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Ruthenium(II)-Complex-Catalyzed Acceptorless Double Dehydrogenation of Primary Amines to Nitriles

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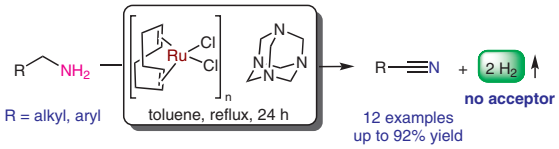

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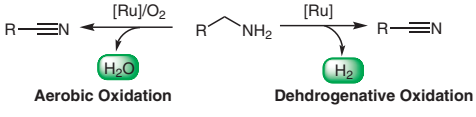
Abstract Acceptorless dehydrogenative oxidation of primary amines into nitriles using an *in situ* complex derived from commercially available dichloro(1,5-cyclooctadiene) ruthenium(II) complex and simple hexamethylenetetramine has been demonstrated. The synthetic protocol is highly selective and yields the nitrile compounds in moderate to excellent yields and produces hydrogen as the sole byproduct.

Key words ruthenium, amine, nitrile, dehydrogenation

Nitrile compounds play a vital role in the field of synthetic chemistry for the synthesis of several industrially important products.[1] As a result; several methods are available for the synthesis of nitrile compounds. Some of the important traditional methods available for the synthesis of nitrile compounds include Sandmeyer-type reaction, ammoxidation reaction, Rosenmund–von Braun reaction, and other methods which use stoichiometric amounts of oxidizing agents such as MnO_2, HgO–I_2, DDQ, IBX, S, and many others.[2,3] All the traditional methods suffer from several drawbacks such as the use of toxic reagents/reactants, poor atom economy, and harsh reaction conditions.[2,3] Among several existing methods for the synthesis of nitrile compounds from a variety of starting materials, oxidation of amines using transition-metal catalysts provides direct access. The transition-metal-catalyzed oxidation of amines involves two different pathways, namely aerobic oxidation and dehydrogenative oxidation. The aerobic oxidation of amines works in the presence of transition-metal catalyst in combination with an external oxygen source and produces water as the side product.[4] Though, this method is very efficient in producing nitriles, sometimes it suffers from selectivity issues forming other possible side product such as amide.[4a] The second methodology which involves the metal-catalyzed dehydrogenative oxidation was found to be very superior compared to aerobic oxidation and other traditional methods as it is very clean, producing hydrogen as the sole byproduct, and has high atom economy (Scheme 1). Moreover, the metal-catalyzed dehydrogenative oxidation methodology was identified as a potential candidate in the field of hydrogen storage and transportation as amines are considered as liquid organic hydrogen carriers (LOHCs).[5]



Scheme 1 Ruthenium-catalyzed oxidation of primary amine

Notwithstanding its potential applications, the reported catalyst systems for the dehydrogenation of amines, especially the dehydrogenation of primary amine to form nitriles, are scarce. To the best of our knowledge only three catalyst systems are available in the literature for the acceptorless and dehydrogenative oxidation of primary amines to form nitrile compounds. The complexes are pyridine-based PNN-pincer ruthenium complex by Szymczak and co-workers,[6] Ru(*p*-cymene) system reported by Bera and co-workers,[7] and $[Ru(benzene)Cl_2]_2$ reported by our group (Scheme 2).[8]

In transition-metal-catalyzed organic transformations, the role of additives is crucial in deciding the selectivity and efficiency of the catalyst system. The added additive works in tandem with metal catalyst by providing different reaction pathway by activating catalyst and/or substrate(s).[9] It has been reported in the literature that hexamethylenetetramine (HMTA) upon decomposition can act as a source of small molecules such as NH_3, H_2, HCN, HCHO, CO, CO_2, and many others, which makes HMTA an interesting molecule in organic synthesis.[10] Recently, we have reported the first

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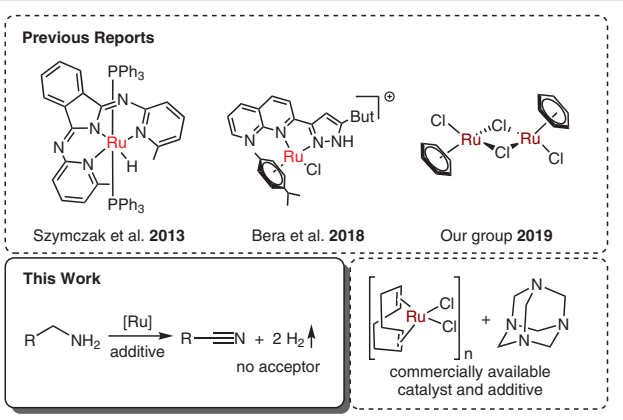


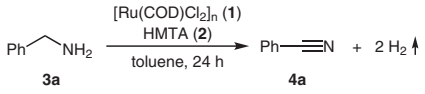
Scheme 2 Ruthenium-catalyzed double dehydrogenation of amines

example of hexamethylenetetramine (HMTA) being simultaneously acting as both base as well as hydride donor in $[Ru(benzene)Cl_2]_2$-catalyzed acceptorless amine dehydrogenation reaction.[8] In view of extending the chemistry of HMTA as a cheap and versatile additive, we explored its reactivity in combination with other ruthenium complexes. Herein, we report the efficient conversion of primary amines into nitriles using the commercially available $[Ru(COD)Cl_2]_n$ as the pre-catalyst and simple HMTA as the additive. Experimental studies proved that the oxidation of primary amines to nitriles involves double dehydrogenation pathway with the evolution of hydrogen as the sole by-product.

Encouraged by the activity of $[Ru(benzene)Cl_2]_2$ for the dehydrogenative oxidation of amines, we tested the activity of $[Ru(COD)Cl_2]_n$ (**1**) in combination with HMTA (**2**) for the dehydrogenation of amines. The dehydrogenation of benzylamine (**3a**) to form benzonitrile (**4a**) was taken as the model reaction, and several reactions were carried out to optimize the reaction conditions as depicted in Table 1.

Initially, 5 mol% of **1** was tested for the conversion of **3a** into **4a** in the absence of any additive under toluene reflux conditions for 24 h, which resulted in the formation of nitrile product **4a** in poor yield (Table 1, entry 1). When HMTA (**2**) was employed in the absence of Ru complex, no formation of product was observed (entry 2). However, when the activity of 0.5 mol% of **1** combination with 0.5 mol% **2** was tested, it led to increase in the yield of **4a** (entry 3). Further increase in catalyst/additive loading resulted in the increased yield of the product, and excellent yields were obtained while using 3 mol% both **1** and **2** (entries 4–6). After identifying the suitable catalyst and additive ratio and amount, other parameters such as reaction solvent, temperature, and time were optimized and identified that toluene reflux conditions for 24 h were ideal for the dehydrogenative oxidation of amine to form nitrile (entries 7–11).

Table 1 Optimization of Reaction Conditions for Catalytic Dehydrogenation of Benzylamine (**3a**)

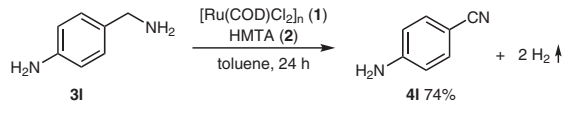


Entry	[Ru] (mol%)	HMTA (mol%)	Solvent	Temp (°C)	Time (h)	Yield of **4a** (%)[a]
1	5	–	toluene	110	24	27
2	–	5	toluene	110	24	–
3	0.5	0.5	toluene	110	24	56
4	1	1	toluene	110	24	70
5	2	2	toluene	110	24	85
6	3	3	toluene	110	24	97
7	3	3	THF	64	24	0
8	3	3	CH_2Cl_2	40	24	2
9	3	3	toluene	80	24	54
10	3	3	toluene	80	6	42
11	3	3	toluene	80	12	56

[a] GC yields using dodecane as the internal standard and average of at least two runs.

After optimizing the reaction conditions for the double dehydrogenation of amines to form nitriles, we explored the substrate scope of our catalyst system as shown in Table 2.

Initially, in view of testing the electronic effect on the yield of nitrile product, a series of substituted benzylamine substrates were tested. The presence of electron-donating substituents such as methyl (**3b**) and methoxy (**3c**) groups in the *para* position gave the corresponding nitrile products **4b** and **4c**, respectively, in excellent yields (Table 2, entries 2 and 3). The slight decrease in the yields of nitrile product was observed when electron-withdrawing substituents, namely chloro (**3b**), fluoro (**3e**), and nitro (**3f**), were present in the para position (entries 4–6). Moreover, the halogen and nitro groups were retained in the nitrile products indicating the very good functional group tolerance of our catalyst system. The presence of substituents such as methyl (**3g**) and chloro (**3h**) groups in the *ortho* position gave the nitrile products **4g** and **4h** in moderate yields, showing the developed catalyst system is sensitive towards the steric factor (entries 7 and 8). The dehydrogenation of few alkyl amines was also tested and all of them gave the corresponding nitrile products in very good yields (entries 9–11).

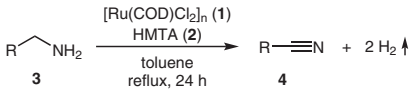


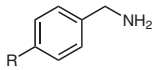
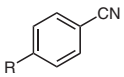
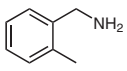
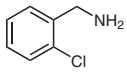
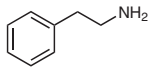
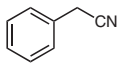
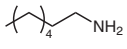
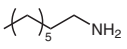
Scheme 3 Dehydrogenation of 4-aminobenzylamine

In order to check the selectivity and functional group tolerance, the double dehydrogenation of 4-aminobenzylamine (**3l**) having both $H_2N–CR_2$ and $H_2N–CH_2–$ groups was attempted using the present catalyst system (Scheme 3). The reaction resulted in the formation of 4-aminobenzonitrile (**4l**) as the only product in good yield. This result shows the very good selectivity of our catalyst system. In addition, this also proves the oxidation reaction involving the dehydrogenative pathway without forming 4-nitrobenzonitrile, which is possible during aerobic oxidation in the presence of any external oxygen source.

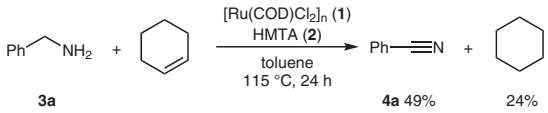
Further, to confirm the evolution of hydrogen gas and dehydrogenative pathway, the double dehydrogenation of benzylamine was conducted using the present catalyst system in the presence of a hydrogen acceptor such as cyclohexene. In a typical closed-vessel reaction, **1** (3 mol%), **2** (3 mol%), benzylamine, and cyclohexene in 1:10 equivalent ratio were taken heated at 115 °C for 24 h using toluene as the solvent (Scheme 4). This resulted in the formation of cyclohexane in 24% yield.

Table 2 Dehydrogenative Oxidation of Amines to Nitriles[a]



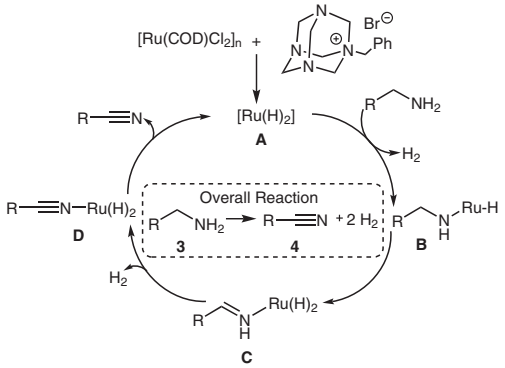
Entry	Substrate **3**	Product **4**	Isolated yield (%)[b]
			
1	**3a** R = H	**4a**	88
2	**3b** R = CH_3	**4b**	92
3	**3c** R = OCH_3	**4c**	90
4	**3d** R = Cl	**4d**	82
5	**3e** R = F	**4e**	80
6	**3f** R = NO_2	**4f**	79
7	 **3g**	 **4g**	73
8	 **3h**	 **4h**	70
9	 **3i**	 **4i**	83
10	 **3j**	 **4j**	80
11	 **3k**	 **4k**	82

[a] Reactions were carried out with amine substrate (0.47 mmol), $Ru(COD)Cl_2$ (3 mol%), and HMTA (3 mol%) in toluene (0.6 mL) under reflux.
[b] Isolated yields and average of at least two runs.



Scheme 4 Dehydrogenation of benzylamine in the presence of cyclohexene

The above reaction suggested that the reaction involved hydrogen evolution and followed the dehydrogenative pathway (Scheme 4). Based on the literature report and our experimental results, the following mechanism has been proposed for the double dehydrogenation of primary amines to form nitrile compounds (Scheme 5). In our previous report we proved the formation of $Ru(H)_2$ species as the catalytically active species during dehydrogenation of primary amines while using $[Ru(benzene)Cl_2]_2$ as the pre-catalyst and HMTA as the additive.[8] Further, we experimentally proved that HMTA acted simultaneously as a source of base as well as hydride donor. According to the proposed mechanism the catalytically active species $[Ru(H)_2]$ (**A**) is generated from a reaction between complex **1** and additive **2**. The active catalyst **A** upon reaction with primary amine, followed by elimination of hydrogen molecule lead to the formation of amine-coordinated Ru–hydride complex **B**. The complex **B** undergoes β-elimination to form the imine-coordinated Ru–dihydride intermediate **C**. The formation of imine-coordinated Ru complex was observed in the in situ ^1H NMR study of dehydrogenation of benzylamine using the present catalyst system (Figure S13 in the Supporting Information). The complex **C** upon elimination of hydrogen molecule and β-elimination resulted in the formation of nitrile-coordinated ruthenium complex **D**. The complex **D** further undergoes reductive elimination to yield the nitrile product and regenerate the active catalyst **A**.



Scheme 5 Mechanism for the oxidation of amine to nitrile

In conclusion, the double dehydrogenation of several primary amines to form nitrile products using an *in situ* catalyst system generated from $[Ru(COD)Cl_2]_n$ as the pre-catalyst and HMTA as the additive was developed.[11–13] The present catalyst system is highly atom economic as it avoids the use of any oxidizing agent/hydrogen acceptor and yielded the nitrile products even in good to excellent yields. The mechanism studies revealed that the reaction involves dehydrogenative pathway with the evolution of hydrogen molecule.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1708016.

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(11) **General Procedure for the Dehydrogenation of Amine**
Ruthenium(II) chloride 1,5-cyclooctadiene **1** (3 mol%), HMTA (**2**, 3 mol%), amine **3** (0.25 mL), and dry toluene (1.0 mL) were placed in a Schlenk tube. The reaction mixture was stirred under open conditions to nitrogen and refluxed for 24 h. After completion of the reaction all toluene were evaporated under vacuo, the oxidized products **4** were isolated from crude mixture with the help of column chromatography using hexane/EtOAc as eluent. The formation of products was confirmed by comparing the ^{1}H NMR data with literature reports.

(12) **General Procedure for the Dehydrogenation of Benzylamine 3 in the Presence of Cyclohexene**
In a 50 mL closed-vessel reactor, ruthenium(II) chloride 1,5-cyclooctadiene **1** (0.004 g, 0.013 mmol), HMTA (**2**, 0.002 g, 0.013 mmol), amine **3** (0.05 mL, 0.5mmol), cyclohexene (0.4 mL, 5 mmol), and dry toluene (0.6 mL) were taken. The resulting mixture was heated at 110 °C for 24 h. After completion of the reaction, the solution was cooled to room temperature and extracted with CH_2Cl_2 then analyzed through gas chromatography; yield of benzonitrile **4** 49% and cyclohexane 24%.

(13) **General Procedure for *in situ* ^{1}H NMR Study to Show Formation of Imine Intermediate**
In N_2 atmosphere benzylamine **3** (0.05 mL, 0.46 mol), ruthenium(II) chloride 1,5-cyclooctadiene (**1**, 0.004 g, 3 mol%) HMTA (**2**, 0.002 g, 3 mol%), and toluene-d_8 as a solvent (0.4 mL) were taken in the NMR tube. The reaction mixture was heated at 110 °C for 12 h, and then the reaction mixture was cooled to room temperature before collecting the NMR data.