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Journal of Molecular Catalysis A: Chemical 140 (1999) 107–113

JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL

Regio control in ruthenium catalysed aminomethylation

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Received 6 March 1998; accepted 26 June 1998

Abstract

The potential of various ruthenium compounds for aminomethylation has been investigated. The reaction of propene, CO/H_2 and piperidine was taken as model reaction to produce *N*-butylpiperidines **1a** and **1b**. The influence of coordinated amine on the product selectivity was examined in stoichiometric experiments using ruthenium–piperidine complexes **6** and **7**. We could show that solvent effects are essential. In acetonitrile, we were able to obtain high product selectivities of up to 99% and linearities of 95% at 55 bar and 120°C.

Keywords: Aminomethylation; Amines; Ruthenium; Homogeneous catalysis

1. Introduction

Aliphatic amines are important organic intermediates for the chemical industry [1]. From both economic and scientific points of view, there is still a high interest in finding a versatile and direct preparation route. While the direct route via hydroamination of olefins still remains one of the major challenges in catalysis [2], the aminomethylation discovered by Reppe in 1949 [3] provides a direct route to amines starting from olefinic feedstock. From a mechanistic point of view, aminomethylation has to be regarded as a three-step reaction comprising: (i) hydroformylation of the olefin to the aldehyde, (ii) condensation of the aldehyde with the amine, (iii) hydrogenation of the resulting enamine/imine to the amine. The reaction equation for the linear product is shown in Scheme 1.

The industrial interest in this reaction is obvious from the patent literature [4–6]. Mixed metal systems were applied in the aminomethylation by Iqbal (Fe/Rh) [7] and Laine (Fe/Rh and Fe/Ru) [8]. Remarkably, best activities were obtained with rhodium carbonyl systems, but linearities were better with ruthenium [8]. The same tendency between Rh and Ru was observed by Jachimowicz and Raksis [9]. Hardly any regio differentiation in the aminomethylation was observed with $RuCl_3 * 3\ H_2O$ [10]. Baig et al. [11] presented rhodium systems with good efficiency under low pressure and a two step-route towards primary amines was recently

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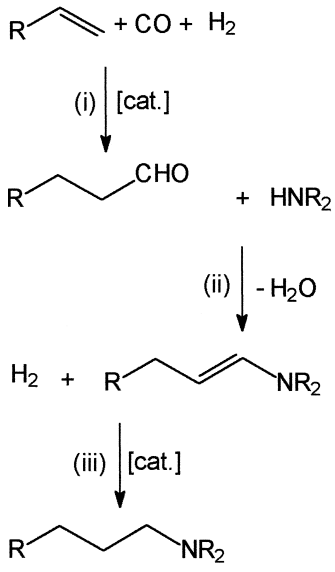
1381-1169/99/$ - see front matter
PII: S1381-1169(98)00230-1



Scheme 1.

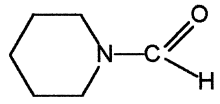
presented by Knifton [12]. Further work in this field is found in patents, see Refs. [13–15].

2. Results and discussion

In the course of our studies on aminomethylation catalysed by ruthenium compounds, we aimed at understanding the selectivity control towards the linear product. As ruthenium compounds led to high *n*:*i*-ratios, we concentrated on investigating the effects of different Ru systems. Various compounds were tested in the model reaction of propene with $CO/2\ H_2$ and piperidine (Scheme 2), leading to *n*-*N*-butylpiperidine **1a** and *iso*-*N*-butylpiperidine **1b**. Propene was chosen, because it is the simplest monoolefin where *n*:*i*-regio control can be observed and piperidine is very stable under reaction conditions.

2.1. Solvent effects on aminomethylation using $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ **2**

Complex $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ **2** (Scheme 3) was chosen for investigation because it is known for its hydrogenation activity [16]. It gave 85% conversion in the model reaction (Scheme 2) with an overall selectivity of 65% towards *N*-butylpiperidines **1** ($n{:}i = 9$) in THF (Table 1, entry 1). No enamines could be detected even at shorter reaction times (1 h; 3 h). Aldehydes, common side products in rhodium catalysed aminomethylation, were not observed as long as piperidine was present. We conclude that condensation and hydrogenation are fast compared with hydroformylation which seems to be rate-determining here. This fact establishes the advantage ruthenium offers in this reaction, since no side reactions of aldehydes are observed. The only side product is *N*-formylpiperidine **3,** formed via carbonylation of piperidine.



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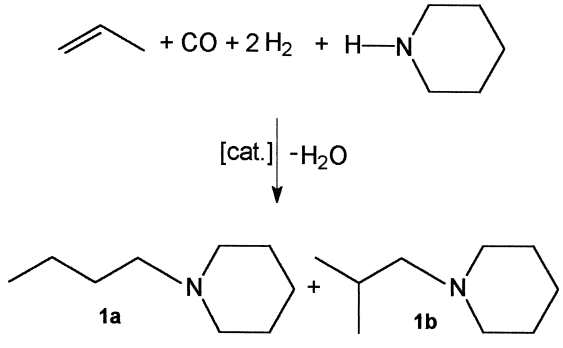
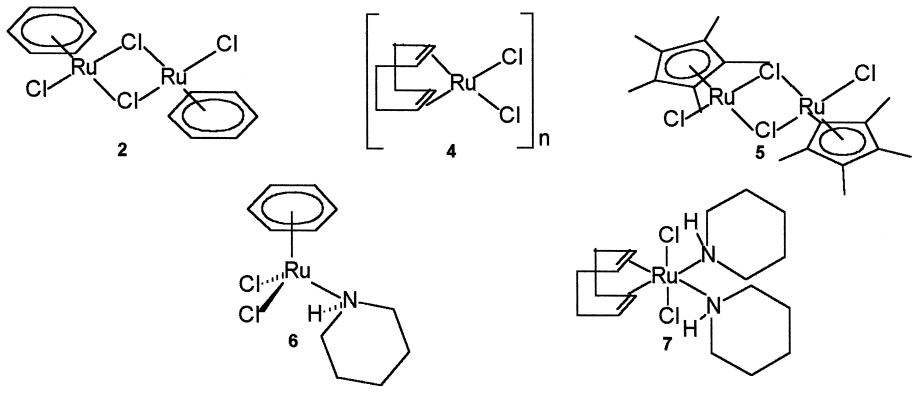
Good linearities in the product were obtained in all polar solvents used such as THF, *N*-ethylpiperidine, methanol and acetonitrile (Table 1). The least suitable solvent was *N*-ethylpiperidine giving only low selectivity. The best performance of **2** was found in acetonitrile with 99% selectivity and 95% linearity ($n{:}i = 18$) for 59% conversion (Table 1, entry 5). Most strikingly, the formation of *N*-formylpiperidine **3** was almost completely suppressed in CH_3CN. In methylene chloride, formation of piperidinium chloride $[C_5H_{10}NH_2]^+Cl^-$ was the major reaction.

Regarding the coordination capability of the solvents, it is the more strongly coordinating



Scheme 2.



Scheme 3.

solvent that favours high linearities and high selectivities.

2.2. Ligand dissociation

Under reaction conditions, benzene dissociation from complex **2** is observed rendering free coordination sites at the metal centre. Furthermore, it can be assumed that the dimer splits under reaction conditions giving an additional coordination site. For comparison with complex **2**, the similar complexes $[(COD)RuCl_2]_n$ **4** and $[(\eta^5\text{-}C_5Me_5)RuCl_2]_2$ **5** were studied (Scheme 3). While complexes **2** and **4** give equivalent results, the activity of complex **5** is lower. This is in line with the observation that COD dissociates under reaction condition as does the benzene ligand in **2**, whereas the anionic ligand Cp* in complex **5** is more strongly bound to the metal centre which results in lower yields (Table 2).

2.3. Role of coordinated piperidine

The role of coordinated piperidine on the course of aminomethylation was studied by applying the new complex $[(\eta^6\text{-}C_6H_6)Ru(C_5H_{11}N)Cl_2]$ **6** and complex $[(COD)Ru(C_5H_{11}N)_2Cl_2)$ **7**. Comparison of **6** and **7** with the piperidine-free complexes **2** and **4** shows that coordinated piperidine retards the reaction (Table 3).

2.4. Stoichiometric experiments

To determine the role of piperidine as ligand, stoichiometric experiments with complexes **6** and **7** without external piperidine were carried

Table 1
Solvent effects on aminomethylation[a]

Entry	Solvent	Conversion (%)	Yield (%)	Selectivity (%)[b]	*n*:*i*
1	THF	85	55	65	9
2	*N*-ethyl-piperidine	57	23	40	6
3	DMF	88	52	59	13
4	MeOH	27	25	93	18
5	CH_3CN	59	59	99	18

[a] 0.05 mmol complex **2**, 10 ml solvent, 10 mmol piperidine, 10 bar propene, 45 bar $CO/2\ H_2$, 120°C, 16 h.
[b] Only detected side product is **3**.
Conversion = 1-(n(piperidine)/ n_0(piperidine)); yield = n(*N*-ethylpiperidine)/ n_0(piperidine).

Table 2
Ligand dissociation effects on aminomethylation with complexes **2**,**4**,**5**[a]

Entry	Catalyst	Conversion (%)	Yield (%)	Selectivity (%)	*n*:*i*
1	**2**	59	59	99	18
2	**4**	65	64	98	18
3	**5**	26	26	98	15

[a] 0.1 mmol [Ru], 10 ml CH_3CN, 10 mmol piperidine, 10 bar propene, 45 bar $CO/2\ H_2$, 120°C, 16 h.
Conversion = 1-(n(piperidine)/ n_0(piperidine)); yield = n(*N*-ethylpiperidine)/ n_0(piperidine).

Table 3
Influence of coordinated amine on aminomethylation[a]

Entry	Catalyst	Conversion (%)[a]	Yield (%)	Selectivity (%)[b]	*n*:*i*
1	**6**	75	39	52	9
2	**2**	85	55	65	9
3	**7**	50	45	90	9
4	**4**	58	53	92	9

[a]0.1 mmol [Ru], 10 ml THF, 10 mmol piperidine, 10 bar propene, 45 bar CO/2 H_2, 120°C, 16 h.
[b]The only detected side product is **3**.
Conversion = 1-(*n*(piperidine)/ n_0(piperidine)); yield = *n*(*N*-ethylpiperidine)/ n_0(piperidine).

Table 4
Stoichiometric aminomethylation experiments with **6** and **7**[a]

Entry	Catalyst	Solvent	Yield (%)[b]	Selectivity (%)	*n*:*i*
1	**6**	THF	77	100	1
2	**6**	CH_3CN	60	100	1
3	**6**	DMF	68	100	2
4	**7**	THF	60	100	1
5	**7**	CH_3CN	54	100	1
6	**7**	DMF	51	100	2

[a]1.0 mmol [Ru], 10 ml solvent, 10 bar propene, 45 bar CO/2 H_2, 120°C, 16 h.
[b]Calculated on [Ru].
Conversion = 1-(*n*(piperidine)/ n_0(piperidine)); yield = *n*(*N*-ethylpiperidine)/ n_0(piperidine).

out (Table 4). In all cases, good yields of up to 77% and selectivities up to 100% were obtained. *N*-formylpiperidine **3**, formed as side product in catalytic experiments, was not observed. However, the discrepancy of the regioselective discrimination in these stoichiometric experiments without external piperidine (*n*:*i* = 1–2) with the catalytic runs (*n*:*i* = 9–18, Table 1) is quite striking. It shows that coordinated piperidine takes part in the reaction, but the linear product is not favourably formed via the ruthenium centre. This effect was observed in THF, CH_3CN and DMF (Table 4). Several assumptions could be brought forward to explain this phenomenon. For instance, the coordinated piperidine could influence the hydroformylation step towards lower *n*:*i*-ratios. Another reason for the higher *n*:*i*-ratios in the catalytic runs with external amine could be seen in the faster condensation of linear aldehydes with the amines shifting the equilibria towards the desired *n*-product.

From that we concluded that high linearities can be achieved if amine coordination at the metal centre is circumvented. This finding is in line with the good results obtained in acetonitrile (Table 1). This strongly coordinating molecule prevents amine coordination which leads to high *n*:*i*-ratios and also blocks side reactions via the metal centre.

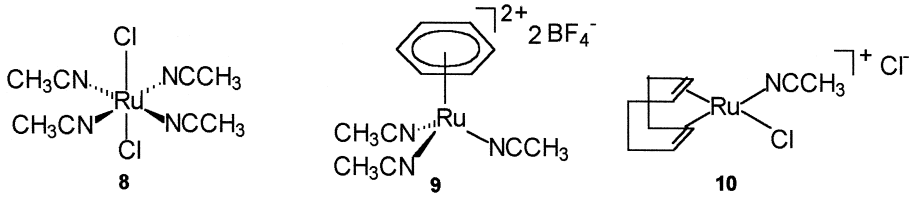
2.5. ruthenium–acetonitrile-complexes

To investigate the effect of acetonitrile coordination, experiments with ruthenium–acetonitrile-complexes were carried out. The complexes used are shown in Scheme 4.

Indeed, equal results to those with complex **2** were obtained with complexes **8** und **10** (Table 5, entries 2, 5 and entry 1 for comparison). Complex **8** was used in its neutral and cationic form after abstraction of Cl^- with 1–2 eq. $AgBF_4$. The results were no different (Table 5, entries 2–4). The chlorine-free cationic complex **9** showed low activity (Table 5, entry 5).

2.6. Catalyst behaviour after preformation with CO / 2 H_2

The use of $[Ru_3(CO)_{12}]$ for aminomethylation has already been described in the literature



Scheme 4.

Table 5
Ruthenium–acetonitrile complexes in the aminomethylation[a]

Entry	Catalyst	Conversion (%)	Yield (%)	Selectivity (%)[b]	*n*:*i*
1	**2**	59	58	99	18
2	**8**	63	62	98	18
3	**8**+1 eq. $AgBF_4$	62	60	97	19
4	**8**+2 eq. $AgBF_4$	60	58	97	19
5	**9**	37	36	97	15
6	**10**	71	69	97	19

[a]0.1 mmol [Ru], 10 ml CH_3CN, 10 mmol piperidine, 10 bar propene, 45 bar CO/H_2, 120°C, 16 h.
[b]Only side product is **3**.
Conversion = 1-(n(piperidine)/ n_0(piperidine)); yield = n(*N*-ethylpiperidine)/ n_0(piperidine).

[8,9]. Since the first step of aminomethylation is the hydroformylation of the olefin, it is very likely that metal carbonyls are the active species. The question arises whether the observed activities are dependent on the rate in which carbonyl species are formed and whether they are all alike. Therefore, we investigated the catalytic activity of complexes $[Ru_3(CO)_{12}]$ **11**, $[(\eta^6\text{-}C_6H_6)_2RuCl_2]_2$ **2**, $[(COD)RuCl_2]_n$ **4** and $[(COD)Ru(C_3H_5)_2]$ **12** against their performance after they had been preformed under 40 bar $CO/2\ H_2$ at 120°C for the times given in Table 6. Prior to their application to the reaction, the preformed catalysts were examined by IR-spectroscopy. The catalytic results showed linearities of 95% in all cases.

Overall, there is no general dependency of the catalytic activity on the preformation time. While activity increases with preformation with complex **2**, preformation has hardly any effect on complex **4**. Complex **12** is less active after preformation and activity of **11** decreases with preformation. The IR-data show some reappearing bands. However, no conclusion as to the active species can yet be drawn.

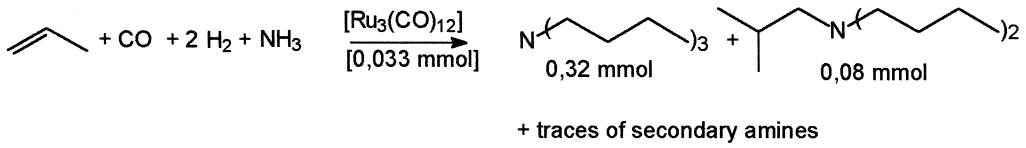
2.7. Amine variation

As mentioned before, a model reaction with piperidine was chosen here with the aim at understanding the regio control of the reaction. In principle, this reaction can be transferred to a range of substrates as has been shown in the literature [8–11]. So in a further experimental series, for example, we obtained analogous results with di-*n*-butylamine using the ruthenium catalysts as above. *N*-butylamine reacted more slowly. Here, *N*-*n*-butylformamide was observed as a major side product with overall selectivities of 30%.

Table 6
Influence of $CO/2\ H_2$ preformation on aminomethylation[a]

Entry	Catalyst	T_{pref} (h)	Yield (%)	Selectivity (%)	ν (CO)(cm^{-1})[b]
1	**2**	0	59	96	–
2	**2**	1	72	98	2083; 2068; 2022
3	**2**	4	96	99	2125w; 2067; 2047; 1972; (1828w)
4	**2**	8	70	97	2125w; 2070sh; 2048; 1972
5	**2**	64	83	97	2078sh; 2043sh; 2020; 1990; 1955
6	**4**	0	62	99	–
7	**4**	1	57	97	2048w
8	**4**	4	59	94	2125, 2070w, 2048
9	**12**	0	82	99	–
10	**12**	1	69	99	2063; 2030; 2001
11	**11**	0	95	99	2084; 2066; 2026
12	**11**	1	80	98	2063, 2037, 2020, 2000
13	**11**	4	73	99	2063; 2040w sh; 2020; 2001; 1976
14	**11**	8	92	97	2064, 2050, 2020, 2005, 1828

[a]0.1 mmol [Ru], 10 ml CH_3CN, 10 mmol piperidine, 10 bar propene, 45 bar $CO/2\ H_2$, 120°C, 16 h.
[b]Analysed after preformation.
Conversion = 1-(n(piperidine)/n_0(piperidine)); yield = n(*N*-ethylpiperidine)/n_0(piperidine).



Scheme 5.

With ammonia, complexes **2** and **11** showed different behaviour. While complex **2** gave understoichiometric results, catalytic activity was observed with complex **11**. An example is given in Scheme 5. Isomeric butylamines, dibutylamines and tributylamines were detected. No triisobutylamine was observed. *N*-*n*-butylformamide was a side product.

3. Experimental

3.1. General methods

All solvents were distilled prior to use under an argon atmosphere according to common procedures. Piperidine, di-*n*-butylamine and *n*-butylamine were purchased from Aldrich and used as received after deoxygenation. Ruthenium compounds were prepared from $RuCl_3 * 3 H_2O$ according to literature methods (**2, 9**: [17]; **4**: [18]; **5**: [19]; **7**: [20]; **8**: [21]; **10**: [22]).

3.2. Analytical methods

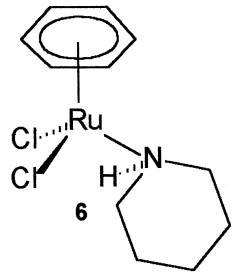
GC-analysis was done on Siemens-Sichromat apparatus using a ca. 50 m Pona HP-FS. IR-spectra were recorded from solutions on a Nicolet P510-spectrometer (4000–400 cm^{-1}).

NMR-data were measured on a Bruker DPX 300: ^1H (300 MHz), ^{13}C (75 MHz) with chemical shifts relative to the solvents used.

Elemental analysis was done on a CHN-Analyser 1106 from Carlo Erba.

*3.3. Preparation of $[(\eta^6\text{-}C_6H_6)Ru(C_5H_{11}N)Cl_2] * CHCl_3$ **6***

A slurry of 2 mmol of $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ **2** and 5 mmol piperidine in 5 ml THF was stirred overnight at RT. Meanwhile, the colour changed from brown/red to yellow. The solid product was filtered, washed with ethanol and acetone and dried in HV. It was recrystallised from chloroform (yield: 85%).



^1H NMR δ ($CDCl_3$) = 1.39–1.60 (m, 6 H, CH_2), 3.02 (m, 2H, NH–CH_{ax}); 3.82 (m, 2 H, NH–CH_{eq}); 5.55 (s, 6 H, Ar–H).

^{13}C NMR δ ($CDCl_3$) = 24.2 (NH–CH_2–CH_2–CH_2); 29.2 (NH–CH_2–CH_2); 56.4 (NH–CH_2); 83.0 (Ar–*C*).

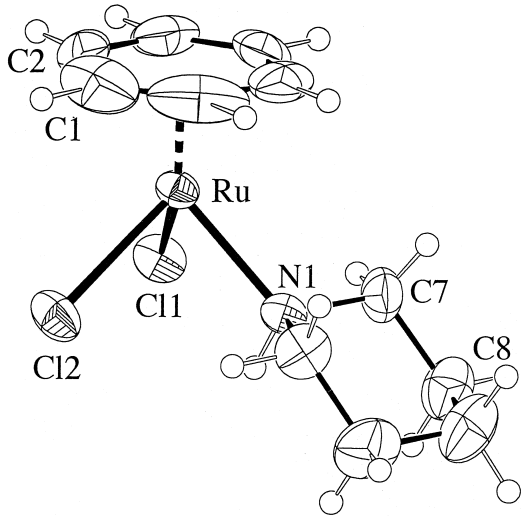


Fig. 1.

IR (KBr; $\nu = 4000–400\ cm^{-1}$) $\nu = 1650–1620s$; 1550m, 1490m, 1440vs; 1200w; 1026s; 1017m; 883m; 838m; 464w; 423w.

Elemental analysis: C (calc. 31.7; found 31.9); H (calc. 3.99; found 3.97); N (calc. 3.08; found 3.06).

Supplementary material: X-ray analysis (Ortep-Plot), see Fig. 1.

3.4. Aminomethylation catalysis

A 75-ml stainless steel autoclave was charged with the catalyst mixture, piperidine, pressurised to 10 bar propene, 45 bar $CO/2\ H_2$ and stirred for 16 h at 120°C. After the reaction, the autoclave was cooled to 0°C, vented carefully, and the reaction mixture was flash distilled and analysed by GC.

Acknowledgements

We are grateful to the BMBF and to the Ministry of NRW, 'Forschungsverbund Katalyse' for financial support. We furthermore thank Degussa for the generous loan of $RuCl_3 * 3\ H_2O$ and Mrs H. Eschmann and Dr. W. Meltzow for their valuable support in GC analysis.

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