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Amino-Alcohol Cyclization: Selective Synthesis of Lactams and Cyclic Amines from Amino-Alcohols

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General considerations

Chemicals and were purchased from Sigma-Aldrich and Acros, $Ru_3(CO)_{12}$ was purchased from Strem and chemicals were used as received The commercially available amino-alcohols (**S1-S4**) were stored under dry conditions in a glovebox. The CataCXium® PCy ligand was synthesized according to a previously reported procedure.[1] Substrates **S5-S8** were synthesized according a literature procedure.[2] 2-(n-alkanol) anilines **S9-S11** were synthesized according a literature procedure.[3] Synthesis and catalysis reactions were performed under an inert Ar atmosphere using standard Schlenk techniques. Product distribution and yield analyses were performed on a Shimadzu GC-17 A instrument with an Ultra 2 column (25 m, 0.2 mm id). GC/MS analyses were conducted on a Shimadzu GCMS-QP2010 SE with a DB-1 MS column (10 m, 0.1 mm id). Amino-alcohol cyclizations were performed in a 10 mL stainless steel autoclave. Reaction profiles were recorded using a homemade 75 mL stainless steel autoclave equipped with a manometer and a sampling unit for 50 µL samples. Samples were subjected directly to GC without further workup.

Procedures for cyclization of amino-alcohols:

Using $RuHCl(CO)(PPh_3)_3$/Xanthos: α,ω-Amino-alcohol (1 mmol) was weighed into a 10 mL stainless steel autoclave applying a blanket of Ar. $RuHCl(CO)(PPh_3)_3$ (1.5 mol%, 0.015 mmol, 14.3 mg) and Xantphos (1.5 mol%, 0.015 mmol, 8.7 mg) were added followed by cyclohexane (0.6 mL). For the reactions using water as an additive, degassed H_2O (10 mmol) was added and the autoclave was closed tightly and heated in an oil bath for the appropriate time. Reactions using ketone as additive were performed using dried, degassed ketone (2 mmol). The reaction mixture was subjected to GC and GC/MS analyses.

Using $Ru_3(CO)_{12}$/Acridine diphosphine: α,ω-Amino-alcohol (1 mmol) was weighed into a 10 mL stainless steel autoclave applying a blanket of Ar. $Ru_3(CO)_{12}$ (0.5 mol%, 0.005 mmol, 3.2 mg) and Acridine diphosphine (1.5 mol%, 0.015 mmol, 6.6 mg) were added followed by cyclohexane (0.6 mL). For the reactions using water as an additive, degassed H_2O (10 mmol) was added and the autoclave was closed tightly and heated in an oil bath for the

appropriate time. Reactions using ketone as additive were performed using dried, degassed ketone (2 mmol). The reaction mixture was subjected to GC and GC/MS analyses.

Using $Ru_3(CO)_{12}$/CataCXium® PCy: α,ω-Amino-alcohol (1 mmol) was weighed into a 10 mL stainless steel autoclave applying a blanket of Ar. $Ru_3(CO)_{12}$ (0.5 mol%, 0.005 mmol, 3.2 mg) and CataCXium PCy (3 mol%, 0.03 mmol, 10.2 mg) were added followed by cyclohexane (0.6 mL). For the reactions using water as an additive, degassed H_2O (10 mmol) was added and the autoclave was closed tightly and heated in an oil bath for the appropriate time. Reactions using ketone as additive were performed using dried, degassed ketone (2 mmol). The reaction mixture was subjected directly to GC and GC/MS analyses without further workup.

Graphs 1 and 2 were produced via a modified procedure: In a Ar-purged Schlenk tube, $Ru_3(CO)_{12}$ (0.5 mol%, 0.075 mmol, 48 mg) and CataCXium® PCy (3 mol%, 0.45 mmol, 153 mg) was dissolved in 9 mL cyclohexane. To this α,ω-amino-alcohol was added. The mixture was then transferred to a 75 mL stainless steel autoclave purged with Ar. The autoclave was closed tightly and was heated to 140ºC using a heating mantle. Samples were taken at t=0.5, 1, 2, 3.75, 5.5, 7.5 10, 21 and 24 h for Graph 1 and at t=0.5, 1, 2, 3.75, 5, 7, 12 and 24 h for graph 2.

Substrates:

The substrates **S1-S4** are commercially available and have been subjected to the catalytic system.

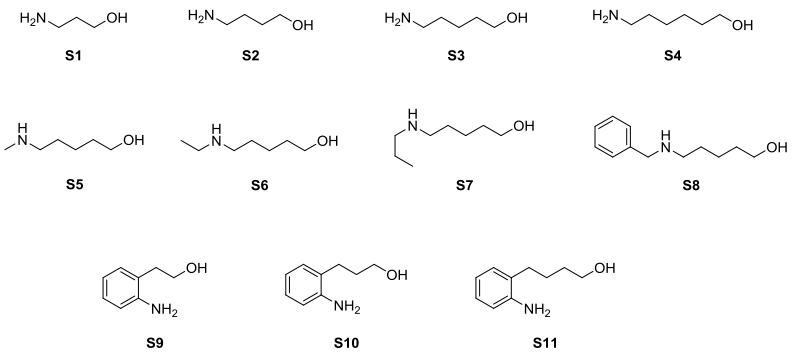

Figure S1: Substrates employed in the cyclization of amino-alcohols to cyclic amines or cyclic amides

Hydrogen scavenger screening

Table S1 summarizes the screening of hydrogen scavengers in order to obtain full selectivity towards the cyclic amide from the corresponding amino-alcohol.

Table S1: Screening for suitable hydrogen scavengers.
Conditions: 1 mmol substrate, additive (2 mmol hydrogen scavenger or 1 mmol H_2O), 0.5 mol% $Ru_3(CO)_{12}$, 3 mol% CataCXium PCy (Ru:P=1:2), 0.6 mL cyclohexane, 140°C, 21 h.

Substrate	Hydrogen Scavenger	Conversion (%) [a]	Amine selectivity	Amide selectivity	Other
S3	Acetone	100	33.5	63.2	3.3 [b]
S3	4-methyl-2-pentanone (MIBK)	100	0	2	98 [b]
S3	2,4-dimethyl-3-pentanone	2.4	100	0	0
S3	cyclohexanone	95.1	74.1	25.9	0
S3	Benzophenone	94.9	16.4	52.8	30.7 [b]
S3	Propiophenone	100	0	100	0
S3	Cyclohexene	95.1	74.1	25.8	0
S3	Phenylacetylene	100	9.8	2.3	87.9
S4	Cyclohexanone	100	15	71.3	13.7 [b]
S4	Cyclohexene	95.7	86.0	11.9	2.1
S4	4-methyl-2-pentanone (MIBK)	95.3	22.3	13.7	64
S4	2-methyl-3-butanone	100	49.1	8.6	42.3
S4	Cyclooctanone	100	83.0	0	17
S4	Cyclopentanone	100	0	0	100 [b]
S4	2,4-dimethyl-3-pentanone	100	92.6	7.6	0
S4	2,6-dimethyl-cyclohexanone	70.4	80.0	20.0	0
S4	Propiophenone	100	67.2	32.8	0
S4	Benzophenone	100	64.2	35.8	0
S4	acetophenone	100	32.6	13.4	54 [b]

[a] Conversion determined by GC, based on amino-alcohol consumption and amine/amide production [b] condensation products

Effects of other additives

Other additives employed in the catalytic conversion of amino-alcohols to cyclic amines or amides are listed in **Table S2**.

Table S2: Effects of different additives on the cyclization of amino-alcohols .
Conditions: 1 mmol substrate, 1 mmol additive, 0.5 mol% $Ru_3(CO)_{12}$, 3 mol% L1 (Ru:P=1:2), 0.6 mL cyclohexane, 140ºC, 21 h.

Substrate	Additive	Conversion (%) [a]	Amine selectivity (%)	Amide selectivity (%)	Other selectivity (%)
S3	No additive	100	69.5	30.5	0
S3	NaH	100	36.4	63.6	0
S3	Mol sieves which?	98.5	89	11	0
S3	$NaHCO_3$	17.5	100	0	0
S3	H_2 p=?	100	99.1	0	0.9 [b]
S3	MeOH	100	36.2	7.8	56.0 [c]
S3	t-amylalcohol	95.9	77.8	22.2	0
S3	t-butanol	92.0	80.3	19.7	0
S3	Phenol	80	100	0	0
S3	p-toluene sulfonic acid	21.7	100	0	0
S3	H_2SO_4	100	0	0	100 [b]
S3	1,4-hydroquinone	100	7.3	51.5	41.2 [b]
S4	Acetic acid	35.7	44.9	0	55.1 [b], [d]
S4	Formic acid	22.7	53.3	34.3	12.4 [b]
S4	HCl	22.5	78.5	0	21.5 [b]

[a] Conversion was determined by GC, based on the amino-alcohol consumption and amine/amide production[b] Unidentified side-products, [c] Mainly N-methylated product [d] cyclic hemiaminal

Analysis

Response factors of 5-amino-1-pentanol (**S3**) and 6-amino-1-hexanol (**S4**) with the corresponding products of these substrates in the cyclization of amino-alcohols were determined and are listed in **Table S3**. The response factors were determined with respect to the amino-alcohol, the cyclic amine and the cyclic amide. Solutions with different concentrations of one chemical and constant for another chemical were prepared. The solutions were subjected to the GC method used for the analysis of the reaction mixture. By plotting the concentration with respect to the peak area, a line graph can be obtained from which the slope is the response factor of the variable chemical.

Table S3: Response factors of reaction products for a 5-carbon and 6-carbon amino-alcohol with respect to the cyclic-amine and the amino-alcohol.

Compound	Response factor / amino-alcohol	Response factor / cyclic amine
6-amino-1-hexanol	N/A	0.70
2-Azepanone	0.72	0.84
Azepane	0.70	N/A
5-amino-1-pentanol	N/A	0.69
2-Piperidinone	0.90	0.81
Piperidine	0.69	N/A

GC-method details

Injection Mode/ ratio:	Split/ 200
Temperature:	270ºC
Carrier Gas:	He
Flow Control Mode:	Pressure
Pressure:	121.0 kPa
Total Flow:	144.0 mL/min
Column Flow:	0.70 mL/min
Liner Velocity:	25.8 cm/sec

Column type:	Ultra-2 serial nr.: US8649351H	
Column length:	25 m, 0.33 µm film thickness, 0.20 mm inner diameter	
Column Max Temp.	310ºC	
Pressure program:	121.0 → 164.0 @ 1.8 kPa/min	164.0 hold 15 min
Temperature program:	80ºC → 270ºC @ 8ºC/min	270 hold 15 min

GC-MS of amine compounds

In **Table S4** GC-MS values are shown for compounds which have been synthesized via the cyclization of amino-alcohols.

Table S4: GC-MS analysis data for the products in the cyclization of amino-alcohols.

Compound	calculated mass (a.u.)	Found mass (a.u)
Azetidine	57.06	57.10
2-pyrrolidinone	85.05	85.10
Pyrrolidine	71.07	71.15
2-piperedinone	99.07	99.15
Piperidine	85.09	85.15
2-Azepanone	113.08	113.20
Azepane	99.10	99.20
Tetrahydroquinoline	133.09	133.10
Quinoline	129.06	129.10
Tetrahydrobenzazepine	147.10	147.15

References

[1] D. Pingen, C. Müller, D. Vogt, *Angew. Chem. Int. Ed.* 2010, **49**, 8130-8133

[2] R. V. Hoffman, J. M. Salvador, *J. Chem. Soc., Perkin Trans. 1* 1989, 1375-1380.

[3] N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* 2007, **72**, 6577-6579.