Palladium-catalyzed cyclocarbonylation of unsaturated amines. Chemo- and stereoselective synthesis of *N*-heteroaryl γ- and δ-lactams

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Dedicated to Professor Giuseppe Bartoli on his 65th birthday

Abstract

Palladium-catalyzed cyclocarbonylation of *N*-heteroaryl-*N*-homoallyl amines led to γ- and δ-lactams with good yields and in a stereo- and regioselective way. The regio- and stereoselectivity of the methodology was investigated by changing the heterocycle attached to the amine and varying the reaction solvent and the metal ligand. In order to explain the obtained results, a cyclocarbonylation mechanism with the participation of the heterocyclic moiety is suggested.

Keywords: *N*-Heteroaryl amine, pyrrolidinone, piperidinone, palladium-cyclocarbonylation, regioselectivity, lactam

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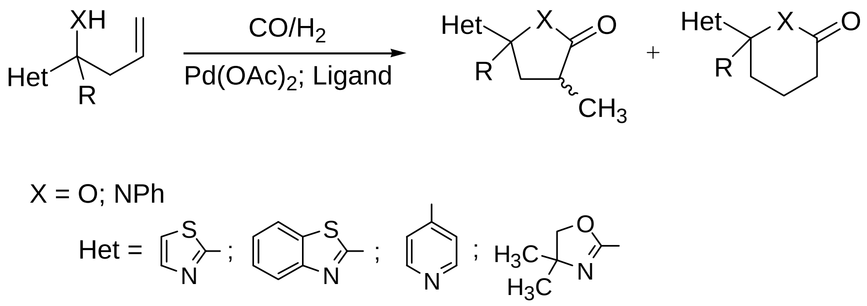
Introduction

The lactam function is a strategic component of many natural compounds showing a biological and pharmacological activity.[1–5] Its importance has led many researchers to investigate new synthetic methodologies for the preparation of azetidinones,[5,6] pyrrolidinones[7–10] and piperidinones.[11,12] Among these preparations, particularly interesting is the metal-catalyzed carbonylation of aminovinyl halides,[13] imines,[14] aziridines,[15] and thiazines[16] leading to β-lactams with regio- and stereo-selectivity. Another convenient synthetic pathway is the intramolecular cyclization of *o*-allylphenols and *o*-allylanilines in the presence of CO/H_2 and Pd(II) complexed by phosphinic ligands as catalyst, which affords bicyclic and polycyclic γ-, δ-, and ε-lactones and lactams, respectively.[17] Recently, we showed that, in an analogous way, the cyclocarbonylation can occur also on homoallylic, propargylic and allenic α-heteroaryl- substituted alcohols and amines leading to variously substituted γ- and δ-lactones and lactams,[18] according to Scheme 1.



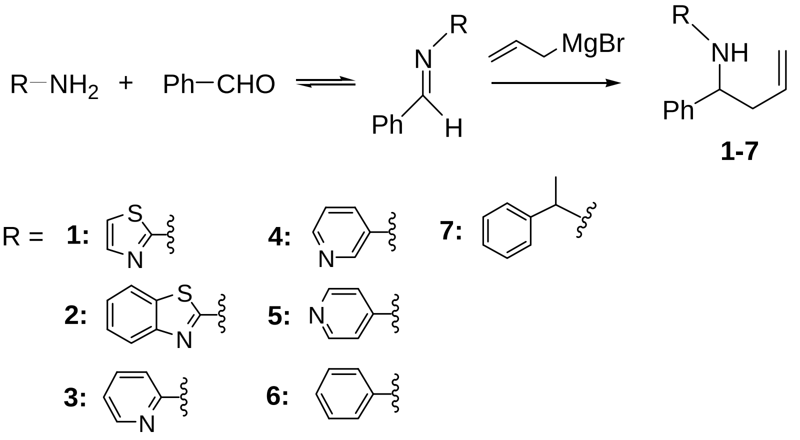
Scheme 1. Cyclocarbonylation of α-(heteroaryl)homoallyl alcohols and *N*-phenyl α-(heteroaryl)homoallyl amines.

When toluene was used as solvent and 1,4-bis(diphenylphosphino)butane (dppb) as ligand we recorded a regioselectivity towards the six-membered ring; moreover, in these conditions, the five-membered ring was formed in the two isomeric forms *cis*- and *trans*- with a certain diastereoselectivity (*trans*>*cis*). It was found, in addition, that the use of CH_2Cl_2 as solvent and R(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (binap) as ligand made the reaction regioselective towards the five-membered ring product. The presence of a heterocycle as a substituent in these structures is potentially useful for subsequent synthetic modifications such as freeing the acyl groups masked by some of the heterocycles.[19]

Comforted by these interesting findings we continued our research by carrying out the cyclocarbonylation on *N*-heteroaryl amines in order to obtain lactams bearing a heterocyclic function on the amide nitrogen. This investigation aims at the understanding of the potentially different regio- and stereoselectivity of the methodology, and at the same time producing, new structures with interesting biological activity or useful synthetic applications.

Results and Discussion

The unsaturated amines **1–7** were prepared (yield > 90%) through the coupling reaction between allyl-magnesium bromide and the imines (Scheme 2) prepared previously according to the Taguchi's method.[20] More details of these syntheses are given in the Experimental Section.

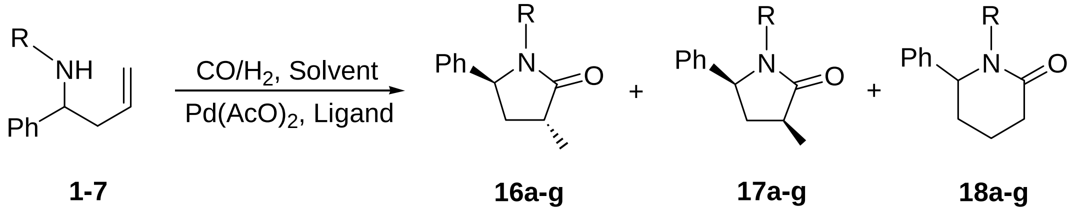


Scheme 2. Synthesis of *N*-aryl-α-(phenyl)homoallyl amines.

Table 1 collects the data on the cyclocarbonylation of the *N*-heteroaryl amines **1–7** leading to γ- and δ- lactams in good yields. The reactions were performed in toluene or CH_2Cl_2, under a pressure (600 psi) of CO and H_2, in the presence of a catalytic amount (10%) of $Pd(AcO)_2$ and dppb or binap as phosphinic ligands, at 120°C for 72–96 h. The relative geometries of the pyrrolidinone isomers were assigned on the basis of 2D-NOESY experiments. The NOE interaction between the CH_3 bonded on the C_3 of the γ-lactam, and the two different protons on the vicinal C_4 was evaluated.

A good regioselectivity was noticed using the substrates **1–3**, having an α-aza heterocycle attached to the amide nitrogen. The reactions carried out in toluene as solvent and with dppb as ligand led to the δ-lactam as the major product (yields of 70–79 %, entries 1, 3, and 5, Table 1). Among the many cyclocarbonylation reactions performed under different conditions (varying the solvent and phosphinic ligand) in order to investigate the regio- and stereochemistry of these substrates, the more effective were those performed using CH_2Cl_2 as solvent and binap as Pd ligand. The differences in yield between the γ- and the δ-adducts obtained from amines **1–3**, increased even more using CH_2Cl_2 as solvent and binap as ligand (yields of δ-lactam 75–88 %, entries 2, 4, and 6). Moreover, for all these reactions a high diastereoselectivity was observed among the pyrrolidinone derivatives. For example, only small amounts of the *cis*- isomer were formed (entries 5, and 6) or it was not formed at all (entries 1–4). Using the other amines, bearing a β- or a γ-*aza* heterocycle (**4**, **5**), or those not having an *aza* group in the nitrogen substituent (**6** and **7**), the percentage of the δ-lactam decreased, sometimes in a significant way (entries 10 and 14), while the γ-lactam yield increased (entries 7–14). Furthermore, the *trans*-/*cis*- ratio within the γ-lactams became almost unity, even by changing the solvent and the ligand.

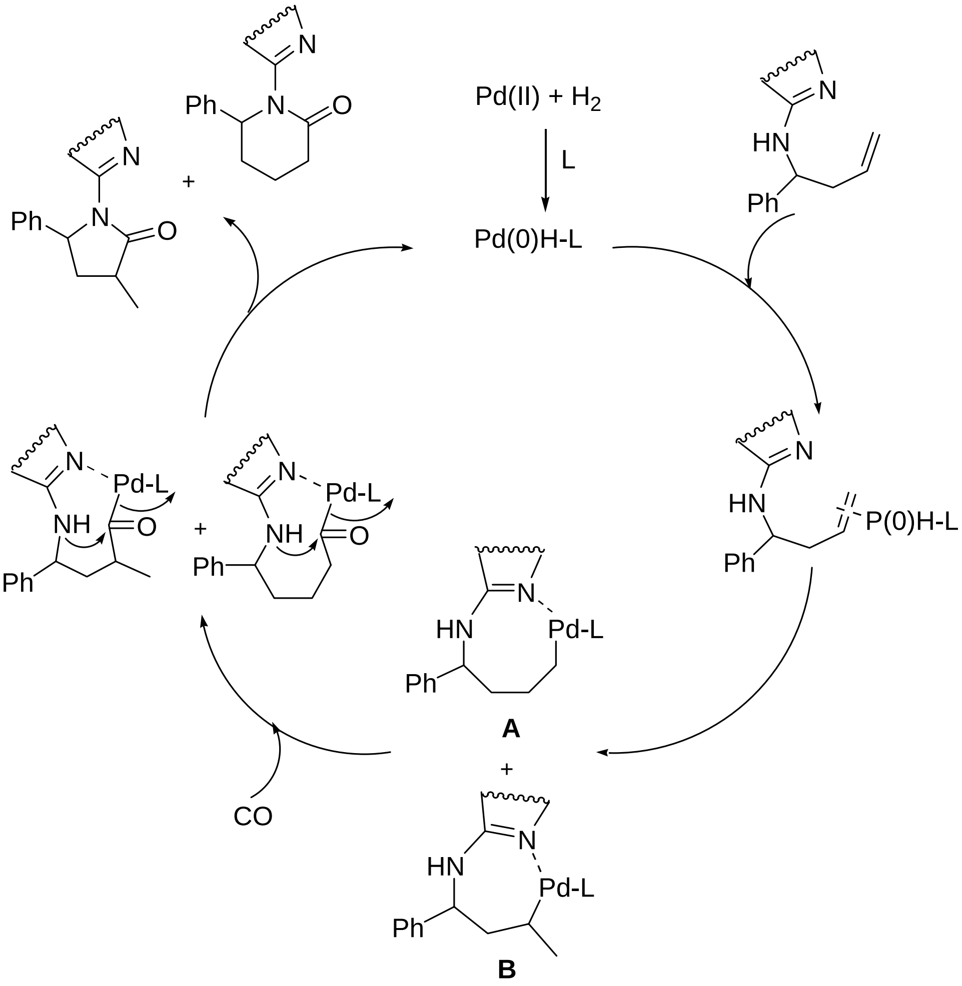
Table 1. Cyclocarbonylation of amines **1–7** under two different reaction conditions



Entry	Amine	Solvent	Ligand	Total yield (%)[a]	Products distribution (%)[b]		
1	**1**	toluene	dppb	90	**16a** (21)	**17a** (–)	**18a** (79)
2	**1**	CH_2Cl_2	binap	88	**16a** (12)	**17a** (–)	**18a** (88)
3	**2**	toluene	dppb	99	**16b** (30)	**17b** (–)	**18b** (70)
4	**2**	CH_2Cl_2	binap	99	**16b** (25)	**17b** (–)	**18b** (75)
5	**3**	toluene	dppb	97	**16c** (24)	**17c** (6)	**18c** (70)
6	**3**	CH_2Cl_2	binap	90	**16c** (19)	**17c** (6)	**18c** (75)
7	**4**	toluene	dppb	82	**16d** (30)	**17d** (25)	**18d** (45)
8	**4**	CH_2Cl_2	binap	77	**16d** (22)	**17d** (18)	**18d** (60)
9	**5**	toluene	dppb	80	**16e** (25)	**17e** (25)	**18e** (50)
10	**5**	CH_2Cl_2	binap	70	**16e** (50)	**17e** (48)	**18e** (2)
11	**6**	toluene	dppb	78	**16f** (30)	**17f** (21)	**18f** (49)
12	**6**	CH_2Cl_2	binap	80	**16f** (20)	**17f** (24)	**18f** (56)
13	**7**	toluene	dppb	79	**16g** (26)	**17g** (23)	**18g** (51)
14	**7**	CH_2Cl_2	binap	78	**16g** (40)	**17g**(40)	**18g** (20)
15	**3**	toluene	–	50	**16c** (20)	**17c** (3)	**18c** (77)
16	**5**	toluene	–	10	**16e** (25)	**17e** (25)	**18e** (50)

[a] Isolated yields. [b] Measured by GC and ^{1}H- NMR spectroscopy.

From the results given above, it seems that the presence or absence of an aza group in the position α– to the heterocyclic functionality, that could participate in the coordination of the Pd during the lactam formation, is of strategic importance. A mechanism presumed for the cyclocarbonylation of *N*-heteroaryl unsaturated amines is reported in Scheme 3. The *aza* group should influence the coordination in the **A** and **B** structures (Scheme 3) and, consequently, the isomers' distribution. For example, the participation of the α-*aza* heterocyclic nitrogen in the Pd coordination during the cyclocarbonylation process could particularly favor the formation of the six-membered ring and the *trans*- diastereomer among the five-membered isomers.



Scheme 3. Suggested mechanism for the cyclocarbonylation of *N*-heteroaryl unsaturated amines.

An attempt was made to carry out the reaction without a ligand, on substrates **3** and **5**. With the amine **3**, which has an α-aza group on the imine nitrogen, the reaction occurred anyway, although with modest transformation yields, and with longer reaction times (120 h), but with the γ-/δ-lactam ratio confirmed (entry 15). A lower yield was noticed when using the amine **5** which still has an *aza* group linked to the aminic nitrogen, but in the γ– position (entry 16). These results support the suggested mechanism reported in Scheme 3, with the strategic participation of the α-*aza* heterocyclic nitrogen to the metal coordination. Also, the higher reaction yields obtained with the substrates **1–3** with respect to the substrates **4–7** should support this hypothesis.

Finally, in order to verify that the Pd participates in the reaction in the oxidation state (0) the reaction reported in entry 15 was repeated using the commercial *tetrakis*(triphenylphosphine)-palladium(0) [$Pd(PPh_3)_4$]. An equally satisfactory yield was noted, and the metallic Pd(0) and the Ph_3PO were observed at the end of the reaction.[21]

In conclusion, we have found that unsaturated *N*-heteroaryl amines undergo a Pd-catalyzed cyclocarbonylation reaction, leading to five- and six- membered ring lactams, with good yield and high stereo- and regioselectivity. The latter can be modified by changing the heterocycle bonded on the amine and by varying the reaction conditions, in particular the solvent and the ligand. This methodology represents a useful path to the synthesis of these new substrates, extensively studied in biology and pharmacology.

Experimental Section

General Procedures. Toluene, dichloromethane, allylmagnesium bromide, palladium(II) acetate, *tetrakis*(triphenylphosphine)-palladium(0), 1,4-bis(diphenylphosphino)butane (dppb), *R*-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (binap), 2-aminothiazole, 2-aminobenzothiazole, 2-aminopyridine, 3-aminopyridine, 4-aminopyridine, aniline, 1-phenylethylamine, and all other chemicals were of commercial grade (Aldrich), and were used without further purification. Benzaldehyde was of commercial grade (Aldrich), and was purified by distillation prior to use. Petroleum refers to the 40–60°C boiling fraction. The ^1H- and ^{13}C-NMR spectra were recorded with a Bruker Avance 400 apparatus (400.13 MHz and 100.62 MHz for ^1H and ^{13}C, respectively), with $CDCl_3$ as solvent and TMS as internal standard ($\delta = 7.24$ ppm for ^1H spectra; $\delta = 77.0$ for ^{13}C spectra). IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC-MS analyses were performed with a Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV (EI). The electrospray ionization (HR–ESI–MS) experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 mL/min) of a solution containing the appropriate sample (10 pmol/ mL), dissolved in a solution of 0.1% acetic acid, methanol/water, 50:50, at the optimum ion voltage of 4,800 V. The pressure of the nitrogen gas flow was set at 30 psi and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V respectively, relative to ground. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. Melting points were measured using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatography was performed on silica gel (63–200 μm), with petroleum/diethyl ether (petrol/Et_2O) or petrol/ethyl acetate (petrol/EtOAc) mixtures as eluents.

Preparation of *N*-aryl-α-(phenyl)homoallyl amines 1–7. The amines **1–5** were prepared by Grignard reaction of allyl magnesium bromide with the corresponding benzylidene-*N*-aryl amines.[18] The former precursors were prepared by the coupling reaction of the corresponding *N*-aryl amines with the benzaldehyde according to Taguchi's procedure.[20] The amines **6** and **7** are known compounds and were prepared as reported in the literature.[22,23]

(1-Phenylbut-3-enyl)-thiazol-2-ylamine (1). Yield 225 mg (98%), yellow solid, mp 105–106°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.58–2.63 (2H, m), 3.65 (1H, s, broad), 4.51 (1H, q, *J* = 7.5 Hz), 5.14–5.21 (2H, m), 5.70–5.80 (1H, m), 6.42 (1H, d, *J* = 3.7 Hz), 7.09 (1H, d, *J* = 3.7 Hz), 7.26–7.35 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.4, 59.4, 107.3, 119.1, 126.6, 127.6, 128.6, 133.5, 138.9, 141.3, 169.4; GC-MS *m/z* (%): 230 (M^+, 25), 189 (100), 162 (38), 131 (34), 111 (32), 91 (68); IR (film, cm^{-1}) 3402 (br.), 3003, 2979, 2874, 1534, 1491, 1111; chromatographic eluent: petrol/Et_2O = 1/1; Anal. Calcd. $C_{13}H_{14}N_2S$: C, 67.79; H, 6.13; N, 12.16; S, 13.92. Found: C, 67.70; H, 6.19; N, 12.20; S, 13.95.

Benzothiazol-2-yl-(1-phenylbut-3-enyl)amine (2). Yield, 266 mg (95%): yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.62 (2H, t, *J* = 7.1 Hz), 4.10 (1H, q, *J* = 7.1 Hz), 4.66 (1H, t (br.), *J* = 6.6 Hz), 5.04–5.09 (2H, m), 5.70–5.77 (1H, m), 6.99–7.03 (2H, m), 7.21–7.27 (2H, m), 7.29–7.33 (2H, m), 7.36–7.38 (2H, m), 7.49 (2H, d, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 41.9, 59.3, 118.6, 118.7, 120.7, 121.3, 125.8, 126.5, 127.5, 128.6, 130.5, 133.4, 141.2, 151.9, 167.5; GC-MS *m/z* (%): 280 (M^+, 42), 239 (100), 212 (30), 150 (51), 119 (38), 91 (51); IR (film, cm^{-1}) 3379 (br.), 3074, 3030, 2978, 2923, 1606, 1567, 1446, 1247; chromatographic eluent: petrol/Et_2O = 1/1; HRMS Calcd. $C_{17}H_{16}N_2S$: 280.10358. Found: 280.10348.

(1-Phenylbut-3-enyl)pyridin-2-ylamine (3). Yield, 223 mg (>99%), yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.56–2.63 (2H, m), 4.63 (1H, q, *J* = 7.1 Hz), 5.09 (1H, s, broad), 5.12–5.19 (2H, m), 5.74–5.76 (1H, m), 6.14 (1H, d, *J* = 8.4 Hz), 6.51–6.55 (1H, m), 7.23–7.35 (6H, m), 8.06 (1H, d, *J* = 5.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.7, 55.7, 106.6, 113.2, 118.5, 126.3, 127.1, 128.5, 134.0, 137.4, 142.9, 148.2, 158.0; GC-MS *m/z* (%): 224 (M^+, 5), 184 (65), 183 (100), 128 (13), 105 (20), 91 (23), 78 (93); IR (film, cm^{-1}) 3254 (br.), 3077, 3027, 2977, 2929, 2877, 1600, 1505, 1446, 1324, 1288, 1154; chromatographic eluent: petrol/Et_2O = 1/1; HRMS Calcd. $C_{15}H_{16}N_2$: 224.13148. Found: 224.13151.

(1-Phenylbut-3-enyl)pyridin-3-ylamine (4). Yield: 213 mg (95%), yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.47–2.55 (1H, m), 2.59–2.65 (1H, m), 4.28 (1H, s, broad), 4.36 (1H, q, *J* = 7.8, Hz), 5.16 (1H, d, *J* = 9.9 Hz), 5.19 (1H, d, *J* = 17.0 Hz), 5.70–5.80 (1H, m), 6.66–6.69 (1H, m), 6.94 (1H, dd, *J* = 4.6, 8.4 Hz), 7.22–7.34 (5H, m), 7.89 (1H, dd, *J* = 1.1, 4.6 Hz), 7.97 (1H, d, *J* = 3.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 43.1, 56.8, 118.6, 119.2, 122.5, 123.5, 126.2, 127.3, 128.7, 134.1, 136.7, 138.7, 142.4, 143.2; GC-MS *m/z* (%): 224 (M^+, 2), 183 (100), 105 (10), 91 (7), 78 (12); IR (film, cm^{-1}) 3265 (br.), 3061, 3030, 3010, 2979, 2927, 2859, 1590, 1483, 1305, 794, 758, 702; chromatographic eluent: petrol/Et_2O = 1/1; HRMS Calcd. $C_{15}H_{16}N_2$: 224.13148. Found: 224.13152.

(1-Phenylbut-3-enyl)pyridin-4-ylamine (5). Yield: 213 mg (95%), yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.50–2.56 (1H, m), 2.59–2.64 (1H, m), 4.42–4.47 (1H, m), 4.72 (1H, s, broad), 5.15–5.21 (2H, m), 5.69–5.76 (1H, m), 6.33 (2H, d, *J* = 6.3 Hz), 7.23–7.35 (5H, m), 8.09 (2H, d, *J* = 6.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.7, 56.1, 108.4, 118.8, 126.1, 127.4, 128.7, 133.8, 141.9, 149.8, 152.4; GC-MS *m/z* (%): 224 (M^+, 1), 183 (100), 128 (7), 105 (41), 78 (48); IR (film, cm^{-1}) 3238 (br.), 3027, 2984, 2933, 1605, 1519, 1351, 1217, 989, 812, 701; chromatographic eluent: petrol/EtOAc = 1/9; HRMS Calcd. $C_{15}H_{16}N_2$: 224.13148. Found: 224.13140.

General Procedure for the preparation of γ– and δ– lactams 16a–g, 17a–g, 18a–g. A mixture of 1.0 mmol of **1–15**, 0.04 mmol of $Pd(AcO)_2$, and 0.1 mmol of ligand was dissolved in 5 mL of solvent and placed in a 45 mL autoclave. The autoclave was purged, pressurized (300 psi of CO + 300 psi of H_2), and then heated. The reaction was then cooled to R.T., worked up by addition of water (5 mL) and extracted with Et_2O (3x5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude products were purified by column chromatography (silica gel, petrol/Et_2O or petrol/EtOAc in the appropriate ratio) to afford the pure γ and δ-lactams **16a–g, 17a–g, 18a–g**; overall yields: 70–99%.

3-Methyl-5-phenyl-1-thiazol-2-ylpyrrolidin-2-one (16a). Yield in toluene: 49 mg (19%); yield in CH_2Cl_2: 28 mg (11%); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, d, *J* = 7.0 Hz), 2.29–2.39 (2H, m), 2.89–2.95 (1H, m), 5.72 (1H, dd, *J* = 1.5, 7.2 Hz), 6.97 (1H, d, *J* = 3.5 Hz), 7.15 (2H, d, *J* = 8.9 Hz), 7.23–7.37 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.1, 35.2, 37.9, 60.6, 113.6, 125.2, 127.5, 128.8, 137.9, 140.5, 158.0, 176.2; GC-MS *m/z* (%): 258 (M^+, 100), 230 (6), 189 (33), 174 (10), 127 (72); IR (film, cm^{-1}) 3031, 2928, 2855, 1703, 1508, 1466, 1325, 1279, 1173, 907; chromatographic eluent: petrol/EtOAc = 9/1; HRMS Calcd. $C_{14}H_{14}N_2OS$: 258.08282. Found: 258.08279.

6-Phenyl-1-thiazol-2-ylpiperidin-2-one (18a). Yield in toluene: 183 mg (71%); yield in CH_2Cl_2: 199 mg (77%); yellow solid, mp 122–123°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70–1.81 (2H, m), 2.20–2.35 (2H, m), 2.66–2.84 (2H, m), 6.26–6.28 (1H, m), 6.93 (1H, d, *J* = 3.2 Hz), 7.10 (2H, d, *J* = 7.6 Hz), 7.16–7.37 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.5, 30.3, 32.1, 60.1, 114.9, 125.7, 127.1, 128.5, 137.2, 141.0, 158.7, 169.9; GC-MS *m/z* (%): 258 (M^+, 100), 230 (15), 202 (63), 187 (13), 127 (28), 100 (44); IR (film, cm^{-1}) 3010, 2958, 2927, 2855, 1653, 1499, 1448, 1319, 1254, 1185, 962; chromatographic eluent: petrol/EtOAc = 9/1; HRMS Calcd. $C_{14}H_{14}N_2OS$: 258.08282. Found: 258.08275.

1-Benzothiazol-2-yl-3-methyl-5-phenylpyrrolidin-2-one (16b). Yield in toluene: 92 mg (30%); yield in CH_2Cl_2: 77 mg (25%); white solid, mp 170–171°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, *J* = 7.0 Hz), 2.32–2.42 (2H, m), 2.89–2.97 (1H, m), 5.86 (1H, dd, *J* = 6.9, 9.5 Hz), 7.19–7.36 (7H, m), 7.67 (1H, d, *J* = 8.0 Hz), 7.80 (1H, d, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.0, 35.6, 37.7, 60.7, 121.2, 121.6, 123.8, 125.4, 125.8, 127.5, 128.7, 132.4, 140.3, 148.8, 156.2, 177.0; GC-MS *m/z* (%): 308 (M^+, 100), 280 (16), 239 (50), 177 (69), 162 (53), 149 (20); IR (film, cm^{-1}) 3067, 3021, 2983, 2936, 2876, 1712, 1513, 1443, 1386, 1228, 1220;

chromatographic eluent: petrol/EtOAc = 7/3; *Anal*. Calcd. $C_{18}H_{16}NOS$: C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 70.01; H, 5.20; N, 9.20; S, 10.31.

1-Benzothiazol-2-yl-6-phenylpiperidin-2-one (18b). Yield in toluene: 212 mg (69%); yield in CH_2Cl_2: 228 mg (74%); yellow solid, mp 165–166°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74–1.80 (2H, m), 2.24–2.35 (2H, m), 2.70–2.86 (2H, m), 6.46 (1H, dd, *J* = 3.0, 4.6 Hz), 7.15–7.34 (7H, m), 7.65 (1H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.5, 30.1, 32.4, 60.2, 120.9, 121.6, 123.8, 125.6, 125.8, 127.1, 128.5, 133.5, 140.9, 148.1, 158.4, 171.0; GC-MS *m/z* (%): 308 (M^+, 100), 280 (14), 252 (56), 149 (50), 119 (31); IR (film, cm^{-1}) 3014, 2959, 1664, 1495, 1443, 1400, 1256; chromatographic eluent: petrol/EtOAc = 7/3; Anal. Calcd. $C_{18}H_{16}NOS$: C, 70.10; H, 5.23; N, 9.08; S, 10.40. Found: C, 70.03; H, 5.25; N, 9.17; S, 10.33.

3-Methyl-5-phenyl-1-pyridin-2-ylpyrrolidin-2-one (16c, 17c). 16c. Yield in toluene: 58 mg (23%); yield in CH_2Cl_2: 43 mg (17%); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, d, *J* = 7.0 Hz), 2.22–2.27 (2H, m), 2.80–2.87 (1H, m), 5.89 (1H, dd, *J* = 3.0, 7.0 Hz), 6.93 (1H, dd, *J* = 2.0, 6.8 Hz), 7.17–7.29 (5H, m), 7.67 (1H, t, *J* = 7.5 Hz), 8.19 (1H, d, *J* = 4.7 Hz), 8.47 (1H, d, *J* = 8.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.4, 36.6, 37.0, 58.7, 115.3, 119.4, 125.5, 126.9, 128.5, 137.5, 142.1, 147.6, 151.1, 177.7; GC-MS *m/z* (%): 252 (M^+, 100), 195 (18), 174 (28), 121 (88), 106 (70), 79 (65); IR (film, cm^{-1}) 3065, 3029, 3010, 2934, 2875, 1702, 1588, 1470, 1435, 1391, 1305; chromatographic eluent: petrol/EtOAc = 1/9; HRMS Calcd. $C_{16}H_{16}N_2O$: 252.12638. Found: 252.12641; **17c:** yield in toluene: 15 mg (6%); yield in CH_2Cl_2: 13 mg (5%); white solid, mp 75–76°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, d, *J* = 6.6 Hz), 1.63–1.66 (1H, m), 2.77–2.83 (2H, m), 5.61 (1H, dd, *J* = 2.8, 7.6 Hz), 6.90 (1H, t, *J* = 6.6 Hz), 7.14–7.24 (5H, m), 7.64 (1H, t, *J* = 8.0 Hz), 8.04 (1H, d, *J* = 8.4 Hz), 8.13 (1H, d, *J* = 4.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.6, 37.5, 38.1, 60.2, 117.7, 119.8, 125.9, 126.9, 128.4, 137.2, 143.1, 147.6, 151.0, 177.7; GC-MS *m/z* (%): 252 (M^+, 100), 195 (16), 174 (24), 121 (72), 106 (56), 79 (50); IR (film, cm^{-1}) 3065, 3031, 3010, 2971, 2933, 1699, 1589, 1471, 1435, 1370, 1234; chromatographic eluent: petrol/EtOAc = 1/9; HRMS Calcd. $C_{16}H_{16}N_2O$: 252.12638. Found: 252.12629.

6-Phenyl-1-pyridin-2-ylpiperidin-2-one (18c). Yield in toluene: 171 mg (68%); yield in CH_2Cl_2: 171 mg (68%); yellow solid, mp 107–108°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76–1.90 (2H, m), 2.02–2.09 (1H, m), 2.29–2.38 (1H, m), 2.58–2.77 (2H, m), 5.89 (1H, t, *J* = 5.2 Hz), 6.94–6.97 (1H, m), 7.13–7.26 (5H, m), 7.53–7.58 (2H, m), 8.31 (1H, dd, *J* = 1.2, 5.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.3, 31.7, 33.1, 60.6, 121.0, 123.0, 126.5, 127.0, 128.2, 136.7, 141.7, 148.0, 153.5, 171.1; GC–MS *m/z* (%): 252 (M^+, 36), 224 (8), 195 (100), 155 (11), 120 (15), 93 (17), 78 (21); IR (film, cm^{-1}) 3064, 3008, 2957, 2878, 1647, 1589, 1469, 1403, 1288; chromatographic eluent: petrol/EtOAc = 1/9; Anal. Calcd. $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.17; H, 6.35; N, 11.05.

3-Methyl-5-phenyl-1-pyridin-3-ylpyrrolidin-2-one (16d, 17d). 16d. Yield in toluene: 63 mg (25%); yield in CH_2Cl_2: 43 mg (17%); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, *J* = 7.1 Hz), 2.25–2.35 (2H, m), 2.85 (2H, m), 2.85 (1H, sextet, *J* = 7.1 Hz), 5.22 (1H, dd, *J* = 3.7, 6.5 Hz), 7.18–7.34 (6H, m), 8.10–8.13 (1H, m), 8.29 (1H, d, *J* = 4.6 Hz), 8.66 (1H, d, *J* = 2.4

Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 15.6, 35.5, 37.7, 60.8, 123.2, 125.5, 127.8, 127.9, 129.1, 135.3, 140.2, 141.9, 145.2, 177.7; GC-MS *m/z* (%): 252 (M$^+$, 75), 251 (100), 237 (5), 175 (21), 117 (22), 91 (15), 78 (19); IR (film, cm^{-1}) 3060, 3030, 3010, 2971, 2936, 2876, 1700, 1588, 1486, 1386; chromatographic eluent: petrol/Et$_2$O = 3/7; HRMS Calcd. $C_{16}H_{16}N_2O$: 252.12638. Found: 252.12628. **17d:** yield in toluene: 50 mg (20%); yield in CH$_2$Cl$_2$: 35 mg (14%); brown solid, mp 115–117°C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.37 (3H, d, *J* = 6.9 Hz), 1.66–1.74 (1H, m), 2.73–2.88 (2H, m), 5.18 (1H, dd, *J* = 6.9, 9.0 Hz), 7.15–7.28 (6H, m), 7.79–7.82 (1H, m), 8.25 (1H, dd, *J* = 1.4, 4.7 Hz), 8.52 (1H, d, *J* = 2.4 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 16.2, 37.5, 39.0, 61.4, 123.1, 126.4, 128.0, 129.0, 129.9, 134.6, 140.2, 143.7, 145.6, 177.4; GC-MS *m/z* (%): 252 (M$^+$, 67), 251 (100), 237 (5), 175 (19), 117 (27), 91 (18), 78 (24); IR (film, cm^{-1}) 3060, 3031, 3010, 2968, 2929, 2875, 2855, 1703, 1585, 1485, 1367; chromatographic eluent: petrol/Et$_2$O = 3/7; Anal. Calcd. $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.10; H, 6.30; N, 11.15.

6-Phenyl-1-pyridin-3-ylpiperidin-2-one (18d). Yield in toluene: 93 mg (37%); yield in CH$_2$Cl$_2$: 116 mg (46%); yellow oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.80–2.06 (3H, m), 2.32–2.41 (1H, m), 2.63–2.78 (2H, m), 5.01 (1H, t, *J* = 5.4 Hz), 7.14–7.35 (6H, m), 7.47 (1H, dd, *J* = 2.4, 6.7 Hz), 8.33 (1H, d, *J* = 4.6 Hz), 8.43 (1H, d, *J* = 2.2 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 17.7, 32.3, 32.6, 65.0, 123.2, 126.7, 127.7, 128.7, 130.8, 134.9, 140.6, 147.2, 148.2, 171.0; GC–MS *m/z* (%): 252 (M$^+$, 66), 251 (100), 117 (45), 94 (61), 78 (36); IR (film, cm^{-1}) 3060, 3031, 3009, 2960, 2933, 2875, 2855, 1645, 1585, 1480, 1406, 1340, 1300; chromatographic eluent: petrol/Et$_2$O = 3/7; HRMS Calcd. $C_{16}H_{16}N_2O$: 252.12638. Found: 252.12640.

3-Methyl-5-phenyl-1-pyridin-4-ylpyrrolidin-2-one (16e, 17e). 16e. Yield in toluene: 50 mg (20%); yield in CH$_2$Cl$_2$: 88 mg (35%); white solid, mp 147–148°C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.29 (3H, d, *J* = 7.0 Hz), 2.27 (2H, dd, *J* = 5.2, 10.0 Hz), 2.78–2.85 (1H, m), 5.20 (1H, dd, *J* = 4.9, 5.2 Hz), 7.16–7.19 (2H, m), 7.27–7.37 (3H, m), 7.53 (2H, d, *J* = 5.0 Hz), 8.43 (2H, d, *J* = 5.0 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 15.4, 35.8, 37.6, 60.3, 113.7, 125.3, 128.0, 129.3, 136.8, 145.5, 150.5, 178.0; GC-MS *m/z* (%): 252 (M$^+$, 100), 251 (94), 175 (51), 117 (35), 78 (30); IR (film, cm^{-1}) 3031, 2966, 2930, 1714, 1593, 1504, 1383, 1223, 1193, 1000; chromatographic eluent: petrol/EtOAc = 1/9; Anal. Calcd. $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.12; H, 6.28; N, 11.12. **17e:** yield in toluene: 50 mg (20%); yield in CH$_2$Cl$_2$: 86 mg (34%); white solid, mp 108–110°C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.35 (3H, d, *J* = 6.9 Hz), 1.65–1.68 (1H, m), 2.72–2.76 (1H, m), 2.82–2.89 (1H, m), 5.16 (1H, dd, *J* = 7.7, 7.8 Hz), 7.16–7.19 (2H, m), 7.22–7.31 (3H, m), 7.37 (2H, d, *J* = 4.9 Hz), 8.40 (2H, d, *J* = 5.0 Hz); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 16.3, 37.8, 38.5, 61.0, 115.6, 125.8, 128.7, 129.2, 141.2, 145.0, 150.0, 179.0; GC-MS *m/z* (%): 252 (M$^+$, 95), 251 (100), 175 (37), 117 (37), 78 (32); IR (film, cm^{-1}) 3024, 2929, 2855, 1712, 1592, 1504, 1363, 1227; chromatographic eluent: petrol/EtOAc = 1/9; Anal. Calcd. $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.10; H, 6.27; N, 11.12.

6-Phenyl-1-pyridin-4-ylpiperidin-2-one (18e). Yield in toluene: 101 mg (40%); yield in CH$_2$Cl$_2$: 2 mg (1%); yellow solid, mp 149–150°C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.77–1.89 (2H, m), 2.03–2.10 (1H, m), 2.29–2.37 (1H, m), 2.65–2.75 (2H, m), 5.10 (1H, t, *J* = 5.0 Hz), 7.14–

7.28 (5H, m), 7.32 (2H, d, *J* = 6.5 Hz), 8.40 (2H, d, *J* = 6.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.3, 32.1, 32.9, 63.6, 120.4, 126.3, 127.7, 128.8, 140.7, 149.5, 150.3, 170.8; GC-MS *m/z* (%): 252 (M^+, 90), 251 (100), 196 (25), 183 (58), 78 (32); IR (film, cm^{-1}) 3030, 3010, 2960, 1655, 1590, 1494, 1398, 1299, 1168, 1137, 999; chromatographic eluent: petrol/EtOAc = 1/9; Anal. Calcd. $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.20; H, 6.35; N, 11.14.

3-Methyl-1,5-diphenylpyrrolidin-2-one (16f, 17f). 16f. Yield in toluene: 60 mg (24%); yield in CH_2Cl_2: 40 mg (16%); yellow solid, mp 96–97°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, d, *J* = 7.1 Hz), 2.11–2.21 (2H, m), 2.74 (1H, sextet, *J* = 7.1 Hz), 5.11 (1H, dd, *J* = 3.3, 7.1 Hz), 6.96 (1H, t, *J* = 7.4 Hz), 7.12–7.25 (7H, m), 7.45 (2H, d, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.8, 35.8, 37.8, 61.4, 121.0, 124.4, 125.6, 127.5, 128.6, 128.9, 138.7, 141.2, 177.2; GC-MS *m/z* (%): 251 (M^+, 100), 250 (77), 236 (10), 174 (57), 117 (45), 78 (40); IR (film, cm^{-1}) 3067, 3030, 3011, 2972, 2934, 2875, 1695, 1599, 1495, 1390; chromatographic eluent: petrol/Et_2O = 4/6; Anal. Calcd. $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.20; H, 6.78; N, 5.50. **17f:** yield in toluene: 40 mg (16%); yield in CH_2Cl_2: 48 mg (19%); yellow solid, mp 132–133°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 6.8 Hz), 1.54–1.62 (1H, m), 2.63–2.77 (2H, m), 5.09 (1H, dd, *J* = 3.3, 7.1 Hz), 6.96 (1H, t, *J* = 7.4 Hz), 7.12–7.25 (7H, m), 7.45 (2H, d, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.8, 35.8, 37.8, 61.4, 121.0, 124.4, 125.6, 127.5, 128.6, 128.9, 138.7, 141.2, 177.2; GC-MS *m/z* (%): 251 (M^+, 100), 250 (63), 236 (7), 174 (34), 117 (32), 77 (25); IR (film, cm^{-1}) 3068, 3032, 3011, 2971, 2934, 2877, 1690, 1599, 1500, 1369; chromatographic eluent: petrol/Et_2O = 4/6; Anal. Calcd. $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.19; H, 6.80; N, 5.53.

1,6-Diphenylpiperidin-2-one (18f). Yield in toluene: 95 mg (38%); yield in CH_2Cl_2: 113 mg (45%); yellow solid, mp 123–124°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65–1.76 (1H, m), 1.80–1.90 (1H, m), 1.91–1.97 (1H, m), 2.22–2.29 (1H, m), 2.54–2.68 (2H, m), 4.93 (1H, t, *J* = 5.1 Hz), 7.05 (2H, d, *J* = 7.1 Hz), 7.12–7.19 (6H, m), 7.21 (1H, dd, *J* = 3.3, 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.5, 32.2, 32.5, 65.0, 126.6, 126.9, 127.2, 127.4, 128.4, 128.7, 141.3, 142.3, 170.7; GC-MS *m/z* (%): 251 (M^+, 100), 250 (38), 182 (39), 117 (26), 93 (86); IR (film, cm^{-1}) 3067, 3033, 3007, 2956, 2928, 2857, 1638, 1596, 1495, 1410, 1344; chromatographic eluent: petrol/Et_2O = 4/6; Anal. Calcd. $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.21; H, 6.82; N, 5.54.

3-Methyl-5-phenyl-1-(1-phenylethyl)pyrrolidin-2-one (16g+17g). Inseparable mixture of two *trans*- and *cis*- diastereomers (*dr* = 1/1 by ^{1}H NMR of the crude products); overall yield in toluene: 109 mg (39%); yield in CH_2Cl_2: 173 mg (62%); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, *J* = 7.3 Hz), 1.14 (3H, d, *J* = 7.1 Hz), 1.16 (3H, d, *J* = 7.1 Hz), 1.63 (3H, d, *J* = 7.3 Hz), 1.92–2.00 (2H, m), 2.64–2.79 (2H, m), 4.12 (1H, dd, *J* = 1.0, 8.7 Hz), 4.51 (1H, dd, *J* = 3.9, 7.9 Hz), 4.80 (1H, q, *J* = 7.3 Hz), 5.49 (1H, q, *J* = 7.3 Hz), 6.90–7.30 (20H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 17.7, 17.8, 34.8, 35.5, 38.0, 38.5, 50.7, 52.8, 58.1, 59.9, 126.3, 126.7, 127.0, 127.3, 127.4, 127.6, 128.0, 128.4, 128.6, 140.4, 141.2, 141.9, 143.5, 177.8, 178.1; GC-MS *m/z* (%): 279 (M^+, 100), 264 (18), 174 (65), 160 (85), 105 (60); IR (film, cm^{-1}) 3066, 3031, 3009, 2979, 2934, 1671, 1495, 1455, 1417; chromatographic eluent: petrol/Et_2O = 9/1; HRMS Calcd. $C_{19}H_{21}NO$: 279.16243. Found: 279.16250.

6-Phenyl-1-(1-phenylethyl)piperidin-2-one (18g). Yield in toluene: 112 mg (40%); yield in CH_2Cl_2: 45 mg (16%); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, J = 7.3 Hz), 1.45–1.70 (3H, m), 2.45–2.63 (2H, m), 4.28 (1H, t, J = 7.3 Hz), 6.15 (1H, q, J = 7.3 Hz), 7.05 (2H, d, J = 7.0 Hz), 7.18–7.30 (8H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 15.7, 17.1, 31.5, 31.6, 51.6, 56.3, 126.6, 127.1, 127.4, 127.5, 128.3, 128.4, 141.0, 143.0, 170.7; GC-MS *m/z* (%): 279 (M^+, 88), 160 (52), 120 (100), 105 (60); IR (film, cm^{-1}) 3060, 3031, 3007, 2957, 1616, 1494, 1444, 1170; chromatographic eluent: petrol/Et_2O = 9/1; HRMS Calcd. $C_{19}H_{21}NO$: 279.16243. Found: 279.16248.

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