Supercritical Carbon Dioxide as Solvent and Temporary Protecting Group for Rhodium-Catalyzed Hydroaminomethylation

Klaus Wittmann,[a] Wolfgang Wisniewski,[a] Richard Mynott,[a] Walter Leitner,*[a] Christian Ludger Kranemann,[b] Thorsten Rische,[b] Peter Eilbracht,*[b] Sander Kluwer,[c] Jan Meine Ernsting,[c] and Cornelis J. Elsevier*[c]

Abstract: Supercritical carbon dioxide ($scCO_2$) acts simultaneously as solvent and temporary protecting group during homogeneously rhodium-catalyzed hydroaminomethylation of ethyl methallylic amine. Cyclic amines are formed as the major products in $scCO_2$, whereas the cyclic amide is formed preferentially in conventional solvents. Multinuclear high-pressure NMR spectroscopy revealed that this selectivity switch is mainly due to reversible formation of the carbamic acid in the solvent CO_2, which reduces the tendency for intramolecular ring closure at the Rh–acyl intermediate. These results substantiate the general concept of using $scCO_2$ as a protective medium for amines in homogeneous catalysis and demonstrate for the first time its application for selectivity control.

Keywords: hydroaminomethylation · hydroformylation · homogeneous catalysis · supercritical fluids · protecting groups

Introduction

Compressed (liquid or supercritical) carbon dioxide is finding increasing interest as an environmentally benign reaction medium that has unique properties for homogeneously metal-catalyzed synthesis.[1, 2] The use of supercritical carbon dioxide ($scCO_2$) seems particularly attractive, since it results not only in the replacement of the organic solvent, but also may affect the underlying chemical transformation. At present, there are only few examples for such effects[2d,e] and a better understanding of possible interactions of the reaction medium CO_2 with catalytic pathways is urgently required.

A number of studies have focussed on late transition metal catalyzed carbonylation reactions in the presence of compressed CO_2, recent examples include the carbonylation of methanol,[3] Pd-catalyzed carbonylations of aryl halides,[4] and the Pauson–Khand reaction.[5] The industrially important hydroformylation has been investigated intensively, and catalytic systems compatible with the use of compressed CO_2 include unmodified cobalt[6] or rhodium[7b] catalysts, phosphane-modified rhodium catalysts,[7, 8, 9, 10] heterogenized rhodium systems,[11] and even chiral catalysts for asymmetric synthesis.[12] The rhodium-catalyzed cyclohydrocarbonylation of homoallylic amides has been investigated in the presence of carbon dioxide at temperatures and pressures beyond the critical data of CO_2.[13]

Herein, we report on the successful application of $scCO_2$ as a reaction medium for the intramolecular hydroaminomethylation of an unprotected secondary allylic amine. In particular, we demonstrate that the reversible interaction of CO_2 with the N–H functionality dramatically changes the product selectivity during the intramolecular hydroaminomethylation of ethyl methallylic amine. A mechanistic rationale for this remarkable effect is provided and supported by high-pressure multinuclear NMR studies of the substrate/CO_2 interaction.

[a] Dr. W. Leitner, K. Wittmann, W. Wisniewski, Dr. R. Mynott
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim (Germany)
Fax: (+49) 208-306-2993
E-mail: leitner@mpi-muelheim.mpg.de

[b] Prof. Dr. P. Eilbracht, Dr. C. L. Kranemann, Dr. T. Rische
Universität Dortmund
Otto-Hahn-Strasse 6, 44221 Dortmund (Germany)
Fax: (+49) 231-755-5363
E-mail: eilbrach@citrin.chemie.uni-dortmund.de

[c] Prof. Dr. C. J. Elsevier, M.Sc. S. Kluwer, Dipl.-Chem. J. M. Ernsting
Universiteit van Amsterdam
Instituut voor Moleculaire Chemie
Faculteit der Natuurwetenschappen, Wiskunde en Informatica
Nieuwe Achtergracht 166, 1018 WV Amsterdam (The Netherlands)
Fax: (+31) 20-525-6456
E-mail: else4@anorg.chem.uva.nl

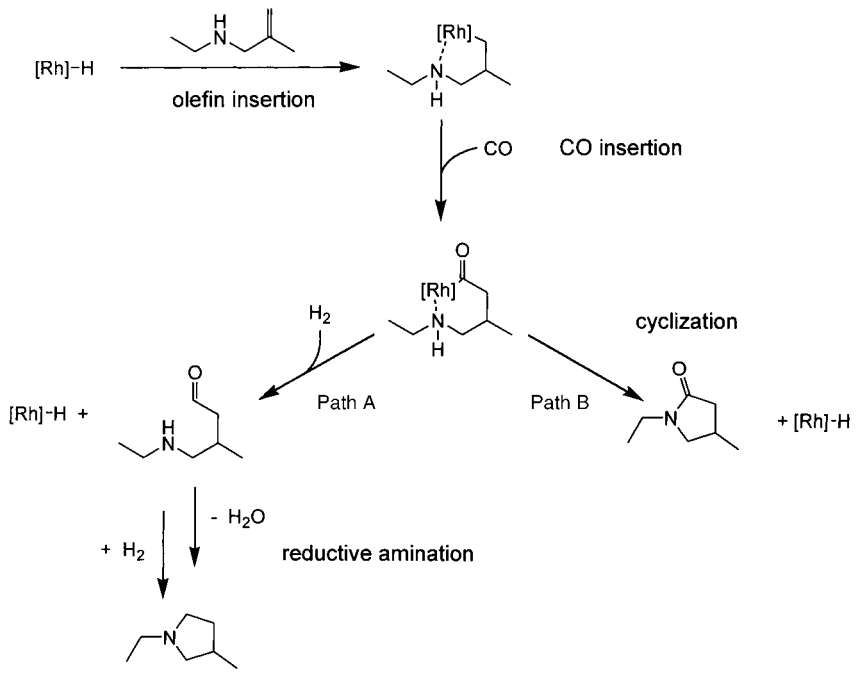
Results and Discussion

Mechanistic considerations: The hydroaminomethylation sequence converts olefins to saturated amines under hydroformylation conditions in the presence of a primary or secondary amine.[14] In the first part of the sequence, the olefin reacts with synthesis gas (CO/H_2) under the catalytic

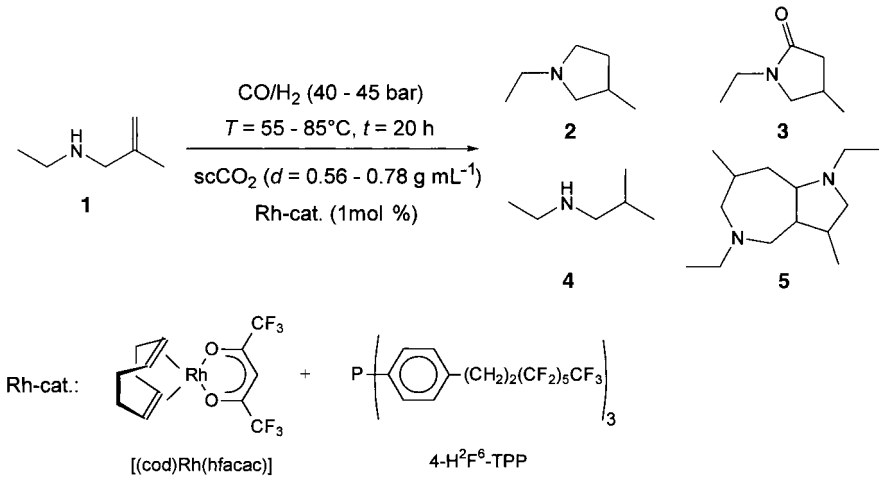
0947-6539/01/0721-4584 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 21

influence of a rhodium center to give an aldehyde. This primary product undergoes a subsequent condensation reaction with the amine, followed by hydrogenation of the resulting imine or enamine which is also catalyzed by the transition metal compound. Intramolecular versions of this reductive amination of in situ generated oxo–aldehydes provide an interesting approach to the synthesis of nitrogen-containing heterocycles and macroheterocycles.[15]

According to this sequence, the intramolecular hydroaminomethylation of ethyl methallylic amine should lead to the corresponding pyrrolidine as shown on Path A of Scheme 1. However, it was observed earlier that this substrate reacts exclusively to give the cyclic amide when subjected to hydroformylation conditions in conventional organic solvents.[16] The five-membered ring lactam is formed in the coordination sphere of the catalyst by nucleophilic attack of the nitrogen atom at the carbonyl group in the intermediate rhodium acyl species (Path B, Scheme 1). In liquid organic solvents, this intramolecular cyclization is faster than the hydrogenolysis of the rhodium acyl moiety, thus preventing the subsequent condensation/hydrogenation sequence that would lead to the saturated heterocycle (Path A, Scheme 1). Based on our earlier findings concerning the catalytic olefin metathesis of secondary amines,[17] we speculated that if the hydroaminomethylation of ethyl methallylic amine could be carried out successfully in $scCO_2$ as the solvent, then chemical interaction of the N–H group and CO_2 would reduce the nucleophilicity of the nitrogen atom and thus suppress the cyclization pathway B.



Scheme 1. Mechanistic rationale for the competing formation of pyrrolidine or cyclic amide products during hydroaminomethylation of ethyl methallyic amine.



Scheme 2. Conversion of ethyl methallylic amine **1** under hydroaminomethylation conditions in $scCO_2$ as the reaction medium.

Rhodium-catalyzed hydroaminomethylation of ethyl methallylic amine in supercritical carbon dioxide: Scheme 2 shows the general reaction conditions and the products detected during hydroaminomethylation of ethyl methallylic amine **1** in $scCO_2$. Detailed results are summarized in Table 1. Initially, we used an unmodified rhodium catalyst as reference in the optimized procedure in organic solvents (Table 1, entry 1). The active species was formed in situ from [(cod)Rh(hfacac)] (cod = 1,5-cyclooctadiene, hfacac = hexafluoroacetylacetonate) under hydroformylation conditions in $scCO_2$. To keep the total pressure within practical limits when working in $scCO_2$, the temperature and synthesis gas pressure had to be significantly reduced (Table 1, entry 2). Despite these mild conditions, almost quantitative conversion of **1** was achieved, with compounds **2, 3**, and **4** being formed in an approximate 3:3:2 ratio. The formation of pyrrolidine **2** as the main compound is fully in line with our mechanistic rationale and the proposal that CO_2 acts as a protecting group. However, hydrogenation of **1** to give the saturated amine **4** was now a prominent side reaction, probably resulting from the H_2 being more readily available in the supercritical phase than in liquid organic solvents.[2] Increasing the CO/H_2 ratio retarded the

Table 1. Rhodium-catalyzed hydroaminomethylation of ethyl methallylic amine **1** in supercritical CO_2.[a]

Entry	**1** [g]	T [°C]	p_{syngas} [bar]	CO:H_2	P:Rh	t [h]	$d(CO_2)$[b] [g mL^{-1}]	Conv.[c] [%]	Product distribution [%][c] **2**	**3**	**4**	**5**
1	1.43	110	110	9:2	–	24	dioxane	>95	<1	93	<1	—
2	1.48	80	40	1:1	–	20	0.56	92	41	34	25	–
3	0.75	55	40	2:1	–	21	0.68	81	41	37	22	–
4	0.74	55	40	2:1	3:1	21	0.67	94	35	62	3	–
5	0.75	60	40	1:1	3:1	20	0.68	65	37	58	5	–
6	0.73	60	40	1:2	3:1	20	0.68	61	64	18	5	13
7	0.74	78	40	1:2	3:1	20	0.71	70	56	<1	6	38
8	0.75	79	45	1:4	3:1	20	0.67	60	40	<1	8	52
9	0.15	80	40	1:2	3:1	44	0.78	77	76	7	4	13

[a] See Experimental Section for details. [b] Determined from the weight of CO_2 in the reaction vessel ($V = 25$ mL). [c] Determined by GC.

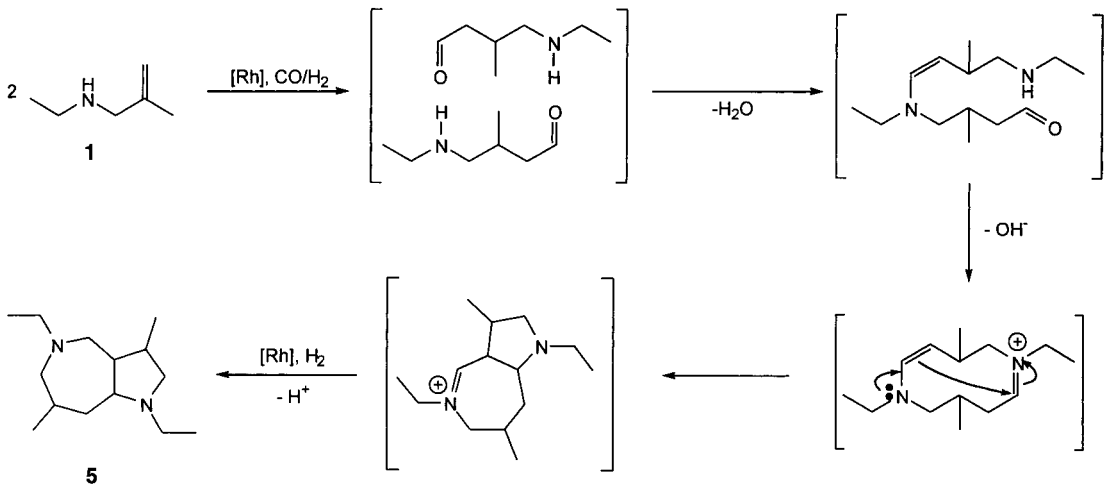
reaction slightly but did not significantly alter the product ratio (Table 1, entry 3).

The use of a phosphane-modified catalyst, formed in situ from [(cod)Rh(hfacac)] and the "CO_2-philic" analogue of triphenylphosphane, 4-H^{2}F^6-TPP, [7a] allowed the undesired hydrogenation pathway to be suppressed while retaining a reasonable activity (Table 1, entry 4). Although less of the lactam **3** was formed than when using the conventional solvent system, it was still the major product (ratio 1.8:1 relative to **2**). Increasing the partial pressure of hydrogen resulted in almost complete suppression of lactam formation, but at the same time a new product was observed in significant yields (Table 1, entries 4–6). This new compound, like **3**, contains a five-membered saturated nitrogen heterocycle, but this is now part of the bicyclic bisamino structure **5**. Under certain conditions the bicyclic saturated heterocycle could even be obtained as the major product (Table 1, entries 6–8).

The unusual heterocycle **5** was formed as a mixture of diastereomers, one of which could be isolated in pure form by TLC and was fully characterized by mass spectrometry and NMR spectroscopy (see Experimental Section). A plausible reaction sequence for the formation of **5** is shown in Scheme 3. The primary steps in this sequence are largely identical with the formation of the pyrrolidine (Scheme 1, Path A), except that the pathway of condensation of the amine and the aldehyde group is *intermolecular* rather than *intramolecular*. A subsequent Mannich-type aldol addition of the resulting dimer leads to the formation of the transannular C–C bond, creating the bicyclic skeleton. Rhodium-catalyzed hydrogenation closes the sequence, again in analogy to the pyrrolidine pathway.

The initial dimerization by *intermolecular* condensation may be facilitated by solute/solute clustering of the amino aldehyde through hydrogen bonding in the nonpolar $scCO_2$ environment at higher concentrations. In accord with this, the formation of **5** could be significantly suppressed at lower substrate concentration (Table 1, entries 7, 9). Further studies on the stereochemistry and the potential synthetic utility of the hitherto not observed dimerization of 4-amino-pentanals are in progress.

Under the conditions of entry 9 in Table 1, a selectivity for the monocyclic pyrrolidine **2** of 76% was achieved at 77% conversion of **1**. In general, path B is shut down effectively in $scCO_2$ and more than 90% of the products are of type **2** and **5** under various conditions. These saturated heterocycles are formed exclusively by path A in Scheme 1.[18] Thus, the catalytic experiments described herein demonstrate nicely that it is possible to exploit the specific chemical and physicochemical properties of $scCO_2$ in a rational way to alter the course of a catalytic reaction dramatically. In the present case, the switch from path B to A is thought to result mainly from the reversible chemical interaction of CO_2 with the N–H group. To gain more evidence for this concept, we

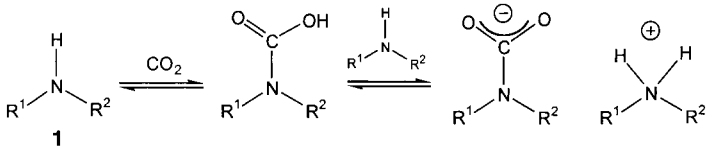


Scheme 3. Reaction sequence for the intermolecular condensation/hydrogenation pathway leading to the formation of **5** in $scCO_2$.

0947-6539/01/0721-4586 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 21

investigated the behavior of **1** in $scCO_2$ by high-pressure NMR spectroscopy.

High-pressure NMR spectroscopic investigation of 1 in $scCO_2$: Depending on the basicity of the amine and the reaction conditions, the reaction of the N–H unit with CO_2 can lead to carbamic acids or the corresponding ammonium carbamates (Scheme 4)[19] and the equilibria involved have an



Scheme 4. Possible equilibria for the interaction of N–H units with CO_2.

impact on the physical and chemical behavior of amines in $scCO_2$.[17, 20, 21, 22] The high-pressure NMR spectroscopic investigations described below indicate that the carbamic acid is the preferred species formed from substrate **1** and $scCO_2$ under conditions closely related to the catalytic experiments.

The top trace of Figure 1 shows the standard 300 MHz ^{1}H NMR spectrum of **1** in [D_8]THF (concentration 1 mmol L^{-1}) at room temperature under air at ambient pressure. The assignment of the signals is straightforward, the N–H proton giving rise to a somewhat broadened signal at approximately $\delta = 1.4$. A ^{1}H NMR spectrum of **1** recorded on the same instrument in $scCO_2$ (40 °C, 120 bar) using a high-pressure sapphire NMR tube with built-in pressure sensor[23] is depicted as the bottom trace in Figure 1. Despite some loss of resolution under these conditions, the individual groups are readily observed and assigned in this spectrum. Most significantly, the signal of the N–H proton is absent under these conditions and has been replaced by a new signal at $\delta = 12.4$ with a relative intensity of one proton. The signals of both the CH_2 groups directly adjacent to the nitrogen center of **1** exhibit a significant high frequency shift of $\Delta\delta = 0.6$, whereas the more remote groups are less affected.

The large shift of the N–H proton to high frequency ($\Delta\delta =$ 11) observed on dissolving **1** in $scCO_2$ is consistent with the formation of the carbamic acid. In contrast, when **1** is converted to the ammonium ion by protonation in [D_6]benzene and [D_6]acetone, smaller high frequency shifts of 5.8 and 5.0 ppm, respectively, are observed.[24] Furthermore, while the differences between the CH_2 signals of the amine and the ammonium ion are very small, their resonances in $scCO_2$ are more similar to the chemical shifts observed in N-acetylated secondary allylic amines. Nevertheless, it cannot be ruled out completely that the carbamic acid is in a fast equilibrium with small amounts of the other species.

The interaction of the basic nitrogen center with CO_2 is reflected also in the spectroscopic data of the quadrupolar nucleus ^{14}N ($I = 1$).[25] The ^{14}N NMR spectra of **1** in [D_6]acetone (top trace) and in the presence of $scCO_2$ (bottom trace) are depicted in Figure 2. In conventional solution, the free amine shows a signal at $\delta(^{14}N) = -349$ with an approximate linewidth at half height of 180 Hz. In the presence of $scCO_2$, the signal of the major component appears at higher

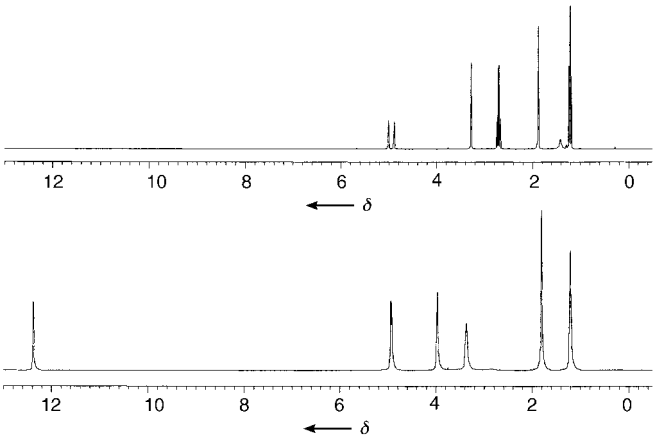


Figure 1. ^{1}H NMR spectra of **1** in [D_8]THF (25 °C, top trace) and in $scCO_2$/[D_8]THF (180 bar, 50 °C, bottom trace).

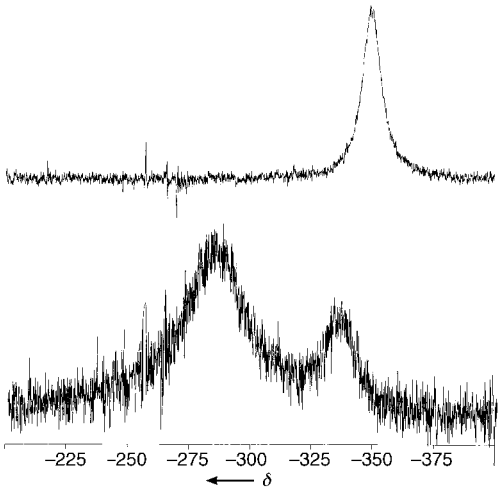


Figure 2. ^{14}N NMR spectra of **1** in [D_6]acetone (25 °C, top trace) and $scCO_2$/[D_6]acetone (110 bar, 40 °C, bottom trace).

frequency ($\delta = -285$), an induced shift of $\Delta\delta = 64$ ppm, indicating again the formation of the carbamic acid as the major species.[26] In contrast to the ^{1}H NMR spectra, a smaller signal of a second species is visible under the somewhat different experimental conditions of the ^{14}N NMR investigation. The chemical shift ($\delta = -336$) and the linewidth ($\Delta\nu_{1/2} = 340$ Hz) of this smaller signal strongly suggest the presence of the ammonium ion of **1**,[24] although an unambiguous distinction from the free amine is difficult considering the difference in the type of solvent and the typically very small differences in nitrogen shifts between amines and ammonium ions.

Conclusion

Hydroaminomethylation of ethyl methallylic amine can be carried out efficiently in supercritical carbon dioxide ($scCO_2$) as the reaction medium using unmodified or phosphane-modified "CO_2-philic" rhodium catalysts. The reaction occurs at considerably lower temperatures and lower synthesis gas pressures than usually required for this transformation in conventional solvents. Most significantly, the product distri-

bution obtained in $scCO_2$ differs remarkably from that observed in organic liquid solvents: whereas the cyclic amide is obtained as the major product in conventional solvents, saturated nitrogen heterocycles are formed preferentially in $scCO_2$. The reaction conditions can be optimized further to yield either the pyrrolidine or a new bicyclic framework as the major saturated heterocyclic product.

There are presently only very few examples for such a remarkable change of the preferred reaction pathway upon replacing organic solvents with $scCO_2$, and our understanding of these effects on a molecular level is even more limited.[2] In the present case, high-pressure ^1H and ^{14}N NMR spectroscopy were used to demonstrate that the selectivity switch results primarily from the protection of the N–H unit in the amine by the reversible formation of the carbamic acid in the presence of CO_2. The intriguing possibility for selectivity control substantiates the general concept of using $scCO_2$ as protective medium for amines in catalytic chemical synthesis, which may find application in various C–C bond-forming reactions.[17]

Experimental Section

Safety warning: The use of highly compressed gases such as supercritical fluids must be conducted only with suitable high pressure equipment under appropriate safety conditions.

Catalytic experiments: In a typical experiment, ethyl methallylic amine (**1**, 0.74 g, 7.5 mmol), [(cod)Rh(hfacac)] (30 mg, 0.07 mmol), and 3-H^2F^6-TPP (300 mg, 0.23 mmol) were placed in a home-built stainless steel high-pressure reactor ($V = 25$ mL) equipped with thick-walled borosilicate windows for visual control of the phase behavior of the reaction mixture. The mixture was pressurized with a 1:2 mixture of CO and H_2 to $p_{syngas} =$ 40 bar and filled with CO_2 (17.8 g) by means of a compressor. The reactor was heated to reach an inside temperature of $T = 78\,^\circ C$ within 30 min, and the homogeneous single-phase reaction mixture was stirred at this temperature for 20 h. Systematic variations of the reaction conditions were carried out as summarized in Table 1.

For standard workup, the reactor was allowed to cool to room temperature and then slowly depressurized, venting the gas stream through a cold trap at $-60\,^\circ C$. The contents of the reactor and the trap were collected by washing with diethyl ether and the combined solutions analyzed by gas chromatography (GC: Fisons 8130 with 30 m CP sil-5 capillaries, GC/MS: Finnigan ITD 800 (MS)). For individual characterization and assignment of the reaction products, a representative crude reaction mixture was isolated as above and worked up by kugelrohr distillation.

1-Ethyl-3-methylpyrrolidine (2): *GC-MS*: *m*/*z* (%): 112 (24, $[M^+ - 1]$), 98 (100), 82 (10), 71 (14), 56 (24); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.95$ (d, 3H, $^3J = 6.8$ Hz), 1.03 (t, 3H, $^3J = 7.3$ Hz), 1.27 (m, 1H), 1.89 (m, 1H), 1.96 (m, 1H), 2.17 (m, 1H), 2.38 (m, 3H), 2.63 (m, 1H), 2.77 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): $\delta = 13.9$ (CH_3), 20.3 (CH_3), 31.7 (CH), 32.5 (CH_2), 50.3 (CH_2), 53.8 (CH_2), 62.0 (CH_2); GC-FTIR: $\tilde{\nu} = 2966$ (s), 2791 (s), 1458 (m), 1387 (m), 1330 (m), 1178 (m), 841 (w), 664 (w), 620 (w) cm^{-1}.

1-Ethyl-4-methyl-pyrrolidin-2-one (3): Spectroscopic data were identical do those reported in reference [16].

Ethyl isobutylamine (4): GC-MS: *m*/*z* (%): 102 (14, $[M^+ + 1]$), 58 (100); GC-FTIR: $\tilde{\nu} = 2965$ (s), 2889 (m), 2820 (m), 1463 (m), 1384 (m), 1136 (m), 1037 (w), 973 (w), 909 (w), 852 (w), 821 (w), 695 (w), 657 (w) cm^{-1}.

1,5-Diethyl-3,7-dimethylperhydropyrrolo[3,2-*c*]azepine (5): The compound was present in the crude product as a mixture of diastereomers as indicated by GC-MS. A representative diastereomer was isolated by preparative thin-layer chromatography on silica. The NMR signals were assigned on basis of H,H- and C,H-correlation as well as ^{13}C-DEPT spectra. GC-MS: *m*/*z* (%): 225 (67, $[M^+ + 1]$), 179 (12), 164 (7), 138 (38), 124 (14), 112 (100), 56 (5); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.04$ (m, 12H; $4 \times CH_3$), 1.38 (m, 1H; NCHC*H*H), 1.69 (t, $^3J = 9.4$ Hz, 1H; NC*H*HCHCHH), 1.85 (m, 1H; NCHCH*H*), 1.93 (m, 1H; NCHC*H*), 1.98 (m, 1H; NCHCHC*H*), 2.13 (m, 2H; NCHHC*H*CHH, NC*H*HCH$_3$), 2.18 (m, 1H; NC*H*HCHCHCH), 2.32 (m, 2H; NC*H*HCHCH, NC*H*HCH$_3$), 2.48 (m, 2H; NC*H*, NCH*H*CH$_3$), 2.63 (m, 2H; NCH*H*CHCH, NCH*H*CHCHCH), 2.85 (m, 1H; CH*H*CH$_3$), 3.26 (dd, $^3J = 8.7$ Hz, $^3J = 6.6$ Hz, 1H; NCH*H*CHCHH); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): $\delta = 13.7$ ($2 \times NCH_2CH_3$), 18.8 ($CHCH_3$), 21.4 ($CHCH_3$), 31.1 (NCH_2CHCH_2), 33.8 (NCH_2CHCH), 36.1 ($NCHCH_2$), 48.5 (NCHCH), 49.2 (NCH_2CH_3), 50.5 (NCH_2CH_3), 58.3 (NCH_2CHCH), 62.2 (NCH_2CHCH_2), 63.1 (NCH_2CHCH), 66.8 (NCH); GC-FTIR: $\tilde{\nu} = 2963$ (s), 2882 (m), 2793 (s), 1458 (m), 1384 (m), 1322 (m), 1173 (m), 1038 (w), 914 (w), 859 (w), 810 (w), 688 (w) cm^{-1}.

High-pressure NMR spectrosocpic investigations: Measurements were carried out using a 5 mm or 10 mm sapphire NMR tube with an titanium pressure head equipped with a needle valve and a pressure sensor.[23] The tubes were always kept behind a protective shield and/or inside a cylinder made from polymethacrylate[27] during handling, filling, transport, and insertion into the magnet of the spectrometer. ^1H NMR spectra were measured at the NMR facilities of the MPI Mülheim and chemical shifts are given relative to TMS using the residual signal of the deuterated lock solvent as internal reference. ^{14}N NMR spectra were measured at the NMR facilities of the University of Amsterdam or the MPI Mülheim and chemical shifts are given relative to $MeNO_2$ (0 ppm), using either $MeNO_2$ itself or Me_4NCl (−335.7 ppm) as the external references.

Ethyl methallylic amine (**1**, ca. 100 μL) was placed in the tube together with $[D_8]$THF (ca. 150 μL) as the lock solvent. The tube was charged with a weighed amount of liquified CO_2 (0.28 g) to adjust an average density of about 0.70 g L^{-1}. The tube was carefully lowered into the preheated (40 °C) standard 5 mm probehead of a Bruker AMX400 NMR spectrometer and ^1H NMR spectra were recorded without spinning after constant shim parameters were reached. The ^{14}N NMR spectra were measured on a Bruker DRX300 NMR spectrometer following the same procedure but using a 10 mm tube and $[D_6]$acetone as the lock solvent.

Acknowledgement

Financial support of this work by the DFG (Gerhard-Hess-Award to W.L.), the State of Nordrhein-Westfalen, the Fonds der Chemischen Industrie, and the COST-D10 program of the EU (cooperation Mülheim/Amsterdam) is gratefully acknowledged.

[1] *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**.
[2] a) P. G. Jessop, T. Ikariya, R. Noyori, *Science* **1995**, *269*, 1065; b) D. A. Morgenstern, R. M. leLacheur, D. K. Morita, D. L. Borkowsky, S. Feng, G. H. Brown, L. Luan, M. G. Gross, M. J. Burk, W. Tumas, in *Green Chemistry* (Eds.: P. T. Anastas, T. C. Williamson), American Chemical Society, Washington DC, *ACS Symp. Ser.* **1996**, *626*, p. 132; c) E. Dinjus, R. Fornika, M. Scholz, in *Chemistry under Extreme or Non-Classical Conditions* (Eds.: R. van Eldik, C. D. Hubbard), Wiley, New York, **1996**, p. 219; d) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, *99*, 457; e) W. Leitner, *Top. Curr. Chem.* **1999**, *206*, 107.
[3] R. J. Sowden, M. F. Sellin, N. DeBlasio, D. J. Cole-Hamilton, *Chem. Commun.* **2000**, 2511.
[4] Y. Kayaki, Y. Noguchi, S. Iwasa, T. Ikariya, R. Noyori, *Chem. Commun.* **2000**, 1235.
[5] N. Jeong, S. H. Hwang, Y. W. Lee, J. S. Lim, *J. Am. Chem. Soc.* **1997**, *119*, 10549.
[6] a J. W. Rathke, R. J. Klingler, T. R. Krause, *Organometallics* **1991**, *10*, 1350; b) Y. Guo, A. Akgerman, *J. Supercrit. Fluids* **1999**, *15*, 63.
[7] a) S. Kainz, D. Koch, W. Baumann, W. Leitner, *Angew. Chem.* **1997**, *109*, 1699; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1628; b) D. Koch, W. Leitner, *J. Am. Chem. Soc.* **1998**, *120*, 13398.
[8] a) D. R. Palo, C. Erkey, *Ind. Eng. Chem. Res.*, **1998**, *37*, 4203; b) D. R. Palo, C. Erkey, *Organometallics* **2000**, *19*, 81.
[9] a) I. Bach, D. J. Cole-Hamilton, *Chem. Commun.* **1998**, 1463; b) M. F. Sellin, D. J. Cole-Hamilton, *J. Chem. Soc. Dalton Trans.* **2000**, 1681.
[10] P. G. Jessop, D, C. Wynne, S. DeHaai, D. Nakawatase, *Chem. Commun.* **2000**, 693.

  0947-6539/01/0721-4588 $ 17.50+.50/0

[11] N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Poliakoff, *Chem. Commun.* **2000**, 1497.
[12] G. Franciò, W. Leitner, *Chem. Commun*. **1999**, 1663.
[13] I. Ojima, M. Tzamarioudaki, C. Y. Chuang, D. M. Iula, Z. Li, "Catalytic Carbonylations in Supercritical Carbon Dioxide" in *Catalysis of Organic Reactions* (Ed.: F. E. Herkes), Marcel Dekker, New York, **1998**, p. 333.
[14] P. Eilbracht, L. Bärfacker, C. Buß, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev*. **1999**, *99*, 3329.
[15] C. L. Kranemann, P. Eilbracht, *Eur. J. Org. Chem*. **2000**, 2367, and references therein.
[16] T. Rische, L. Bärfacker, P. Eilbracht, *Eur. J. Org. Chem*. **1999**, 653.
[17] a) A. Fürstner, D. Koch, K. Langemann, W. Leitner, C. Six, *Angew. Chem.* **1997**, *109*, 2562; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2466; b) A. Fürstner, L. Ackermann, K. Beck, H. Hori, D. Koch, K. Langemann, M. Liebl, C. Six, W. Leitner, *J. Am. Chem. Soc.* **2001**, *123*, in press.
[18] Lactone **3** is not hydrogenated to **2** under hydroaminomethylation conditions.
[19] M. Aresta, D. Ballivet-Tkatchenko, M. C. Bonnet, D. Boschi, F. Calderazzo, R. Faure, L. Labella, F. Marchetti, *Chem. Commun.* **2000**, 1099, and references therein.
[20] For an early discussion of the possible interference of this equilibrium with transition metal catalysis in $scCO_2$ see ref. [2b].
[21] The interaction of amines with CO_2 has also been observed for certain products arising from imine hydrogenation in $scCO_2$, but was found to be detrimental in this case. See: S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, *J. Am. Chem. Soc.* **1999**, *121*, 6421.
[22] Related examples involving this equilibrium in $scCO_2$: a) A. W. Francis, *J. Phys. Chem.* **1954**, *58*, 1099; b) M. Ashraf-Khorassani, L. T. Taylor, P. Zimmermann, *Anal. Chem.* **1990**, *62*, 1177; c) O. Aaltonen, in *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999** Chapter 4.9, pp. 414–445; d) M. Yoshida, N. Hara, S. Okuyama, *Chem. Commun.* **2000**, 151.
[23] a) S. Gaemers, H. Luyten, J. M. Ernsting, C. J. Elsevier, *Magn. Reson. Chem.* **1999**, *37*, 25. For reviews on high-pressure NMR techniques and/or their application to chemistry in supercritical fluids see: b) J. W. Rathke, R. J. Klingler, R. E. Gerald II, D. Fremgen, K. Woelk, S. Gaemers, C. J. Elsevier in *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**, Chapter 3.2, p. 165–194; c) S. Gaemers, C. J. Elsevier, *Chem. Soc. Rev.* **1999**, *28*, 135; d) I. T. Horváth, J. M. Millar, *Chem. Rev.* **1991**, *91*, 1339; e) D. C. Roe, *J. Magn. Res.* **1985**, *63*, 388.
[24] The ammonium ion of **1** was generated in situ by protonation with excess trifluoracetic acid at room temperature. ^1H NMR ([D_6]acetone, 400 MHz): $\delta = 0.98$ (t, 3H; CH_3), 1.64 (s, 3H; CH_3), 2.46 (q, 2H; CH_2), 3.00 (s, 2H; CH_2), 4.80 (s, 1H; CH), 4.91 (s, 1H; CH), 6.41 (s, 2H; NH_2); ^{14}N NMR ([D_6]acetone, 28.9 MHz): $\delta = -337$($\Delta\nu(1/2) =$ 525 Hz).
[25] a) J. M. Robert, R. F. Evilia, *J. Am. Chem. Soc.* **1985**, *107*, 3733; b) S. Gaemers, C. J. Elsevier, *Magn. Reson. Chem.* **2000**, *38*, 650.
[26] We were unable to locate ^{14}N or ^{15}N data for free carbamic acids in the literature. Some ^{15}N shifts of related compounds: $Me_2NC(O)OMe$, $\delta = -314.2$; S. Berger, S. Braun, H.-O. Kalinowski, *NMR Spectroscopy of the of the Non-metallic Elements*, Wiley, Chichester, **1996**, 142; $H_2N(COH)_2^+$, $\delta = -310.7$; G. A. Olah, T. Heiner, G. Rasul, G. K. S. Prakash, *J. Org. Chem.* **1998**, *63*, 1993.
[27] C. J. Elsevier, *J. Mol. Catal.* **1994**, *92*, 285.

Received: February 14, 2001 [F3071]