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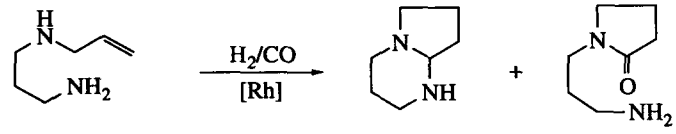
Control of Chemo- and Regio-Selectivity in Rhodium Catalysed Reactions of Unsaturated Amines with H_2/CO

David J. Bergmann, Eva M. Campi, W. Roy Jackson, Quentin J. McCubbin and Antonio F. Patti

Department of Chemistry, Monash University, Clayton, Victoria 3168, Australia

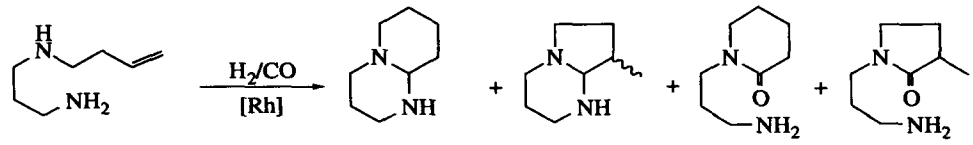
Abstract: The rhodium catalysed reactions of *N*-allyl- and *N*-butenyl-1,3-diaminopropanes give single products arising from exclusive hydroformylation at the terminal carbon when the hindered bisphosphite ligand, BIPHEPHOS is used. Reactions using a high carbon monoxide : hydrogen ratio (9 : 1) and triphenylphosphine as ligand give predominantly lactams arising from carbonylation but with poor control of regioselectivity. © 1997 Elsevier Science Ltd.

Aliphatic polyamines such as spermine and spermidine are widely distributed in nature and their oxdation products have been the subject of both physiological and pharmacological interest.[1] Enzymatic and chemical oxidation can lead to formation of either bicyclic heterocycles, e.g. (2)[2] or lactams, e.g. (3).[1]



(1) (2) (3)

An attractive general route to these classes of compounds involves hydroformylation/cyclisation or carbonylation of alkenyl-1,3-diaminopropanes, e.g. the *N*-allyl compound (1). However, in general, rhodium catalysed reactions of unsaturated amines with H_2/CO often give mixtures of isomers resulting from low chemo- and regioselectivity.[3,4] Thus, e.g. although rhodium-catalysed reaction of (1) with H_2/CO, 1:1 using PPh_3 as ligand is regiospecific an almost equimolar mixture of products arising from hydroformylation (2) and carbonylation (3) is obtained (Table 1). The problem is more acute in reactions of the homologous *N*-butenyl compound (4) which under similar conditions gives a mixture of four products, two regioisomers (5) and (6) arising from hydroformylation and two (7) and (8) from carbonylation. (Table 2)

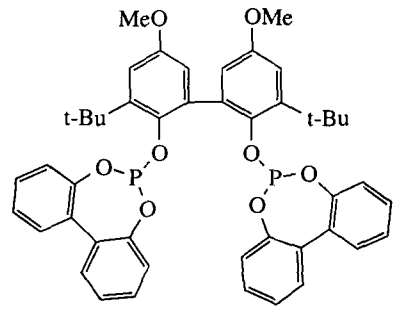


(4) (5) (6) (7) (8)

Table 1. Effect of Ligand Variation and Gas Ratio on Chemoselectivity of Reaction of (1)

Ligand	Ratio H2/CO	Product Distribution		
		Hydroformylation (2)	:	Carbonylation (3)
PPh_3	1 : 1	40	:	60
PPh_3	9 : 1	95	:	5
BIPHEPHOS	1 : 1	100	:	-
PPh_3	1 : 9	10	:	90
P(*o*-tol)$_3$	1 : 1 or 1 : 9	15	:	85

We wish to report that use of the hindered bisphosphite, BIPHEPHOS (9)[5,6] as ligand gives complete control of both chemo- and regioselectivity. Thus reaction of (4) with H_2/CO (1:1) using $[Rh(OAc)_2]_2$ and BIPHEPHOS (9) gave only the product (5) resulting from terminal hydroformylation in quantitative yield.[7]



(9)

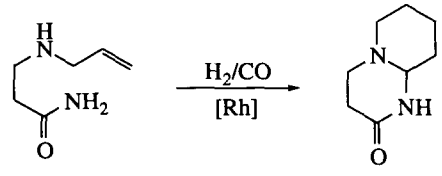
Similarly reaction of the N-allyl compound (1) using BIPHEPHOS was now chemospecific and only the bicyclic heterocycle (2) was obtained, again in quantitative yield. The high regioselective preference for terminal hydroformylation of a range of alkenes using BIPHEPHOS as ligand has been reported previously[6] and has been applied to the synthesis of indolizidine and pyrrolizidine alkaloids.[8] The dramatic change in chemoselectivity has not been noted previously. High chemoselectivity for hydroformylation products ($\geq$ 95%) could also be achieved by using triphenylphosphine as a ligand but with a H_2/CO gas ratio of 9:1. However, the regioselectivity of the products from the reaction of (4) was now only 70:30 for (5):(6). an alternative method of achieving high selectivity for hydroformylation products ($\geq$ 95%) involved the use of more basic phosphines, e.g. Bu_3P or $(C_6H_{11})_3P$ but again regioselectivity was no greater than 75% of (5). In contrast, the reaction of (4) using BIPHEPHOS with H_2/CO gas ratios of 9:1, 1:1 or 1:9 gave in all cases only hydroformylation products and only with 9:1 H_2/CO was *ca.* 5% of the branched isomer (6) obtained; both reactions using 1:1 and 1:9 H_2/CO gave exclusive terminal product.

Table 2. Effect of Ligand Variation and Gas Ratio on Chemo- and Regioselectivity of Reaction of (4)

Ligand	Ratio H2/CO	Product Ratio	Ratio of isomers	
		Hydroformylation (5,6) : Carbonylation (7,8)	Hydroformylation linear (5) : branched (6)	Carbonylation linear (7) : branched (8)
PPh_3	1 : 1	60 : 40	85 : 15	25 : 75
PPh_3	9 : 1	≥95 : ≤ 5	70 : 30	-
PBu_3	1 : 1	> 95 : < 5	75 : 25	-
$P(C_6H_{11})_3$	1 : 1	> 95 : < 5	65 : 35	-
BIPHEPHOS	1 : 1	100 : 0	100 : 0	-
PPh_3	1 : 9	20 : 80	>95 : < 5	55 : 45
P(*o*-tol)$_3$	1 : 1 or 1 : 9	5 : 95	95 : 5	30 : 70

Attempts to increase the chemoselectivity in favour of carbonylation first involved increasing the CO/H_2 ratio to 9:1, a method previously used successfully by Ojima and his co-workers.[3] Reaction of (1) using this gas mixture with Ph_3P as ligand gave a 90:10 ratio of (3):(2) and a reaction of (4) gave a ratio of 80:20 of carbonylation ((7) and (8)) to hydroformylation ((5) and (6)) products. Use of tris-*o*-tolylphosphine as ligand with CO/H_2 ratios of either 1:1 or 9:1 gave higher selectivities for carbonylation, 85% from (1) and 95% from (4) but in all of these reactions regioselectivity was at best moderate ranging from 30(7):70(8) to no selectivity at all.

The above methodology was applied successfully to the preparation of 1,5-diaza-6-oxo-bicyclo[4.3.0]nonane (11) from the *N*-allylaminopropanamide (10). This compound has potential for further functionalisation and conversion into interesting multi-ring heterocycles.



(10) (11)

ACKNOWLEDGEMENTS

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7. Typical procedure for hydroformylation of amine (1) involved stirring a solution of rhodium(II) acetate dimer (5.8 mg, 0.013 mmol), PPh_3 (13.0 mg, 0.057 mmol) and the amine (1) (300 mg, 2.6 mmol) in benzene (10 ml) in a 100 ml stainless steel Parr autoclave pressurised to 400 psi with H_2/CO (1:1 molar ratio) and heated to 80°C for 20 h. After cooling and releasing the pressure, the soluton was concentrated and analysed by ^1H and ^{13}C n.m.r. spectroscopy. The products were separated and purified by distillation to give the bicyclononane (2) as an oil. The lactam (3) was isolated as its acetamide by acetylation of the distillation residue.

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