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The mechanism of the mild rhodium-catalyzed carbonylation and cyclization of *N*-alkylallylamines to γ-butyrolactams under CO/H_2

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Abstract

The carbonylation and cyclization of *N*-alkylallylamines to γ-butyrolactams is efficiently achieved by use of $RhCl_3 \cdot 3H_2O/PPh_3$ or $RhCl(CO)(PPh_3)_2$ as catalyst precursors under mild conditions (70°C, 10 bar) when CO/H_2 (4:1) mixtures are used instead of pure CO. Mechanistic studies on the Rh and the analogous Ir system allowed the deduction of a major catalytic cycle in which the active species is $RhCl(CO)_2(PPh_3)_2$ and the role of H_2 is the decomposition of an intermediate containing a coordinated carbamoyl fragment derived from a nucleophilic attack of the amine to a coordinated CO.

Keywords: Rhodium; Carbonylation; Cyclization; Allylamines; Lactams; Mechanism

The synthesis of 5-membered ring lactams by homogeneous carbonylation and cyclization of allylamines by Co [1,2] and Rh [2,3] complexes under stringent reaction conditions (150–340°C, 136–300 atm CO) has been known for some time. The use of a 1:1 mixture of CO/H_2 allowed milder Rh-catalyzed reactions for the preparation of 5-membered [4] and 6-membered [5,6] ring lactams. Other Rh-catalyzed reactions of unsaturated amines with CO/H_2 have led to hydroformylation of the C=C bond [7] or mixtures of hydroformylation and carbonylation products [8]. Very little information has been provided concerning the active species or the reaction pathways involved in these reactions. We now report a highly efficient mild Rh-catalyzed carbonylation/cyclization of *N*-alkylallylamines to γ-butyrolactams, as well as studies which have allowed us to deduce a hitherto unknown mechanism for this interesting transformation. The most important catalytic results are summarized in Eq. 1:

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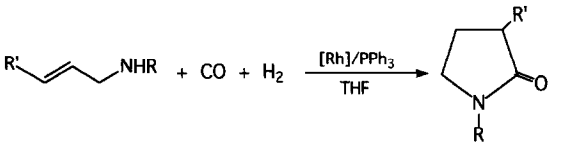


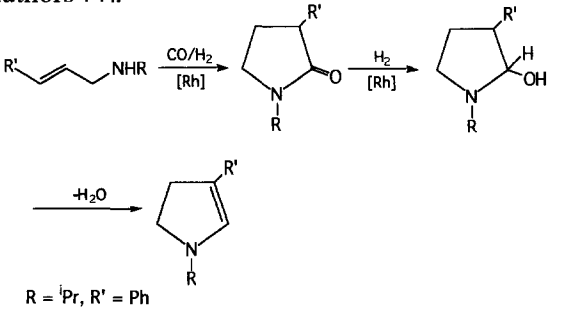
(1) (2)

(1)

1, 2	R	R'	t (h)	conv. (%) [a]	yield (%) [b]
a	H	H	–	–	–
b	Me	H	12	88	64
c	iPr	H	6	96	88
d	Ph	H	24	–	–
e	iPr	Me	24	80	40
f	iPr	Ph	24	70	53 [c]

[a] Defined as % substrate consumed.
[b] Defined as conv. × selectivity (select. = % lactam in total products).
[c] This represents the combined yields of **2f**, **2f'**, and **2f''** (see text).

Reaction of allylamine (**1a**) led to a complex mixture of heavy oligomerization products. However, *N*-substituted derivatives did lead to the desired reaction in the presence of catalytic amounts of $RhCl_3 \cdot 3H_2O/PPh_3$ [1] producing the lactams in good to excellent yields. Thus, *N*-methylallylamine (**1b**) produced 1-methyl-2-pyrrolidinone (**2b**), the only other major product of the reaction interestingly being 1-methyl-3,5-lutidinium chloride. *N*-isopropylallylamine (**1c**) produced the best results for the lactam **2c**, with only 8% of the hydrogenation product, *N*-isopropyl-n-propylamine, whereas 1-allylaniline (**1d**) did not react under our working conditions. *N*-alkylallylamines substituted at the terminal olefinic position also reacted efficiently to produce the corresponding 3-substituted lactams; thus *N*-isopropylcrotylamine (**1e**) was converted to **2e**, the byproducts consisting of C=C bond migration isomers of the starting allylamine, plus heavy oligomerization products; *N*-isopropylcinnamylamine (**1f**) was transformed into 3-phenyl-1-isopropylpyrroline (**2f'**) as the major product, accompanied by small amounts of the corresponding pyrrolidine (**2f''**); in view of our results with all other substrates we believe this reaction to involve initial formation of the lactam **2f** followed by CO bond hydrogenation and subsequent dehydration as depicted in Eq. 2. We cannot, however, rule out the possibility of a direct hydroformylation of the C=C bond followed by intramolecular nucleophilic attack of the nitrogen to the aldehyde group and subsequent dehydration of the resulting hemiamidal, as has been proposed by other authors [4].

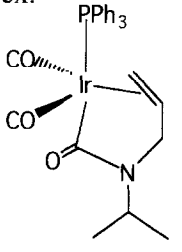


(2)

Concerning the mechanism of the formation

[1] Optimum reaction conditions are as follows: THF, $V_{tot} = 25$ cm^3, 70°C, 10 bar CO/H_2 (4:1), [Rh]:[PPh_3]:[substrate] 1:4:250. Reactions carried out in glass lined stainless steel autoclaves (Parr); products analyzed by GC–MS (Kratos MS 25) and ^{1}H and ^{13}C NMR (Bruker AM 300).

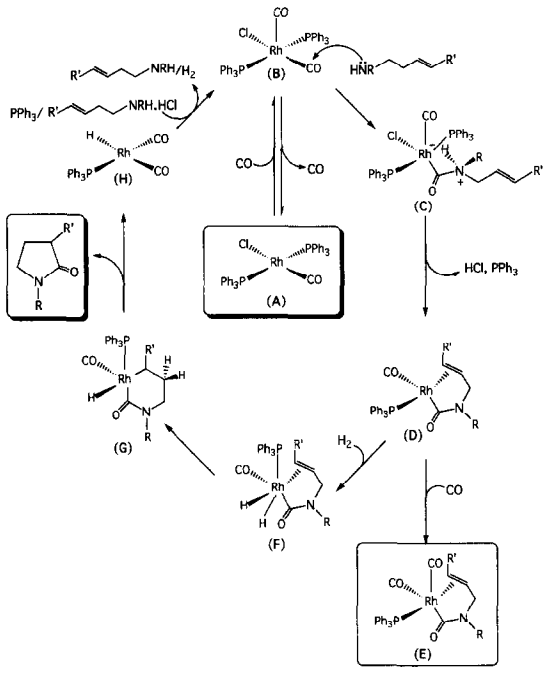
of lactams, the following observations are interesting: (i) Under pure CO the reaction is very slow (ca. 10% conv. of **1c** in 12 h). (ii) At the end of successful catalytic runs the metal is recovered in the form of $RhCl(CO)(PPh_3)_2$, which is also an excellent catalyst precursor for the conversion of **1c** to **2c** (ca. 100% conv., 95% select. in 12 h). No intermediates could be observed in the catalytic mixtures or from model reactions of $RhCl(CO)(PPh_3)_2$ with the amine in the absence or presence of CO. (iii) The complex $HRh(CO)(PPh_3)_3$ which is very probably present under our reaction conditions does not catalyze the reaction between the allylamine and pure CO, in agreement with previous reports on the carbonylation of 4-aminopent-1-ene [5]; it does catalyze, however, the formation of the lactam under a CO/H_2 atmosphere but at a rate 5 times lower than those observed for $RhCl_3 \cdot 3H_2O/PPh_3$ or $RhCl(CO)(PPh_3)_2$; this strongly indicates that the presence of chloride is important and that the monohydride is not the major active species, although it may be contributing to the overall catalysis. (iv) When $IrCl(CO)(PPh_3)_2$ was allowed to react with the amine **1c** under similar conditions the lactam **2c** was slowly formed (ca 25% conv. in 12 h); more interestingly, the metal was recovered as a mixture of $IrH(CO)(PPh_3)_3$ and the new Ir complex (**3**) [2], a stable derivative related to the catalytic cycle which contains a metallacycle that can obviously lead to the product lactam. Related Rh carbonyl complexes containing a coordinated unsaturated amine have been reported to produce lactams upon treatment with HCl and $P(OMe)_3$ [9]. (v) In situ NMR experiments showed that preformed $Ir(H)_2Cl(CO)(PPh_3)_2$ [10] does not react with the allylamine **1c** upon heating, but instead it loses H_2 and reverts back to $IrCl(CO)(PPh_3)_2$; neither the latter complex nor $IrH(CO)(PPh_3)_3$ reacted with the amine under similar conditions. On the other hand, $IrCl(CO)_2(PPh_3)_2$ generated by bubbling CO through a hot solution of Vaska's compound [11] did react with the amine to yield complex **3**, demonstrating that the major active species is not a hydride but a polycarbonylated complex.



(3)

In the light of these results, we propose the mechanism depicted in Scheme 1 for the formation of γ-butyrolactams: $RhCl(CO)(PPh_3)_2$ (**A**) (preformed or generated in situ) reacts with CO to yield the coordinatively saturated dicarbonyl derivative **B**; nucleophilic attack of the amine to coordinated CO produces **C**, which is transformed into the metallacyclic Rh(I) complex **D** by loss of HCl and displacement of a phosphine to coordinate the C=C bond of the carbamoyl fragment. Complex **D** can react with CO to yield a peripheral species **E**, the Ir analogue of which has been isolated and characterized. On the other hand, reaction of **D** with H_2 leads to the dihydride **F**; transfer of one hydride to the less substituted carbon of the double bond leads to complex **G** containing a six-membered ring metallacycle. Reductive C–C coupling from **G** liberates the lactam and the monohydride complex **H**. Since we have shown that the major

[2] Selected data for complex **3**: Anal. Found: C, 50.51; H, 4.25; N, 2.33. Calcd. for $C_{27}H_{26}NO_3PIr$: C, 50.93; H, 4.27; N, 2.20. IR (Nujol) (cm^{-1}): 2041 (vs) and 1986 (vs), ν_{CO} (terminal); 1579 ν_{CO} (carbamoyl). NMR: ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, ^{13}C-DEPT, $^1H-^1H$ 2D-COSY, $^{13}C-^1H$ and $^{31}P-^1H$ 2D-HETCOR spectra allowed the total and unequivocal assignment of all the signals as follows: δ, ^1H: 0.94, d, *J* 6.8 Hz and 1.01, d, *J* 6.8 Hz, $-CH-CH_3$; 1.42, m, *J* 7.8 Hz, 1.7 Hz, $=CH_aH$; 1.97, m, *J* 7.8 Hz, 1.7 Hz, $=CHH_b$; 2.23, m, $=CH-$; 3.35, m, *J* 11.3 Hz, 4.0 Hz, $-N-CH_aH-$; 3.49, d, *J* 11.3, $-N-CHH_b-$; 4.51, hept, *J* 6.8 Hz, $-N-CH(CH_3)_2$; 7.38, m, PPh_3. ^{13}C: 175.2, d, J_{C-P} 7.9 Hz and 174.2, d, J_{C-P} 7.9 Hz, CO (terminal); 172.9, d, J_{C-P} 103.2 Hz, CO (carbamoyl), 47.0, $N-CH_2-$; 42.1, $=CH-$; 41.0 $-CH-$; 21.8, $=CH_2-$; 20.6 and 20.0, $-CH_3$. ^{31}P, −5.98, s. The stereochemical assignment depicted in **3** has also been confirmed by an X-ray diffraction study, although the crystals were of poor quality and therefore the structure could not be refined to a crystallographically acceptable level.



Scheme 1.

mechanism is not based on a monohydride, and in view of the fact that the metal is recovered from the catalytic runs nearly quantitatively as $RhCl(CO)(PPh_3)_2$, we envisage a reaction of **H** with HCl and PPh_3 to regenerate **B** and restart the cycle. In the presence of an excess of the amine, all the HCl formed from $RhCl_3 \cdot 3H_2O$ and/or released in the transformation of **C** into **D** will be in the form of the amine hydrochloride which is the actual species reacting with the hydride. We have verified that $RhH(CO)(PPh_3)_3$ readily reacts with e.g., NH_4Cl in THF to yield $RhCl(CO)(PPh_3)_2$ quantitatively.

Some additional comments concerning this proposal are in order: The formation of **D** from **B** may alternatively be envisaged via displacement of a phosphine by the N-donor atom of the allylamine, followed by N–H activation and subsequent CO insertion into the M–N bond, accompanied by loss of HCl. Although we cannot rule out this possibility, examples of N–H activation are rare, particularly for Rh [12,13] whereas nucleophilic attack of secondary amines to M–CO bonds leading to stable carbamoyl fragments by loss of a proton is known to occur readily [14,15]; we therefore favor the pathway shown in Scheme 1. Perhaps the most interesting point in our mechanism is the role of H_2 which has been noted but never explained in previous related work [4–6]. Our results suggest that H_2 intervenes *after* the metallacycle **D** has been formed. This intermediate **D** can add either H_2 (more readily for Rh than Ir, which explains the difference in the catalytic behavior and in the isolable species for the two metals) or CO (as demonstrated for **3**, the stable Ir analogue of **E**). Hydride transfer from Rh to a C=C bond, as in the transformation of **F** into **G**, is well documented and agrees also with Jackson's observations [5,6] in the closely related carbonylation of 5-aminopent-1-enes under D_2/CO which yields six-membered ring lactams deuterated in the 3-methyl group. Finally, the monohydride **H**, formed towards the end of the catalytic cycle, reacts readily with the amine hydrochloride to yield the stable $RhCl(CO)(PPh_3)_2$ isolated at the end of the catalytic runs; in the case of iridium the M–H bond is stronger, and the analogue of intermediate **H** is rather stabilized as $IrH(CO)(PPh_3)_3$ which was isolated from the model reactions.

Besides the transient occurrence of intermediate **H**, Rh(I) hydrides such as $RhH(CO)(PPh_3)_3$ and $RhH(CO)_2(PPh_3)_2$ are known to be formed under CO/H_2 in the presence of amines [16]; it is therefore possible to imagine an alternative but closely related cycle for lactam formation starting from a monohydride, as has been proposed for the carbonylation of allylamines to lactams catalyzed by Rh carbonyl clusters which do not contain chloro or phosphine ligands [4,5]. The lower activities observed by us when using a chloride-free rhodium–hydride catalyst seem to indicate that the presence of a chloro ligand has a beneficial effect on the catalysis and that a catalytic cycle based on hydrides is not the principal route operating in our system.

In conclusion, we have obtained an excellent system for the mild catalytic synthesis of γ-

butyrolactams from allylamines, and uncovered the most relevant aspects of a hitherto unknown mechanism which we believe to be the major reaction pathway for this important transformation; at present we are performing further catalytic and mechanistic studies as well as trying to render the catalyst enantioselective by the introduction of chiral ligands.

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