Ruthenium-Catalyzed Reactions

Concomitant Monoreduction and Hydrogenation of Unsaturated Cyclic Imides to Lactams Catalyzed by Ruthenium Compounds**

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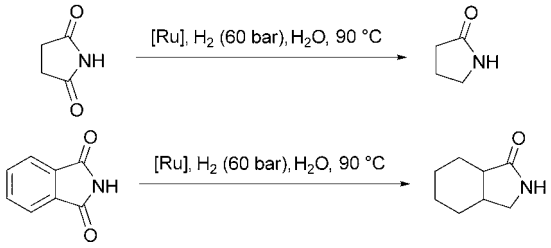
Catalytic transformations of multifunctional molecules now offer access to a variety of useful intermediates. However, there are still some important unsolved problems. This is the case of the transformation of cyclic imides into lactams through selective monoreduction of one carbonyl group which is still a challenge in organic synthesis. Strong reducing reagents such as $LiAlH_4$ have been used to perform complete reduction with formation of cyclic amines,[1] and only in the special case of highly substituted cyclic acylureas (hydantoins) was the monoreduction into ureas obtained.[2] The monoreduction of phthalimides into isoindolinone derivatives has been performed in moderate to good yields under acidic conditions in the presence of stoichiometric amounts of reducing metals such as Sn[3] or Zn.[4] Their catalytic reduction in the presence of hydrogen has been carried out with Raney nickel as catalyst, but under drastic conditions (180 °C, 190 bar H_2).[5] In water, under hydrogen pressure at 100 °C, *N*-methylsuccinimide was transformed into 2-pyrrolidinone in the presence of water-soluble ruthenium precatalysts such as $RuCl_3 \cdot 3H_2O$, $[RuCl_2(dmso)_4]$, or $[Ru(dmp)(H_2O)_2](PF_6)_2$ (dmp = 2,9-dimethylphenanthroline), but in modest yields (< 28 %).[6]

Herein we report that the ruthenium precatalysts $[RuCl_2(p\text{-cymene})]_2$ and $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ are efficient catalyst precursors for the monoreduction of cyclic imides in water under hydrogen pressure. Moreover, they make possible the concomitant monoreduction and hydrogenation of unsaturated cyclic imides into saturated lactams (Scheme 1).



Scheme 1. [Ru] = $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ and $[RuCl_2(p\text{-cymene})]_2$.

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This represents a new example of a multifunctional catalytic system able to perform two chemical transformations[7] (reduction of carbonyl groups and hydrogenation of double and aromatic bonds) with the same reagent (H_2) and with atom economy, to release only water, which is the solvent of the reaction.

The reaction of succinimide **1** (5 mmol) in distilled water (10 mL) in the presence of $[Ru_4H_6(p\text{-cymene})_4]Cl_2$[8] (1 mol%) under hydrogen (60 bar) for 13 h led to its complete and selective conversion into 2-pyrrolidinone **2**, which was isolated in 87% yield (Table 1, entry 1). No further reduction into the amine was detected. Under similar conditions, the unsaturated maleimide **3** quantitatively provided the same lactam **2** in 86% isolated yield, whereas the unsaturated tetrahydrophtalimide **4** underwent complete conversion into the bicyclic lactam **5** after 22 h of reaction (Table 1, entry 3). These reactions showed that the catalytic system operating in water is able to perform the selective monoreduction of one carbonyl group of a cyclic imide and the hydrogenation of activated and nonactivated olefinic bonds. The concomitant reduction and hydrogenation of aromatic substrates was also attempted and phthalimide **6** was converted into the aliphatic lactam **5**, which was isolated in 78% yield, after 24 h under similar catalytic conditions (Table 1, entry 4). The saturated imide **7** was also detected as a minor reaction product. Furthermore, ^{1}H NMR analyses and chiral gas-chromatography studies showed that the hydrogenation was diastereoselective and that the formed product **5** resulted from a pure *cis* addition of hydrogen to a formal junction C=C bond.

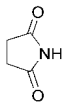
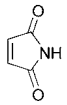
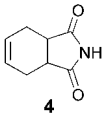
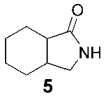
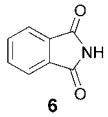
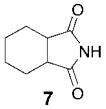
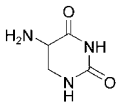
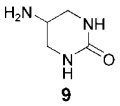
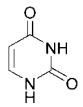
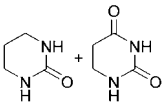
This ruthenium-based catalytic system tolerated the presence of functional groups such as primary amines as it performed the transformation of the 5-aminouracil **8** into the novel 5-amino tetrahydropyrimidin-2-one **9** through selective reduction of the acyl carbonyl group of the starting acylurea structure. The example reported in Table 1, entry 6 revealed that the reduction of the carbonyl group was more difficult to perform than the hydrogenation of the carbon–carbon double bond of uracil **10**, as after complete conversion the tetrahydropyrimidin-2-one **11** was isolated in only 70% yield together with only 30% of the saturated hydantoin **12**.

$[Ru_4H_6(p\text{-cymene})_4]Cl_2$ was prepared by treatment of $[RuCl_2(p\text{-cymene})]_2$ in water at 60 °C under 60 bar of hydrogen pressure,[8] thus under conditions very close to those of the catalytic conditions described above. The hypothesis of a common or closely related intermediates that are active in catalysis in both the previous catalytic system and during the stoichiometric transformation of $[RuCl_2(p\text{-cymene})]_2$ was evaluated. The hydrogenation of the cyclic imides **3**, **4**, **6**, **8**, and **10** in water in the presence of $[RuCl_2(p\text{-cymene})]_2$ (1–2 mol%) as catalyst precursor at 90 °C under hydrogen (60 bar; Table 1) took place even more efficiently than with $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ as precatalyst to give **2**, **5**, **7**, **9**, and **11**. Indeed, with half the amount of potentially active ruthenium sites, complete conversions and transformations into lactams were reached within shorter reaction times. For instance, the complete conversion of the imide **10** into the sole tetrahydropyrimidin-2-one **11** was obtained within 24 h which indicates a more efficient carbonyl-reduction reaction. Note that it had already been shown that the binuclear system was more active than the corresponding hydride cluster for the simple hydrogenation of aromatic hydrocarbons.[9]

With both catalysts, the hydrogenation of N-substituted phthalimides and phthalic anhydride only led to the hydrogenation of the aromatic ring. This shows that the presence of the NH bond of the cyclic imides plays a crucial role in the reduction of one carbonyl group.

A screening of the temperature and H_2 pressure parameters in the presence of $[RuCl_2(p\text{-cymene})]_2$ as catalyst precursor indicated that the hydrogenation of the aromatic ring of phthalimide **6** took place even at low temperature (50 °C) and low pressure (10 bar), whereas the reduction of

Table 1: Monoreduction/hydrogenation of cyclic imides in the presence of $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ and $[RuCl_2(p\text{-cymene})]_2$ as catalyst precursors.[a]

Entry	Substrate	Product	$[Ru_4H_6(p\text{-cymene})_4]Cl_2$		$[RuCl_2(p\text{-cymene})]_2$	
			t [h]	Isolated Yield[b] [%]	t [h]	Conversion [%]
1	 **1**	 **2**	13	87	–	–
2	 **3**	 **2**	13	86	3	100
3	 **4**	 **5**	22	97	15	100
4	 **6**	**5** +  **7**	24	78 (**5**)	15[c]	76 (**5**) 24 (**7**)
5	 **8**	 **9**	24	66	13	100
6	 **10**	 **11** **12**	23	70 (**11**) 30 (**12**)	24	100 (**11**)

[a] General conditions: imide (1 mmol), $[Ru_4H_6(p\text{-cymene})]Cl_2$ (1 mol%), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), water (5–10 mL), hydrogen (60 bar), 90 °C. [b] Complete conversion. [c] Catalyst (2 mol%).

the carbonyl group required high temperatures (Table 2). In hydrogenation with molecular metal catalysts, the question of the colloidal or nanoparticle nature relative to the molecular nature of the active species is raised.[10,11] Mercury is known to

Table 2: Reaction of phthalimide **6** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2 mol%).[a]

$P(H_2)$ [bar]	T [°C]	t [h]	**7/5**
60	90	15	24:76
30	90	23	20:80
10	90	21	25:75
60	50	23	78:22
60	90	15	17:83[b]

[a] **6** (1 mmol), H_2O (5 mL), complete conversion of **6.** [b] Reaction performed in the presence of mercury.

poison heterogeneous catalysts by formation of an amalgam with metals.[11] We have found that the transformation of **6** with a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$ in the presence of mercury under our most severe conditions (90 °C, 60 bar) during 15 h led to quantitative conversion of the phthalimide **6** to form **7** and **5** in the ratio 17:83, which is very close to that observed in the absence of mercury (Table 2). This result tends to corroborate the involvement of molecular catalytic species rather than colloids or nanoparticles in this type of hydrogenation process under the temperature and hydrogen pressure conditions used.

We have revealed a new catalytic activity of easy to prepare or commercially available ruthenium complexes and solved the problem of selective monoreduction of cyclic imides into lactams. Moreover, these complexes generate catalytic systems that are able to promote two catalytic reactions in one pot: the hydrogenation of carbon–carbon double bonds, including aromatic structures, and the monoreduction of cyclic imides. These catalytic systems might be very helpful for selective reduction of imides and desymmetrization transformations.

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