One-pot ruthenium catalyzed synthesis of spiro[pyrrolidin-2-one] derivatives by a [2 + 2 + 1] cycloaddition of ketimines, carbon monoxide and ethylene†‡

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The reaction of chiral *N*,*N*′-bis(aryl)tetrahydropyrrolo-[2,1-*c*][1,4]oxazine-3,4-diylidenediamines with carbon monoxide and ethylene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ leads to the formation of spiro-lactams by a formal [2 + 2 + 1] cycloaddition reaction, whereas the imine double bond next to the oxazine nitrogen atom remains unreacted; the same spiro-lactams may be synthesized if iron carbonyl complexes of the *N*,*N*′-bis(aryl)tetrahydropyrrolo-[2,1-*c*][1,4]oxazine-3,4-diylidenediamines are introduced as the starting compounds.

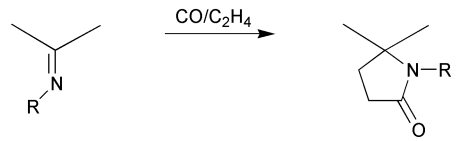
Spiro-lactams have been described as the key intermediates in the total synthesis of several natural products[1] *e.g.* cephalotaxine or aldosterone antagonists, where the lactam ring system is attached to the D-ring of a steroid core.[2] Spiro[pyrrolidine-3,3′-indole] and spiro[pyrrolidine-3,3′-oxindole] derivatives are known as natural products with high cytostatic potential.[3] On the other hand, Murai *et al.* have synthesized functionalized γ-butyrolactones by a formal [2 + 2 + 1] cycloaddition reaction from a ketone, ethylene and CO.[4] It has also been described that the reaction of CO and/or olefins with unsaturated imines catalyzed by $Ru_3(CO)_{12}$ proceeds *via* C–H activation steps in the β-position with respect to the C–N double bond, followed by insertion reactions of CO and the olefins into the carbon metal bond. These reactions lead to functionalized imines or in some cases *via* intramolecular cyclization reactions to dihydropyrrol-2-one or dihydrobenzoisoindol-1-one derivatives, respectively.[5] Similar reactions have also been reported starting from N-heterocyclic compounds or aromatic ketones, respectively.[6]

If the cycloaddition reaction described by Murai and coworkers were also to work in the case of ketimines as starting compounds, one would formally end up with spiro-lactams if the organic substituents R and R′ of the ketimines formed a cyclic moiety (Scheme 1).

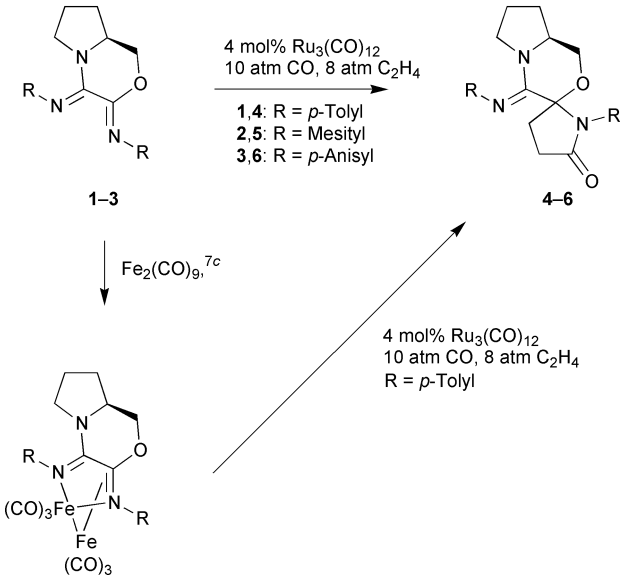
In addition, it would be of interest to perform this reaction with chiral ketimines in order to achieve stereoselective reactions, which in most cases are necessary in the synthesis of natural products. Therefore we chose the chiral *N*,*N*′-bis(aryl)-tetrahydropyrrolo[2,1-*c*][1,4]oxazine-3,4-diylidenediamines, which may be easily prepared from *N*,*N*′-bis(aryl)oxalimidoyl chlorides, and *S*-prolinol[7] as the starting compounds. In our earlier work we were able to show that these ligands react with $Fe_2(CO)_9$ to produce dinuclear iron carbonyl complexes in which the $Fe_2(CO)_6$ moiety is coordinated to the diimine ligand in an unsymmetrical fashion.[7c] One of the iron atoms is coordinated by both imine nitrogen atoms *via* their lone pairs whereas the second metal is coordinating the imine double bond next to the oxazine oxygen atom in side-on fashion (Scheme 2). This unsymmetrical coordination mode of a 1,4-diazadiene ligand has also been described in the literature.[8]

Scheme 2 shows the reaction of the diimine ligands **1**–**3** with CO and ethylene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ to produce the spiro-lactams **4**–**6**. This reaction may be described as a formal [2 + 2 + 1] cycloaddition reaction of a ketimine with CO and ethylene to give a pyrrolidin-2-one system. Remarkably, only one of the imine moieties of the starting compounds does react. The cycloaddition only takes place at the C–N double bond neighboring the oxazine oxygen atom. This imine moiety is also the one that coordinates the second iron atom in a side-on fashion if **1**–**3** are reacted with stoichiometric amounts of $Fe_2(CO)_9$ (Scheme 2).[7c] So the reaction discriminates between the two imine subunits of the starting material whereas in principle both should be reactive.

Crystallization from toluene produced crystals of one of the diastereomers of **4** suitable for X-ray structure analysis.[9] The result is depicted in Fig. 1. The molecular structure shows the tetrahydropyrrolo[2,1-*c*][1,4]oxazine system which was already present in **1**. Now one of the former imine carbon atoms is the spiro-atom to which the pyrrolidone ring formed by the cycloaddition is attached (C6). The bonds from the pyrrolidone nitrogen atom (N2) towards the surrounding carbon atoms are in the single bond size-range with the bond to the carbonyl carbon atom (C10) being slightly shorter due to partial delocalization of π-electron density from the C–O double bond to the nitrogen. The bonds of C8 and C9 which represent the former ethylene molecule are also clearly single bonds. As expected, the planes through the oxazine and the pyrrolidone ring systems show a



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b0/b008290m/

‡ Dedicated to Prof. Ernst-Gottfried Jäger on the occasion of his 65th birthday.

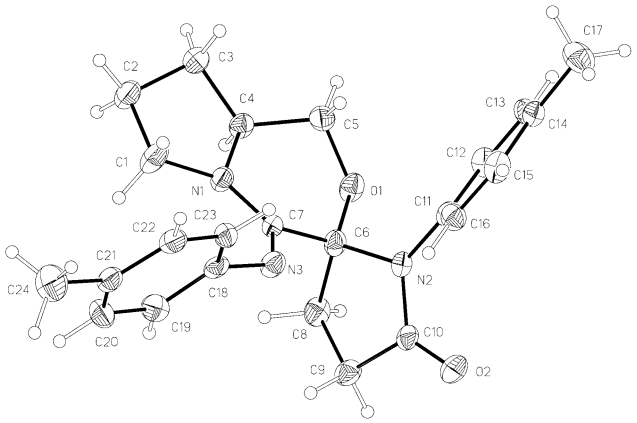


Fig. 1

nearly perpendicular arrangement. The second imine function of **1** did not react with CO and/or ethylene and thus the bond N3–C7 still shows a value typical for a double bond. **4** crystallizes in the chiral space group $P2_12_12_1$, so that in this crystal only the stereoisomer shown in Fig. 1 is present in which the *S*-configuration of prolinol still is preserved and the spiro-carbon atom (C6) shows a *R*-configuration.

NMR spectra of the crude reaction mixture of **4** show the presence of two isomers in a 1.5 : 1 ratio. The HMBC spectrum of the reaction mixture clearly proves that these isomers are diastereomers corresponding to the two different configurations possible at the new stereogenic center at C6. The spectra only show crosspeaks between the two different spiro-carbon atoms and the corresponding methylene protons at C5 (Fig. 1). If the second isomer was a regioisomer in which the reaction had taken place at the imine double bond next to the oxazine nitrogen atom, one would also expect to observe crosspeaks between the methylene moiety at C5 and the imine carbon atom next to the oxazine oxygen atom which then would have been preserved.

In the case of **4** the diastereomers may be separated by crystallization. NMR spectra of the crystals that were characterized also by X-ray diffraction show only one set of signals corresponding to the diastereomer which is the major component of the crude reaction mixture. The carbon resonances of the tetrahydropyrrolo[2,1-*c*][1,4]oxazine moiety do not differ very much from the corresponding signals in **1**,[6] with the exception, of course, of C6, which now is observed at δ = 94.3. The resonances of C8 and C9 give rise to signals at δ = 29.6 and 35.6, respectively.

The resonances of the second diastereomer show nearly identical chemical shifts compared to the one shown in Fig. 1. The most significant differences are the signals corresponding to the spiro-atom itself, which now is observed at δ = 95.5 and the resonances of the carbon atoms of C8 and C9, which are observed at δ = 35.5 and 21.3, respectively. The same observations can be made in the NMR spectra of the mixtures of diastereomers of **5** and **6**. For all compounds **4**–**6** the diastereomer which shows the signal of the spiro-carbon atom at higher field is the major component of the product mixture.

As mentioned previously, the reaction of **1**–**3** with $Fe_2(CO)_9$ yields dinuclear iron carbonyl complexes in which the two imine subunits are differently coordinated to the organometallic fragments (Scheme 1).[7c] In these complexes the imine double bond that is next to the oxazine oxygen atom is the one that is coordinated to both iron centers, whereas the other imine subunit is only bound to one $Fe(CO)_3$ moiety. So we tried to react the complex derived from **1** with CO and ethylene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ under the same conditions as for the free ligands **1**–**3**. This reaction results in the quantitative formation of **4** also as a mixture of diastereomers in the same ratio as if the starting compound was **1**. This shows that the unsymmetrical coordination mode in the dinuclear iron complexes may well be of some relevance in the catalytic cycle leading to the spiro-lactams **4**–**6** and may also be responsible for the observed regioselectivity.

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9 *Crystal and intensity data for* **4**: 183 K, yellow crystal, crystal size 0.3 × 0.1 × 0.02 mm, orthorhombic, a = 8.2350(4), b = 11.1009(6), c = 23.009(2) Å, V = 2103.4(2) Å^3, Z = 4, F(000) = 832, ρ_{calc} = 1.230 g cm^{-3}, spacegroup $P2_12_12_1$, abs. coeff. 0.079 mm^{-1}, θ limit 3.55–27.51°, ϕ- and ω-scan, 11462 refl. measured, 4734 independent refl., 3079 obs. refl. $F_o^2 > 2\sigma(F_o^2)$, 268 parameters, GOF = 1.069, R_1 = 0.0830, wR_2 = 0.1507, final diff. map electron density [e Å^{-3}] 0.214. CCDC 151894. See http://www.rsc.org/suppdata/cc/b0/b008290m/ for crystallographic files in .cif format.