Supplementary Material

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

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Materials and Methods

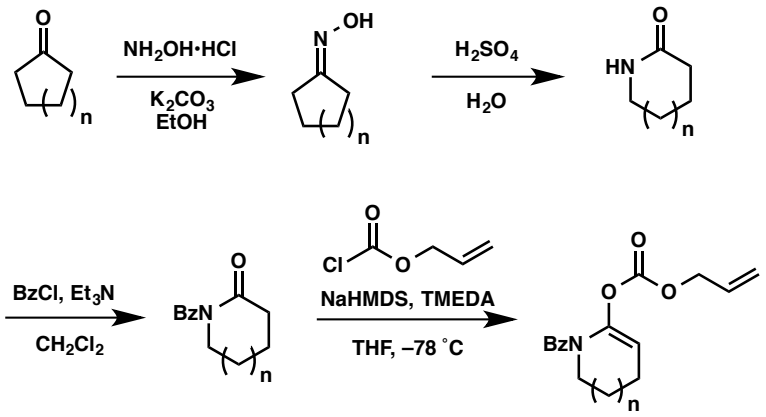
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[1] Reaction progress was monitored by thin-layer chromatography (TLC) which 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. ^1H 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 ^1H 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 x 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][2] and tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) [$Pd_2(pmdba)_3$][3] were prepared by known methods.

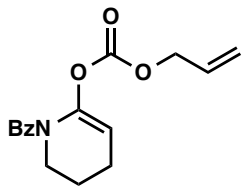
Synthesis of Enol Carbonate Substrates

The following scheme shows a synthetic scheme of enol carbonates (Scheme S1). Lactams were prepared in two steps from cyclic ketones. Subsequent benzoyl protection and acylation of the lactams led to the formation of enol carbonates. Synthesis of 7-membered substrates started from commercially available ε-caprolactam. To introduce 2-substituted allyl groups, the corresponding allyloxycarbonyl imidazoles were used instead of allyl chloroformate. 2-Chloroallyl group was successfully introduced using the typical procedure, while 2-methylallyl and 2-phenylallyl groups could not be introduced.

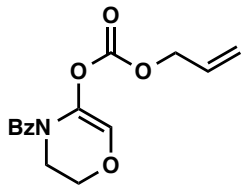
Scheme S1. Typical synthetic scheme of enol carobonates



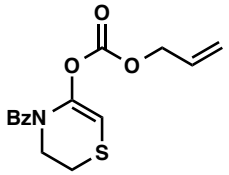
General procedure for the preparation of enol carbonate. To a solution of amide (10 mmol, 1.0 equiv) in THF (100 mL) was added a 2.5 M solution ^{n}BuLi in THF (11 mmol, 1.1 equiv) at –78 ºC. The resulting solution was stirred at –78 ºC for 30 min. Then, benzoyl chloride (11 mmol, 1.1 equiv) was added at –78 ºC. After completion of the addition, the reaction mixture was allowed to warm to room temperature. All volatiles were removed in vacuo. After the addition of EtOAc, the organic layer was washed with 1 M HCl, saturated $NaHCO_3$ aq and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 15→50% EtOAc in hexanes) to give the Bz-protected amide. To a stirred solution of NaHMDS (3 mmol, 1.5 equiv) in THF (30 mL) was added a solution of Bz-protected amide (2 mmol, 1.0 equiv) and TMEDA (2.2 mmol, 1.1 equiv) in THF dropwise via syringe at –78 ºC. After stirring for 30 min, allyl chloroformate (2.2 mmol, 1.1 equiv) was added at –78 ºC. The reaction was quenched by the addition of NH_4Cl aq, and then the resulting mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give the enol carbonate.



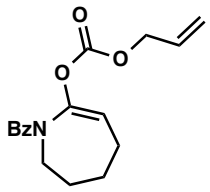
*Allyl (1-benzoyl-1,4,5,6-tetrahydropyridin-2-yl) carbonate (**7a**)*. Compound **7a** was obtained from piperidin-2-one according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.55 (m, 2H), 7.48 (m, 1H), 7.45–7.39 (m, 2H), 5.84 (m, 1H), 5.35–5.24 (m, 2H), 5.11 (t, *J* = 3.8 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.88–3.82 (m, 2H), 2.35 (td, *J* = 6.6, 3.8 Hz, 2H), 1.97–1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 152.0, 140.9, 136.0, 130.9, 130.7, 128.2, 127.7, 119.3, 102.4, 69.1, 46.0, 23.1, 21.8. IR (Neat Film, NaCl) 3520, 3290, 2917, 1765, 1644, 1451, 1367, 1263, 1224, 1039 cm^{-1}. HRMS (ESI/APCI) m/z calc'd for $C_{16}H_{18}NO_4$ $[M+H]^+$: 288.1230, found 288.1227.



*Allyl (4-benzoyl-3,4-dihydro-2H-1,4-oxazin-5-yl) carbonate (**7b**)*. To a solution of ethanol amine (197 mmol, 1.1 equiv) in ^{i}PrOH (100 mL) was portionwise added small pieces of sodium (197 mmol, 1.1 equiv). The mixture was heated at 50 °C for 5 h, and the resulting yellow solution was cooled in an ice-water bath. Ethyl chloroacetate (179 mmol, 1.0 equiv) was dropwise added at 0 °C, and the resulting yellow suspension was heated at 80 °C for 2 h. Insoluble materials were removed by paper filtration and washed with ^{i}PrOH. The combined filtrate and washings were concentrated *in vacuo*, and the resulting brown solids were recrystallized from ^{i}PrOH/EtOAc to afford 3-morpholinone in 52% yield. To a solution of 3-morpholinone (9.9 mmol, 1.0 equiv) in THF (100 mL) was added a 2.5 M solution ^{n}BuLi in THF (10.9 mmol, 1.1 equiv) at –78 ºC. The resulting solution was stirred at –78 ºC for 30 min. Then, benzoyl chloride (10.9 mmol, 1.1 equiv) was added at –78 ºC. After completion of the addition, the reaction mixture was allowed to warm to room temperature. All volatiles were removed *in vacuo*. After the addition of EtOAc, the organic layer was washed with 1 M HCl, saturated $NaHCO_3$ aq and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 15→50% EtOAc in hexanes) to give the Bz-protected amide in 71% yield. To a stirred solution of LHMDS (3 mmol, 1.5 equiv) in THF (30 mL) was added a solution of Bz-protected amide (2 mmol, 1.0 equiv) in THF dropwise via syringe at –78 ºC. After stirring for 30 min, allyl chloroformate (2.2 mmol, 1.1 equiv) was added at –78 ºC. The reaction was quenched by the addition of saturated NH_4Cl aq, and then the resulting mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give the enol carbonate in 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2H), 7.49–7.38 (m, 3H), 6.31 (s, 1H), 5.80 (ddt, *J* = 16.5, 10.4, 5.8 Hz, 1H), 5.29–5.22 (m, 2H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.18–4.14 (m, 2H), 3.93–3.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 152.8, 135.3, 131.1, 131.0, 128.4, 128.1, 128.0, 126.6, 119.5, 69.5, 66.53, 42.6. IR (Neat Film, NaCl) 3062, 2944, 2884, 1769, 1698, 1653, 1602, 1580, 1493, 1448, 1393, 1362, 1319, 1256, 1215, 1097, 1045 cm^{-1}. HRMS (ESI/APCI) m/z calc'd for $C_{15}H_{16}NO_5$ $[M+H]^+$: 290.1023, found 290.1024.

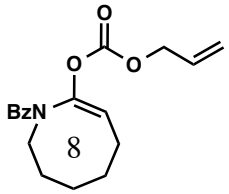


*Allyl (4-benzoyl-3,4-dihydro-2H-1,4-thiazin-5-yl) carbonate (**7c**)*. To a solution of 2-aminoehtane-1-thiol (4.5 g, 40 mmol, 1.0 equiv) and K_2CO_3 (5.5 g, 40 mmol, 1.0 equiv.) in EtOH (80 mL) was added ethyl chloroacetate (40 mmol, 1 equiv). The resulting solution was stirred at room temperature for 2 h and at 75 ºC for 24 h. After filtration, all volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc) to give thiomorpholin-3-one as white solid in 18% yield. To a cold solution (–78 ºC) of thiomorpholin-3-one (780 mg, 6.7 mmol, 1 equiv) in THF (20 mL) was added ^{n}BuLi (2.5 M in hexane, 0.85 mL, 7.3 mmol, 1.1 equiv) dropwise. After stirring for 30 min, benzoyl chloride (7.3 mmol, 1.1 equiv) was added at –78 ºC. The reaction mixture was warmed to room temperature and quenched by the addition of 1M HCl, and then resulting mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give Bz-protected lactam as yellow solid in 85% yield. To a stirred solution of NaHMDS (2.05 g, 11.2 mmol, 2.0 equiv) in THF (50 mL) was added a solution of Bz-protected lactam (1.25 g, 5.6 mmol, 1.0 equiv) and TMEDA (840 μL, 5.6 mmol, 1.1 equiv) in THF (10 mL) dropwise via syringe at –78 ºC. After stirring for 30 min, allyl chloroformate (590 mL, 5.6 mmol, 1.0 equiv) was added at –78 ºC. The reaction was quenched by the addition of saturated NH_4Cl aq, and then the resulting mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 40% EtOAc in hexanes) to give the enol carbonate as yellow oil in 39% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.52 (m, 2H), 7.47 (m, 1H), 7.42–7.37 (m, 2H), 5.76 (ddt, J = 17.5, 10.1, 5.8 Hz, 1H), 5.70 (s, 1H), 5.28–5.20 (m, 2H), 4.44 (dt, J = 5.8, 1.4 Hz, 2H), 4.19–4.14 (m, 2H), 3.16–3.10 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 151.8, 135.4, 135.0, 131.0, 130.6, 128.3, 127.4, 119.5, 100.4, 69.2, 42.6, 28.5. IR (Neat Film, NaCl) 3067, 2942, 2359, 1764, 1664, 1638, 1601, 1579, 1491, 1448, 1364, 1320, 1276, 1244, 1226, 1190, 1162, 1138, 1100, 1029 cm^{-1}. HRMS (ESI/APCI) m/z calc'd for $C_{15}H_{16}NO_4S$ $[M+H]^+$: 306.0795, found 306.0786.

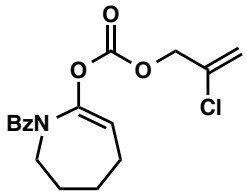


*Allyl (1-benzoyl-4,5,6,7-tetrahydro-1H-azepin-2-yl) carbonate (**7d**)*. Compound **7d** was obtained from ε-caprolactam according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2H), 7.48 (m, 1H), 7.44–7.37 (m, 2H), 5.85 (ddt, J = 16.4, 10.9, 5.7 Hz, 1H), 5.47 (t, J = 6.8 Hz, 1H), 5.35–5.25 (m, 2H), 4.53 (d, J = 5.7 Hz, 2H), 3.97 (br s, 2H), 2.34 (td, J = 6.8, 4.3 Hz, 2H), 1.92 (br s, 2H), 1.75–1.68 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 152.6, 146.1, 136.0, 131.0, 130.5, 128.3, 127.0, 119.4, 112.2,

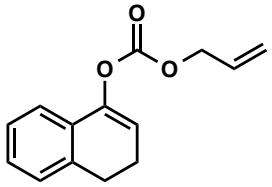
69.1, 46.5, 29.8, 24.9, 23.9. IR (Neat Film, NaCl) 2943, 2359, 1761, 1653, 1448, 1374, 1325, 1243, 1172, 1134, 1094 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1387, found 302.1372.



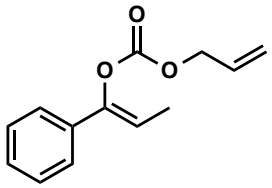
*(E)-Allyl (1-benzoyl-1,4,5,6,7,8-hexahydroazocin-2-yl) carbonate (**7e**).* In a 100 mL flask equipped with magnetic stirrer and containing 30 mL of EtOH, cycloheptanone (50 mmol) and $NH_2OH \cdot HCl$ (80 mmol) were dissolved. To the above solution was added K_2CO_3 (40 mmol) in H_2O (30 mL) dropwise. The mixture was stirred at 50 ºC for 2 h. After removal of all volatiles, aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give cycloheptanone oxime in 61% yield. To a hot solution (110 ºC) of H_2SO_4 (10 mL) in H_2O (3 mL) was added cycloheptanone oxime (20 mmol) dropwise or several portions. After completion of the addition, the reaction mixture was cooled to 0 ºC and neutralized with NaOH. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give the corresponding amide in 69% yield. To a solution of amide (10 mmol, 1.0 equiv) in THF (100 mL) was added a 2.5 M solution ^{n}BuLi in THF (11 mmol, 1.1 equiv) at –78 ºC. The resulting solution was stirred at –78 ºC for 30 min. Then, benzoyl chloride (11 mmol, 1.1 equiv) was added at –78 ºC. After completion of the addition, the reaction mixture was allowed to warm to room temperature. All volatiles were removed in vacuo. After the addition of EtOAc, the organic layer was washed with 1 M HCl, saturated $NaHCO_3$ aq and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2, 15→50% EtOAc in hexanes) to give the Bz-protected amide in 91% yield. To a stirred solution of NaHMDS (3 mmol, 1.5 equiv) in THF (30 mL) was added a solution of Bz-protected azocan-2-one (2 mmol, 1.0 equiv) and TMEDA (2.2 mmol, 1.1 equiv) in THF dropwise via syringe at –78 ºC. After stirring for 30 min, allyl chloroformate (2.2 mmol, 1.1 equiv) was added at –78 ºC. The reaction was quenched by the addition of saturated NH_4Cl aq, and then the resulting mixture was extracted with ether. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give the enol carbonate in 36% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.45 (m, 1H), 7.39 (dd, J = 8.2, 6.6 Hz, 2H), 5.97 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 5.50–5.30 (m, 3H), 4.67 (dt, J = 5.9, 1.4 Hz, 2H), 3.87 (br s, 2H), 2.14–2.07 (m, 2H), 1.98–1.93 (m, 2H), 1.84–1.73 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 153.4, 141.2, 135.8, 131.0, 130.3, 127.9, 127.1, 119.7, 118.7, 69.2, 48.2, 26.8, 25.4. IR (Neat Film, NaCl) 3059, 2932, 2855, 1759, 1660, 1601, 1579, 1493, 1447, 1360, 1333, 1235, 1218, 1190, 1156, 1116, 1085, 1026 cm^{-1}. HRMS (ESI/APCI) m/z calc'd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found 316.1544.



*1-Benzoyl-4,5,6,7-tetrahydro-1H-azepin-2-yl (2-chloroallyl) carbonate (**7f**)*. Compound **7f** was obtained from ε-caprolactam with 2-chloroallyloxycarbonyl imidazole[17] according to the general procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.51 (m, 2H), 7.47 (m, 1H), 7.43–7.38 (m, 2H), 5.50 (t, *J* = 6.7 Hz, 1H), 5.46–5.40 (m, 2H), 4.58 (s, 2H), 3.97 (br s, 2H), 2.34 (td, *J* = 6.8, 4.4 Hz, 2H), 1.92 (br s, 2H), 1.77–1.63 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 152.0, 145.9, 135.8, 134.48, 130.49, 128.2, 126.9, 115.7, 112.2, 69.4, 46.4, 29.7, 24.8, 23.7. IR (Neat Film, NaCl) 2943, 2855, 1766, 1660, 1651, 1579, 1492, 1446, 1372, 1352, 1326, 1260, 1242, 1195, 1173, 1134, 1095, 1011 cm^{-1}. HRMS (ESI/APCI) m/z calc'd for $C_{17}H_{19}ClNO_4$ $[M+H]^+$: 336.0997, found 336.0995.



*Allyl (3,4-dihydronaphthalen-1-yl) carbonate (**8a**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.16 (m, 4H), 6.04 (ddt, *J* = 17.2, 10.5, 5.9 Hz, 1H), 5.86 (t, *J* = 4.7 Hz, 1H), 5.47 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.37 (ddd, *J* = 10.5, 1.2, 1.2 Hz, 1H), 4.76 (dt, *J* = 5.9, 1.4 Hz, 2H), 2.92 (t, *J* = 8.3 Hz, 2H), 2.50 (td, *J* = 8.3, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 146.1, 136.4, 131.2, 130.1, 128.1, 127.6, 126.5, 120.6, 119.4, 115.3, 69.1, 27.4, 22.0. IR (Neat Film, NaCl) 3066, 3023, 2942, 2889, 2835, 1760, 1656, 1489, 1451, 1360, 1338, 1223, 1185, 1135, 1013 cm^{-1}. HRMS (FAB+) m/z calc'd for $C_{14}H_{13}O_3$ $[M-H]^-$: 229.0865, found 229.0859.



*(Z)-Allyl (1-phenylprop-1-en-1-yl) carbonate (**8b**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.43 (m, 2H), 7.42–7.35 (m, 2H), 7.35–7.29 (m, 1H), 6.01 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.92 (q, *J* = 7.0 Hz, 1H), 5.44 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.35 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1H), 4.74 (dt, *J* = 5.7, 1.4 Hz, 2H), 1.84 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 147.3, 134.7, 131.2, 128.5, 128.2, 124.3, 119.2, 113.0, 69.0, 11.3. IR (Neat Film, NaCl) 3060, 2919, 2356, 1759, 1674, 1495, 1446, 1381, 1318, 1225, 1185, 1116, 1077 cm^{-1}. HRMS (FAB+) m/z calc'd for $C_{13}H_{13}O_3$ $[M-H]^-$: 217.0865, found 217.0866.

References

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