Easy ruthenium-catalysed oxidation of primary amines to nitriles under oxidant free conditions

Thierry Achard, Julien Egly, Michel Sigrist, Aline Maisse-François, Stéphane Bellemin-lapponnaz

► To cite this version:

Thierry Achard, Julien Egly, Michel Sigrist, Aline Maisse-François, Stéphane Bellemin-lapponnaz. Easy ruthenium-catalysed oxidation of primary amines to nitriles under oxidant free conditions. Chemistry - A European Journal, 2019, 25 (58), pp.13271-13274. 10.1002/chem.201902557 . hal-02330378

HAL Id: hal-02330378

<https://hal.science/hal-02330378>

Submitted on 23 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Easy ruthenium-catalysed oxidation of primary amines to nitriles under oxidant free conditions

Thierry Achard,^a Julien Egly,^a Michel Sigrist,^a Aline Maise-François,^a Stéphane Bellemin-Laponnaz^a

Abstract: A dehydrogenation of primary amine to give the corresponding nitrile under oxidant- and base-free conditions catalysed by simple $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$ with no extra ligand is reported. The system is highly selective for alkyl amine whereas benzylamine derivatives gave the nitrile product together with the imine in ratio ranging from 14:1 to 4:1 depending on the substrate. Preliminary mechanistic investigations have been performed to identify the key factors that govern the selectivity.

Nitrile is a valuable functional group which gives rise to different class of organic molecules.¹ Structurally diverse nitrile-containing compounds are present in many natural products,² medicinal drugs,³ and involved in industrial processes.⁴ Conventional approaches for nitrile synthesis^{1b} such as Sandmeyer reaction,⁵ the Rosenmund-von Braun reaction,⁶ the dehydration of amides/oximes,⁷ metal-catalysed cyanation,⁷ oxidation of primary amine using iodine based⁸ or metal-catalysts^{9,10} and others^{7, 11} generally involve complicated operations, heavy metal waste, toxic reagents (e.g., KCN or CuCN), with restricted reactivity and poor selectivity¹² or harsh reaction conditions.

Acceptorless Dehydrogenation (AD)¹³ of primary amine has emerged as an elegant alternative in which a double dehydrogenation takes place, producing H_2 gas as the sole by-product and thus produces non-toxic waste. However, relatively few catalysts have been reported for the dehydrogenation of amine^{13a, 14} in contrast to alcohol.^{13, 15} Among those, only few avoid the use of excess oxidant and they achieve either low conversion or require exogenous additives (bases and/or sacrificial hydrogen acceptor) under harsh conditions.¹⁴ Beside this, the reaction selectivity remains an issue due to the competition between the second dehydrogenation and the transamination pathway.^{13, 16}

So far, only a few rare examples are known in the literature for the highly selective transformation of primary amine into nitrile under acceptorless and oxidant-free conditions (Scheme 1).¹⁷ The first example was reported in 2013 by Szymczak^{17a} with bis(2-pyridylimino)isoindolate Ru(II) hydride derivative **1** as catalyst. Ru p-cymene NHC complexes **2** were found active albeit with moderate selectivity,^{17d} however the catalyst can be recycled for alternative hydrogen storage purpose.¹⁸ Finally, very recently Ru(II) p-cymene pyrazole **3** system displayed good

selectivity however it requires the addition of a strong base to achieve high reactivity.^{17e}

Scheme 1. Selective formation of nitrile without hydrogen acceptor additive and under oxidant free condition.

While evaluating ruthenium complexes with various ancillary ligands for this reaction, we found that a simple Ru(II) precursor (i.e. $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$) may act as an efficient catalyst. Indeed, in some metal-catalysed reactions the addition of ancillary ligands is unnecessary, since the substrate itself can serve as a ligand.¹⁹ Herein, we explored the amine dehydrogenation under oxidant- and base-free conditions with $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$ as precatalyst. Under optimised conditions alkyl amines were selectively converted into the nitrile derivatives. Benzyl amine substrates also gave the expected product albeit together with little of the imine. We also conducted some experiments to have better insight into the active species.

Initially, we studied the model reaction using benzylamine²⁰ to establish an efficient catalytic system for benzonitrile synthesis (Table 1). The reactions were conducted for 24h at 110 °C in 1,2-dichlorobenzene (ODCB) in an open vessel under inert atmosphere.²¹ Several classical Ru precursors were then evaluated and a complete disappearance of the amine was observed in all cases (5 mol% cat., Entries 1-5). However, among them only $[\text{Ru}(\text{p-cym})\text{Cl}_2]_2$ was found to selectively generate the benzonitrile as the sole product thanks to the analysis of both ¹H NMR and GC spectra of reaction mixtures. Consistent with Szymczak observation,^{17a-c} only trace of nitrile was observed in a closed system under our conditions (Entry 6).

[a] Dr. T. Achard, J. Egly, M. Sigrist, Dr. A. Maise-Francois, Dr. S. Bellemin-Laponnaz
Département des Matériaux Organiques
Institut de Physique et Chimie des Matériaux de Strasbourg
(IPCMS) Université de Strasbourg, CNRS UMR-7504
23 rue du Loess, BP 43, 67034 Strasbourg Cedex 2, France
E-mail: thierry.achard@ipcms.unistra.fr; bellemin@unistra.fr

Supporting information, including general experimental procedures, additional schemes and figures, characterization data and NMR spectra for this article, is given via a link at the end of the document.

In addition, under our conditions with an atmosphere of O₂, in a closed system, the reaction is less selective producing undesired benzaldehyde (ca. 10%) as by-product.^{8b, 12e-g} Further optimisation studies showed that dry 1,2-dichlorobenzene, 1M concentration of amine and 2.5 mol% of ruthenium was the best combination among a variety of solvents, concentrations and catalyst loadings (see SI).²²

Table 1. Evaluation of benzylamine oxidation under varying conditions.^[a]

Entry 1 ^[a]	[Ru]	Conv (%) ^[b]	Selectivity (%) ^[b]	
			4	5
1	Ru(acac) ₃	100	80	20
2	[CpRu(CH ₃ CN) ₃][PF ₆]	100	75	25
3	Ru ₃ (CO) ₁₂	100	73	27
4	[Ru(benzene)Cl ₂] ₂	100	86	14
5	[Ru(<i>p</i> -cym)Cl ₂] ₂	100	100	0
6 ^[c]	[Ru(<i>p</i> -cym)Cl ₂] ₂	5% <	0	100
7 ^[d]	[Ru(<i>p</i> -cym)Cl ₂] ₂	100	86	11 ^[e]

[a] Reaction conditions: benzylamine (0.2 mmol), 5 mol% cat. based on Ru and 1,2-dichlorobenzene (0.2 mL), 110 °C, 24h, open vessel under argon atmosphere; [b] Conversion and selectivity were determined by ¹H RMN, internal reference hexadecane; [c] Closed system under argon atmosphere. [d] H₂O (0.2 mmol). [e] presence of 3% of benzaldehyde

Next, a series of amine substrates was examined under the optimized conditions (Tables 2 and 3). Non-benzylic amines generated corresponding nitriles as the exclusive product in good yield after chromatographic purification on SiO₂ (**6-15**). Only the crowded adamantylamine was found less selective by producing small amount of non-desired imine in a ratio of 6 to 1 in the crude product. Nonetheless, the expected product (**16**) was isolated in 65% yield. Aliphatic amines showed good reactivity, whether for short or long carbon chains. Both geranylamine and oleylamine gave geranyl nitrile (**11**) and oleonitrile (**12**) in 50 and 67% yield, respectively, where double bonds remained unaltered.

Electronic and steric effects were evaluated through different substitution pattern on benzylic substrates (Table 3). Whereas benzylamine gave benzonitrile as a sole product, introduction of substituents onto the phenyl ring induced the formation of imines as secondary product. In all cases, amines were totally consumed to generate nitriles together with imines at different ratios. The presence of a substituent in *para* is well tolerated by the system giving good level of selectivity. In contrast, the presence of a substituent in *ortho*- or *meta*-position led to a decrease of selectivity (compare **17** with **18**, **19** with **20** and **21** or **22** with **23**). This lower selectivity can be attributed either to the coordinating nature or the steric bulk of the *ortho*-groups, which might interfere with the metallic centre. Electron-withdrawing groups cause a greater loss of nitriles selectivity, notably for the most electron attractive p-CF₃ group (**26**) that

gave a 4/1 nitrile/imine ratio. Those moderate yields are due to the hydrolysis of imine derivatives into aldehydes, during the purification step, which possess very close R_f with the corresponding benzyl-nitriles compounds and thus make their separation very difficult.

Table 2. Substrate scope for [Ru(*p*-cym)Cl₂]₂ catalyzed oxidation of primary alkyl amine to nitrile.^[a]

[a] Reaction conditions: amine (0.2 mmol), 1.25 mol% [Ru(*p*-cym)Cl₂]₂, and 1,2-dichlorobenzene (0.2 mL), 110 °C, 24h in open vessel under argon atmosphere. Yields refer to isolated products.

Table 3. Substrate scope for [Ru(*p*-cym)Cl₂]₂ catalyzed oxidation of benzylic amines to nitriles.^[a]

[a] Reaction conditions: amine (0.2 mmol), 1.25 mol% [Ru(*p*-cym)Cl₂]₂, and 1,2-dichlorobenzene (0.2 mL), 110 °C, 24h in open vessel under argon atmosphere. Yields refer to isolated products.

The reactivity of dibenzylamine and indoline has also been studied under our experimental conditions (SI, Figure S8). The use of [Ru(*p*-cym)Cl₂]₂ complex afforded the selective imine product for dibenzylamine however the reaction was rather slow compared to primary amine as only 25% conversion was achieved after 24h of reaction. On the other hand, indoline was cleanly converted into the sole indole as shown by both ¹H NMR and GC analyses.

To shed light on the reaction mechanism, we conducted various experiments. First, the reaction profile of benzylamine dehydrogenation catalysed by [Ru(*p*-cym)Cl₂]₂ followed over time shows that the system requires a 3h induction period likely to form the *catalytic active species* (see SI). This is also consistent with our observation that in each catalytic test, immediately after adding the amine substrate, the solution turned yellow and then gradually dark-red after a few hours at 110 °C.

The homogeneous nature of the catalytic system was confirmed by the addition of ≈ 300 equivalents of Hg(0) which did not affect the formation of benzonitrile.²³ In addition, a poisoning experiment using 0.5 equivalent of 1,10-phenanthroline vs. [Ru] induced an increase of imine formation with a product distribution of 3/1 nitrile/imine. However, addition of up to 50 equivalents of 1,10-phenanthroline did not poison the reaction, but instead promoted the formation of the sole imine product.

Nitrile functional groups are well known in coordination chemistry to be good ligand for transition metals thereby they can contribute to the activity of the catalyst or compete with the substrate and inhibit the system. Addition of 4 equivalents of benzonitrile vs. [Ru] in the media led to a slight increase of the reaction rate of benzylamine (51% conv. after 6h instead of 33% conv.). However, competitive binding of nitrile to active Ru species appeared while using a large excess of benzonitrile (2000 equivalents vs. [Ru]) where only 62% conversion was observed after 24h.

In the presence of the only N-Benzylidenebenzylamine **5** and the ruthenium complex, no reaction occurred. Additionally, the reaction carried out in presence of imine **5** and *n*-octylamine showed total consumption of the amine after 24h and produced benzonitrile **4**, *n*-octylnitrile **7** and the transamination product **27** (confirmed by both GC and ¹H NMR spectra analysis) along unreacted **5** (scheme 2).²⁴ Other cross coupling imine and auto-coupling products from *n*-octylamine were never observed. This cross experiment indicates that the short-lived intermediate aldimine from *n*-octylamine undergo quick second dehydrogenation step rather than the transamination process.

Scheme 2. Competition experiment between imine **3** and octylamine under oxidant free condition

Finally, NMR experiments were achieved by the sequential addition of benzylamine to a CD₂Cl₂ solution of [Ru(*p*-cym)Cl₂]₂ and evolution was followed by ¹H NMR over the time. After addition of 2.4 equiv. of BnNH₂, a rapid formation of neutral complex Ru(*p*-cym)Cl₂(BnNH₂) was observed (Figure 1, c).²⁵ The slight excess of benzylamine (signal at 3.88 ppm) allows the system to evolve slowly towards the formation of a new species (see d). ¹H NMR spectra shows appearance of two new sets of characteristic signals of coordinated benzylamine respectively at δ 4.20 and 3.98 ppm for the benzylic protons and at 6.35 and 2.32 ppm for those of the NH₂. In other hands, typical signals of coordinated *p*-cymene were shifted downfield. The mixture of the two complex did not evolved even after 4 days for which [(BnNH₂)Ru(*p*-cym)Cl₂] is the major specie (see d). Finally, addition of two more equivalents of amine lead to the total conversion of the remaining [(BnNH₂)Ru(*p*-cym)Cl₂] in a new ruthenium complex (Figure 1, e) and the complex did not evolved even after 48h. 2D NMR analyses of the mixture advocate the formation of a cationic [Ru(*p*-cym)Cl(BnNH₂)₂]⁺Cl⁻ complex on which two BnNH₂ molecules are coordinated. Noteworthy, doing the same experiment with octylamine provided similar ruthenium cationic species (see SI).

Figure 1. In situ formation of [Ru(*p*-cym)Cl(BnNH₂)₂]⁺Cl⁻. (a) isolated complex [Ru(*p*-cym)Cl₂(BnNH₂)₂]; (b) complex [Ru(*p*-cym)Cl₂]₂; (c) addition of 2.4 equiv of BnNH₂; (d) after 19h; (e) after 4 days; (f) addition of 2 equiv of BnNH₂, spectrum after 19 h..

At 110°C, the well-defined complex [(BnNH₂)Ru(*p*-cym)Cl₂] stayed totally unchanged. However, addition of 10 equivalents of BnNH₂ to reaction mixture lead to the total consumption of both the [(BnNH₂)Ru(*p*-cym)Cl₂] complex and BnNH₂; no more Ru(*p*-

cym) species were detected by ^1H NMR and we observed free cymene ligand in solution along the formation of benzonitrile. Same result was obtained starting with the $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ precursor. In each case, the characteristic N-H and C-H signals, around 9-8 ppm, for the coordinated aldimine intermediate has never been observed.²⁶ We propose that the coordination of the amine is directly followed by a loss of H_2 to afford an aldimine intermediate which remains bound to the ruthenium center. This species presumably undergoes a faster dehydrogenation reaction, to afford a Ru-nitrile adduct, than either its direct attack by benzylamine or its release in the media to conduct to imine compound. Then rather labile nitrile on ruthenium might be substituted by amine substrate at low nitrile concentration but this process exchange might be slow down at high concentration. In summary, we have developed a straightforward access to nitrile from amine by employing a commercially available ruthenium precursor with no need of additional ligand. This reaction features no oxidant or base and is highly selective with alkylamine derivatives. Good activity was also observed with benzyl amine albeit with some imine as by-product. Further studies to improve the system are currently underway in our laboratory.

Acknowledgements

We gratefully acknowledge the funding from Région Grand Est.

Keywords: dehydrogenation • nitrile • acceptorless dehydrogenation • ruthenium • homogenous catalysis

- [1] (a) R. C. Larock, in: *Comprehensive Organic Transformations: a Guide to Functional Group Preparations*, Wiley-VCH, Weinheim, **1989**, pp 819–995. (b) A. J. Fatiadi, in: *Preparation and Synthetic Applications of Cyano Compounds*, (Eds.: S. Patai, Z. Rappoport), Wiley-VCH, New York, **1983**.
- [2] (a) F. F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597-606; (b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902-7917.
- [3] A. Kleemann, J. Engel, B. Kutscher, D. Reichert, in *Pharmaceutical Substance: Synthesis Patents, Applications*, 4th edn., Georg Thieme Verlag, Stuttgart, **2001**
- [4] Pollak, P.; Romeder, G.; Hagedorn, F.; Gelbke, H.-P. *Nitriles. In Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH: Weinheim, Germany, **2012**
- [5] T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1635.
- [6] K. W. Rosenmund, E. Struck, *Ber. Dtsch. Chem. Ges.* **1919**, *2*, 1749–1756
- [7] G. B. Yan, Y. Zhang, J. B. Wang, *Adv. Synth. Catal.* **2017**, *359*, 4068-4105.
- [8] (a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299-5358; (b) T. Najam, S. S. A. Shah, K. Mehmood, A. U. Din, S. Rizwan, M. Ashfaq, S. Shaheen, A. Waseem, *Inorg. Chim. Acta* **2018**, *469*, 408-423.
- [9] Sheldon, R. A.; Kochi, J. K. in *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: San Diego, **1981**; pp 387-397
- [10] M. T. Schumperli, C. Hammond, I. Hermans, *Acs Catalysis* **2012**, *2*, 1108-1117.
- [11] (a) J. Kim, H. J. Kim, S. Chang, *Angew. Chem. Int. Ed.* **2012**, *51*, 11948-11959; (b) R. Ray, A. S. Hazari, G. K. Lahiri, D. Maiti, *Chemistry-an Asian Journal* **2018**, *13*, 2138-2148.
- [12] (a) F. Porta, C. Crotti, S. Cenini, G. Palmisano, *J. Mol. Catal.* **1989**, *50*, 333-341; (b) W. P. Griffith, B. Reddy, A. G. F. Shoair, M. Suriaatmaja, A. J. P. White, D. J. Williams, *J. Chem. Soc., Dalton Trans.* **1998**, 2819-2825; (c) S. Yamazaki, Y. Yamazaki, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 301-303; (d) S. Aiki, A. Taketoshi, J. Kuwabara, T.-a. Koizumi, T. Kanbara, *J. Organomet. Chem.* **2011**, *696*, 1301-1304; (e) J. Kim, S. S. Stahl, *Acs Catalysis* **2013**, *3*, 1652-1656.
- [13] (a) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681-703; (b) C. Gunanathan, D. Milstein, *Science* **2013**, *341*; (c) C. Chen, F. Verpoort, Q. Y. Wu, *RSC Advances* **2016**, *6*, 55599-55607; (d) P. Pandey, I. Dutta, J. K. Bera, *Proc. Natl. Acad. Sci., India, Sect. A Phys. Sci.* **2016**, *86*, 561-579; (e) R. H. Crabtree, *Chem. Rev.* **2017**, *117*, 9228-9246.
- [14] D. L. J. Broere, *Physical Sciences Reviews* **2018**, *3*.
- [15] (a) T. C. Johnson, D. J. Morris, M. Wills, *Chem. Soc. Rev.* **2010**, *39*, 81-88; (b) S. Siddiki, T. Toyao, K. Shimizu, *Green Chem.* **2018**, *20*, 2933-2952.
- [16] A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410-1459.
- [17] (a) K. N. T. Tseng, A. M. Rizzi, N. K. Szymczak, *J. Am. Chem. Soc.* **2013**, *135*, 16352-16355; (b) K. N. T. Tseng, N. K. Szymczak, *Synlett* **2014**, *25*, 2385-2389; (c) L. V. A. Hale, T. Malakar, K.-N. T. Tseng, P. M. Zimmerman, A. Paul, N. K. Szymczak, *Acs Catalysis* **2016**, *6*, 4799-4813; (d) D. Ventura-Espinosa, A. Marza-Beltran, J. A. Mata, *Chem. Eur. J* **2016**, *22*, 17758-17766; (e) I. Dutta, S. Yadav, A. Sarbajna, S. De, M. Holscher, W. Leitner, J. K. Bera, *J. Am. Chem. Soc.* **2018**, *140*, 8662-8666.
- [18] M. Grellier, S. Sabo-Etienne, *Dalton Trans.* **2014**, *43*, 6283-6286.
- [19] (a) G. Franc, A. Jutand, *Dalton Trans.* **2010**, *39*, 7873-7875; (b) L. A. Perego, R. Blicke, A. Groue, F. Monnier, M. Taillefer, I. Ciofini, L. Grimaud, *Acs Catalysis* **2017**, *7*, 4253-4264.
- [20] Reproducibility of the reaction selectivity requires well dried amine.
- [21] The schlenk valve is put in the open position and connects to an argon inlet via the vacuum ramp to allow the evacuation of the H_2 formed during the reaction
- [22] The ODBC polar solvent improved the solubility of the active species compared to toluene for which the formation of a black solid is always observed during the reaction. 0.2 mL of ODBB was chosen as the standard volume because it allows better separation by SiO_2 chromatography than with larger volumes, thus giving isolated yields greater than 1 or 3 mL.
- [23] (a) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem* **2003**, *198*, 317-341; (b) R. H. Crabtree, *Chem. Rev.* **2012**, *112*, 1536-1554.
- [24] M. Ciaccia, S. Di Stefano, *Org. Biomol. Chem.* **2015**, *13*, 646-654.
- [25] P. Govindaswamy, Y. A. Mozharivskyj, M. R. Kollipara, *Polyhedron* **2004**, *23*, 3115-3123.
- [26] G. Albertin, S. Antoniutti, J. Castro, *J. Organomet. Chem.* **2010**, *695*, 574-579.