Hydrogenation Catalysts Hot Paper

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Tailor-Made Ruthenium-Triphos Catalysts for the Selective Homogeneous Hydrogenation of Lactams

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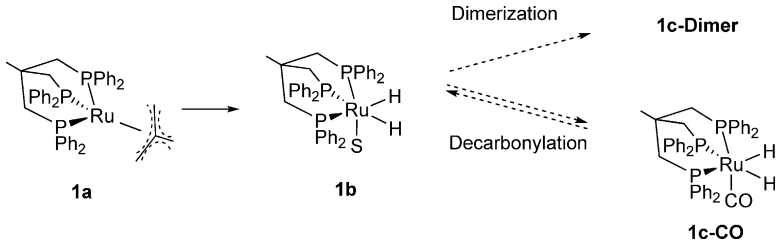
Abstract: *The development of a tailored tridentate ligand enabled the synthesis of a molecular ruthenium-triphos catalyst, eliminating dimerization as the major deactivation pathway. The novel catalyst design showed strongly increased performance and facilitated the hydrogenation of highly challenging lactam substrates with unprecedented activity and selectivity.*

Catalytic hydrogenation using molecular catalysts based on defined organometallic complexes has been advanced to be an essential tool for the chemical synthesis in research laboratories as well as on the industrial scale.[1] Very effective catalysts could be tailored for the addition of hydrogen to complex organic substrates, largely based on fundamental mechanistic insight on a molecular level. Moreover, recent research efforts have illustrated that ruthenium complexes of the multidentate triphos (1,1,1-tri(diphenylphosphinomethyl)ethane) ligand demonstrate potential for the development of highly active and stable homogeneous species.[2] Especially for the reduction of challenging functionalities, the ruthenium-triphos systems could be established as important molecular catalyst,[2b,c] finding increasing application in numerous research groups.[3] This important advancement moved these molecular catalysts into the spotlight for novel transformations and in special cases closer to processing conditions of heterogeneous catalyst systems.[4] Nevertheless, the hydrogenation of non-activated aliphatic amides remains an enormous challenge for molecular catalysts and especially the reductive cleavage of lactams requires novel dedicated catalysts. The group of Bergens introduced the catalyst $[Ru(Ph_2P(CH_2)_2NH_2)_2(\mu^3\text{-}C_3H_5)]BF_4$ for the hydrogenation of *N*-phenylpyrrolidin-2-one, enabling the formation of the respective amino alcohol with C–N cleavage with high turnover number (TON).[5] Most recently the group of Milstein presented N,N,P-pincer ruthenium complexes for the conversion of glycine anhydride into ethanolamine in high yield.[6] The reduction of lactams to cyclic amines is still demanding, but the groups of Mashima and Saito could already use a bis-bidentate $(P,N)_2$-Ru system to accomplish this transformation and obtained the cyclic products in low to moderate yield.[7] Therefore, effective homogeneous catalysts for the hydrogenolysis of lactams towards cyclic amines remain largely elusive and the development of novel transition-metal compounds for this challenging catalytic transformation needs to be established. Herein we describe a rationally developed novel triphos-type ligand that enables this transformation in hitherto unprecedented efficacy.

In our recent effort we could establish the highly versatile and stable ruthenium complex [Ru(triphos)(tmm)] (**1a**, tmm = trimethylenemethane) as active catalysts system.[2c,8] Initial mechanistic evaluation of the active hydride species **1b** revealed two reaction pathways as important targets for tailoring an improved catalyst (Scheme 1).[2c,d] The minor reaction pathway is strongly substrate dependent via the formation of the dihydrido carbonyl complex [Ru(triphos)-$(CO)(H)_2$] (**1c-CO**), originating from the decarbonylation of intermediate aldehydes or alcohols. However, **1c-CO** can be easily reactivated and recycled towards **1b**.[2a] The major pathway results in deactivation and is based on the irreversible formation of a ruthenium dimer, resulting in the very stable and catalytically inactive hydride bridged dimeric complex (**1c-Dimer**).[2c,d]



Scheme 1. Major reaction pathways of ruthenium-triphos-based catalysts in hydrogenation reactions.

Catalyst deactivation via the formation of stable dimers, trimers, or higher aggregates represents a wide-ranging problem in homogeneous catalysis.[9] A general approach to avoid the buildup of such structures is based on the design of sterically demanding ligands using the respective repellent forces for keeping the monomeric catalysts maintained in solution.[10] However, the design of these enlarged ligands still has to enable the coordination of the substrates, preserving high catalytic activity.

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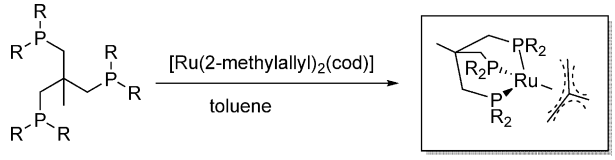
Consequently, a substitution of the aromatic ring in *meta*- or *para*-position was envisaged as promising lead structure, avoiding the formation of the ruthenium dimer, while tolerating the coordination of the substrate in the presence of molecular hydrogen in the transition state. The synthesis of the respective triphos derivatives was achieved following a similar procedure to that first reported by Kabachnik et al. in 1986 and modified by Huttner et al. in 1994.[11] This synthetic pathway involved the substitution of 1,1,1-tris-(chloromethyl)ethane with an in situ prepared solution of a deprotonated secondary aryl phosphine in DMSO. This procedure was successfully employed in the preparation of the triphos-derivatives, **L2** and **L3**, in which the reaction conditions were dependent on the nature of the phosphine nucleophile.

The synthesis of the corresponding triphos η^4-trimethylenemethane complexes **1a**–**3a** (Scheme 2) proceeded by heating the ligand (**L1**–**L3**) with one equivalent of [Ru(2-methylallyl)$_2$(1,5-cyclooctadiene)] for 16 h.[2c] The introduction of alkyl substituents on the aryl groups of the phosphorus atoms strongly influenced the solubility of the ruthenium complexes. Complexes **1a** and **2a** were easily precipitated out of the toluene reaction solution by the addition of pentane (yield **1a**: 76%, **2a**: 84%). However, the solubility of complex **3a** was significantly higher and this complex had to be purified by removal of toluene and repeated washing with heptane (yield 88%).



Ligand	Catalyst	R
L1	1a	Phenyl
L2	2a	4-methylphenyl
L3	3a	3,5-dimethylphenyl

Scheme 2. Synthesis of molecular ruthenium catalysts **1a**, **2a**, and **3a**.

Suitable crystals of complex **2a** and **3a** for X-ray diffraction (XRD) measurement were grown via recrystallization from a toluene or pentane solution and the structures are shown together with **1a** in Figure 1.[2c] The introduction of different alkyl moieties in the aryl groups of the ligand had only a minor influence to the coordination of the triphos ligand (average Ru–P distance: **1a** 2.279 Å, **2a** 2.276 Å, **3a** 2.282 Å). The most important difference between compounds **1a**–**3a** is the steric shielding of the ruthenium center, expected to influence the formation of the inactive ruthenium dimer. The comparison of the three different [Ru(triphos)(tmm)] complexes showed that the introduction of a *para*-methyl group in compound **2a** slightly increased the steric shielding of the ruthenium center. In complex **3a** the methyl groups in *meta* position clearly give a deeply imbedded ruthenium center and decrease the "accessible surface" of the metal center.[12] Moreover, owing to the hindered rotation of the

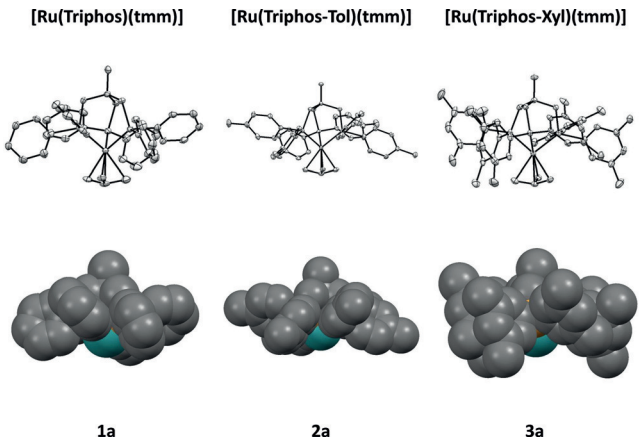
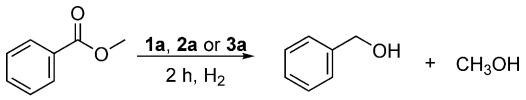


Figure 1. Crystal structures of **1a**, **2a**, and **3a**; Ru turquoise.

phenyl groups, the shielding cannot be decreased by alignment of the rings, unlike in **1a** or **2a**, which should have an additional distinct impact on prevention of dimerization.

To compare the catalytic performance of the newly developed catalysts, the hydrogenation of methyl benzoate was selected as prototypical test reaction (Scheme 3).[2c]



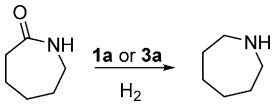
1a: 25 %
2a: 37 %
3a: 98 %

Scheme 3. Catalytic hydrogenation of methyl benzoate with catalysts **1a**, **2a**, and **3a**.

All three catalysts **1a**–**3a** showed full conversion after 16 h at a substrate to catalyst ratio of 100/1. Upon reducing the reaction time to 2 h, the hydrogenation with [Ru(**L3**)-(tmm)] (**3a**) still led to a yield of 98%, whereas catalysts **1a** and **2a** showed yields below 40%. The expected avoidance of dimerization upon steric increase in the ligand could be confirmed by $^{31}P\{^1H\}$-NMR spectroscopic investigations of the reaction solutions after full conversion. The reaction solution obtained with catalyst **1a** showed mostly the signals for the respective dimer. Less dimer together with [Ru(**L2**)-(CO)(H)$_2$] could be detected with catalyst **2a**. The $^{31}P\{^1H\}$-NMR spectrum of the solution after a hydrogenation of methyl benzoate with [Ru(**L3**)(tmm)] showed only the formation of the carbonyl complex, which is consistent with the expected inhibition of the dimer formation by the steric demand of the ligand (see Supporting Information for details).

Subsequently, the effect on catalytic performance was further substantiated in the hydrogenation of cyclic amides and therefore ε-caprolactam was chosen as a challenging substrate. For this type of substrates currently no molecular catalysts enables the selective hydrogenation to the azepane product. The results obtained with catalysts **1a** and **3a** are

Table 1: Hydrogenation of ε-caprolactam with catalysts **1a** and **3a**.[a]



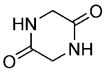
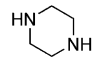
Entry	Catalyst [mol%]	Additive [mol%]	Conversion [%]	Yield [%]	TON
1	**1a** (1.0)	–	traces	–	–
2	**3a** (1.0)	–	12	12	12
3	**1a** (1.0)	MSA (1.5)	25	13	25
4	**1a** (5.0)	MSA (7.5)	62	59	12
5[b]	**3a** (0.5)	MSA (1.5)	99	95	200
6[c]	**3a** (0.2)	MSA (1.5)	69	67	345

[a] Reaction conditions: 1.0 mmol ε-caprolactam, 160 °C, 100 bar H_2, 16 h, 3 mL THF, [b] 2.0 mmol ε-caprolactam, [c] 5.0 mmol ε-caprolactam.

presented in Table 1. Without additional additives, **1a** only gave traces of the desired product, whereas **3a** already gave a 12% yield of azepane product (Table 1, entry 1 and 2). Activating catalysts **1a** with methanesulfonic acid (MSA) improved the yield to 25% and increasing the catalyst loading to 5 mol% resulted in 59% azepane (Table 1, entry 3 and 4). Using only 0.5 mol% **3a** resulted in full conversion and a yield of 95% with a TON of 200 (Table 1, entry 5), clearly emphasizing the superior performance of the tailored catalyst. Further reduction of the catalyst loading to 0.2 mol% gave a TON of 345 with a yield of 67% (Table 1, entry 6).

To further substantiate the general reactivity of **3a**, a series of diverse lactams was hydrogenated with a catalyst loading of 1 mol% **3a** (Table 2). In this transformation butyrolactam could be converted into pyrrolidine within 16 h in a yield of 98% (Table 2, entry 1). Increasing the cyclic

Table 2: Hydrogenation of selected lactams with catalyst **3a**.[a]

Entry	1	2	3	4	5[b]
Substrate					
Product					
Yield	98 %	99 %	95 %	99 %	84 %

[a] Reaction conditions: 1.0 mol % **3a**, 1.5 mol % MSA, 160 °C, 100 bar H_2, 16 h. [b] 180 °C.

chain further to δ-valerolactam maintained the exceptional activity and piperidine was obtained in 99% yield (Table 2, entry 2). Also ε-caprolactam could be hydrogenated with 1 mol% catalyst to azepane in 95% yield (Table 2, entry 3). Furthermore, piperazin-2-one was hydrogenated with 99% yield and even the challenging substrate glycine anhydride could be reduced to piperazine in 84% yield at 180 °C reaction temperature.

In summary, the performance of the recently established [Ru(triphos)(tmm)] catalyst could be extended to show unprecedented activity and selectivity in catalytic hydrogenation of challenging lactam substrates. A tailor-made triphos-ligand enhanced the performance by successfully avoiding the deactivation through dimer formation. With this rationally developed molecular catalysts the performance in ester hydrogenation was significantly improved and the challenging reduction of lactams to cyclic amines could be achieved, paving the way towards efficient catalysts recycling and multiphase reaction systems. Further investigations on the application of this next generation of triphos-catalysts in other transformation are ongoing in our laboratory.

Experimental Section

The lactam substrate (1.0 mmol) was weighed under air in a glass insert equipped with a stir bar and placed in a 10 mL steel autoclave. [Ru(**L3**)(tmm)] (9.5 mg, 10.0 μmol, 0.01 equiv) was weighed in a 10 mL Schlenk tube, dissolved in THF (1.6 mL) followed by the addition of MSA (1.48 mg, 15.0 μmol, 0.015 equiv). The resulting solution was transferred via syringe to the autoclave in an argon counter stream. The autoclave was pressurized at room temperature with 100 bar of hydrogen, placed in an alumina cone and the reaction mixture was stirred for 16 h at 160 °C. Afterwards the reaction was allowed to cool in an ice bath and carefully vented to the atmosphere. The yield was determined by ^{1}H NMR spectroscopy using mesitylene as internal standard.

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