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Palladium-catalyzed asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines

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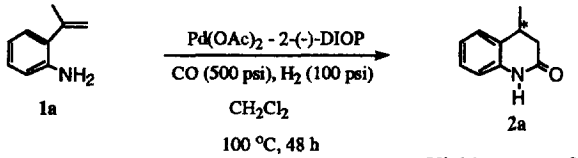
Abstract: The asymmetric cyclocarbonylation of 2-vinylanilines catalyzed by palladium with chiral phosphines was investigated. The reaction of 2-(1-methylvinyl)anilines using a catalyst system consisting of $Pd(OAc)_2$-2(−)-DIOP gave 3,4-dihydro-4-methyl-2(1H)-quinolin-2-ones in up to 54% enantiomeric excess. © 1997 Elsevier Science Ltd

Homogeneous transition metal catalyzed reactions are one of the most useful methods in organic syntheses because high chemo-, regio-, and stereochemical control can be achieved using catalysts modified by many types of ligands. Asymmetric transformations are of value when one can obtain enantiomerically enriched compounds by using catalytic amounts of expensive chiral ligands as the source of chirality. Numerous studies have been made on asymmetric hydrogenation, carbon–carbon bond forming reactions, hydrosilylation, and carbonylation, and relatively high enantioselectivity has been achieved for the first three types of reactions.[1] Although asymmetric hydroformylation, hydrocarboxylation, and hydroesterification of prochiral olefins, in particular vinyl arenes by Rh, Pd or Pt complexes,[1] have been actively investigated because of the potential of α-arylpropionic acids as antiinflammatory agents, much less attention has been paid to asymmetric cyclocarbonylation. One example is the palladium-catalyzed asymmetric cyclocarbonylation of allyl alcohols using bppm as a chiral ligand to form optically active γ-lactones.[2] Recently, we reported the cyclocarbonylation of 2-vinyl- and 2-allylanilines by palladium catalysts leading to 5-, 6-, and 7-membered lactams, the product selectivity depending on the nature of the catalyst system.[3] The asymmetric version of this reaction is a challenging goal from the viewpoint of the synthesis of optically active fused lactams. We wish to report our findings on the asymmetric cyclocarbonylation of 2-vinylanilines by palladium catalysts.



1a **2a** (1)

Yield 91 %
Optical Purity 33 %ee
$[\alpha]_D^{20}$ -13.5 (c 3.0 CH_3OH) (S)[4]

In order to evaluate the effectiveness of chiral ligands, 2-(1-methylvinyl)aniline (**1a**) was chosen as the initial substrate for the present asymmetric reaction since our previous studies indicated that the reaction of **1a** using bidentate ligands such as 1,4-bis(diphenylphosphino)butane (dppb) gave the 6-membered ring lactam, 3,4-dihydro-4-methyl-2(1H)-quinolin-2-one (**2a**) exclusively. When the carbonylation of **1a** (1.0 mmol) was performed using $Pd(OAc)_2$ (0.01 mmol) in the presence of (−)-DIOP ((−)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) (0.02 mmol) in CH_2Cl_2 at 100°C for 48 h under carbon monoxide and hydrogen pressure (P_{CO}=500 psi, P_{H_2}=100 psi), the expected 6-membered lactam, **2a** was isolated in 91% yield (eq. 1). Its enantiomeric excess

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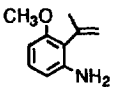
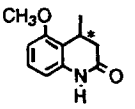
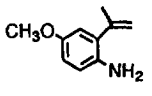
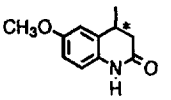
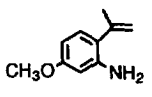
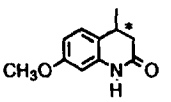
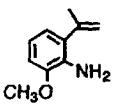
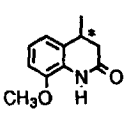
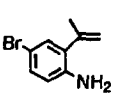
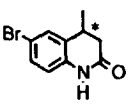
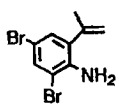
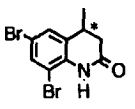
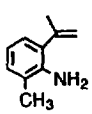
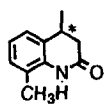
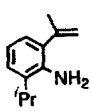
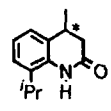
Table 1. Asymmetric cyclocarbonylation of substituted 2-(1-methylvinyl)anilines **1b–i** catalyzed by $Pd(OAc)_2$-2(−)-DIOP[a]

Substrate	Product	Chemical Yield (%)[b]	Optical Purity (% ee)[c]	$[\alpha]_D^{20}$
 **1b**	 **2b**	64	0	—
 **1c**	 **2c**	97	20	-2.8 (c 3.1 CH_3OH)
 **1d**	 **2d**	91	20	-7.3 (c 2.9 CH_3OH)
 **1e**	 **2e**	99	54	-11.8 (c 3.0 CH_3OH)
 **1f**	 **2f**	97	31	-7.8 (c 2.1 $CHCl_3$)
 **1g**	 **2g**	48	43	-9.2 (c 2.6 $CHCl_3$)
 **1h**	 **2h**	98	32	-16.4 (c 3.0 $CHCl_3$)
 **1i**	 **2i**	99	—[d]	-13.3 (c 3.2 CH_3OH)

[a] Reaction conditions; [1]:[$Pd(OAc)_2$]:[(-)-DIOP]=1:0.01:0.02. CH_2Cl_2 (5 ml), CO 500 psi, H_2 100 psi, 100 °C, 48 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR using $Eu(hfc)_3$(**2b-d, f**), and $Eu(dcm)_3$(**2h**). (HPLC analysis by chiral stationary phase column (**2e**). The value for **2g** was assessed by ^{1}H-NMR using $Eu(hfc)_3$ by reduction to **2a** with 5eq. of t-BuLi followed by protonation.). [d] Not determined.

was determined to be 33% ($[\alpha]^{20}_D$ −13.5 (c 3.0 CH_3OH)) by ^{1}H-NMR using optically active $Eu(hfc)_3$ (tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III)) shift reagent; the signal of the methyl group at the C-4 position, which was originally a doublet, was observed as a pair of doublets in the presence of $Eu(hfc)_3$. Several other commercially available chiral ligands, (−)-bppm (98% yield, 9% ee), (+)-BINAP ((R)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (43% yield, 7% ee), and R,R-BDPP ((2S,3S)-(−)-bis(diphenylphosphino)butane) (20% yield, 6% ee) were inferior to (−)-DIOP in terms of enantioselectivity. When the reaction was effected at 80°C using $Pd(OAc)_2$-2(−)-DIOP, the chemical yield was reduced (37% after 48 h), while the enantiomeric excess did not change significantly (35% ee). The enantioselectivity was not influenced by the amount of (−)-DIOP (1, 2, 6

eq) or palladium precursors ($Pd_2(dba)_3 \cdot CHCl_3$, $Pd(acac)_2$, $Pd(CF_3COO)_2$, π-allylpalladiumchloride dimer) employed whereas it was slightly sensitive to the ratio of carbon monoxide and hydrogen pressure. Thus, an increase in the ratio of hydrogen pressure (PCO=100 psi, PH_2=500 psi) reduced the enantioselectivity to 18% ee with 99% isolated yield. Although the reaction resulted in very low chemical yield (37%) in the absence of hydrogen, the optical purity was still maintained (33% ee).[4,5]

2-(1-Methylvinyl)anilines **1b–e** having a methoxy group at different positions, and 4-bromo-2-(1-methylvinyl)aniline (**1f**), were carbonylated under the optimum conditions found for **1a**, in order to assess the electronic and steric effects of the substituent on the enantioselectivity. The results are summarized in Table 1. While the substituents at the 4- and 5-position (**1c**, **1d**, and **1f**) showed some effect on the enantioselectivity, more interesting observations were made using **1b** and **1e**. While the reaction of **1b** was not enantioselective affording racemic lactam **2b**, the carbonylation of **1e** proceeded in a more enantioselective manner than that of **1a** forming **2e** in nearly quantitative yield, and in 54% ee. The carbonylation of 6-substituted 2-(1-methylvinyl)anilines (**1g–i**) was also examined. The carbonylation of **2h** and **2i** occurred smoothly to produce the corresponding 6-membered lactams in excellent yield whereas the reaction of **1g** afforded the lactams in moderate yield. Unfortunately, attempts to determine the optical purity of lactam **2i** by NMR using $Eu(hfc)_3$, and by chiral HPLC (CHIRACEL OD) were unsuccessful. However, the measured optical rotation value implies that chiral induction takes place in this reaction.

In conclusion, the asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines proceeded by means of $Pd(OAc)_2$ in the presence of (−)-DIOP to give 4-methyl-3,4-dihydroquinolin-2-one derivatives in up to 54% ee.

Acknowledgements

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