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Enantioselective cyclocarbonylation of 2-vinylanilines to six-membered ring lactams

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Abstract—A catalyst system based on Pd(OAc)$_2$/(2*S*,4*S*)-(−)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine has been found to effect asymmetric cyclocarbonylation of 2-vinylanilines to enantiomerically enriched six-membered ring lactams in excellent yield. The reaction was effected under an atmosphere of CO (500 psi) and H_2 (100 psi) in methylene chloride for 48 h; the chiral six-membered ring lactams were isolated in up to 98% yield and 84% ee. The stereoselectivity was influenced by the structure of the substrate and the reaction conditions. The enantiopurity of the lactam was further improved by recrystallization with 99% ee obtained in some cases.

1. Introduction

Transition metal catalyzed carbonylation reactions are important organic transformations,[1] and provide efficient entries to a variety of useful functionalized heterocyclic compounds.[2] In particular, the selective synthesis of lactams, fused to an aromatic ring, has been of interest for many years due to their presence in biologically and pharmacologically active compounds.[3] Cyclocarbonylation reactions were investigated as part of our research in organic reactions using palladium catalysts.[4] Asymmetric synthesis achieved by a catalyst with a bound or added chiral ligand is a valuable method in organic synthesis, and in recent years, some excellent enantioselectivities have been reported for asymmetric carbonylation reactions.[5] Few publications have appeared on asymmetric cyclocarbonylation reactions of 2-vinylanilines to form enantiomeric enriched lactams. In an earlier study, we found that good catalytic reactivity can be attained in the cyclocarbonylation of vinylanilines to form six-membered ring lactams catalyzed by palladium acetate with a 1,4-bisphosphine ligand. Unfortunately, the chiral version of the process using Pd(OAc)$_2$ as the catalyst and (−)-DIOP as the chiral ligand gave, at maximum, 54% ee.[6] The ligand (−)-BPPM, which possesses a rigid carbon skeleton, showed higher catalytic activity with palladium but much lower enantiodiscrimination for this reaction with 98% yield and 9% ee. However, (−)-BPPM has successfully been applied in asymmetric cyclocarbonylation reactions of allylic alcohols to butyrolactones, and the chiral γ-butyrolactone was obtained in up to 84% ee.[4e] We reasoned that such low selectivity might be attributed to the diminishing asymmetry of the ligand itself by introducing the *t*-butoxycarbonyl group on the nitrogen atom of the pyrrolidine ring. Based on the considerations above, we revisited this reaction by utilizing the chiral phosphine ligand [(2*S*,4*S*)-(−)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine] (−)-DDPP, its structure being similar to that of BPPM, but having greater asymmetric properties. We therefore carried out the reaction using (−)-DDPP anticipating greater chiral discrimination in the palladium catalyzed synthesis of six-membered ring lactams. Herein, we report a significant improvement in the asymmetric synthesis of six-membered ring lactams through the cyclocarbonylation of 2-vinylanilines catalyzed by palladium acetate and (−)-DDPP.

2. Results and discussion

The 2-vinylanilines **1a**, **1c**–**f** and **1j** employed in this reaction (Scheme 1) were prepared by the Grignard reaction of 2-aminoacetophenone with the appropriate

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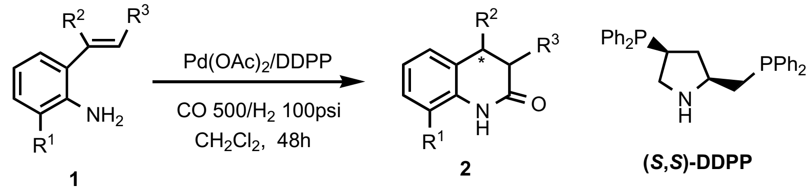


a, $R^1=R^3=H$, $R^2=Ph$,
b, $R^1=R^3=H$, $R^2=CH_3$
c, $R^1=R^3=H$, $R^2=o\text{-}MeC_6H_4$
d, $R^1=OCH_3$, $R^2=Ph$, $R^3=H$
e, $R^1=R^3=H$, $R^2=m\text{-}MeC_6H_4$
f, $R^1=OCH_3$, $R^2=CH_3$, $R^3=H$
g, $R^1=R^2=H$, $R^3=Ph$
h, $R^1=R^2=H$, $R^3=CH_3$
i, $R^1=OCH_3$, $R^2=H$, $R^3=CH_3$
j, $R^1=R^3=H$, R^2=1-naphthyl

Scheme 1.

iodo compounds followed by dehydration, Compounds **1g**–**1i** were synthesized by the Wittig reaction of aldehydes with methyltriphenylphosphonium bromide.[7]

In order to find suitable reaction conditions, which could be applied to a variety of anilines so as to achieve high stereoselectivities, we selected 2-(1-phenylvinyl)-aniline **1a** as the model substrate for reaction optimization. The catalyst precursor for the asymmetric cyclocarbonylation was prepared in situ by treatment of palladium acetate with (−)-DDPP under argon at room temperature, followed by the reaction with **1a**, carbon monoxide (500 psi), and hydrogen (100 psi) at a specified reaction temperature. The results show that the solvent and amount of catalyst used, as well as the structure of the substrate, influence the enantiomeric excess of the product. Initially, we examined the reaction by using different solvents (Table 1).

Amongst the chiral ligands we examined,[8] (2*S*,4*S*)-(−)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine (DDPP) was found to be the best for this reaction. The enantioselectivity was significantly influenced by the catalyst loading and the solvent. When 1 mol% $Pd(OAc)_2$ and 2 mol% of DDPP were used, only 50% enantiomeric excess was obtained (entry 4), while 84% ee resulted when using 2 mol% of $Pd(OAc)_2$ and 8 mol% chiral ligand. To our knowledge, this is the highest enantioselectivity reported to date for the asymmetric cyclocarbonylation of 2-vinylanilines to form six-membered ring lactams. The cyclocarbonylation reaction of 2-(1-phenylvinyl)aniline, effected under the same reaction conditions in dichloromethane, gave 96% yield and 57% ee. However, when benzene was used as the solvent, only 56% yield and 31% ee was obtained, while toluene afforded 68% yield and 30% ee.

The cyclocarbonylation of various anilines catalyzed by the $Pd(OAc)_2$/(*S*,*S*)-DDPP system was effected under the optimized conditions (Table 2).

The results clearly show that the structure of the substrate affects the ee of the corresponding lactam. For example, changing the olefin substituent from methyl **1b** to phenyl **1a**, increased the ee from 58% to 84%. We also considered aminostyrenes with a substituent at the olefinic carbon containing the aryl unit **1c**–**1e**. The cyclocarbonylation of **1c** did not proceed at 120 °C, but occurred smoothly at 135 °C to afford **2c** in 78% ee (entry 3), while **2d** and **2e** afforded the lactams in 74% ee (entry 4), and 70% ee (entry 5), respectively. No reaction occurred for **1j**, which had a 1-naphthyl substituent. The use of reactants containing a substituent at the other *ortho*-position to the amino group gave lower ee. The reaction of 3-methoxyl-2-(1-phenylvinyl)aniline **1d** afforded 3,4-dihydro-8-methoxyl-4-phenyl-2-(1H)-quinolin-2-one **2d** in 93% yield and 74% ee. Cyclocarbonylation of **1f** gave **2f** in 98% yield and 41% ee. 2-Vinylanilines **1g**–**1i** containing substituents at the terminal C=C bond position gave lactams in low to moderate enantioselectivity due to significant steric effects. Cyclocarbonylation of **1g** with a phenyl group at the 2 position of the double bond afforded the lactam in 60% yield and 50% ee, while use of **1h** gave the lactam in 55% yield and 18% ee. A similar result was observed for the reaction of **1i** to form **2i** (40% yield and 16% ee).

Table 1. Palladium catalyzed asymmetric cyclocarbonylation of 2(1-phenylvinyl)aniline **1a** to **2a**[a]

Entry	Solvent	$Pd(OAc)_2$ (mol%)	DDPP (mol%)	Yield (%)	Ee (%)[b]
1	CH_2Cl_2	2	8	98	84
2	CH_2Cl_2	2	4	90	79
3	CH_2Cl_2	1	4	96	57
4	CH_2Cl_2	1	2	85	50
5	$ClCH_2CH_2Cl$	1	4	40	34
6	Benzene	1	4	56	31
7	Toluene	1	4	68	30
8	Ether	1	4	10	28

[a] Reaction conditions: 2-(1-phenylvinyl)-aniline **1a** (1.0 mmol), CO (500 psi), H_2 (100 psi), 5 mL solvent, 120 °C, 48 h.

[b] Ee was determined by HPLC using a Chiracel OD column.

Table 2. Palladium catalyzed asymmetric cyclocarbonylation of various anilines in the presence of $Pd(OAc)_2$-(*S*,*S*)-DDPP[a]

Entry	Aniline	Temperature (°C)	Lactam[b]	Yield (%)	Ee (%)[c]	$[\alpha]_D^{22}$ in $CHCl_3$
1	**1a**	120	**2a**	98	84 (>99)[d]	+15.8 (*c* 1.40)
2	**1b**	100	**2b**	98	58 (>99)[d]	+47.4 (*c* 2.89)
3	**1c**	135	**2c**	98	78	+35.3 (*c* 1.04)
4	**1d**	125	**2d**	93	74	+21.6 (*c* 0.96)
5	**1e**	125	**2e**	90	70	+10.2 (*c* 2.00)
6	**1f**	110	**2f**	98	41	+9.25 (*c* 2.50)
7	**1g**	110	**2g**	60	50	+8.7 (*c* 2.50)
8	**1h**	110	**2h**	55	18	−2.1 (*c* 1.66)
9	**1i**	110	**2i**	40	16	−1.6 (*c* 2.00)
10	**1j**	150	**2j**	0	—	—

[a] Reaction conditions: aniline (1 mmol), $Pd(OAc)_2$ (0.02 mmol), (*S*,*S*)-DDPP (0.08 mmol), CO (500 psi), H_2 (100 psi), 48 h.

[b] (*R*)-configuration was assigned to **2b**, and (*S*)-configuration to **2h** by comparison of the sign of the specific rotation with the reference value.[9] The absolute configurations of lactams **2a**, **2c**–**2g** and **2i** were not determined.

[c] Determined by HPLC using chiracel OD and chirapak AS columns.

[d] The data reported in parentheses are the ee values of lactams after recrystallization.

As products **2a** and **2b** in this study are crystalline, the ee can be improved to >99% after recrystallization. The single X-ray diffraction is shown in Figures 1 and 2,[10] in which the absolute configuration of **2b** was assigned to be *R* by comparison of the sign of the specific rotation with the known value.[9]

A possible mechanism for the enantioselective cyclocarbonylation of vinylanilines to six-membered ring lactams is given in Scheme 2. First, a palladium(0) complex is formed, and undergoes insertion into the N–H bond of the substrate, affording palladium hydride **3**. Subsequent coordination of the carbon–carbon double bond to the palladium hydride leads to the intermediate **4**. Intramolecular hydropalladation of the latter gives the two diastereomers, **5a** and **5b**. Finally, carbon monoxide insertion into the Pd–C bond followed by reductive elimination, forms the six-membered lactam ring with regeneration of the palladium complex. The enantiodetermination step in this asymmetric cyclocarbonylation involves intramolecular hydropalladation. In the experiment using (*S*,*S*)-DDPP as the chiral phosphine ligand, the chirality of the ligand was governed by the disposition of the phenyl ring on the phosphorus atoms, which is the major element of the steric interaction between the ligand and substrate. In this case, the formation of **5b** is expected to be disfavored because of steric interactions between the methyl group of aniline and the phenyl rings of the ligand, which are not present in the cyclization of **5a**; therefore **5a** can react further to form the lactam **2b** (*R*).

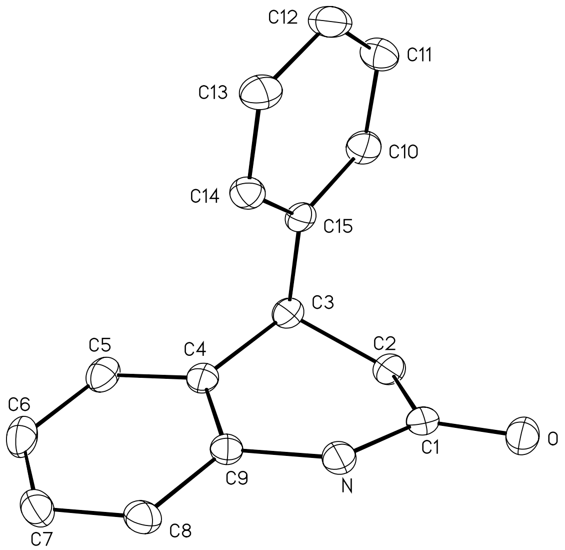


Figure 1. ORTEP view of compound **2a**.

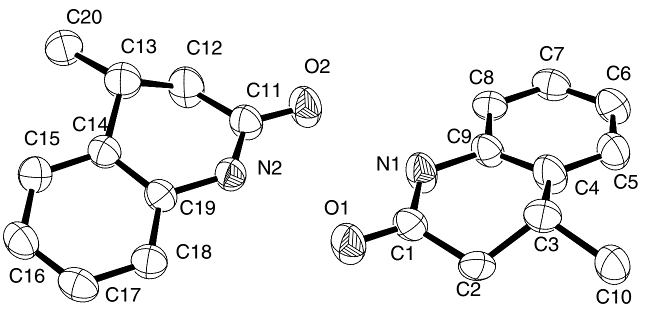


Figure 2. ORTEP view of compound **2b**.

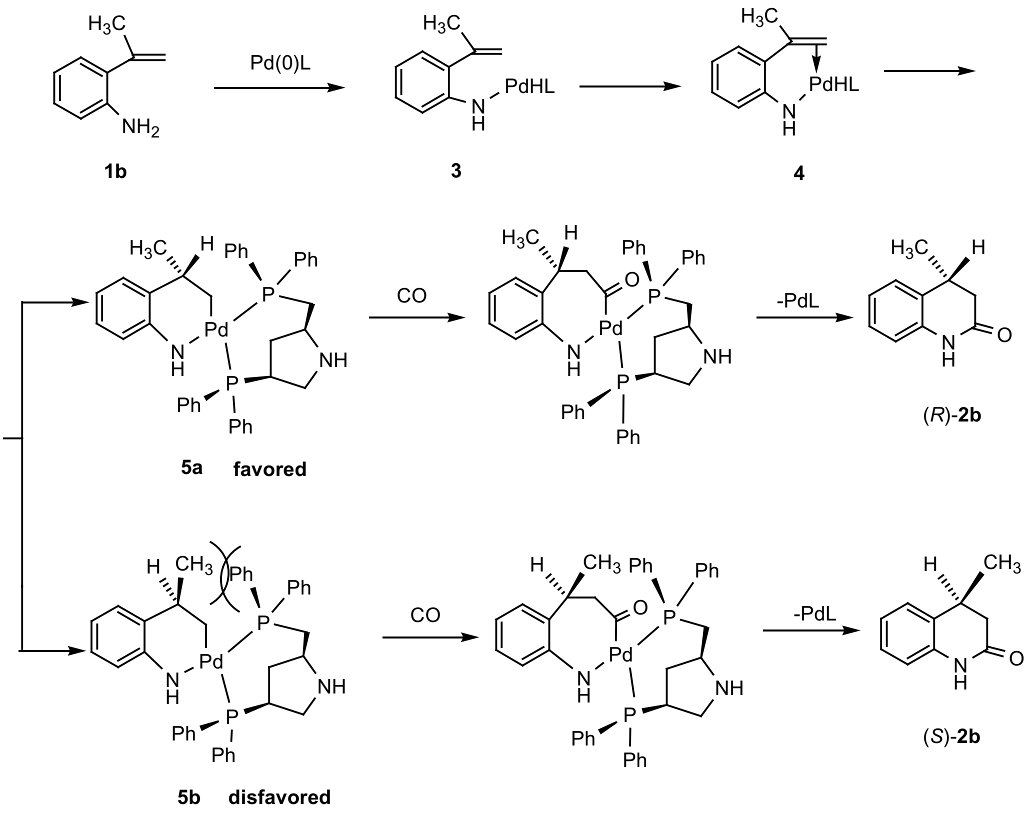
3. Conclusion

In summary, $Pd(OAc)_2$/(−)-DDPP can catalyze the cyclocarbonylation of 2-vinylanilines to form six-membered ring lactams in good enantioselectivities, with recrystalization affording enantiomerically pure products in selected cases.

4. Experimental section

4.1. General methods

All NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on Varian XL-300 spectrometer. Infrared spectra were recorded on a Bomen MB 100-C15 Fourier transform spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra were obtained on a



Scheme 2.

VG 7070E spectrometer. A Fisher–Johns apparatus was used for melting point determinations. Optical rotations were measured on a Perkin–Elmer polarimeter in a 10 cm cell at 22 °C. Enantiomeric excesses were achieved using a Waters 2996 series HPLC equipped with Chiralcel OD or a Chiralpak AS column.

Materials: Dichloromethane was freshly distilled under nitrogen from CaH_2. 2-(1-Methylvinyl) aniline **1b** was commercially available, and other anilines prepared by literature methods.[7]

4.2. General procedure for the cyclocarbonylation of 2-vinylanilines

A mixture of 1.0 mmol of aniline, 0.02 mmol palladium acetate and 0.08 mmol of (*S*,*S*)-DDPP was dissolved in 5 mL of dry solvent and placed in an autoclave containing a glass liner. The autoclave was purged with CO (500 psi) and H_2 (100 psi), and then heated and stirred for 48 h. The reaction was then cooled to room temperature, filtered through silica gel and concentrated by rotary evaporation. The product was isolated by silica gel chromatography using hexane/ethyl acetate 4:1 as the eluate.

4.2.1. 3,4-Dihydro-4-phenyl-2-(1H)-quinolin-2-one 2a. Mp: 170–172 °C; 84% ee; $[\alpha]_D^{22} = +15.8$ (*c* 1.40, $CHCl_3$); IR (neat): ν 1709 (cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.92 (d, 2H, $J = 6.8$ Hz), 4.29 (t, 1H, $J = 7.6$ Hz), 6.86–6.97 (m, 3H), 7.16–7.34 (m, 6H), 9.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.0, 32.0, 116.1, 123.7, 127.0, 127.6, 128.2, 128.4, 128.7, 129.3, 137.4, 141.8, 171.3; MS (*m*/*z*): 223 [M^+]; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0987.

4.2.2. 3,4-Dihydro-4-methyl-2-(1H)-quinolin-2-one 2b. Mp: 92–95 °C; 58% ee; $[\alpha]_D^{22} = +47.4$ (*c* 2.89, $CHCl_3$); IR (neat): ν 1686 (cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, $J = 7.0$ Hz), 2.37 (dd, 1H, $J = 7.1$ Hz), 2.70 (dd, 1H, $J = 5.9$ Hz), 3.20 (m, 1H), 6.74 (d, 1H, $J = 8.2$ Hz), 7.14 (d, 1H, $J = 8.8$ Hz), 7.22 (t, 2H, $J = 7.4$ Hz), 9.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.7, 30.6, 38.3, 115.8, 123.3, 126.4, 127.5, 128.6, 136.5, 171.9; MS (*m*/*z*): 161 [M^+]; HRMS(EI): calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0840.

4.2.3. 3,4-Dihydro-4-*o*-tolyl-2-(1H)-quinolin-2-one 2c. Pale yellow oil; 78% ee; $[\alpha]_D^{22} = +35.3$ (*c* 1.04, $CHCl_3$); IR (neat): ν 1689 (cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.85 (d, 2H, $J = 7.9$ Hz), 4.54 (t, 1H, $J = 8.2$ Hz), 6.73 (d, 1H, $J = 7.6$ Hz), 6.90 (m, 3H), 7.43 (m, 4H), 8.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 19.9, 66.2, 115.9, 123.8, 127.0, 127.1, 127.5, 127.7, 128.2, 128.4, 131.2, 136.5, 137.7, 139.4, 171.2; MS (*m*/*z*): 237 [M^+]; HRMS (EI): calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1137.

4.2.4. 3,4-Dihydro-8-methoxy-4-phenyl-2-(1H)-quinolin-2-one 2d. Mp: 110–111 °C; 74% ee; $[\alpha]_D^{22} = +21.6$ (*c* 0.96, $CHCl_3$); IR (neat): ν 1672 (cm^{-1}); ^1H NMR

(300 MHz, CDCl$_3$): δ 2.88 (d, 2H, $J = 8.6$ Hz), 3.87 (s, 3H), 4.27 (t, 1H, $J = 7.5$ Hz), 6.52 (d, 1H, $J = 7.6$ Hz), 6.77 (d, 1H, $J = 8.3$ Hz), 6.89 (t, 1H, $J = 7.9$ Hz), 7.17 (d, 1H, $J = 7.4$ Hz), 7.27 (m, 4H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.6, 46.9, 55.8, 109.3, 109.4, 120.2, 122.2, 122.8, 124.1, 126.9, 127.2, 127.7, 127.8, 129.5, 141.5, 179.9; MS (*m/z*): 253 [M$^+$]; HRMS (EI): calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1085.

4.2.5. 3,4-Dihydro-4-(*m*-tolyl)-2-(1H)-quinolin-2-one 2e. Mp: 122–123 °C; 70% ee; $[\alpha]_D^{22} = +10.2$ (*c* 2.00, CHCl$_3$); IR (neat): v 1686 (cm^{-1}); ^{1}H NMR(300 MHz, CDCl$_3$): δ 2.32 (s, 3H), 2.91 (d, 2H, $J = 7.3$ Hz), 4.26 (t, 1H, $J = 7.6$ Hz), 6.88–7.24 (m, 8H), 9.49 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.5, 38.4, 41.9, 115.8, 123.3, 124.8, 126.7, 127.8, 127.9, 128.3, 128.5, 128.7, 137.0, 138.5, 141.4, 171.3; MS (*m/z*): 237 [M$^+$]; HRMS (EI): calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1155.

4.2.6. 3,4-Dihydro-8-methoxy-4-methyl-2-(1H)-quinolin-2-one 2f. Mp: 100–102 °C; 41% ee; $[\alpha]_D^{22} = +9.25$ (*c* 2.50, CHCl$_3$); IR (neat): v 1687 (cm^{-1}); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.26 (d, 3H, $J = 7.0$ Hz), 2.37 (dd, 1H, $J = 7.1$ Hz), 2.67 (dd, 1H, $J = 5.9$ Hz), 3.10 (q, 1H, $J = 6.8$ Hz), 3.86 (s, 3H), 6.76 (dd, 2H, $J = 8.2$ Hz, $J = 7.6$ Hz), 6.94 (t, 1H, $J = 7.9$ Hz), 7.80 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.1, 31.2, 38.7, 56.1, 109.3, 118.9, 123.3, 123.9, 125.9, 146.2, 170.2; MS (*m/z*): 191 [M$^+$]; HRMS (EI): calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0933.

4.2.7. 3,4-Dihydro-3-phenyl-2-(1H)-quinolin-2-one 2g. Mp: 168–169 °C; 50% ee; $[\alpha]_D^{22} = +8.7$ (*c* 2.50, CHCl$_3$); IR (neat): v 1706 (cm^{-1}); ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.35 (d, 2H, $J = 7.2$ Hz), 3.89 (t, 1H, $J = 7.8$ Hz), 6.60–7.30 (m, 9H), 8.50 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 33.4, 44.5, 118.1, 120.7, 125.5, 127.9 128.2, 128.6, 129.6, 130.3, 136.4, 142.3, 170.9; MS (*m/z*): 223 [M$^+$]; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0990.

4.2.8. 3,4-Dihydro-3-methyl-2-(1H)-quinolin-2-one 2h. Mp: 126–127 °C; 18% ee; $[\alpha]_D^{22} = -2.1$ (*c* 1.66, CHCl$_3$); IR (neat): v 1686 (cm^{-1}); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.40 (d, 3H, $J = 6.4$ Hz), 2.52–2.74 (m, 2H), 2.98–3.12 (m, 1H), 6.71–7.30 (m, 4H), 8.95 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 16.6, 32.6, 37.5, 115.8, 122.9, 125.8, 127.5, 129.6, 133.5, 172.0; MS (*m/z*): 161 [M$^+$]; HRMS(EI): calcd for $C_{10}H_{11}NO$ 161.0841, found 161.0836.

4.2.9. 3,4-Dihydro-8-methoxy-3-methyl-2-(1H)-quinolin-2-one 2i. Oil; 16% ee; $[\alpha]_D^{22} = -1.6$ (*c* 2.00, CHCl$_3$); IR (neat): 1689 (cm^{-1}); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.30 (d, 3H, $J = 6.6$ Hz), 2.64–2.74 (m, 2H), 2.93–3.02 (m, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 6.75–6.79 (m, 2H), 6.90–6.98 (m, 1H), 7.75 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 15.3, 33.3, 34.7, 55.6, 108.8, 119.9, 122.5, 123.9, 130.2, 145.5, 173.1; MS (*m/z*): 191 [M$^+$]; HRMS (EI): calcd for $C_{11}H_{13}NO_2$ 191.0946, found 191.0935.

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8. We have examined other ligands for this reaction, (−) –JOSIPHOS was less effective affording 35% yield and 40% ee. Other commercially available ligands, such as the TROST ligand, DUPHOS, CARBOPHOS and QUINAP showed no activity for the Pd-catalyzed cyclocarbonylation reaction.
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10. CCDC 218861 for compound **2a** and CCDC 218862 for compound **2b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336-033 or email: deposit@ccdc.cam.ac.uk.