4d** was isolated by flash chromatography (SiO_2, 10% EtOAc in hexanes) as a yellow oil. 83% yield. R_f = 0.44 (17% EtOAc in hexanes). 85% ee, $[\alpha]_D^{25}$ -33.9 (*c* 1.90, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 7.55–7.49 (m, 2H), 7.46 (m, 1H), 7.40–7.34 (m, 2H), 5.78 (m, 1H), 5.11–5.03 (m, 2H), 4.56 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.44 (ddd, *J* = 14.8, 10.7, 0.9 Hz, 1H), 2.83 (m, 1H), 2.55 (m, 1H), 2.12–1.96 (m, 3H), 1.90 (m, 1H), 1.74–1.44 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 174.5, 136.8, 136.2, 131.4, 128.1, 127.7, 117.1, 45.9, 44.5, 36.4, 30.2, 28.8, 28.7. IR (Neat Film, NaCl) 3073, 3030, 2931, 2857, 1681, 1641, 1600, 1583, 1513, 1490, 1450, 1396, 1360, 1322, 1282, 1220, 1189, 1177, 1141, 1114, 1044, 1018, 1001 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489, found 258.1494. SFC conditions: 5% MeOH, 3.0 mL/min, Chiralcel AD-H column, λ = 254 nm, t_R (min): major = 4.48, minor = 4.88.

4.1.5. 3-Allyl-1-benzoylazocan-2-one (4e)—Reaction performed in toluene at 23°C. Compound **4e** was isolated by flash chromatography (SiO_2, 10% EtOAc in hexanes) as a yellow oil. 84% yield. R_f = 0.50 (17% EtOAc in hexanes). 59% ee, $[\alpha]_D^{25}$ -8.6 (*c* 0.37, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.22 (m, 5H), 5.80 (ddt, *J* = 17.2, 10.5, 6.9 Hz,

1H), 5.18–5.02 (m, 2H), 4.19 (ddd, *J* = 15.1, 4.3, 3.0 Hz, 1H), 3.85 (ddd, *J* = 15.1, 12.6, 2.8 Hz, 1H), 3.01 (m, 1H), 2.53 (m, 1H), 2.21–2.05 (m, 2H), 1.92–1.70 (m, 4H), 1.70–1.35 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.7, 174.9, 136.8, 136.1, 131.3, 128.1, 127.9, 117.4, 45.1, 44.0, 38.0, 36.7, 31.2, 25.9, 24.5. IR (Neat Film, NaCl) 3067, 2928, 2857, 1679, 1619, 1493, 1448, 1392, 1319, 1285, 1246, 1176, 1125, 1091 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found 272.1656. SFC conditions: 5% MeOH, 3.0 mL/min, Chiralcel OJ-H column, λ = 254 nm, t_R (min): major = 2.97, minor = 3.87.

4.1.6. 1-Benzoyl-3-(2-chloroallyl)azepan-2-one (4f)—Reaction performed in toluene at 23 °C. Compound **4f** was isolated by flash chromatography (SiO_2, 15% EtOAc in hexanes) as a yellow oil. 42% yield. R_f = 0.37 (17% EtOAc in hexanes). 91% ee, $[\alpha]_D^{25}$ -78.1 (*c* 1.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.50 (m, 2H), 7.46 (m, 1H), 7.41–7.29 (m, 2H), 5.26 (d, *J* = 1.2 Hz, 1H), 5.19 (d, *J* = 1.2 Hz, 1H), 4.58 (dd, *J* = 15.1, 5.1 Hz, 1H), 3.50 (dd, *J* = 15.1, 11.0 Hz, 1H), 3.23 (m, 1H), 2.85 (ddd, *J* = 14.6, 6.4, 1.0 Hz, 1H), 2.32 (ddd, *J* = 14.6, 7.7, 0.7 Hz, 1H), 2.15–1.99 (m, 2H), 1.89 (m, 1H), 1.78–1.55 (m, 2H), 1.48 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 174.5, 140.0, 136.7, 131.6, 128.2, 127.9, 115.5, 44.7, 43.5, 41.6, 29.6, 28.9, 28.7. IR (Neat Film, NaCl) 2931, 2857, 1683, 1636, 1450, 1397, 1358, 1321, 1274, 1220, 1188, 1148, 1126 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{16}H_{19}ClNO_2$ $[M+H]^+$: 292.1099, found 292.1104. SFC conditions: 5% MeOH, 3.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 5.89, minor = 4.97.

4.1.7. 2-Allyl-3,4-dihydronaphthalen-1(2H)-one (9a)—Reaction performed in toluene at 40 °C. Compound **9a** was isolated by flash chromatography (SiO_2, 0 to 3% EtOAc in hexanes) as a pale colorless oil. 91% yield. R_f = 0.40 (9% EtOAc in hexanes). 90% ee, $[\alpha]_D^{25}$ +26.6 (*c* 0.61, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36–7.16 (m, 2H), 5.95–5.75 (m, 1H), 5.18–5.01 (m, 2H), 3.00 (dd, *J* = 7.8, 4.5 Hz, 2H), 2.76 (m, 1H), 2.55 (m, 1H), 2.36–2.16 (m, 2H), 1.87 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 144.2, 136.4, 133.3, 132.8, 128.8, 127.7, 126.8, 116.9, 47.4, 34.2, 28.8, 28.2. IR (Neat Film, NaCl) 3073, 2976, 2929, 1686, 1682, 1640, 1600, 1455 1435, 1359, 1293, 1280, 1220, 1156 cm^{-1}. HRMS (ESI/APCI+) m/z calc'd for $C_{13}H_{15}O$ $[M+H]^+$: 187.1117, found 187.1110. SFC conditions: 0.5% MeCN, 3.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 8.11, minor = 7.74.

4.1.8. 2-Methyl-1-phenylpent-4-en-1-one (9b)—Reaction performed in toluene at 23 °C. Compound **9b** was isolated by flash chromatography (SiO_2, 0 to 3% EtOAc in hexanes) as a colorless oil. Quant. R_f = 0.43 (10% EtOAc in hexanes). 81% ee, $[\alpha]_D^{25}$ -32.9 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02–7.97 (m, 2H), 7.60 (m, 1H), 7.55–7.47 (m, 2H), 5.83 (m, 1H), 5.14–5.02 (m, 2H), 3.60 (m, 1H), 2.61 (m, 1H), 2.25 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 136.4, 135.8, 132.9, 128.7, 128.3, 116.8, 40.4, 37.6, 17.0. IR (Neat Film, NaCl) 3077, 2975, 2933, 2358, 1682, 1641, 1596, 1579, 1447, 1374, 1360, 1239, 1209 cm^{-1}. HRMS (ESI/APCI+) m/z calc'd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1117, found 175.1113. SFC conditions: 0.5% MeCN, 3.0 mL/min, Chiralcel OD-H column, λ = 254 nm, t_R (min): major = 3.97, minor = 4.42.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, the Caltech Center for Catalysis and Chemical Synthesis, and Caltech for financial support. Y.K. expresses his special thanks to the International Engineering Science Consortium for financial support. Y.N. thanks Toray Industries Inc. for a postdoctoral fellowship. N.O. is grateful for a postdoctoral fellowship provided by Hiroshima International University. The authors thank Scott Virgil (Caltech) for instrumentation assistance and Dr. Douglas C. Behenna (Caltech) for initial experimental results.

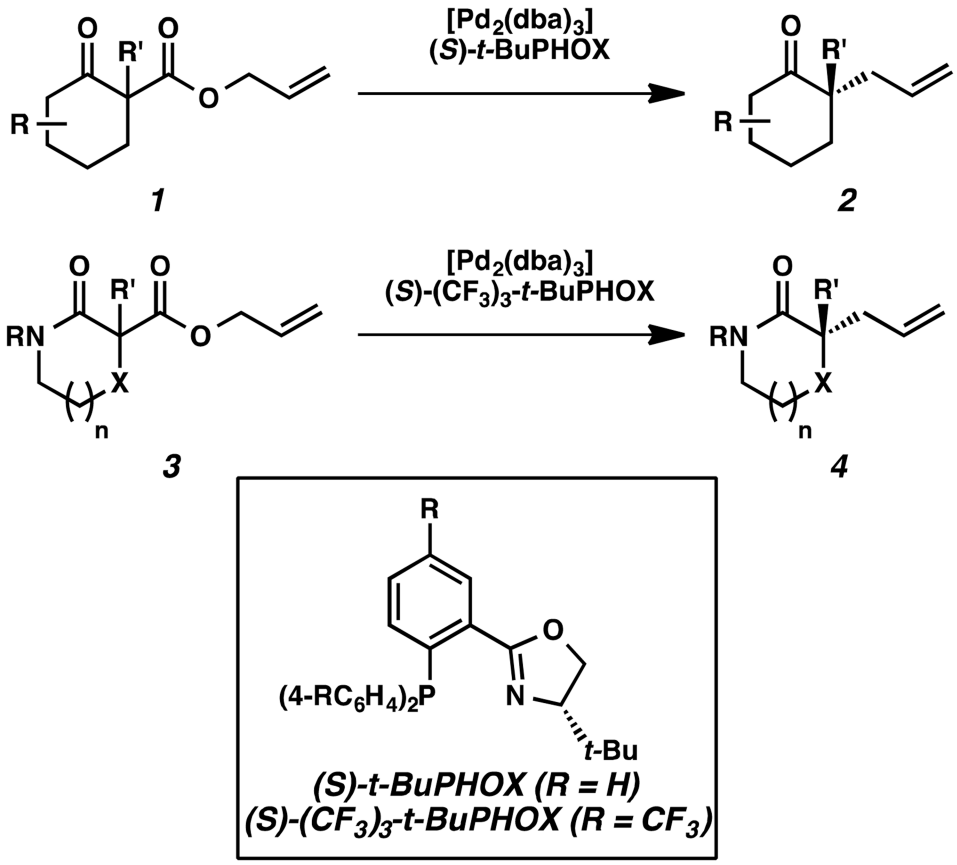
7. References and notes

1. For selected reviews, Wender PA, Miller BL. Organic Synthesis: Theory Applications. Hudlicky T. JAI PressGreenwich, CT1993; 2:27.Trost BM. Angew Chem, Int Ed. 1995; 34:259–281.Wender PA, Verma VA, Paxton TJ, Pillow TH. Acc Chem Res. 2008; 41:40–49. [PubMed: 18159936] Newhouse T, Baran PS, Hoffmann RW. Chem Soc Rev. 2009; 38:3010–3021. [PubMed: 19847337]
2. For reviews see: Trost BM, Brennan MK. Synthesis. 2009:3003–3025.Trost BM, Crawley ML. Top Organomet Chem. 2012; 38:321–340.
3. (a) Trost BM, van Vranken DL. Chem Rev. 1996; 96:395–422. [PubMed: 11848758] (b) Trost, BM.; Lee, C. Catalytic Asymmetric Synthesis. 2nd. Ojima, I., editor. Wiley-VCH; New York: 2000. p. 593(c) Trost BM, Crawley ML. Chem Rev. 2003; 103:2921–2944. [PubMed: 12914486] (d) Miyabe H, Yamamoto Y. Synlett. 2005:1641–165.
4. (a) Tani K, Behenna DC, McFadden RM, Stoltz BM. Org Lett. 2007; 9:2529–2531. [PubMed: 17536810] (b) Krout MR, Mohr JT, Stoltz BM. Org Synth. 2009; 86:181–193. [PubMed: 20072718]
5. (a) Behenna DC, Stoltz BM. J Am Chem Soc. 2004; 126:15044–15045. [PubMed: 15547998] (b) Moher JT, Behenna DC, Harned AM, Stoltz BM. Angew Chem, Int Ed. 2005; 44:6924–6927.
6. Behenna DC, Mohr JT, Sherden NH, Marinescu SC, Harned AM, Tani M, Seto M, Ma S, Novák Z, Krout MR, McFadden RM, Roizen JL, Enquist JA Jr, White DE, Levine SR, Petrova KV, Iwashita A, Virgil SC, Stoltz BM. Chem Eur J. 2011; 17:14199–14223. [PubMed: 22083969]
7. (a) McFadden RM, Stoltz BM. J Am Chem Soc. 2006; 128:7738–7739. [PubMed: 16771478] (b) Enquist JA Jr, Stoltz BM. Nature. 2008; 453:1228–1231. [PubMed: 18580947] (c) Day JJ, McFadden RM, Virgil SC, Kolding H, Alleva JL, Stoltz BM. Angew Chem, Int Ed. 2011; 50:6814–6818.(d) Hong AY, Stoltz BM. Angew Chem, Int Ed. 2012; 51:9674–9678.(e) Liu Y, Liniger M, McFadden RM, Roizen JL, Malette J, Reeves CM, Behenna DC, Seto M, Kim J, Mohr JT, Virgil SC, Stoltz BM, Beilstein. J Org Chem. 2014; 10:2501–2512.(f) Numajiri Y, Pritchett BP, Chiyoda K, Stoltz BM. J Am Chem Soc. 2015; 137:1040–1043. [PubMed: 25578104]
8. McDougal NT, Streuff J, Mukherjee H, Virgil SC, Stoltz BM. Tetrahedron Lett. 2010; 51:5550–5554. [PubMed: 21076623]
9. (a) Behenna DC, Liu Y, Yurino T, Kim J, White DE, Virgil SC, Stoltz BM. Nat Chem. 2012; 4:130–133. [PubMed: 22270628] (b) Korch KM, Eidamshaus Behenna DC, Nam S, Horne D, Stoltz BM. Angew Chem, Int Ed. 2015; 54:179–183.(c) Numajiri Y, Jiménez-Osés G, Wang B, Houk KN, Stolz BM. Org Lett. 2015; 17:1082–1085. [PubMed: 25714704]
10. (a) Zhang K, Peng Q, Hou XL, Wu YD. Angew Chem, Int Ed. 2008; 47:1741–1744.(b) Trost BM, Michaelis DJ, Charpentier J, Xu J. Angew Chem, Int Ed. 2012; 51:204–208.
11. Keith JA, Behenna DC, Mohr JT, Ma S, Marinescu SC, Oxgaard J, Stoltz BM, Goddard WAIII. J Am Chem Soc. 2007; 129:11876–11877. [PubMed: 17824701]
12. (a) Ukai T, Kawazura H, Ishii Y, Bonnet JJ, Ibers JA. J Organomet Chem. 1974; 65:253–266.(b) Fairlamb IJS, Kapdi AR, Lee AF. Org Lett. 2004; 6:4435–4438. [PubMed: 15548044]
13. For a previous example using the Pd•PHOX system, see: Hanessian S, Chénard E. Org Lett. 2012; 14:3222–3225. [PubMed: 22668074]

14. Pangborn AM, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. Organometallics. 1996; 15:1518–1520.

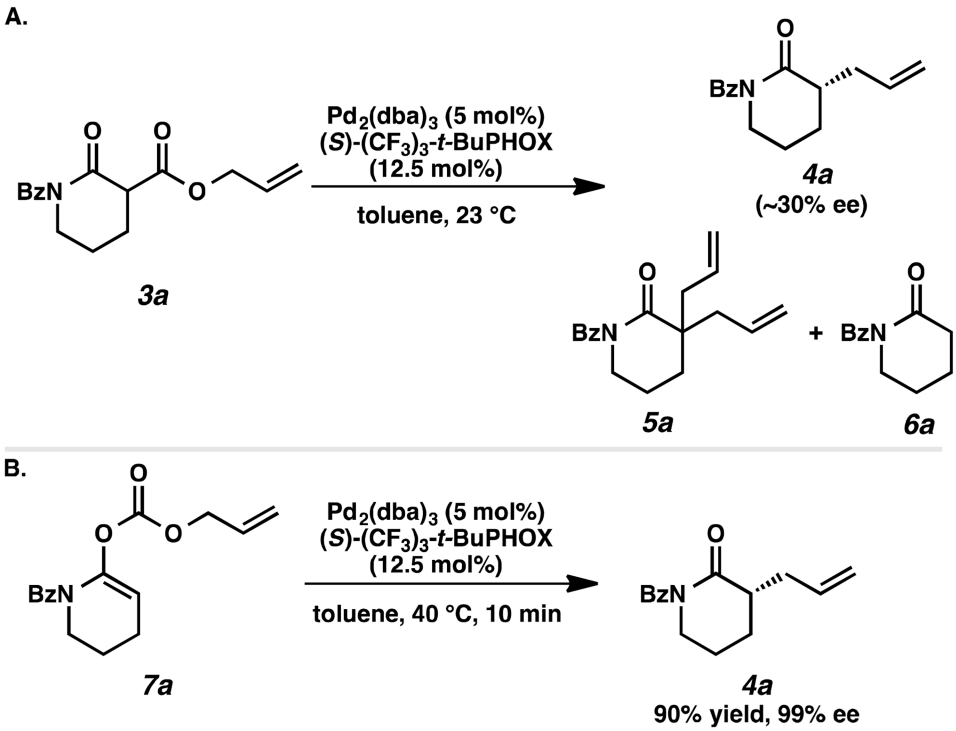
15. McDougal NT, Streuff J, Mukherjee H, Virgil SC, Stoltz BM. Tetrahedron Lett. 2010; 51:5550–5554. [PubMed: 21076623]

16. (a) Ukai T, Kawazura H, Ishii Y, Bonnet JJ, Ibers JA. J Organomet Chem. 1974; 65:253–266.(b) Fairlamb IJS, Kapdi AR, Lee AF. Org Lett. 2004; 6:4435–4438. [PubMed: 15548044]



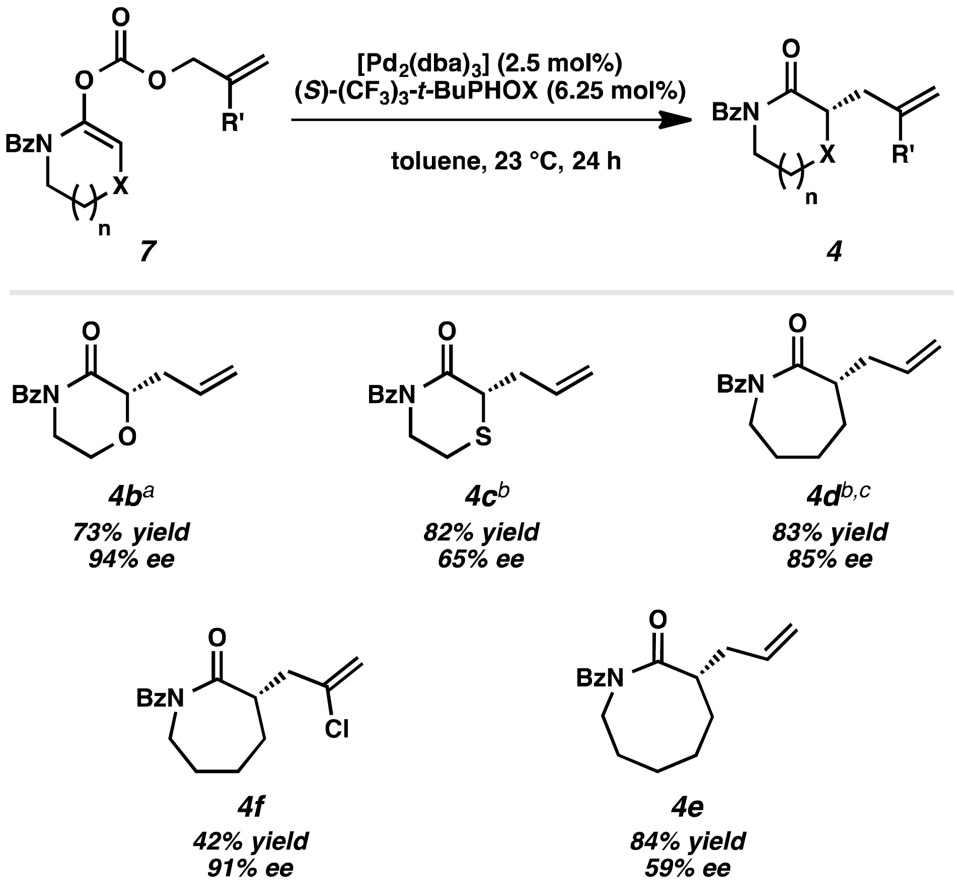
Scheme 1.

Allylic alkylation of ketones and lactams using Pd(0) complex and chiral P–N ligand system



Scheme 2.

Comparison of β-amidoester (**3a**) and enol carbonate (**7a**).



Scheme 3.

Substrate scope of enol carbonates. Reaction conditions: A mixture of **7** (0.20 mmol), $Pd_2(dba)_3$ (0.005 mmol), and (*S*)-$(CF_3)_3$-*t*-BuPHOX (0.0125 mmol) in toluene (0.033 M) was stirred at 23 °C for 24 h. Yield was isolated yield and enantiomeric excess was determined by chiral SFC analysis. [a]Performed at 50 °C. [b]Performed at 40 °C. [c]$[Pd_2(pmdba)_3]$ was used as a catalyst.