Homogeneous Catalysis

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Ruthenium-Catalyzed Modular Synthesis of Cyclic Tertiary Amines from Lactams

*Stefan Westhues, Markus Meuresch, and Jürgen Klankermayer**

Abstract: *Reported is the development of a novel catalytic cascade reaction facilitating the modular synthesis of cyclic tertiary amines from simple lactam substrates and secondary alcohols. Using a single molecular ruthenium-triphos catalyst in the presence of molecular hydrogen enabled the versatile formation of various amines in high yield with excellent selectivity. Extending the reaction system to using an alcohol as the hydrogen transfer reagent allowed the reduction of lactams without the need for molecular hydrogen.*

The development of versatile organic synthetic protocols and the creation of sustainable processes represent central challenges in the field of molecular catalysis. Especially the effective production of amines, an essential class of organic intermediates on the pathway to pharmaceutically relevant products, is of great importance to the synthetic chemist. The respective amine functionality is present in many active principal drugs, agrochemicals, and numerous specialty chemicals. Particularly, tertiary cyclic amines are promising lead structures towards the synthesis of novel anticonvulsants, kinase inhibitors, and antiviral compounds.[1–4]

Novel access to these important molecules could in principle be established by the utilization of versatile amides or lactam starting materials. Lactams can be synthesized from easily accessible amino acids and the most prominent example, ε-caprolactam, the precursor to Nylon 6, is a widely used synthetic polymer with an annual production of approximately 4.5 billion kilograms.[5] Moreover, recent biobased synthetic pathways were developed, thus enabling the possibility to produce these compounds by new benign routes.[6,7] Consequently, the creation of cyclic tertiary amines starting from lactams could pave the way to novel sustainable pathways towards this class of products.

A convenient synthesis using this approach is represented by the reduction of lactams to the corresponding amine. Traditionally, conventional reducing agents like $NaBH_4$ or $LiAlH_4$ are used in stoichiometric amounts, but very recently, practical catalytic methods using molecular catalysts were established. Using the tailored ruthenium catalyst [Ru(triphos-xyl)(tmm)] enabled the hydrogenolysis of non-activated lactams with unprecedented activity and selectivity.[8]

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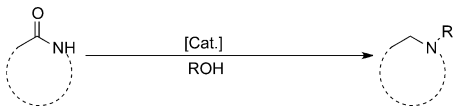
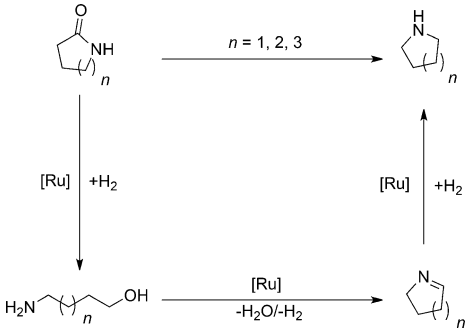
Herein, an effective novel one-step approach for the synthesis of cyclic tertiary amines using only a lactam in combination with a selected alcohol, in the presence of a single molecular ruthenium catalyst, is presented (Scheme 1).



Scheme 1. Direct modular synthesis of cyclic tertiary amines from lactams and alcohols.

The study was initiated with a mechanistic investigation of the reduction of lactams with the developed [Ru(triphos-xyl)(tmm)] catalyst.[8] Supported by recent findings on the reduction of amides, from the group of Beller,[9] the formation of amino alcohols from the hydrogenation of a lactam with a ruthenium catalyst was proposed (Scheme 2). In detail, the



Scheme 2. Proposed reaction mechanism for the hydrogenolysis of lactams with a homogeneous ruthenium catalyst.

C–N bond of the lactam is reductively cleaved, resulting in the corresponding linear amino alcohol. Subsequently, based on a hydrogen-borrowing mechanism, the amino alcohol is initially oxidized to the respective aldehyde species, followed by a Schiff base reaction. The formed cyclic imine is then hydrogenated, thus resulting in the cyclic amine product. Consequently, in a first set of experiments, the amino alcohols 4-aminobutanol, 5-aminopentanol, and 6-aminohexanol were used as substrates under standard hydrogenolysis conditions to yield the respective secondary cyclic amines together with the formation of water, thus corroborating the initial step in the proposed pathway. The subsequent *N*-alkylation with alcohols by a "hydrogen borrowing mechanism" is well

established and various groups have presented the successful alkylation of aliphatic and aromatic amines with a large variety of alcohols.[9–14] Furthermore, the suggested cyclization of aminoalcohols to azacycloalkanes was already demonstrated by Hakata et al. and the group of Bartók, using a [$RuCl_2(PPh_3)_4$] catalyst.[15,16] Moreover, the cyclization of five-, six-, and seven-membered rings is likely driven by the ring stabilization energy.

Taking into consideration the versatility of the novel [Ru(triphos-xyl)(tmm)] catalyst in the hydrogenolysis of amides, as well as the *N*-alkylation of amines with alcohols, a novel one-step cascade reaction yielding tertiary amines from secondary amides was envisaged,[10] thus avoiding large amounts of stoichiometric reducing agents and harmful alkyl halides (Scheme 1).[17–19] Consequently, a set of non-activated lactams (**L1**–**L5**) in combination with secondary alcohols (**A1**–**A4**) was investigated (Figure 1).

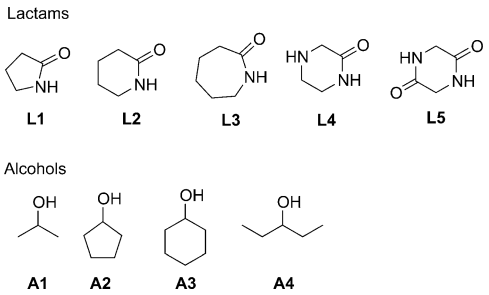
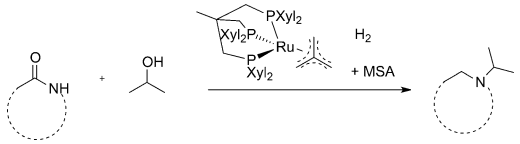


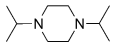
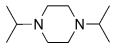
Figure 1. Overview of used lactams and alcohols in the formation of cyclic amines.

The reactions of the lactams **L1**–**L3** were carried out in 2 mL isopropyl alcohol (**A1**) by employing 1 mol% [Ru(triphos-xyl)(tmm)] and 1.5 mol% methanesulfonic acid (MSA) at 200 °C and 100 bar H_2 for 16 hours, yielding *N*-isopropylpyrrolidine, *N*-isopropylpiperidine, and *N*-isopropylazepane with an excellent selectivity of 95–96% (Table 1, entries 1–3). The challenging reactions of **L4** and **L5** to deliver *N*,*N*-diisopropylpiperazine were accomplished under related reaction conditions with 87 and 69% selectivity (entries 4 and 5). Moreover, the reaction of 1-amino-5-pentanol and piperidine in the presence of isopropyl alcohol resulted in the formation of *N*-isopropylpiperidine, thus further supporting the initially proposed mechanism.

Based on these stimulating results, the extended application of selected alcohols in this transformation was targeted. In detail, cyclopentanol (**A2**) and cyclohexanol (**A3**) were used in presence of 2 mol% [Ru(triphos-xyl)(tmm)] and 3 mol% MSA at 200 °C and 100 bar H_2 for 16 hours (Table 2). With this catalytic system, the starting material **L1** was selectively converted into *N*-cyclopentylpyrrolidine in 78% and *N*-cyclohexylpyrrolidine in 80% yield (entries 1 and 2). Enlarging the ring size of the lactam, by using **L2** and **L3**, resulted in an increased selectivity of 73–90% (entries 3–6). Moreover, starting from **L4**, the challenging dialkylated products *N*,*N*-dicyclopentylpiperazine and *N*,*N*-dicyclohexylpiperazine could be obtained with a selectivity of up to 73% (entries 8 and 9). Furthermore, with piperazine-2,5-dione

Table 1: Ruthenium-catalyzed formation of cyclic tertiary amines from selected lactams using molecular hydrogen, isopropyl alcohol, and the [Ru(triphos-xyl)(tmm)] catalyst.[a]



Entry	Lactam	Product	Conv. [%][b]	Sel. [%][b]
1	**L1**		> 99	95 (89)[c]
2	**L2**		> 99	95 (91)[c]
3	**L3**		> 99	96 (92)[c]
4	**L4**		> 99	87 (81)[c]
5	**L5**		> 99[c]	69

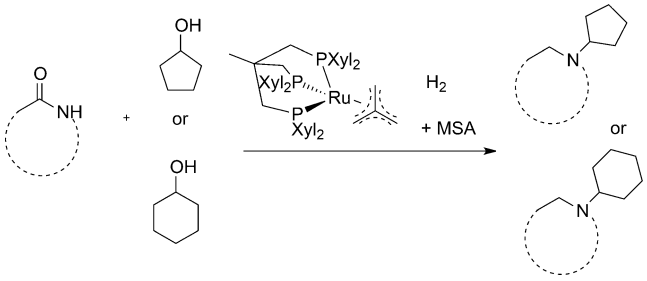
[a] Reaction conditions: Lactam (1.0 mmol), [Ru(triphos-xyl)(tmm)] (1.0 mol%), MSA (1.5 mol%), isopropyl alcohol (**A1**; 2.0 mL), H_2 (100 bar), 200 °C. [b] Conversion and selectivity determined by ^1H and quantitative ^{13}C NMR spectroscopy using mesitylene as an internal standard. [c] Yield of isolated ammonium chloride salts.

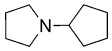
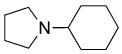
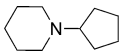
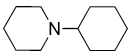
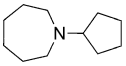
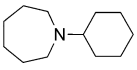
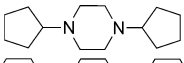
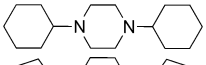
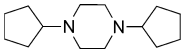
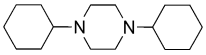
(**L5**), a promising selectivity of 50 and 43% towards *N*,*N*-dicyclopentylpiperazine and *N*,*N*-dicyclohexylpiperazine, respectively, was obtained (entries 9 and 10).

In the final set of experiments, reactions to deliver the cyclic tertiary amines were performed in the absence of molecular hydrogen, that is, simply isopropyl alcohol was used for alkylation and transfer hydrogenation.[20–23] By applying the reaction conditions established in the previous reactions, the high volatility of the reagents resulted in low isolated product at ambient pressure. Consequently, a reaction system with 100 bar argon pressure enabled to fully determine all products and to close the mass balance. In these experiments the formation of *N*-alkylated azacycloalkanes could be established from lactams using only isopropyl alcohol and [Ru(triphos-xyl)(tmm)]. The lactams **L1**–**L3** resulted in full conversion and a selectivity of up to 94% (Table 3, entries 1–3), observing only the formation of two equivalents acetone as the coupled product, and thus demonstrating the first effective hydrogen-transfer hydrogenolysis of amides. Astonishingly, these results are comparable to the reactions using molecular hydrogen as a reducing agent (Table 1). Moreover, the challenging substrates **L4** and **L5** were converted into the respective cyclic tertiary amines with a selectivity of 82 and 52% (Table 3, entries 4 and 5). Finally, with 3-pentanol as a sterically more demanding secondary alcohol, *N*-3-pentylpyrrolidine, *N*-3-pentylpiperidine, and *N*-3-pentylazepane were obtained with yields of up to 97% (see the Supporting information for more details).

In conclusion, a novel catalytic synthesis of cyclic tertiary amines from various lactams was established. The recently introduced [Ru(triphos-xyl)(tmm)] catalyst enabled the effective hydrogenolysis of the lactam substrates to the corresponding azacycloalkane products in excellent yield. First mechanistic investigations suggested an initial C–N bond cleavage, followed by *N*-alkylation of the amino alcohols, thus

Table 2: Ruthenium-catalyzed formation of cyclic tertiary amines from selected lactams using molecular hydrogen, cyclopentanol/cyclohexanol, and the [Ru(triphos-xyl)(tmm)] catalyst.[a]



Entry	Substrate	ROH	Product	Conv.[b] [%]	Sel.[b] [%]
1	**L1**	**A2**		85	92 (63)[c]
2	**L1**	**A3**		86	93
3	**L2**	**A2**		>99	90
4	**L2**	**A3**		>99	89
5	**L3**	**A2**		>99	87
6	**L3**	**A3**		>99	73
7	**L4**	**A2**		>99	73 (59)[c]
8	**L4**	**A3**		>99	55 (47)[c]
9	**L5**	**A2**		>99	50
10	**L5**	**A3**		>99	43

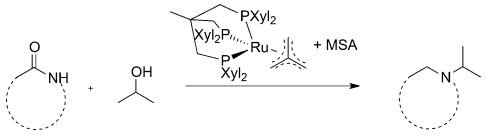
[a] Reaction conditions: Lactam (1.0 mmol), [Ru(triphos-xyl)(tmm)] (2.0 mol%), MSA (3 mol%), alcohol (2.0 mL), H_2 (100 bar); 200°C. [b] Conversion and selectivity determined by quantitative ^{13}C NMR spectroscopy using mesitylene as an internal standard. [c] Products are isolated as ammonium chloride salts after column chromatography on silica and are reported between brackets.

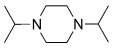
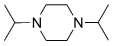
yielding, formally, C=O bond cleavage products. By taking into consideration the possibility of catalytic *N*-alkylation of amines with alcohols, the lactam reduction in the presence of alcohols selectively yielded the desired cyclic tertiary amines. Moreover, the complex cascade reaction also proceeded in the absence of molecular hydrogen by using an alcohol as a hydrogen transfer reagent, thus essentially facilitating the applicability of this sequence in organic synthesis.

Experimental Section

General procedure for the synthesis of tertiary amines from lactams: The lactams were weighed into a glass insert equipped with a stir bar and subsequently placed in a high pressure steel autoclave. [Ru(triphos-xyl)(tmm)] (9.5 mg, 0.01 mmol), MSA (1.48 mg, 0.015 mmol), lactam (1.0 mmol) and alcohol (2 mL) were added through a cannula under argon. Once the autoclave was sealed (and pressurized with 100 bar of hydrogen) it was placed in an alumina cone and the reaction mixture was stirred for 16 hours at 200°C. Afterwards the reaction was cooled in an ice bath and the pressure was carefully released. The crude reaction mixture was analyzed by ^1H and quantitative ^{13}C NMR spectroscopy, using mesitylene as internal standard.

Table 3: Ruthenium-catalyzed formation of cyclic tertiary amines from selected lactams, using only isopropyl alcohol and the [Ru(triphos-xyl)(tmm)] catalyst.[a]



Entry	Substrate	Product	Conv. [%][b]	Sel. [%][b]
1	**L1**		>99	94
2	**L2**		>99	93
3	**L3**		>99	94
4	**L4**		>99	82
5	**L5**		>99	52

[a] Reaction conditions: Lactam (1.0 mmol), [Ru(triphos-xyl)(tmm)] (1.0 mol%), MSA (1.5 mol%), isopropyl alcohol (**A1**; 2.0 mL), Ar (100 bar); 200°C. [b] Conversion and selectivity determined by ^1H and quantitative ^{13}C NMR spectroscopy using mesitylene as an internal standard.

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Keywords: heterocycles · homogeneous catalysis · hydrogenation · lactams · ruthenium

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