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The ruthenium catalyzed formation of chiral dihydropyrrolones from α,β-unsaturated imines: extending the reaction to terminal alkenes and investigating the formation of pyrroles as side-products

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Abstract—The reaction of α,β-unsaturated imines derived from cinnamaldehyde with CO and various alkenes produces chiral 1,3-dihydropyrrolone derivatives. As a byproduct the formation of 2,3-disubstituted pyrroles is observed in every reaction. If the imines are reacted with ethylene only, products with an ethyl group at C-3 of the imine chain are formed. The implications of these findings on the reaction mechanism are discussed.

1. Introduction

C–H activation reactions provide the possibility to achieve highly atom economic catalytic C–C bond formation processes in a very efficient way.[1] So during the last years quite a number of catalytic reactions have been described in which a C–H activation reaction initiates the catalytic cycle.[2] Amongst others the group of Murai and co-workers have been successful in this field of chemistry describing not only alkylation and carbonylation reactions of aromatic ketones and imines, but also of substrates in which the C–H activation proceeds at a sp^3-hybridized carbon atom.[3–5] In these reactions the C–H activation step is believed to take place in terms of an *ortho*-metallation.

We and the Murai group have independently investigated the reactivity of cinnamaldehyde derivatives in catalytic C–H bond activation reactions. It was shown by Murai and co-workers that the reaction of these acyclic unsaturated imines with CO catalyzed by $Ru_3(CO)_{12}$ yields 1,5-dihydropyrrolone derivatives (Scheme 1).[6] On the other hand, we were able to produce chiral 1,3-dihydropyrrolones in a selective reaction cascade from the same imines, CO and ethylene.[7] Recently, Chatani et al. used the same reaction we described earlier to check whether it is applicable to other olefins than ethylene and if there is an influence of the aromatic substituent at the C-terminal end of the imine chain.[8]

We want to report our results on the reaction of α,β-unsaturated imines with CO and olefins in the presence of catalytic amounts of $Ru_3(CO)_{12}$ since in contrast to Chatani we found that terminal alkenes work very well in this reaction when their lower reactivity is considered in the choice of the reaction conditions. In addition, we were able to identify 2,3-disubstituted pyrroles as the byproducts of the catalytic reactions. Their formation requires the cleavage of one carbon monoxide moiety. The corresponding oxygen atom is transferred to another CO ligand to produce CO_2. The implications of these findings on a proposed reaction mechanism are discussed.

2. Results and discussion

Scheme 1 summarizes all compounds that might be produced in catalytic reactions from imines based on cinnamaldehyde with CO and/or ethylene as co-substrates. If CO is used as the only substrate 1,5-dihydropyrrolones of type **A** are formed.[6] The reaction with CO and ethylene produces the 1,3-dihydropyrrolones **C** as the main products.[7,8] In this paper we will focus on the fact that the reaction of cinnamaldehyde imines with ethylene as the only substrate leads to the formation of compounds **B** and we will show that compounds **C** are formed in excellent yields from α-olefins in general. We will also comment on

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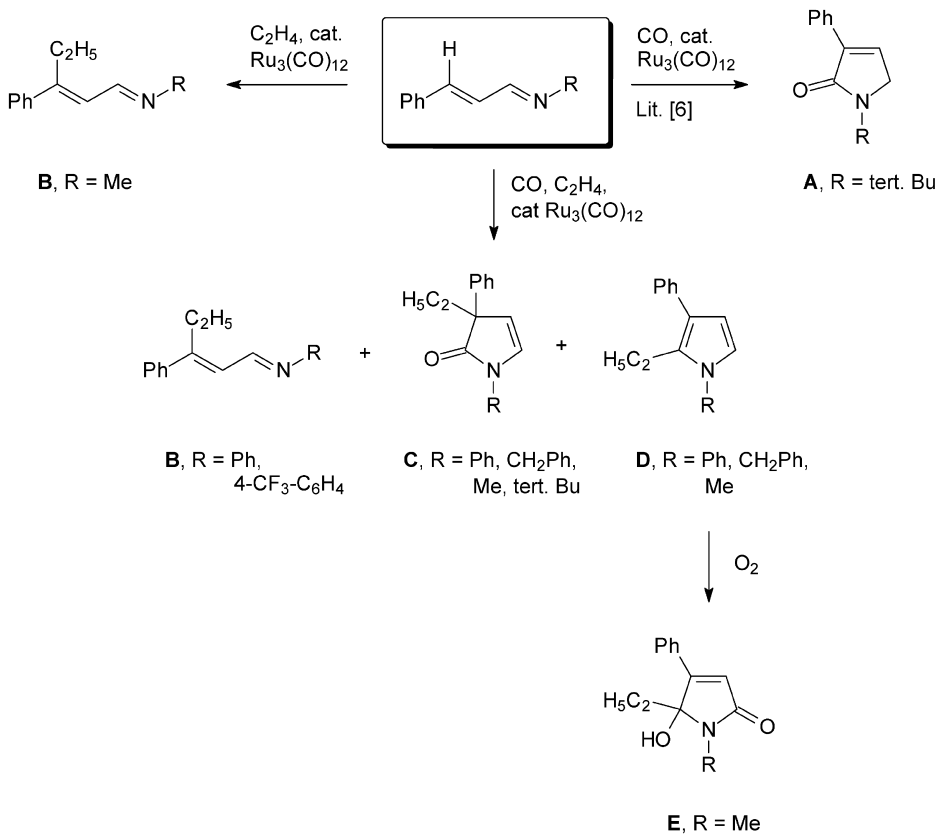


Scheme 1.

the formation of pyrroles **D** and their formal oxidation products **E** in the same reaction mixtures.

Table 1 summarizes all new compounds that were prepared during the investigations we are reporting. Since we noticed earlier that an enhanced basicity at the imine nitrogen atom increases the yield of the pyrrolones of type **C**, we chose benzyl and methyl substituents in this position.

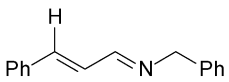
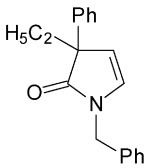
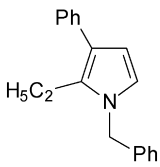
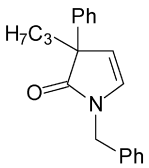
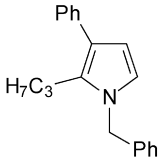
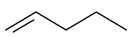
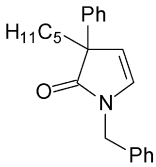
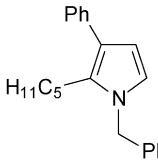
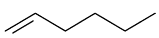
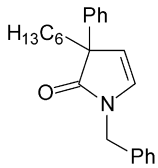
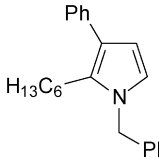
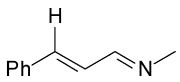
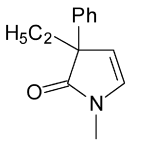
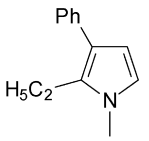
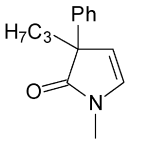
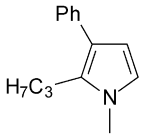
It can be seen from Table 1 that α-olefins together with CO and the corresponding unsaturated imines **1** or **2** produce chiral 1,3-dihydropyrrolone derivatives **3a–f** in good yields. In a recent paper by Chatani and co-workers it was stated that terminal olefins such as 1-hexene do not react at all in these kind of reactions if imines with *tert* butyl groups attached to the imine nitrogen atom are used.[8] This observation was used by the authors as an evidence for a direct carbonylation at C-3 of the imine chain. We find that the reaction works very well with imines bearing benzyl or methyl substituents if the CO pressure is lowered, reaction time is prolonged and the concentration of the olefinic substrate is raised compared with the standard conditions that we used in reactions involving ethylene. These findings correspond very well with the expected reduced reactivity of substituted alkenes reducing the rate constants of all elementary steps of the catalysis in which the alkenes are involved. Following the principle of Le Chatelier, reducing the concentration of the more reactive substrate (CO) combined with increasing the concentration of the less reactive partner (alkene) compensates this effect.

In the reaction of substituted olefins of course the problem of *n*/*iso* selectivity arises. As illustrated in Table 1, a long alkyl chain of the α-olefin results in a high *n*/*iso* ratio as it is expected. For details concerning the reaction conditions cf. Section 4.

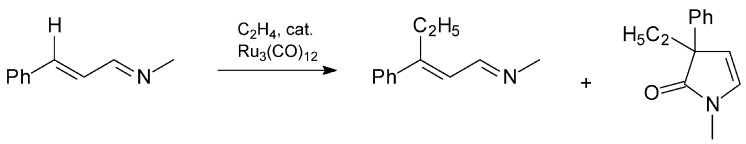
If only one of the substrates is introduced to the reaction mixture products are observed that originate from the formal insertion of CO or ethylene, respectively, into the C–H bond at C-3 of the imine chain. CO reacts to give 1,5-dihydropyrrolones (Scheme 1, type **A**)[6] whereas ethylene produces non-cyclic imines that are alkylated at C-3 (Scheme 1, type **B**). Scheme 2 shows the reaction of **2** with ethylene in the presence of 4 mol% $Ru_3(CO)_{12}$.

We observed the formation of the alkylated product **5** as a mixture of the *s-cis* and *s-trans* isomer as well as the formation of **3e** in low yields. The portion of **3e** formed in this reaction corresponds very well with the amount of CO introduced by the precatalyst $Ru_3(CO)_{12}$. In addition, this reaction is the only one in which no $Ru_3(CO)_{12}$ was recovered during the work-up of the reaction mixture. In all experiments in which CO and alkenes were used $Ru_3(CO)_{12}$ was recovered nearly quantitatively. Traces of $Ru(CO)_5$ were identified by IR-spectroscopy in the residue inside the vacuum trap after all volatile material had been removed from the crude reaction mixture. In one of our recent papers we reported that compounds **B** formed preferably with electron-withdrawing substituents at the imine nitrogen atom also if CO and ethylene are present together.[7a] So obviously CO and ethylene are competing for the position at the imine where the transition metal induced C–H activation occured in order to form a new C–C bond there.

Table 1. Reaction of cinnamadehyde imines with CO and olefins catalyzed by $Ru_3(CO)_{12}$[a]

Imine	Olefin	γ-lactam (type **C**)	Pyrrole (type **D**)
 **1**	═	 **3a** (92%)	 **4a** (6%)
1		 **3b** (90%, n/iso=60/40)	 **4b** (8%, n/iso=90/10)
1		 **3c** (81%, n/iso=90/10)	 **4c** (4%)[b]
1		 **3d** (80%, n/iso=90/10)	 **4d** (5%)[b]
 **2**	═	 **3e** (80%)	 **4e** (18%)
2		 **3f** (82%, n/iso=55/45)	 **4f** (16%, n/iso=80/20)

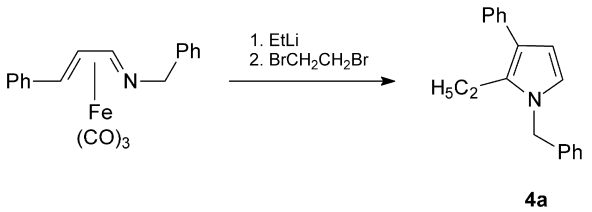
[a] Yields and the *n*/*iso* ratio are determined from ^{1}H NMR data of the crude reaction mixtures.
[b] *iso*-Isomer not detectable by NMR.



2 **5** **3e**

Scheme 2.

The most important fact concerning mechanistic insights into this catalytic reactions is the observation of the disubstituted pyrroles **4a**–**f** as byproducts. Obviously only the carbon atom of carbon monoxide has been introduced to the product molecules whereas the oxygen atom is not present in compounds **4a**–**d** which have been identified by the signals corresponding to the aromatic protons at C-1 and C-2 of the pyrrole ring. The use of ^{13}CO unequivocally



Scheme 3.

proofs this proposition (cf. Section 4). If the reaction is carried out with **2** as the starting compound, **4e** and **4f** are produced in about 20% yield and may thus be purified by column chromatography. In addition, **4a** was prepared via an alternative route and the spectroscopic properties compared with the spectra from mixtures of **3a** and **4a**. There are only a few methods reported in the literature that lead to the formation of 2,3-disubstituted pyrroles. We chose a synthetic procedure reported by Thomas et al. because of the obvious relevance of this method to the problem of understanding the formation of **4a**–**f** in the reactions we are reporting herein.[9] Scheme 3 shows that the stoichiometric reaction of **1** being η^4-coordinated to a $Fe(CO)_3$ moiety with ethyllithium and subsequent quenching of the reaction mixture with dibromoethane yields the pyrrole **4a**. It is noteworthy that the first step of this reaction sequence is typically encountered in the preparation of Fischer type carbene complexes.

We performed the synthesis of **3e** and **4e** using ^{13}CO in order to verify that the carbonyl group in **3e** and C-2 in **4e**, respectively, originate from the substrate CO. The spectroscopic data of the labeled compounds clearly demonstrate that this is indeed the case. The intensity of the signals of the corresponding carbon atoms is significantly increased while the intensity ratios of all other signals remain unchanged. In addition, typical C–C coupling constants are observed. In analogy, signals corresponding to the protons attached to neighboring carbon atoms also exhibit additional coupling in the proton NMR (cf. Section 4).

We were also able to obtain crystals suitable for X-ray structure analysis of the hydroxy-pyrrolone **E**, which formally is an oxidation product of the pyrrole **4e** (Scheme 1, Fig. 1).[10]

Nevertheless, compound **E** together with the spectroscopic evidence undoubtley proves, that the byproducts **4a**–**f** are 2,3-disubstituted pyrroles. The molecular structure of **E** shows, that the oxidation of the corresponding pyrrole **4e** led to the incorporation of two oxygen atoms into the molecule. One of them forms a carbonyl function at C1, the other oxygen atom is incorporated in a hydroxy group at C4 of the heterocycle. There are some similar reactions reported in the literature where a pyrrole was transformed to a hydroxy-pyrrolone by oxidation with O_2, but the reaction mixture had to be irradiated in the presence of a photosensitizer or radical initiators like AIBN had to be added in order to induce the reaction.[11] The bond lengths and angles of compound **E** are of expected values showing the C2–C3 bond to be a double bond as well as the C1–N1 single bond being shortened due to delocalization of electron density from the carbonyl group towards the pyrrolone nitrogen atom as expected for lactams. Compound **E** is chiral since during the oxidation reaction a new stereogenic center at C4 has been formed. Figure 1 shows the (*S*)-enantiomer of **E**. As it can be seen from the achiral space group ($Pna2_1$) and as it is expected due to achiral reaction conditions of course a racemic mixture of both enantiomers of **E** has formed.

Chatani and co-workers reported the synthesis of a tricyclic pyrrole derivative from the catalytic reaction of 5-cyclohex-1-enyl-3,4-dihydro-2*H*-pyrrole with CO and ethylene.[8] In

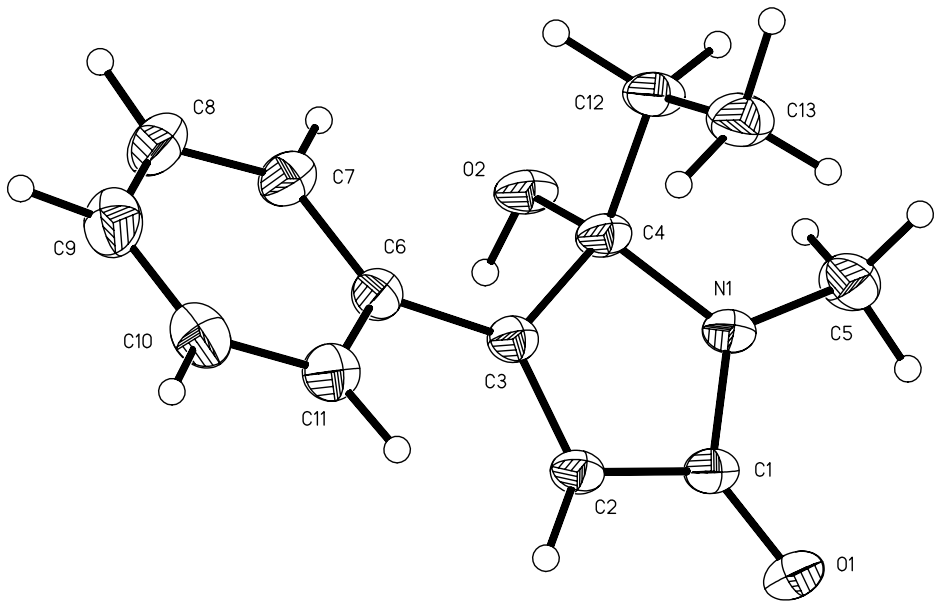


Figure 1. Molecular structure of **E**; selected bond lengths [pm] and angles [°]: C1–N1 134.5(3), C1–C2 147.1(3), C2–C3 133.6(3), C3–C4 153.1(3), C4–N1 147.4(3), C1–O1 123.5(3), C4–O2 141.7(3); N1–C1–C2 106.7(2), C1–C2–C3 110.3(2), C2–C3–C4 108.9(2), C3–C4–N1 101.2(2), C4–N1–C1 112.4(2), C1–N1–C5 124.5(2), C4–N1–C5 122.8(2), N1–C1–O1 125.0(2), C2–C1–O1 128.3(2), C2–C3–C6 127.5(2), C4–C3–C6 123.5(2), N1–C4–O2 110.0(2), N1–C4–C12 112.1(2), C3–C4–O2 112.4(2), C3–C4–C12 114.2(2).

analogy to the formation of **4a–f** the CO triple bond has been cleaved and only the carbon atom remains in the product molecules. Chatani took this result as a clear evidence for the intermediacy of a ketone in the catalytic cycle which after cyclization and elimination of water produces an tricyclic compound with a pyrrole ring in the center which then tautomerizes to give the more stable observed products. As it can be seen from the formation of **4a–f** there is no possibility to eliminate water, since unlike the reaction Chatani reported there are no further rings attached that might be dehydrogenated. In addition, we were able to proof the formation of the appropriate amount of CO_2 during the catalysis by bubbling the gaseous components of the reaction mixture through an alkaline solution of $BaCl_2$ which precipitated the stoichiometric amount of $BaCO_3$. Therefore, we are convinced that the oxygen of the former CO substrate is transferred to another CO presumably in terms of a metathesis reaction to give CO_2 and is not eliminated as H_2O.

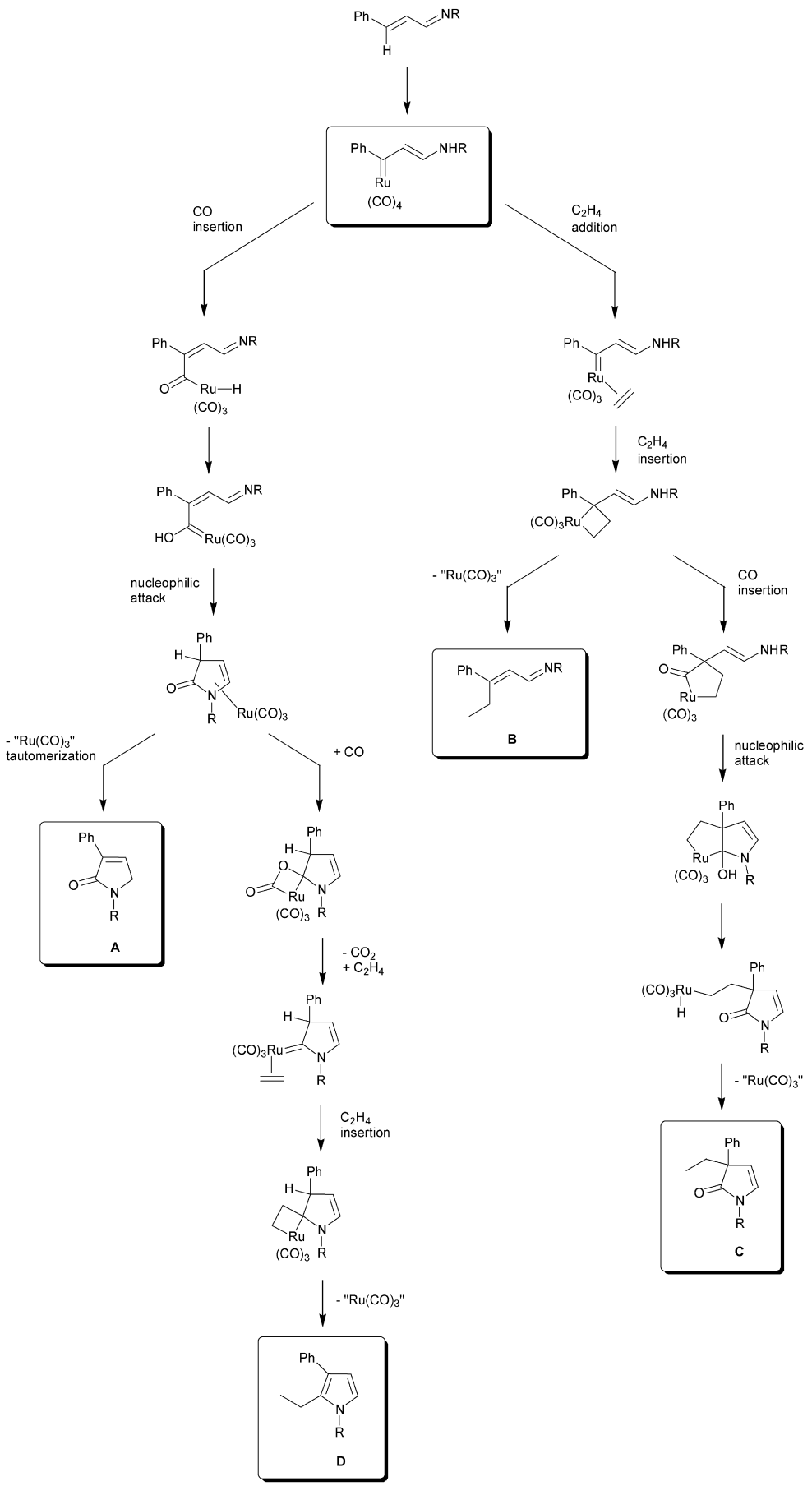
The identification of pyrroles as the side-product in any catalytic formation of pyrrolones by the subsequent reaction of carbon monoxide and an alkene with a α,β-unsaturated imine surely has to be taken into account when proposing a mechanism of these catalytic reactions. It has been established earlier, that the ruthenium induced C–H activation of imines or ketones works as a step-wise process. An equilibrium between a compound in which a Ru–C bond is already established but the hydrogen atom is still present at C-3 of the imine chain and a species in which the hydrogen atom serves as a hydride ligand at ruthenium has been proposed to be responsible for the observation that in one case the insertion of CO and in other reactions the insertion of ethylene is the preferred process.[8] DFT calculations on the C–H activation of benzaldehyde as a model for acetophenone derivatives at ruthenium catalysts also give evidence for a two-step mechanism.[12] It was also pointed out in this reference that the activation barrier between these two intermediates is just slightly above 3 kcal mol^{-1} depending on the basis set used in the calculations. We do not consider this equilibrium to be responsible for the preference of any substrate over the other at a reaction temperature of 160°C. This becomes even more convincing if the fact is taken into account that also in the presence of both CO and ethylene the alkylated products of type **B** may be formed to a considerable extend depending on the electronic properties of the imine which are determined by the organic substituent at the nitrogen atom.[7a]

Two different reaction mechanisms have been proposed for the formation of the pyrrolones **C**. One states that the reaction of CO and ethylene proceeds via the formation of an acyl group which then migrates to C-3 of the imine chain followed by a ring closing reaction. Finally a migration of the ethyl group leads to compounds **C**.[8] The other possibility involves the transfer of CO toward C-3 and after the ring closure—which would then only require a hydrogen migration—in a second catalytic cycle ethylene is inserted into a C–H bond *ortho* the pyrrolone oxygen atom.[7a] In our opinion the data available at the moment is not sufficient to prove or exclude any of these possibilities.

We are convinced that the formation of the byproducts **4a–f** during the catalysis gives important hints for the elucidation of the mechanism of the whole catalytic system. We have clearly demonstrated that during the formation of **4a–f** the C–O bond in carbon monoxide is broken and that the oxygen is transferred toward another CO to produce CO_2. Keeping in mind that the synthesis of analogous pyrroles works by the addition of alkyllithium compounds to CO ligands of an (azadiene)$Fe(CO)_3$ complex, we conclude that carbene species have to be considered as possible intermediates in the mechanism of the formation of compounds type **C** and **D**. To the best of our knowledge this has never been considered up to now. Nevertheless, this proposition would be in excellent agreement with some experimental evidence being reported in recent time. So Bergman et al. showed that the rhodium-catalyzed intramolecular insertion of a alkenyl substituent into the C–H bond of a imidazole substrate proceeds via a carbene intermediate.[13] In addition, Davies and co-workers demonstrated in a series of impressive papers demonstrated that ruthenium or rhodium carbenoids derived from the corresponding diazo compounds may very effectively induce catalytic insertion of the carbene moieties into C–H bonds even of alkanes.[14]

A proposition of a reaction mechanism involving carbene species is depicted in Scheme 4. The formation of a carbene by transferring the hydrogen atom towards the former imine nitrogen atom appears to be reasonable since we observed a hydrogen transfer reaction of this kind in stoichiometric reactions of an α-naphthylimine with $Fe_2(CO)_9$.[15] The proposition of carbene intermediates of course does not rule out an oxidative addition of the imine to a ruthenium center as the initial C–H activation step. The product distribution of the catalytic reaction depends on the fact whether CO or the alkene is inserted into the metal carbene double bond. Both CO and ethylene insertion are straightforward reactions especially when considering intermediates of the Dötz reaction which in this sense seems to be quite related to the reaction described herein.[16] If no additional co-substrate is added, the formation of compounds **A** and **B**, respectively, is easily explained by the proposed mechanism. Addition of CO or ethylene as co-substrates ends up in the formation of compounds **C** and **D**. The formation of CO_2 during the reaction pathway to the pyrroles **D** is rationalized by a metathesis like mechanism leading to a carbene species again which then is able to insert ethylene building up compounds of type **D**. It is also remarkable that the mechanism proposed in Scheme 4 requires only the transfer of hydrogen atoms which is presumably realized via hydride intermediates. Since the pyrroles **D** are side-products in the catalytic reactions the insertion of ethylene obviously is the preferred pathway.

Investigations on the mechanism of the catalytic system reported herein by additional labeling experiments, investigations of the influence of reaction conditions, solvent dependancy, or the influence of different substituents at the imine are the subject of current research in our group. In addition, we are also working on DFT calculations on the mechanism in order to find evidence for the presence of carbene species as intermediates in this reaction sequence.


CO insertion
C_2H_4 addition
C_2H_4 insertion
nucleophilic attack
- "$Ru(CO)_3$" tautomerization
+ CO
- CO_2 + C_2H_4
C_2H_4 insertion
- "$Ru(CO)_3$"
CO insertion
nucleophilic attack
- "$Ru(CO)_3$"
A
B
C
D

Scheme 4.

3. Conclusions

We were able to show that α,β-unsaturated imines react with CO and ethylene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ to give the chiral 1,3-dihydropyrrolone derivatives **3a**–**f** as the main products. In contrast to results recently published α-olefins also work very well.[8] It has also been shown, that the reaction of ethylene without additional CO being present in the reaction mixture leads to an alkylation of the imine chain (type **B**, Scheme 1), whereas the reaction with CO without ethylene leads to 1,5-dihydropyrrolone systems (type **A**, Scheme 1).[6] The implications of these findings on the reaction mechanism were discussed leading to the proposition of a mechanism with carbenes as the crucial intermediates.

4. Experimental

4.1. General

Infrared spectra were recorded on a Perkin Elmer FT-IR System 2000 using 0.2 mm KBr cuvettes. NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50.32 MHz, $CDCl_3$ as internal standard). Mass spectra were recorded on a Finnigan MAT SSQ 710 instrument. High resolution mass spectra were recorded on a Finnigan MAT 95 XL using FAB techniques.GC spectra were aquired from a gas chromatograph Chrompack CP 9000 instrument using He as the mobile phase.

X-Ray crystallographic study. The structure determination of **E** was carried out on an Enraf Nonius Kappa CCD diffractometer, crystal detector distance 25 mm using graphite monochromated Mo K_α radiation. The crystal was mounted in a stream of cold nitrogen. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods and refined by full-matrix least squares techniques against F^2 using the programs SHELXS86 and SHELXL93.[17] Computation of the structure was acomplished with the program XPMA[18] and the molecular illustration was drawn using the program XP.[19] The crystal and intensity data are given in the Supplementary Material. Additional material on the structure analyses is available from the Cambridge Crystallographic Data Centre by mentioning the deposition number CCDC-195942.

Experimental procedures. In a typical reaction a 50 mL autoclave charged with the azadiene (1 mmol), $Ru_3(CO)_{12}$ (0.03 mmol) and toluene (5 mL) was pressurized with carbon monoxide (12 bar) and ethene (8 bar) and heated at 145°C overnight. After the reaction mixture was cooled to room temperature it was transferred to a Schlenk tube and all volatile material was removed under reduced pressure. The remaining oily residue was used to determine yields and *n*/*iso* ratios of the products **3a**–**f** and **4a**–**f**, respectively, by NMR spectroscopy. Column chromatography on silica gel gave **4e** and **4f** as straw yellow oils using mixtures of light petroleum (bp 40–60°C) and $CHCl_3$ (70/30) as the eluent. Elution with ethanol yielded **3e** and **3f** as pale yellow oils. Crystals of **E** formed from pure **4e** upon standing in the freezer at −30°C after several weeks.

Applying the reaction conditions described above but using ethylene only leads to the formation of **5a** and **5b**. **3a** or **3e** are produced as byproducts from the CO present in $Ru_3(CO)_{12}$. Attempts to separate compounds **3** and **5** by destillation or by chromatography have failed so far.

4.1.1. 1,3-Dihydro-1-benzyl-3-ethyl-3-phenyl-2H-pyrrol-2-one (3a). HRMS calcd for $C_{19}H_{19}NO$ (M^+) 277.1467; found 277.1459, Δ=0.8 mmu; MS (EI): *m*/*z* (%): 277 (M^+, 73), 248 ($M^+-C_2H_5$, 43), 91 ($C_7H_7^+$, 100); IR (KBr disk, neat) [cm^{-1}]: ν=3088 w, 3062 m, 3031 m, 2968 m, 2933 m, 2877 m, 1699 s, 1607 m, 1495 m, 1455 m, 1394 m, 1359 m, 1259 m, 1077 w, 1030 w, 698 s. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.84 (t, $^3J_{HH}$=7.4 Hz, 3H, CH_3), 2.07 (q, $^3J_{HH}$=7.4 Hz, 2H, CH_2), 4.61 (m, 2H, CH_2Ph), 5.63 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH)), 6.46 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 7.20–7.53 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz) [ppm]: δ=9.75 (CH_3), 31.78 (CH_2), 46.11 (CH_2), 58.81 (C), 114.03 (CH), 127.17 (CH), 127.45 (CH), 128.10 (CH), 128.20 (CH), 128.91 (CH), 129.18 (CH), 131.40 (CH), 137.14 (C), 140.31 (C), 180.03 (C=O).

4.1.2. 1-Benzyl-2-ethyl-3-phenyl-pyrrole (4a). ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=6.31 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH), 6.61 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH).

4.1.3. 1,3-Dihydro-1-benzyl-3-propyl-3-phenyl-2*H*-pyrrol-2-one (3b, mixture of *n*/*iso* isomers 60/40). HRMS calcd for $C_{20}H_{21}NO$ (M^+) 291.1623; found 291.1628, Δ=0.5 mmu; MS (EI): *m*/*z* (%): 291 (M^+, 69), 248 ($M^+-C_3H_7$, 64), 91 ($C_7H_7^+$, 100); IR (KBr disk, neat) [cm^{-1}]: ν=3087 s, 3062 s, 3031 s, 2960 s, 2932 s, 2872 s, 1695 vs, 1607 s, 1495 s, 1454 s, 1394 s, 1358 s, 1268 m, 1078 m, 1030 m, 757 s, 698 vs. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.81 (d, $^3J_{HH}$=6.8 Hz, 1.2H, CH_3), 0.86 (d, $^3J_{HH}$=6.8 Hz, 1.2H, CH_3), 0.93 (t, $^3J_{HH}$=7.1 Hz, 1.8H, CH_3), 1.26 (m, 1.2H, CH_2), 2.04 (m, 1.2H, CH_2), 2.59 (m, 0.4H, CH), 4.62 (m, 2H, CH_2Ph), 5.67 (d, $^3J_{HH}$=5.1 Hz, 0.4H, =CH), 5.68 (d, $^3J_{HH}$=5.0 Hz, 0.6H, =CH), 6.45 (d, $^3J_{HH}$=5.0 Hz, 0.6H, =CH), 6.51 (d, $^3J_{HH}$=5.1 Hz, 0.4H, =CH), 7.20–7.68 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 50.33 MHz) [ppm]: δ=14.22 (CH_3), 17.68 (CH_3), 18.17 (CH_3), 18.19 (CH_2), 36.11 (CH), 40.67 (CH_2), 45.56 (CH_2), 45.60 (CH_2), 57.86 (C), 62.03 (C), 109.98 (CH), 113.92 (CH), 126.61 (CH), 126.91 (CH), 126.94 (CH), 127.01 (CH), 127.54 (CH), 127.58 (CH), 127.68 (CH), 127.78 (CH), 128.24 (CH), 128.39 (CH), 128.62 (CH), 128.66 (CH), 130.68 (CH), 131.71 (CH), 136.62 (C), 136.67 (C), 140.05 (C), 140.13 (C), 179.42 (C=O), 179.56 (C=O).

4.1.4. 1-Benzyl-2-propyl-3-phenyl-pyrrole (4b, *n*-isomer). ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=6.33 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH), 6.63 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH).

4.1.5. 1,3-Dihydro-1-benzyl-3-pentyl-3-phenyl-2*H*-pyrrol-2-one (3c). HRMS calcd for $C_{22}H_{25}NO$ (M^+) 319.1936; found 319.1932, Δ=0.4 mmu; MS (DCI, H_2O): *m*/*z* (%): 320 (MH^+, 100), 91 ($C_7H_7^+$, 37). IR (KBr disk, neat) [cm^{-1}]: ν=3062 w, 3029 w 2957 m, 2926 s, 2855 m, 1701 vs, 1607 m, 1495 m, 1453 m, 1394 m, 1357 m, 1261 m, 1059 w, 1030 w, 698 s. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.80 (t, $^3J_{HH}$=5.3 Hz, 3H, CH_3), 1.23 (m, 6H, $3CH_2$), 2.00 (m, 2H, CH_2), 4.58 (m, 2H, CH_2Ph), 5.63 (d,

$^3J_{HH}$=5.0 Hz, 1H, =CH), 6.43 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 7.17–7.56 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 50.32 MHz) [ppm]: δ=13.96 (CH_3), 22.45 (CH_2), 24.58 (CH_2), 31.96 (CH_2), 38.53 (CH_2), 45.73 (CH_2), 57.90 (C), 114.06 (CH), 126.69 (CH), 126.99 (CH), 127.68 (CH), 127.81 (CH), 128.48 (CH), 128.75 (CH), 130.79 (CH), 136.79 (C), 140.16 (C), 179.68 (C=O).

4.1.6. 1-Benzyl-2-pentyl-3-phenyl-pyrrole (4c, *n*-isomer). ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=6.35 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH), 6.64 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH).

4.1.7. 1,3-Dihydro-1-benzyl-3-hexyl-3-phenyl-2*H*-pyrrol-2-one (3d). HRMS calcd for $C_{23}H_{27}NO$ (M^+) 333.2091; found 333.2084, Δ=0.7 mmu; MS (EI): *m/z* (%): 333 (M^+, 40), 249 ($M^+-C_6H_{12}$, 53), 248 ($M^+-C_6H_{13}$, 48), 91 ($C_7H_7^+$, 100); IR (KBr disk, neat) [cm^{-1}]: ν=3086 w, 3062 m, 3029 m, 2954 m, 2929 m, 2857 m, 1698 s, 1605 m, 1495 m, 1454 m, 1394 m, 1357 m, 1269 m, 1077 w, 1030 w, 698 s. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) [ppm]: δ=0.83 (t, $^3J_{HH}$=6.7 Hz, 3H, CH_3), 1.19 (m, 8H, 4CH2), 1.98 (m, 2H, CH_2), 4.60 (m, 2H, CH_2Ph), 5.63 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH)), 6.42 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH)), 7.13–7.48 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz) [ppm]: δ=14.05 (CH_3), 22.52 (CH_2), 24.86 (CH_2), 29.44 (CH_2), 31.61 (CH_2), 38.54 (CH_2), 45.70 (CH_2), 57.89 (C), 114.07 (CH), 126.67 (CH), 126.99 (CH), 127.67 (CH), 127.79 (CH), 128.48 (CH), 128.74 (CH), 130.77 (CH), 136.75 (C), 140.11 (C), 179.8 (C=O).

4.1.8. 1-Benzyl-2-hexyl-3-phenyl-pyrrole (4d, *n*-isomer). ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=6.29 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH), 6.59 (d, $^3J_{HH}$=2.9 Hz, 1H, =CH).

4.1.9. 1,3-Dihydro-1-methyl-3-ethyl-3-phenyl-2H-pyrrol-2-on (3e). HRMS calcd for $C_{13}H_{15}NO$ (M^+) 201.1182; found 201.1168, Δ=1.4 mmu; MS (EI): *m/z* (%): 201 (M^+, 100), 172 ($M^+-C_2H_5$, 91); IR (KBr disk, neat) [cm^{-1}]: ν=3088 m, 3059 m, 3024 m, 2967 s, 2934 s, 2877 m, 1697 vs, 1610 m, 1495 m, 1456 m, 1386 s, 1316 s, 1266 m, 1071 m, 1055 m, 769 m, 697 s. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.82 (t, $^3J_{HH}$=7.4 Hz, 3H, CH_3), 2.02 (q, $^3J_{HH}$=7.4 Hz 2H, CH_2), 3.01 (s, 3H, NCH_3), 5.64 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 6.48 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 7.21–7.52 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 50.32 MHz) [ppm]: δ=9.12 (CH_3), 28.78 (CH_2), 31.25 (NCH_3), 58.00 (C), 113.00 (CH), 126.65 (CH), 126.82 (CH), 128.27 (CH), 132.46 (CH), 139.88 (C), 179.76 (C=O).

4.1.10. 1,3-Dihydro-1-methyl-3-ethyl-3phenyl-2H-pyrrol-2-one (3e ^{13}C labeled). HRMS calcd for $^{13}C_1C_{12}H_{15}NO$ (M^+) 202.1211; found 202.1199, Δ=1.2 mmu; MS (EI): *m/z* (%): 202 (M^+, 60), 173 ($M^+-C_2H_5$, 100); IR (KBr disk, neat) [cm^{-1}]: ν=3088 m, 3059 m, 3024 m, 2968 s, 2934 s, 2878 m, 1652 vs, 1610 m, 1495 m, 1456 m, 1384 s, 1314 s, 1266 m, 1071 m, 1052 m, 768 m, 698 s. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.80 (t, $^3J_{HH}$=7.4 Hz, 3H, CH_3), 2.00 (m, $^3J_{HC}$=4.2 Hz, $^3J_{HH}$=7.4 Hz, 2H, CH_2), 3.01 (d, $^3J_{CH}$=2.8 Hz, 3H, NCH_3), 5.63 (dd, $^3J_{HC}$=6.9 Hz, $^3J_{HH}$=4.9 Hz, 1H, =CH), 6.49 (dd, $^3J_{HC}$=5.0 Hz, $^3J_{HH}$=4.9 Hz, 1H, =CH), 7.16–7.51 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 50.32 MHz) [ppm]: δ=9.25 (CH_3), 28.96 (CH_2), 31.38 (NCH_3), 58.16, (d, $^1J_{CC}$=48 Hz, C), 113.19 (d, $^2J_{CC}$=3 Hz, CH), 126.78 (CH), 126.97 (CH), 128.40 (CH), 132.56 (d, $^2J_{CC}$=9 Hz, CH), 139.99 (C), 179.93 (^{13}C=O).

4.1.11. 1-Methyl-2-ethyl-3-phenyl-pyrrole (4e). $C_{13}H_{15}N$ GC–MS: *m/z* (%): 185 (M^+, 100), 170 (M^+-CH_3, 93); IR (KBr disk, neat) [cm^{-1}]: ν=3067 m, 3038 w, 2975 s, 2947 s, 2891 m, 1603 m, 1501 vs, 1416 m, 1352 s, 1247 s, 931 w, 762 m, 695 vs. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=1.25 (t, $^3J_{HH}$=7.5 Hz, 3H, CH_3), 2.74 (q, $^3J_{HH}$=7.4 Hz 2H, CH_2), 3.62 (s, 3H, NCH_3), 6.23 (d, $^3J_{HH}$=2.8 Hz, 1H, =CH), 6.57 (d, $^3J_{HH}$=2.8 Hz, 1H, =CH), 7.15–7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz) [ppm]: δ=14.83 (CH_3), 17.89 (CH_2), 33.74 (NCH_3), 107.31 (CH), 120.83 (C), 121.79 (CH), 125.13 (CH), 127.89 (CH), 128.27 (CH), 131.21 (C), 137.65 (C).

4.1.12. 1-Methyl-2-ethyl-3-phenyl-pyrrole (4e ^{13}C labeled). $^{13}C_1C_{13}H_{15}N$ GC MS: *m/z* (%): 186 (M^+, 100), 171 (M^+-CH_3, 93); IR (KBr disk, neat) [cm^{-1}]: ν=3059 m, 3028 w, 2966 s, 2930 s, 2873 m, 1601 m, 1503 vs, 1412 m, 1352 s, 1245 s, 929 w, 766 m, 699 vs. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=1.2 (dt, $^3J_{HC}$=4.9 Hz, $^3J_{HH}$=7.5 Hz, 3H, CH_3), 2.69 (dq, $^2J_{HC}$=6 Hz, $^3J_{HH}$= 7.5 Hz, 2H, CH_2), 3.58 (d, $^3J_{HC}$=2.5 Hz, 3H, NCH_3), 6.19 (dd, $^3J_{HC}$=5.9 Hz, $^3J_{HH}$=2.8 Hz, 1H, =CH), 6.53 (dd, $^3J_{HC}$=5.3 Hz, $^3J_{HH}$=2.8 Hz, 1H, =CH), 7.10–7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz) [ppm]: δ=14.81 (d, $^2J_{CC}$=1.5 Hz, CH_3), 17.87 (d, $^1J_{CC}$=51 Hz, CH_2), 33.73 (NCH_3), 107.31 (d, $^2J_{CC}$=2 Hz, CH), 120.81 (d, $^2J_{CC}$=7.3 Hz, CH), 121.72 (d, $^1J_{CC}$=69.8 Hz, C), 125.12 (CH), 127.88 (CH), 128.26 (CH), 131.2 (^{13}C), 137.65 (d, $^2J_{CC}$=4 Hz, C).

4.1.13. 1,5-Dihydro-1-methyl-4-phenyl-5-hydroxy-5-ethyl-pyrrol-2-one (E). $C_{13}H_{15}NO_2$ MS: *m/z* (%): 217 (M^+,8), 188 ($M^+-C_2H_5$, 100); IR (KBr pellet) [cm^{-1}]: ν=3171 br, 3054 w, 2972 m, 2935 w, 2878 w, 2831 w, 1686 vs, 1665 s, 1434 s, 1095 s, 1042 m, 857 m, 777 s, 698 m. ^{1}H NMR ($CDCl_3$, 298 K, 400 MHz) [ppm]: δ=0.48 (t, $^3J_{HH}$=7.5 Hz, 3H, CH_3), 2.01 (m, 2H, CH_2), 2.50 (s, 1H, OH), 2.88 (s, 3H, NCH_3), 6.33 (s, 1H, =CH), 7.41(m, 3H, Ph), 7.79 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz) [ppm]: δ=7.31 (CH_3), 23.06 (NCH_3), 27.19 (CH_2), 93.84 (C), 121.63 (CH), 127.38 (CH), 128.87 (CH), 130.12 (CH), 130.99 (C), 157.78 (C), 168.86 (C=O).

4.1.14. 1,3-Dihydro-1-methyl-3-propyl-3-phenyl-2*H*-pyrrol-2-one (3f, mixture of *n/iso* isomers 56/44). HRMS calcd for $C_{14}H_{17}NO$ (M^+) 215.1330; found 215.1320, Δ=1.0 mmu; MS (DI, H_2O): *m/z* (%): 215 (M^+, 58), 172 ($M^+-C_3H_7$, 100) 42 (OCN^+ 66); IR (KBr disk, neat) [cm^{-1}]: ν=3087 w, 3060 w, 3024 w, 2961 s, 2934 m, 2873 m, 1699 vs, 1610 m, 1495 m, 1446 m, 1386 s, 1307 m, 1272 m, 1080 m, 969 w, 969 w, 765 m, 698 s. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.75 (d, $^3J_{HH}$=6.8 Hz, 3H, CH_3), 0.84 (d, $^3J_{HH}$=6.8 Hz, 3H, CH_3), 0.86 (t, $^3J_{HH}$=6.6 Hz, 3H, CH_3), 1.17 (m 2H, CH_2), 1.95 (m 2H, CH_2), 2.46 (m 1H, CH), 2.96 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 5.64 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 5.66 (d,

$^3J_{HH}$=5.0 Hz, 1H, =CH), 6.46 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 6.52 (d, $^3J_{HH}$=5.0 Hz, 1H, =CH), 7.12–7.58 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 50.32 MHz) [ppm]: δ=14.25 (CH_3), 17.68 (CH_3), 18.12 (CH_3), 18.26 (CH_2), 28.81 (CH_2), 28.97 (CH), 36.18 (CH_3), 40.75 (CH_3), 57.71 (C), 61.91 (C), 109.64 (CH), 113.66 (CH), 126.70 (CH), 126.94 (CH), 126.96 (CH), 127.17 (CH), 128.26 (CH), 128.41 (CH), 132.35 (CH), 133.36 (CH), 140.20 (C), 140.25 (C), 179.86 (C=O), 180.00 (C=O).

4.1.15. 1-Methyl-2-propyl-3-phenyl-pyrrole (4f, mixture of *n/iso* isomers 80/20). $C_{14}H_{17}N$ GC–MS: *m/z* (%): 199 (M^+, 84), 184 (M^+-CH_3, 22), 170 ($M^+-C_2H_5$, 100), 42 (C_3H_6, 23); IR (KBr disk, neat) [cm^{-1}]: ν=3055 w, 3027 w, 2959 s, 2930 m, 2871 m, 1602 s, 1555 w, 1504 vs, 1466 m, 1452 m, 1355 m, 1247 m, 1086 w, 942 w, 766 s, 700 vs. ^{1}H NMR ($CDCl_3$, 298 K, 200 MHz) [ppm]: δ=0.97 (t, $^3J_{HH}$=7.3 Hz, 3H, CH_3), 1.31 (d, $^3J_{HH}$=7.2 Hz, 1.5H, $2CH_2$), 1.61 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 3.33 (h, $^3J_{HH}$=7.2 Hz, 0.25H, CH), 3.60 (s, 3H, CH_3), 3.69 (s, 0.75H, CH_3), 6.13 (d, $^3J_{HH}$=2.8 Hz, 0.25H, =CH), 6.25 (d, $^3J_{HH}$=2.8 Hz, 1H, =CH), 6.52 (d, $^3J_{HH}$=2.8 Hz, 0.25H, =CH), 6.58 (d, $^3J_{HH}$=2.8 Hz, 1H, =CH), 7.15–7.42 (m, 6.25H, Ph). ^{13}C NMR ($CDCl_3$, 298 K, 100.65 MHz, only signals arising from the n-propyl isomer are listed) [ppm]: δ=14.89 (CH_3), 23.64 (CH_2), 26.89 (CH_2), 33.81 (CH_3), 107.34 (CH), 120.79 (CH), 122.15 (C), 125.01 (CH), 127.89 (CH), 128.24 (CH), 130.00 (C), 137.78 (C).

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10. Crystal and intensity data for **E**: 183 K, colorless crystal, crystal size 0.3×0.1×0.1 mm^3, orthorhombic, a=7.2407(6), b=17.734(2), c=9.1885(6) Å, V=1179.9(2) $Å^3$, Z=4, $F(000)$=464, ρ_{calc}=1.223 g cm^{-3}, spacegroup $Pna2_1$, abs. coeff. 0.083 mm^{-1}, θ-limit 2.50–27.52°, ϕ- and ω-scan, 6291 refl. measured, 2646 independent refl., R_{int}=0.0607, 1903 obs. refl. $F_o^2>2(F_o^2)$, 205 parameters, GOOF=1.108, R_1=0.0582, wR_2=0.0861, final diff. map electron density [e$Å^{-3}$] 0.179. For full crystallographic data of **E** cf. Supplementary Material.
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