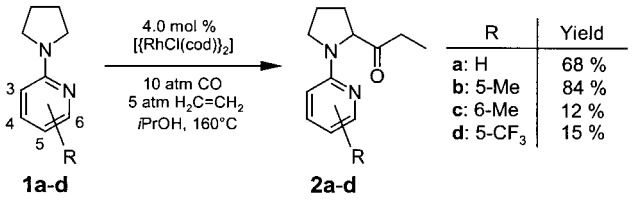
Catalytic C–H Activation of sp^3 C–H Bonds in α-Position to a Nitrogen Atom—Two New Approaches**

Sven Doye*

During the last 10 years, the activation of unreactive bonds by transition metal complexes has developed into a new and independent field of organic chemistry.[1] Whereas initial investigations centered on stoichiometric transformations, the major interest is now focused on the development of procedures for the catalytic activation of unreactive bonds. Among such processes, C–C bond forming reactions involving selective activation of C–H bonds, which cannot be cleaved easily under classical reaction conditions, are particularly challenging. However, in contrast to corresponding reactions of sp^2 C–H bonds only a few transformations that involve the cleavage of sp^3 C–H bonds have been reported. Such transformations are especially interesting when the C–H bond that undergoes reaction is in α-position to nitrogen or oxygen atoms,[2] because important building blocks for organic synthesis can be formed in a single step using this approach.

Recently, two new and promising catalytic procedures for the catalytic activation of sp^3 C–H bonds adjacent to a nitrogen atom have been published by Murai et al.[3] and Ishii et al.[4]

The procedure developed by Murai et al.[3] offers the possibility of [{RhCl(cod)}$_2$]-catalyzed, regioselective carbonylation of several tertiary amines in the α-position to the nitrogen atom. Unfortunately, the optimized reaction conditions (4.0 mol % [{RhCl(cod)}$_2$], 2-propanol, 160 °C, 10 atm CO, 5 atm ethylene, 40–60 h) are relativly harsh (Scheme 1).



R	Yield
a: H	68 %
b: 5-Me	84 %
c: 6-Me	12 %
d: 5-CF_3	15 %

Scheme 1. Carbonylation of various pyrrolidine derivatives developed by Murai et al.[3]

[*] Dr. S. Doye
Institut für Organische Chemie
Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-30-11
E-mail: sven.doye@oci.uni-hannover.de

[**] I thank Professor E. Winterfeldt for his generous support of my research.

However, the fact that the formed products possess significant similarity to α-amino acids is noteworthy to mention.

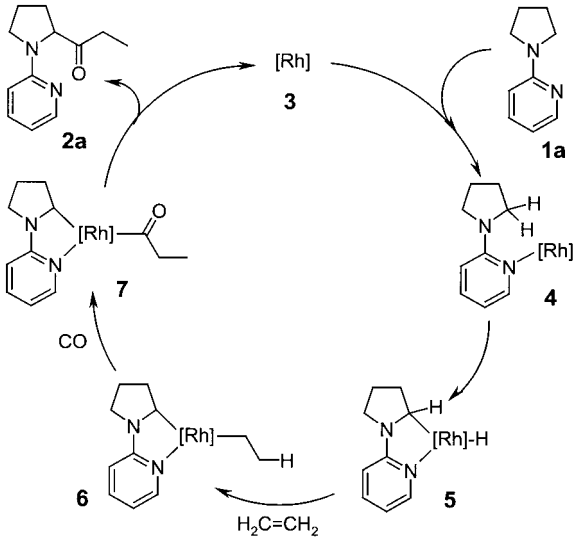
In addition, it is remarkable that the "correct" rhodium complex as catalyst and the solvent (2-propanol) are important for a successful reaction. Previous studies by the same group showed that under comparable reaction conditions the carbonylation of piperazine derivatives performed in toluene in the presence of a catalytic amount of [$Rh_4(CO)_{12}$] takes place via an initial dehydrogenation to tetrahydropyrazine derivatives. Subsequently, the activation of a resulting sp^2 C–H bond leads to the carbonylated and finally isolated tetrahydropyrazine products.[5]

As in the case of known [$Ru_3(CO)_{12}$]-catalyzed carbonylation reactions[6] or the procedure developed in 1998 by Jun et al. for the catalytic alkylation of benzylamines[2b] it is essential for the developed reaction to proceed that a directing group, for example a suitable pyridine substituent, is located close to the reaction center in the substrate.

A detailed investigation of the behavior of several pyrrolidine derivatives (**1a–d**) under the reaction conditions showed that the electronic and steric properties of the directing pyridine substituent, which is in this case directly bound to the amine nitrogen atom, has a significant influence on the reactivity of the substrate. The reaction of **1b**, which bears a relatively electron-rich 5-methylpyridine substituent, takes place with a much higher yield than reactions of substrates possessing a sterically more demanding 6-methylpyridine (**1c**) or an electron-deficient 5-trifluoromethylpyridine (**1d**) substituent (Scheme 1). This finding as well as the fact that the carbonylation takes place at a C–H bond located next to the pyridine substituent, with no other regioisomeric products being observed, leads to the assumption that a coordination of the catalytically active rhodium species to the nitrogen atom of the pyridine ring is an essential step in the catalytic cycle. A corresponding mechanism, which has not been verified by experimental data yet but was proposed by the authors, is shown in Scheme 2.

In this mechanism, the catalytically active rhodium species **3** is initially coordinated to the pyridine nitrogen atom to give complex **4**. The rhodium center in **4** can insert into the neighboring C–H bond that is located in an α-position to the amine nitrogen. The insertion of ethylene into the Rh–H bond in **5** (to give **6**) followed by CO insertion provides access to the rhodium acyl complex **7**. Reductive elimination of the

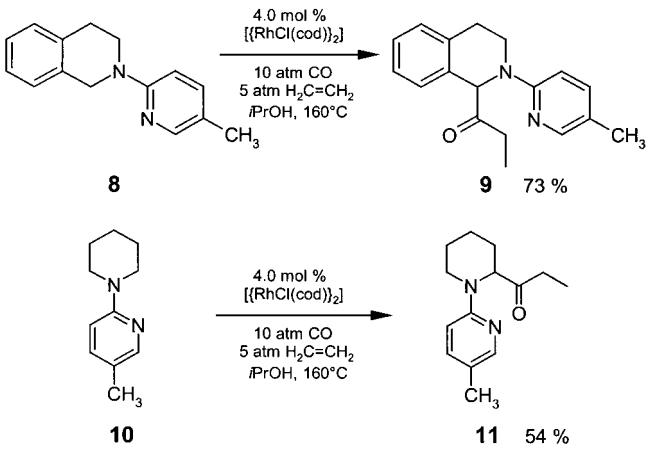
  1433-7851/01/4018-3351 $ 17.50+.50/0



Scheme 2. Proposed mechanism for the [{RhCl(cod)}$_2$]-catalyzed carbonylation of amines.

product **2a** finally leads to the regeneration of the catalytically active species **3**.

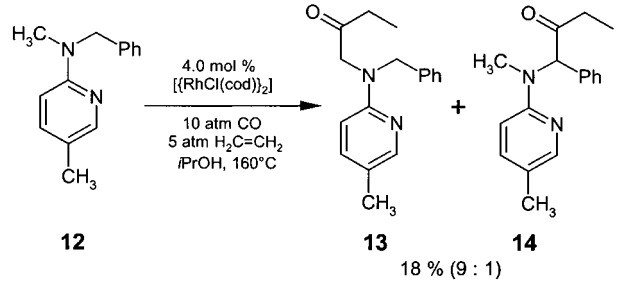
Experiments to transfer the rhodium-catalyzed carbonylation to cyclic amines other than pyrroldine derivatives were only successful for compounds **8** and **10**, both of which bear the well-suited 5-methylpyridine substituent. Interestingly, the carbonylation reaction of the unsymmetrical amine **8** takes place at the benzylic position to give **9** exclusively (Scheme 3).



Scheme 3. [{RhCl(cod)}$_2$]-catalyzed carbonylation of cyclic amines.

Finally, the authors also present the first successful example for the carbonylation of an acyclic amine. In contrast to the mentioned reaction of **8**, the acyclic amine **12** is converted into a mixture of two regioisomers (Scheme 4), of which that carbonylated at the benzylic position is the minor product (**14**). Furthermore, the obtained yield (18%) is lower than that for reactions of cyclic amines.

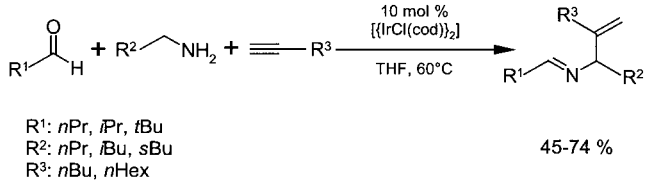
Given the scope and limitations of the described carbonylation procedure, Murai's newly developed process still requires significant work before it can be considered as a widely applicable synthetic method. Nevertheless, the results



Scheme 4. [{RhCl(cod)}$_2$]-catalyzed carbonylation of an acyclic amine.

presented will most probably be the starting point for extensive optimization studies which may finally result in the successful development of a highly elegant and maybe enantioselective method for the synthesis of α-functionalized amines.

The second study published later by Ishii et al.[4] describes a three-component coupling reaction of aldehydes, primary amines, and terminal alkynes in the presence of a catalytic amount of [{IrCl(cod)}$_2$] (10 mol%) to give allylic imines under mild reaction conditions (THF, 60°C) (Scheme 5).



Scheme 5. Three-component coupling reaction of amines, aldehydes, and alkynes developed by Ishii et al.[4]

The authors found that the reaction is initiated by the reaction of the aldehyde with the amine to give the corresponding imine, followed by coordination of the catalytically active Ir^I species to the imine-nitrogen atom. Then, the Ir^I species inserts into the C–H bond adjacent to the nitrogen atom to give an Ir^{III}–H complex, which can subsequently insert the terminal alkyne and reductively eliminate the product.

Impressively, sterically less demanding aldehyds (1-butanal) as well as sterically demanding aldehydes (2-methylpropanal, 2,2-dimethylpropanal) can be coupled with good yields. Furthermore, *n*-alkyl- as well as *sec*-alkylamines can be employed in the reaction successfully, whereas *tert*-butylamine was found to be a poor substrate. In the case of alkynes, the reaction is limited to the use of terminal alkynes, since internal alkynes do not react.

In summary, both developed procedures clearly demonstrate that a selective, catalytic activation of sp^3 C–H bonds in α-position to a nitrogen atom is also possible by the use of rhodium and iridium catalysts. Therefore, the presented results impressively expand this relatively new and elegant synthetic approach towards the synthesis of complex amines. However, we will have to wait for the results of future optimization studies to find out whether the presented new procedures can be sufficiently optimized for a broad application in research and the industrial production of amine derivatives.

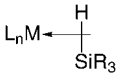
  1433-7851/01/4018-3352 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 18

[1] a) *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, **1999**; b) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808 – 1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698 – 1712; c) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879 – 2932.
[2] a) Y. Lin, D. Ma, X. Lu, *Tetrahedron Lett.* **1987**, *28*, 3249 – 3252; b) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405 – 1406.
[3] N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882 – 12883.
[4] S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602 – 2604; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534 – 2536.
[5] a) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, *16*, 3615 – 3622; b) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Tetrahedron Lett.* **1997**, *38*, 7565 – 7568.
[6] a) N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Org. Chem.* **1997**, *62*, 2604 – 2610; b) Y. Ie, N. Chatani, T. Ogo, D. R. Marshall, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Org. Chem.* **2000**, *65*, 1475 – 1488.

Going Beyond σ Complexation: Nonclassical Interligand Interactions of Silyl Groups with Two and More Hydrides**

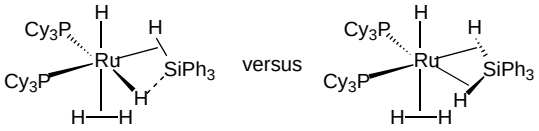
Georgii I. Nikonov*

Transition metal silane σ complexes (**1**) are a well-documented class of nonclassical compounds in which the Si–H bond is considered to be at an intermediate stage in the oxidative addition to a metal center and a direct interaction between the silyl and hydride ligands is present.[1] The question as to whether the silyl ligand can interact simultaneously with more than one hydride has recently received a positive answer.



1

In 1990 the possibility that a silyl group could interact simultaneously with two hydride ligands was proposed for the first time by Crabtree and colleagues to describe the structure of the compound $[(PPh_3)_2ReH_6(SiPh_3)]$.[2] The presence of a $[H_2SiPh_3]^-$ ligand was postulated but the experimental evidence was scarce. Further progress in the identification of multicenter Si – H interactions came from the studies of other polyhydride diphosphane systems. The ruthenium fragment $[(PCy_3)_2RuH_2]$ (Cy = cyclohexyl) was shown to stabilize a variety of dihydrogen and silane σ complexes,[3] a useful entry into this chemistry being Chaudret's bis(dihydrogen) complex $[(PCy_3)_2Ru(H_2)_2H_2]$ (**2**).[4] The research group of Sabo-Etiennie and Chaudret showed that a reaction of **2** with $HSiPh_3$ affords the compound $[(\eta^2\text{-}H_2)(PCy_3)_2RuH_2(\eta^2\text{-}HSiPh_3)]$ (**3**)[5] which was originally formulated as a mixed dihydrogen and silane σ complex. However, its surprising structural features suggest an unusual type of interligand interaction. Firstly, in this complex the very bulky phosphane ligands unexpectedly occupy *cis* rather than the anticipated *trans* positions. Secondly, although the phosphanes lie *trans* to two supposedly different ligands, namely η^2-$HSiPh_3$ and hydride, the observed Ru–P bond lengths do not differ by very much (2.392(2) and 2.406(2) Å). Moreover, density functional theory (DFT) calculations on a model complex with much less sterically demanding phosphanes PH_3 ("$[(\eta^2\text{-}H_2)(PH_3)_2RuH_2(\eta^2\text{-}HSiPh_3)]$") show that the Ru–P bond lengths are also almost identical (2.370 and 2.367 Å), which suggests that an electronic factor is in operation.[5] Finally, the X-ray and DFT-calculated structures of **3** show that the silicon



3 **4**

atom is bound almost equivalently to two hydride units (1.72(3) and 1.83(3) Å observed versus 1.946 and 2.071 Å calculated values) rather than one hydride as the silane σ-complexation model would imply; the distance to the third hydride is much longer (X-ray: 2.40(3) Å, DFT: 2.116 Å). Therefore, **3** contains no more than one classical hydride, the other two are involved in nonclassical bonding to the silyl.

The unusual structural features of **3** were originally attributed to weak bonding between the hydride and silicon ligands which was regarded as "attractive nonbonded interactions".[5] While the nature of these interactions was not clearly defined, several bonding schemes were possible. For example, this unusual bonding between the silyl and hydride groups can be described in terms of an interaction between the fragment $[(PCy_3)_2RuH_2]^+$ and the dihydrosilyl ion $[H_2SiPh_3]^-$ (Figure 1), which leads to the nonclassical complex $[(\eta^2\text{-}H_2)(PCy_3)_2RuH(\eta^3\text{-}H_2SiPh_3)]$ (**4**), rather than the bonding model originally proposed in **3**. The molecular levels of $[H_2SiPh_3]^-$, analogous to the familiar $[H_3]^-$ ion, are shown on the right of Figure 1. Complexation of the $[H_2SiPh_3]^-$ ion to a metal center occurs by electron-density transfer from the orbitals ψ_1 and ψ_2 to metal-centered nonbonding orbitals of symmetry a and b, and back donation of the metal lone pair into ψ_3. This bonding scheme strongly resembles synergic

[*] Dr. G. I. Nikonov
Chemistry Department
Moscow State University
Vorob'evy Gory, 119899, Moscow (Russia)
Fax: (+7)-095-932-88-46
E-mail: nikonov@org.chem.msu.su

[**] Financial support from the Russian Fund for Basic Research is gratefully acknowledged.

  1433-7851/01/4018-3353 $ 17.50+.50/0