Anti-Markovnikov Functionalization of Olefins: Rhodium-Catalyzed Oxidative Aminations of Styrenes**

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Amines and their derivatives are of great importance for organic chemistry as natural products, pharmacological agents, fine chemicals, and dyes. Despite the many uses for amines, the direct addition of ammonia as well as primary and secondary amines to olefins has not been investigated in detail.^[1] The advantage of direct aminations of olefins over classical methods^[2] is that in principle no coupled products are formed, that is every atom from the starting material is still present in the product molecules (100% atom economy).

Aminations of olefins catalyzed by transition metals can follow two different paths (Scheme 1):^[3] a) coordinative binding



Scheme 1. Transition metal catalyzed amination of olefins as exemplified by ethene. a) The first step is the coordinative binding of the olefin to the metal center. b) The first step is the insertion of a metal complex into the N-H bond.

of an olefin, for example ethene, to the central atom of an electron-poor metal complex activates the olefin for a direct attack of the amine; b) oxidative insertion of an electron-rich metal complex into the N-H bond of an amine leads to the corresponding amidohydrido complex with subsequent insertion of an olefin into the metal-nitrogen bond.

Both paths present several problems, and to date, there is no broadly applicable method for the catalytic amination of olefins. Rhodium-catalyzed aminations of ethene and norbornene are well-known,^[4-6] as are palladium-catalyzed intramolecular aminations of amines and amides^[7] as well as recently developed hydroaminations in the presence of lanthanoid complexes.^[8] The metal complexes previously employed for transition metal catalyzed aminations are not very active, and some of the aminations only progress intramolecularly. In addition the Markovnikov products are always favored when unsymmetrical olefins are used. An exception is the intramolecular oxidative amination of o-aminostyrene, in which for reasons of ring strain in the product only attack at a terminal position is possible.^[9]

Here we report on a catalytic system which for the first time enables regioselective intermolecular oxidative anti-Markovnikov aminations of different olefins with secondary amines. Because of the significance of the pharmacologically important structural unit $\operatorname{ArylCH}_2\operatorname{CH}_2\operatorname{NR}_2^{[10]}$ we examined the reaction of styrene with amines. During the course of a catalyst screening we discovered that rhodium complexes with the general formula $[\operatorname{RhL}_4]X$ (L = olefin, phosphane, $X = \operatorname{BF}_4^-$) surprisingly catalyze the selective formation of the enamines 3, that is of the anti-Markovnikov products (Scheme 2)!



Scheme 2. Rhodium-catalyzed regioselective oxidative amination of styrenes. Ar = aryl; R = alkyl, aryl; cod = (Z,Z)-1,5-cyclooctadiene.

Formally this is an oxidation of the olefin, similar to the Wacker process.^[11] Hydrolysis of the enamines leads to phenylacetaldehydes that are regioisomeric to the products of a Wacker oxidation. The reaction conditions were optimized for the model reaction between styrene and piperidine. In the presence of 2.5 mol% [Rh(cod)₂]BF₄ and two equivalents of triphenylphosphane in THF, the desired product N-styrylpiperidine 3 $(Ar = Ph, R_2 = pentane-1, 5-diyl)$ is obtained after 20 h in 55% yield. According to the ¹HNMR spectrum the E isomer is formed exclusively $({}^{3}J = 14 \text{ Hz})$. Hydrogenation of styrene leads to ethylbenzene 5 as a further main product. The other possible amination product, the Markovnikov regioisomer 4, was not detected. Brunet et al. obtained the Markovnikov product of oxidative amination as main product besides the product of the hydroamination reaction when styrene and aniline were converted in the presence of $[{RhCl(PEt_3)_2}_2]/lithium$ anilide.^[12]

The reaction of piperidine with styrene is catalyzed not only by $[Rh(cod)_2]BF_4$, but also by the corresponding norbornadiene (nbd) complex $[Rh(nbd)_2]BF_4$. More strongly coordinating anions such as halide ions suppress enamine formation. Likewise no reaction takes place when $[{RhCl(cod)}_2]/2$ PPh₃ is used as a catalyst. The addition of phosphane to the cationic olefinrhodium complex is essential, as only traces of the product are obtained without PPh₃. The optimal phosphane - rhodium ratio is 2:1. Besides triphenylphosphane, electron-rich, sterically less demanding phosphanes such as tri-n-butylphosphane or tri-ptolylphosphane are highly suitable catalyst ligands. On the other hand, chelating phosphorus and amine ligands completely inhibit the reaction. The choice of solvent is also crucial to the productivity of the catalytic system. The best results are obtained in THF. As expected, the use of polar and coordinating solvents such as dimethyl sulfoxide or dimethylacetamide significantly reduces the activity.

To examine the range of applications for this method, different amines and olefins were transformed under optimized conditions. Table 1 shows that a series of secondary amines can be used for oxidative aminations. The highest reactivity is displayed by cyclic and acyclic aliphatic amines, but *N*-methylani-

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Amine	Yield [%]		
	enamine	ethyl benzene	
diethylamine	40	54	
di-n-butylamine	48	44	
piperidine	55	57	
hexahydroazepine	45	80	
N-methylaniline	9	9	

[a] Ratio of styrene: amine 4:1, 2.5 mol% [Rh(cod)₂]BF₄/2 PPh₃ relative to amine, 20 h reflux in THF.

line, whose nucleophilicity is strongly reduced because of the phenyl ring, can also be made to react.

Surprisingly, electronically different substituents at the aryl ring can significantly influence the efficiency of the reaction (Table 2). Thus a methyl group clearly increases the yield,

Table 2. Variation of olefins in the reaction with piperidine [a].

Olefin	Enamine [b]	Yield [%] Ethyl benzene [c]	Amine after hydrogenation [c]
styrene	55	57	55
4-methylstyrene	75	65	69
3-methylstyrene	75	94	42
4-methoxystyrene	55	49	45(33)
3,4-dimethoxystyrene	44	64	44(35)
2-vinylnaphthalene	99	99	99
4-vinylbiphenyl	24	8	16
4-fluorostyrene	18	13	18(10)
4-trifluoromethylstyrene	14	6	14
acrylamide	18	- [d]	-

[a] Ratio of styrene: amine 4:1, 2.5 mol% $[Rh(cod)_2]BF_4/2$ PPh₃ relative to amine, 20 h reflux in THF. [b] The yield was determined by gas chromatography by percentage area. [c] The yield was determined by gas chromatography using an internal standard. The values in parentheses correspond to yields of isolated product. [d] The yield of the hydrogenated product could not be determined by gas chromatographic methods as the retention time coincides with that of acrylamide.

whereas a methoxy group in the 4-position decreases it. A further methoxy group in 3-position only has a negligible influence on the yield. Distinctly lower yields of enamine are obtained with electron-poor styrenes. Therefore electronic reasons also seem to be responsible for the low reactivity of 4-vinylbiphenyl.

Preliminary experiments aimed at broadening the spectrum of suitable olefins showed that functionalized olefins also undergo the reaction. For example, acrylamide, which without catalyst selectively reacts in a Michael reaction resulting in the hydroamination product, can be transformed into the enamine in 18% yield; however, the hydroamination product is also detected. In principle, further functionalized aliphatic olefins should be convertible into enamines.

The oxidative amination and the simultaneous hydrogenation of a further olefin molecule make a mechanism similar to that of the oxidative silylation seem plausible (Scheme 3).^[13] We postulate that the catalytically active species **6** reacts with the olefin, leading to the formation of the η^2 complex **7**. Nucleophilic attack of the amine on the thus activated olefin affords the Rh-alkylamine compound **8**; β -H elimination then leads to the Rh-H species **9** and the enamine **3**. The active species **6** is then reformed from **9** and a further olefin molecule. Interestingly, only the styrene is hydrogenated, which can be explained by its easy hydrogenability.^[14] Unlike in the palladium-catalyzed oxidative amination with benzoquinone as an oxidant, the



Scheme 3. Postulated mechanism of the oxidative amination. Ar = aryl; R = alkyl, aryl.

olefin added in excess serves as an oxidizing agent. The yield of enamine falls with decreasing styrene-amine ratio.

We have thus developed a method that for the first time allows oxidative aminations of simple olefins. The resulting enamines are reactive intermediates that can be further transformed;^[15] thus, in future new cascade processes should become possible. The excellent regioselectivity of the reaction is of particular importance, as it provides evidence that transition metal catalyzed reactions of simple olefins with nucleophiles in the anti-Markovnikov sense are possible.

Experimental Section

All experiments were carried out under exclusion of air and moisture. The chemicals were dried according to standard procedures and stored under N_2 or argon. [Rh(cod)₂]BF₄ was prepared according to reference[16].

Procedure for the catalysis experiments: $[Rh(cod)_2]BF_4$ (45.0 mg, 0.11 mmol) and PPh₃ (58.0 mg, 0.22 mmol) were suspended in THF (10.0 mL) under argon. Addition of the amine (4.40 mmol) afforded a yellow solution to which the olefin was added. Subsequently the mixture was heated to reflux for 20 h. The reaction mixtures were then either distilled or hydrogenated to the corresponding alkylamines (48 h, 1 bar H₂, 0.5 g 5% Pd/C). After the hydrogenation catalyst had been removed by filtration, the solvent was removed in vacuo and the residue was taken up in dichloromethane (20.0 mL). After extraction with 5% HCl (3 × 20.0 mL) the combined aqueous phases were carefully brought to pH9 by using NaOH pellets and then extracted with dichloromethane (3 × 20.0 mL). The combined organic phases were dried over magnesium sulfate. After the solvent had been removed in vacuo, the product was purified by column chromatography and dried in high vacuum. The products were characterized by ¹H NMR and (DEPT)¹³C NMR spectroscopy as well as by GC-MS. The yields with respect to the amine were determined after gas chromatography with hexadecane as internal standard.

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[Ru₂₀H₄Cu₆Cl₂(CO)₄₈]⁴⁻: A New High Nuclearity Copper-Ruthenium Cluster**

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Mixed-copper alloys are of interest as catalysts, particularly in the selective reforming of petroleum naptha fractions to aromatic hydrocarbons.^[1] We have recently embarked on the study of high nuclearity mixed-metal ruthenium-copper carbonyl clusters, and the three cluster anions characterized so far, $[Ru_8H_2Cu_7Cl_3(CO)_{24}]^{2-}$, $[Ru_{12}H_2Cu_6Cl_2(CO)_{34}]^{2-}$, and $[Ru_{12}Cu_4Cl_2C_2(CO)_{32}]^{2-}$ all have different Ru: Cu ratios, 8:7, 2:1, and 3:1, respective ly.^[2] These mixed-metal clusters illustrate the use of copper cations as linking agents in the formation of high nuclearity mixed-metal clusters. We now report the synthesis and structure of the highest nuclearity ruthenium-copper carbonyl hydrido cluster $[Ru_{20}H_4Cu_6Cl_2(CO)_{48}]^{4-}$, so far characterized crystallographically.

The reaction of the dianion $[Ru_{10}H_2(CO)_{25}]^2$ with excess $[Cu(MeCN)_4]^+$ in CH_2Cl_2 in the presence of $[Bu_4N]OH/H_2O$ and $[(Ph_3P)_2N]Cl$, with stirring at room temperature, leads after purification by thin-layer chromatography to the isolation of 1 in 60–70% yield. Complex 1 was initially

 $[Bu_4N]_4[Ru_{20}H_4Cu_6Cl_2(CO)_{48}] \quad 1$

characterized by spectroscopy,^[3] but in order to establish the structure of the complex a crystal structure analysis was undertaken. Crystals suitable for X-ray analysis were grown from the layered diffusion of ethanol into a solution of 1 in CH₂Cl₂.^[4]

The structure of the tetraanion of 1 (Figure 1) may be viewed as two decaruthenium clusters sandwiching the hexacopper cluster metal core. The geometry of the decaruthenium units in cluster 1 is different from that observed in the precursor dianion $[Ru_{10}H_2(CO)_{25}]^{2-}$.^[5, 6] This geometry can be viewed as the con-



Figure 1. Top: Structure of the anion of 1 showing the atom numbering scheme. Selected bond lengths [Å] and angles [°]: Ru(1)-Cu(1) 2.595(4), Ru(1)-Cu(2) 2.667(5), Ru(1)-Cu(3) 2.720(4), Ru(1)-Ru(2) 2.835(3), Ru(1)-Ru(3) 2.882(3), Ru(1)-Ru(5) 2.994(3), Ru(1)-Ru(6) 3.073(3), Ru(2)-Ru(3) 2.852(4), Ru(2)-Ru(4) 2.855(3), Ru(2)-Ru(5) 2.896(3), Ru(2)-Ru(7) 2.836(4), Ru(2)-Ru(8) 2.837, Ru(2)-Ru(10) 2.807(4), Ru(3)-Cu(2) 2.657(4), Ru(3)-Ru(4) 2.851(3), Ru(3)-Ru(6) 2.924(3), Ru(3)-Ru(9) 2.916(3), Ru(3)-Ru(10) 2.960(3), Ru(4)-Ru(5) 2.842(4), Ru(4)-Ru(6) 2.860(3), Ru(4)-Ru(7) 2.835(3), Ru(5)-Cu(3) 2.608(4), Ru(5)-Ru(6) 2.937(4), Ru(5)-Ru(7) 2.697(4), Ru(6)-Cu(2) 2.678(4), Ru(6)-Cu(3) 2.715(4), Ru(6)-Cu(1a) 2.615(4), Ru(7)-Ru(8) 2.685(4), Ru(8)-Ru(9) 2.925(4), Ru(8)-Ru(10) 2.924(4), Ru(9)-Ru(10) 2.798(4), Cu(1)-Cu(2) 2.668(5), Cu(1)-Cu(3) 2.674(5), Cu(1)-Cu(1a) 2.440(6), Cu(1)-Cu(2a) 2.647(5), Cu(1)-Cu(2a) 7.8.8(2). The atoms denoted "a" are related to the atoms with the same number through the center of symmetry. Bottom: The metal core geometry of 1 showing the position of the chlorine ligands.

densation of two octahedra through the triangular face Ru2-Ru3-Ru4, generating three butterflies, one of which is capped. This is very similar to the metal core geometry found in $[Ru_{11}H(CO)_{27}]^{3-[6, 7]}$ but in this case two of the butterflies are capped. In the cluster precursor $[Ru_{10}H_2(CO)_{23}]^2$ the geometry is that of two trigonal bipyramids fused to an octahedron. The ruthenium metal core arrangement in the anion of 1 has not been observed previously for decanuclear clusters, although the use of Group 11 metals has been shown to introduce a polarity into ruthenium metal frameworks, generating metal geometries not observed in homometal clusters.^[8] The Cu₆ metal core may be described as two tetrahedra fused through a common edge (Cu(1)-Cu(1a)) the center of which is the crystallographic center of symmetry.

The central section of the metal core is reminiscent of that in $[Ru_{12}H_2Cu_6Cl_2(CO)_{34}]^2$, which consists of four fused octahredra; in the case of 1 a further four Ru atoms have condensed on each end. Two chloride ligands each symmetrically bridge two of the copper atoms in the Cu₆ core. The distance between the Cu centers bridged by the two chloride ligands is 2.840(5) Å, and the shortest Cu–Cu distance is between the two central copper atoms Cu(1) and Cu(1a) (2.440(6) Å). The structure of the tetraanion of 1 has 12 asymmetrically bridging carbonyl ligands, each Ru₁₀ unit containing six.

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