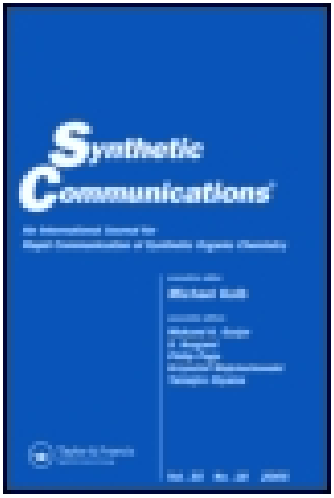

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Palladium-Catalyzed Synthesis of β-Lactams via Carbonylative Cycloaddition of Benzyl and Allyl Halides with Imines

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PALLADIUM-CATALYZED SYNTHESIS OF β-LACTAMS VIA CARBONYLATIVE CYCLOADDITION OF BENZYL AND ALLYL HALIDES WITH IMINES

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Abstract: Benzyl and allyl halides react stereoselectively with imines under carbon monoxide pressure in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride together with triethylamine to afford the corresponding β-lactams in good yields.

It is well-known that the formation of the structural core of β-lactam is the annulation of ketene precursors such as acid chlorides and activated carboxylic acids with imines through a [2+2] cycloaddition process.[1] Transition metal-mediated and -catalyzed versions utilizing various substrates have also been attempted for the formation of the β-lactam skeleton.[2-19] Among them, it is worth while to note the palladium-catalyzed carbonylative [2+2] cycloaddition reaction of allyl diethyl phosphates with imines.[20] However, the ketene precursor seems to be limited to the phosphates, other allylic substrates such as bromide, acetate, phenyl ether, carbonate, and sulfone being not successful for the β-lactam. As our series of studies on transition metal-catalyzed carbonylative cycloaddition reactions for the construction of N-heterocyclic compounds,[21] we here report a palladium-catalyzed

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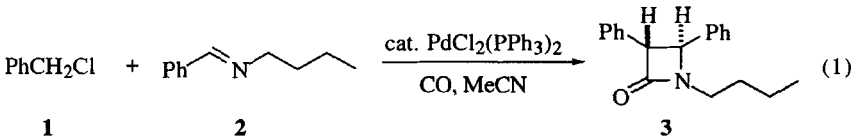
approach for the synthesis of β-lactams which utilize benzyl and allyl halides as a ketene precursor.

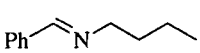
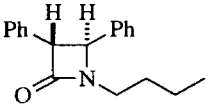
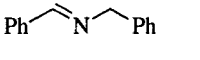
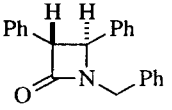
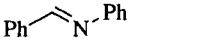
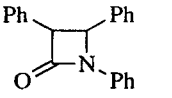
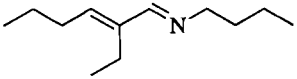
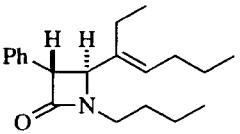
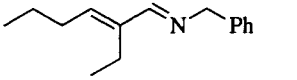
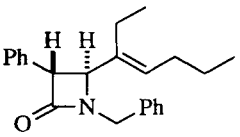
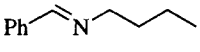
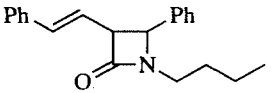
Treatment of benzyl chloride (**1**) with *N*-butylbenzaldimine (**2**) and carbon monoxide (30 atm) in anhydrous acetonitrile in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (2 mol% based on **2**) together with triethylamine at 100 °C for 24 h afforded stereochemically pure *trans*-1-butyl-3,4-diphenylazetan-2-one (**3**) in 73% isolated yield (eq 1). The carbonylative cycloaddition also proceeded using benzyl bromide in place of **1**, but the yield of the β-lactam **3** was lower than that when benzyl chloride was used (Table 1, entry 1).



1 **2** **3** (1)

Table 1 indicates that the structural nature of the imines showed no considerable influence on the yield of the corresponding β-lactams. However, the stereochemical configuration of β-lactam varied as the structural nature of primary amine counterpart of the imines (entries 1-3). The reaction of *N*-benzylbenzaldimine with **1** only resulted in the corresponding *trans*-β-lactam, whereas the reaction of *N*-phenylbenzaldimine with **1** afforded stereoisomeric β-lactams, favoring the formation of *trans*-β-lactam. α,β-Unsaturated imines[22] could also be applied to the present carbonylative cycloaddition with **1** to give the corresponding 4-vinyl-β-lactams without the loss of *trans* stereoselectivity (entries 4,5). This result shows that the conjugation on the aldehyde counterpart of imine does not affect the stereoselectivity of β-lactams. Similar treatment of cinnamyl chloride with

Table 1. Palladium-Catalyzed Synthesis of β-Lactams from **1** and Imines[a]

entry	imine	products	yield[b] (%)
1[c]			48
2			61
3			55[d]
4			53
5			40
6[e]			74[f]

[a] Except as noted, all reactions were carried out with **1** (3 mmol), imine (2 mmol), $PdCl_2(PPh_3)_2$ (0.04 mmol), PPh_3 (0.16 mmol) and triethylamine (5 mmol) in acetonitrile at 100 °C for 24 h.

[b] Isolated yield based on imine.

[c] Benzyl bromide was used in place of **1**.

[d] *Trans* : *cis* = 7 : 3.

[e] Cinnamyl chloride was used in place of **1**.

[f] *Trans* : *cis* = 8 : 2.

imine **2** under the above reaction system afforded stereoisomeric 3-vinyl-β-lactams in high isolated yields, also favoring the formation of *trans*-isomer (entry 6). This result indicates that the stereochemical distribution of 3-vinyl-β-lactams was also affected by halide analogues.

Further application of other halide analogues and imines for synthetic utility is in progress.

EXPERIMENTAL

Typical procedure for palladium-catalyzed synthesis of β-lactams from benzyl chloride and imines: A mixture of benzyl chloride (0.380 g, 3 mmol), *N*-butylbenzaldimine (0.322 g, 2 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol), PPh_3 (0.042 g, 0.16 mmol), and Et_3N (0.506 g, 5 mmol) in anhydrous acetonitrile (10 mL) was placed in a pressure vessel. After the system was flushed and then pressurized with carbon monoxide to 27 atm, the mixture was stirred at 100 °C for 24 h. The yellow reaction mixture was poured into aqueous 5% HCl solution, extracted with dichloromethane (30 mL x 2), and washed with water. The combined organic layer was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left an oil which was separated by column chromatography using ethyl acetate-hexane mixtures as an eluent to give stereochemically pure *trans*-1-butyl-3,4-diphenylazetan-2-one (0.410 g, 73%). The products prepared by the above procedure were characterized spectroscopically as shown below.

***trans*-1-Butyl-3,4-diphenylazetan-2-one (3):** pale yellow oil; IR (neat) 1754 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 1.27-1.37 (m, 2H), 1.45-1.54 (m, 2H), 2.87 (dt, J = 13.8 and 6.9 Hz, 1H), 3.60 (dt, J = 13.8 and 6.9 Hz, 1H), 4.12 (d, J = 2.4 Hz, 1H), 4.48 (d, J = 2.4 Hz, 1H), 7.22-7.49 (m, 10H);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 19.9, 29.5, 39.9, 63.4, 64.7, 126.1, 127.0, 127.2, 128.3, 128.6, 128.8, 134.9, 137.4, 167.8; MS *m/z* (relative intensity) 279 (M^+, 0.3), 250 (0.1), 236 (0.1), 222 (0.1), 204 (0.2), 180 (100), 165 (15), 117 (12), 90 (15), 77 (6), 51 (4). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.56; H, 7.39; N,4.97.

***trans*-1-Benzyl-3,4-diphenylazetan-2-one:** pale yellow oil; IR (neat) 1756 (C=O) cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 3.76 (d, J = 15.5 Hz, 1H), 4.15 (s, 1H), 4.31 (s, 1H), 4.91 (d, J = 15.5 Hz, 1H), 7.13-7.34 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 44.1, 62.6, 64.7, 126.1, 126.9, 127.2, 127.4, 128.1, 128.3, 128.4, 128.5, 128.7, 134.6, 135.2, 136.8, 167.7; MS *m/z* (relative intensity) 313 (M^+, 0.1), 224 (0.7), 179 (100), 180 (89), 165 (14), 117 (9), 91 (16). Anal. Calcd for $C_{22}H_{19}NO$: C, 84.32; H, 6.11; N, 4.47. Found: C, 84.50; H, 6.31; N, 4.40.

***trans*-1,3,4-Triphenylazetan-2-one:** white solid; mp 132-134 °C; IR (KBr) 1746 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, J = 2.6 Hz, 1H), 4.94 (d, J = 2.6 Hz, 1H), 7.20-7.40 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 63.5, 65.0, 117.1, 123.9, 125.8, 127.3, 127.8, 128.6, 128.9, 129.0, 129.2, 134.6, 137.3, 137.4, 165.5; MS *m/z* (relative intensity) 299 (M^+, 2), 180 (100), 165 (17), 104 (3), 77 (25), 51 (12). Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.05; H, 5.54; N, 4.68.

***cis*-1,3,4-Triphenylazetan-2-one:** white solid; mp 172-175°C; IR (KBr) 1736 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (d, J = 6.5 Hz, 1H), 5.46 (d, J = 6.5 Hz, 1H), 7.04-7.43 (m, 15H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 60.2, 60.3, 117.2, 124.0, 127.1 (x2), 127.8, 128.0, 128.2, 128.8, 129.0, 132.0, 134.3, 137.7, 165.6; MS *m/z* (relative intensity) 299 (M^+, 6), 181 (100), 180 (69), 165 (10), 104 (6), 77 (33), 51 (13). Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 83.97; H, 5.85; N, 4.35.

***trans*-1-Butyl-4-[(*E*)-1-ethyl-1-pentenyl]-3-(3-heptenyl)-3-phenylazetan-2-one:** colorless oil; IR (KBr) 1757 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-1.55 (m, 15H), 1.92-2.13 (m, 4H), 2.78-2.87 (m, 1H), 3.44-3.54 (m, 1H), 3.84 (s, 1H), 3.92 (s, 1H), 5.42 (t, *J* = 7.2 Hz, 1H), 7.12-7.29 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 13.4, 13.9, 19.9, 20.1, 22.4, 29.3, 29.5, 39.8, 61.3, 65.4, 127.0, 128.4, 128.9, 130.4, 135.3, 136.9, 168.0; MS *m/z* (relative intensity) 299 (M^+, 2), 270 (1), 256 (6), 200 (67), 182 (22), 171 (100), 157 (54), 128 (65), 117 (23), 91 (62), 77 (12), 55 (24).

***trans*-1-Benzyl-4-[(*E*)-1-ethyl-1-pentenyl]-3-(3-heptenyl)-3-phenylazetan-2-one:** colorless oil; IR (KBr) 1755 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81-1.47 (m, 8H), 1.91-2.11 (m, 4H), 3.74 (d, *J* = 2.6 Hz, 1H), 3.92 (d, *J* = 15.0 Hz, 1H), 4.02 (d, *J* = 2.6 Hz, 1H), 4.85 (d, *J* = 15.0 Hz, 1H), 5.42 (t, *J* = 7.5 Hz, 1H), 7.15-7.35 (m, 10H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 13.9, 20.3, 22.6, 29.4, 44.5, 61.8, 64.8, 127.2, 127.5, 128.4, 128.5, 128.6, 128.7, 129.2, 135.3, 135.7, 136.6, 168.3; MS *m/z* (relative intensity) 333 (M^+, 2), 304 (1), 290 (5), 216 (18), 200 (63), 171 (69), 157 (34), 128 (42), 117 (18), 91 (100), 77 (8).

***trans*-1-Butyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:** white solid; IR (KBr) 1735 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.5 Hz, 3H), 1.28-1.36 (m, 2H), 1.45-1.51 (m, 2H), 2.86 (dt, *J* = 14.0 and 7.0 Hz, 1H), 3.52 (dt, *J* = 14.0 and 7.5 Hz, 1H), 3.75 (d, *J* = 8.0 Hz, 1H), 4.40 (d, *J* = 2.0 Hz, 1H), 6.32 (dd, *J* = 16.0 and 8.0 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 7.19-7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 20.0, 29.5, 40.1, 61.7, 63.4, 122.4, 126.2 (x2), 127.6, 128.3, 128.4, 128.8, 133.8, 136.3, 137.4, 168.0; MS *m/z* (relative intensity) 305 (M^+, 0.1), 206 (100), 191 (18), 178 (6), 165 (6), 144 (12), 128 (31), 115 (42), 104 (7), 77 (11). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.18; H, 7.37; N, 4.54.

***cis*-1-Butyl-4-phenyl-3-[(*E*)-2-phenyl-1-ethenyl]-2-azetanone:** pale yellow oil; IR (KBr) 1744 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.29-1.37 (m, 2H), 1.49-1.55 (m, 2H), 2.95 (dt, J = 14.0 and 7.0 Hz, 1H), 3.57 (dt, J = 14.0 and 7.5 Hz, 1H), 4.27-4.29 (m, 1H), 4.88 (d, J = 5.5 Hz, 1H), 5.60 (dd, J = 16.0 and 8.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.06-7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 19.9, 29.3, 40.1, 57.8, 59.0, 120.7, 125.9, 127.0, 127.1, 127.97, 127.98, 128.3, 134.1, 135.2, 136.4, 168.0; MS *m/z* (relative intensity) 305 (M^+, 1), 206 (100), 191 (19), 178 (7), 165 (5), 144 (22), 128 (29), 115 (49), 104 (7), 77 (14). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.29; H, 7.26; N, 4.49.

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