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One-pot synthesis of γ-lactams in a reaction cascade from α,β-unsaturated imines, CO and ethylene catalysed by $Ru_3(CO)_{12}$†

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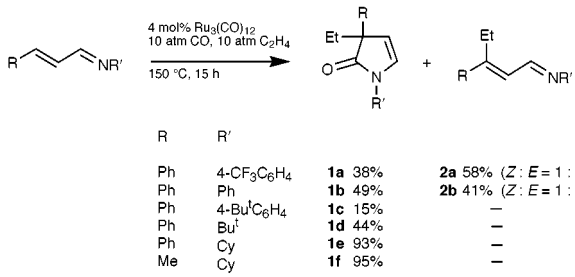
The formation of 1,3-dihydropyrrol-2-one derivatives in moderate to excellent yields may be achieved by sequential insertion of CO and ethylene into C–H bonds of 1-azadienes catalysed by $Ru_3(CO)_{12}$; thus two new C–C bonds and a new center of asymmetry at C3 are produced *via* an intramolecular aldol condensation-like cyclization.

C–H activation reactions induced by transition metal compounds have aroused considerable interest as models for the initial steps of catalytic transformations of the ligands, *e.g.* in C–C coupling reactions. Thus in the past years inter- as well as intramolecular C–H activation reactions have been thoroughly reviewed.[1] In our recent work we investigated the reaction of aromatic imines towards $Fe_2(CO)_9$ which proceeds *via* C–H activation steps and subsequent intramolecular hydrogen migration reactions towards suitable acceptor sites in the ligand, producing di- or trinuclear iron carbonyl complexes.[2] On the other hand, it has been shown previously that aromatic imines may react with CO and/or a wide variety of olefins in the presence of catalytic amounts of $Ru_3(CO)_{12}$ to give the respective substitution products.[3] The C–C coupling reaction selectively takes place in the position *ortho* with respect to the imine substituent, and thus similar C–H activation steps to the ones which we observed in the stoichiometric reactions of the same ligands with $Fe_2(CO)_9$ may well be the initial steps of these catalytic reactions. The reaction of acyclic α,β-unsaturated imines with $Ru_3(CO)_{12}$ yields ruthenium carbonyl complexes, the formation of which also includes C–H activation steps, whereas treatment with $Fe_2(CO)_9$ produces (η^4-azadiene)$Fe(CO)_3$ complexes.[4,5]

Here we report the catalytic synthesis of γ-lactams, namely 1,3-dihydropyrrol-2-one derivatives, from α,β-unsaturated imines, CO and ethylene (Scheme 1).[6] From Scheme 1 it can be seen that variation of the organic substituent at nitrogen leads to different product distributions. Obviously CO and ethylene compete for the azadiene. In the case of the least electron donating organic moieties at the imine nitrogen, in addition to the pyrrol-2-one derivatives **1a** and **1b** two other compounds, **2a** and **2b** respectively, are formed in which one molecule of ethylene has inserted into the C–H bond at the β-carbon atom of the 1-azadiene. If R′ is *p*-$CF_3C_6H_4$ then **2a** is the main product



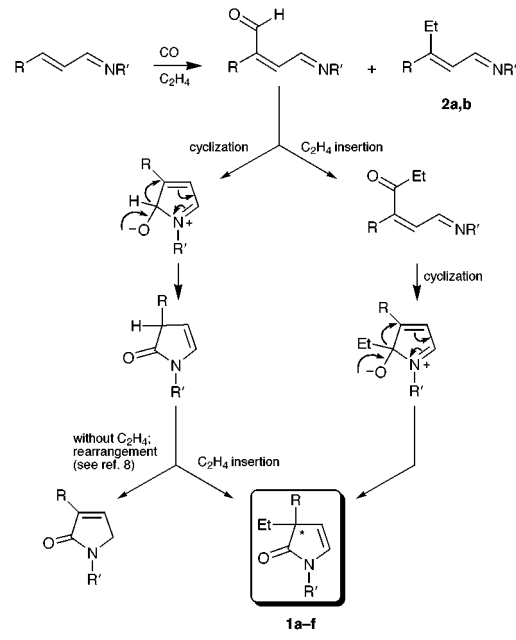
R	R′		
Ph	4-$CF_3C_6H_4$	**1a** 38%	**2a** 58% (*Z* : *E* = 1 : 2.5)
Ph	Ph	**1b** 49%	**2b** 41% (*Z* : *E* = 1 : 1)
Ph	4-$Bu^tC_6H_4$	**1c** 15%	–
Ph	Bu^t	**1d** 44%	–
Ph	Cy	**1e** 93%	–
Me	Cy	**1f** 95%	–

Scheme 1

† Experimental and spectral data for **1a–f** and **2a**,**b** are available from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/1457/

of the reaction. *Z* and *E* isomers are formed as can be demonstrated by IR and NMR spectroscopy. If the imine nitrogen and thus the whole π-system of the azadiene is nucleophilic enough the 1,3-dihydropyrrol-2-one derivatives **1c–f** are formed selectively. In these cases CO is obviously preferred for the first catalytic C–C coupling reaction. In the case of **1c** and **1d** the yields are quite low, presumably because of the higher steric demands of the *tert*-butyl groups. If the organic substituent at nitrogen is cyclohexyl the reaction produces **1e** and **1f** in nearly quantitative yield, so the steric as well as the electronic properties of the azadiene in those cases are ideal. Whether the starting material was cinnamaldehyde or croton aldehyde has no significant effect on the product distribution or the yield.

The formation of **1a–f** obviously proceeds *via* the catalytic incorporation of CO into the C–H bond at the β-carbon atom of the azadiene, followed by a nucleophilic attack of the imine nitrogen lone pair towards the aldehyde carbon closing the pyrrole ring. Compounds **1a–f** are then produced by a second catalytic C–C bond formation reaction by inserting one molecule of ethylene into the C–H bond *ortho* to the new carbonyl group in the 2-position of the pyrrole system (Scheme 2). By this reaction also a new chiral carbon atom at C3 is formed. This reaction sequence seems to us to be more reasonable than the other possibility, which would be for the intramolecular aldol condensation-like cyclization reaction to take place after the insertion of ethylene. If this were the reaction mechanism an ethyl group would have to be transferred from the carbonyl carbon atom to C3 of the pyrrolone system (Scheme 2). In addition, the reaction pathway we propose corresponds very well to the literature, in which C–C coupling



Scheme 2

reactions of olefins in the position *ortho* with respect to carbonyl groups have been reported using acetophenone derivatives as the starting material.[7] Parallel to our work Murai and coworkers very recently published a very similar reaction of azadienes with CO to yield the isomeric 1,5-dihydropyrrol-2-one derivatives.[8] They proposed a reaction mechanism in which as an intermediate a 1,3-dihydropyrrole-2-one derivative is formed which then isomerises to give the thermodynamically more stable 1,5-dihydropyrrol-2-one derivative (Scheme 2). Obviously in our reaction the second catalytic reaction of the pyrrol-2-one intermediate with ethylene to give **1a–f** is much faster than the rearrangement reaction, which we never observed. So this reaction offers the opportunity of selectively synthesising the thermodynamically less stable 1,3-dihydropyrrol-2-ones and in the same reaction building up a new center of chirality. Since γ-lactams are very interesting compounds with respect to pharmaceutical purposes,[9] the selective synthesis of 1,5-dihydropyrrol-2-one derivatives as reported by Murai as well as the synthesis of 1,3-dihydropyrrol-2-one derivatives we describe herein may both be useful synthetic strategies to achieve the selective synthesis of both isomers.

In the ^{1}H-NMR spectra of **1a–f** the most significant features are the two pyrrole hydrogen atoms at C4 and C5 which both give rise to doublets by coupling with each other in the range of δ 5.5 to 5.9 and δ 6.5 to 7.1, and the multiplet structures representing the CH_2 protons of the ethyl group attached to the new chiral center at C3 which clearly indicate that these two hydrogen atoms are diastereotopic. In the crystal structure determination of **1f** both enantiomers are observed to be statistically disordered in the lattice.[10] The bond lengths and angles show the values expected for a 1,3-dihydropyrrol-2-one. In addition, a quite strong intramolecular hydrogen bond is observed between the carbonyl oxygen atom and the methine hydrogen atom of the cyclohexyl substituent, which may be responsible for the downfield shift of the resonance of this hydrogen atom in the ^{1}H-NMR spectra of **1e** and **1f** at about δ 3.9 and the observation of five different CH_2 resonances for the cyclohexyl substituent in the ^{13}C-NMR spectrum of both compounds.

In conclusion we may say that the procedure described above allows the selective synthesis of 1,3-dihydropyrrol-2-one derivatives in a one-step synthesis. These compounds are produced *via* a reaction mechanism including two catalytic C–C bond formation reactions as well as the formation of a new center of chirality. Investigations on the reactivity of chiral azadienes in order to achieve diastereoselective reactions or reactions using catalysts derived from $Ru_3(CO)_{12}$ by substituting one or more CO groups by chiral ligands to achieve enantioselective reactions are under way and we will report these in due course.

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Notes and references

1 (*a*) M. Brookhart and M. L. H. Green, *J. Organomet. Chem.*, 1983, **250**, 395; (*b*) E. C. Constable, *Polyhedron*, 1984, **3**, 1037; (*c*) J. Halpern, *Inorg. Chim. Acta*, 1985, **100**, 41; (*d*) R. H. Crabtree, *Chem. Rev.*, 1985, **85**, 245; (*e*) A. D. Ryabov, *Chem. Rev.*, 1990, **90**, 403; (*f*) *Selective Hydrocarbon Activation*, ed. J. A. Davies, VCH, Weinheim 1990; (*g*) B. A. Arndtsen, R. G. Bergman, T. A. Mobley and T. H. Petersen, *Acc. Chem. Res.*, 1995, **28**, 154; (*h*) R. H. Crabtree, *Chem. Rev.*, 1995, **95**, 987; (*i*) Y. Fujiwara, K. Takagi and Y. Taniguchi, *Synlett*, 1996, 591.

2 (*a*) W. Imhof, *J. Organomet. Chem.*, 1997, **533**, 31; (*b*) W. Imhof, *J. Organomet. Chem.*, 1997, **541**, 109; (*c*) W. Imhof, A. Göbel, D. Ohlmann, J. Flemming and H. Fritzsche, *J. Organomet. Chem.*, in the press; (*d*) W. Imhof, *Organometallics*, in the press.

3 (*a*) F. Kakiuchi, F. Yamauchi, N. Chatani and S. Murai, *Chem. Lett.*, 1996, 111; (*b*) T. Fukuyama, N. Chatani, F. Kakiuchi and S. Murai, *J. Org. Chem.*, 1997, **62**, 5647; (*c*) T. Fukuyama, N. Chatani, J. Tatsumi, F. Kakiuchi and S. Murai, *J. Am. Chem. Soc.*, 1998, **120**, 11 522.

4 (*a*) C. J. Elsevier, W. P. Mul and K. Vrieze, *Inorg. Chim. Acta*, 1992, **198–200**, 689 and literature cited therein; (*b*) W. P. Mul, C. J. Elsevier, L. H. Polm, K. Vrieze, M. C. Zoutberg, D. Heijdenrijk and C. H. Stam, *Organometallics*, 1991, **10**, 2247; (*c*) W. Imhof, *J. Chem. Soc., Dalton Trans.*, 1996, 1429.

5 W. Imhof, A. Göbel, D. Braga, P. De Leonardis and E. Tedesco, *Organometallics*, 1999, **18**, 736.

6 All compounds are characterised by GC, GC-MS, GC-IR and ^{1}H-NMR. In addition, **1e** and **1f** were characterised by ^{13}C-NMR, **1f** also by elemental analysis and X-ray structure determination. See note †.

7 M. Sonoda, F. Kakiuchi, N. Chatani and S. Murai, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 3117.

8 T. Morimoto, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 1758.

9 (*a*) E. R. Gamzu, T. M. Hoover and S. I. Gracon, *Drug. Dev. Rev.*, 1989, **18**, 177; (*b*) S. Bertozzi and P. Salvadori, *Synth. Commun.*, 1996, **26**, 2659.

10 *Crystal data* for $C_{13}H_{21}NO$ **1f**: M = 207.31, orthorhombic, a = 20.476(1), b = 22.094(1), c = 11.4430(4) Å, V = 5176.8(5) Å^3, space group *Fdd*2. Z = 16, 1376 reflections measured, 1376 unique, 1253 observed reflections ($F_o^2 > 2\sigma(F_o^2)$), $R1$ = 0.0562, $wR2$ = 0.1395, GooF = 1.081, largest diff. peak 0.129 e Å^{-3}. CCDC 182/1302. See http://www.rsc.org/suppdata/cc/1999/1457/ for crystallographic data in .cif format.

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