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Acceptorless dehydrogenation of amines to nitriles catalyzed by N-heterocyclic carbene-nitrogen-phosphine chelated bimetallic ruthenium (II) complex



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ABSTRACT

We have developed a clean, atom-economical and environmentally friendly route for acceptorless dehydrogenation of amines to nitriles by combining a new dual N-heterocyclic carbene-nitrogen-phosphine ligand R(CNP)₂ (R = o-xylyl) with a ruthenium precursor [RuCl₂(η^6 -C₆H₆)]₂. In this system, the electronic and steric factors of amines had a negligible influence on the reaction and a broad range of functional groups were well tolerated. All of the investigated amines could be converted to nitriles in good yield of up to 99% with excellent selectivity. The unprecedented catalytic performance of this system is attributed to the synergistic effect of two ruthenium centers chelated by R(CNP)₂ and a plausible reaction mechanism is proposed according to the active species found via in situ NMR and HRMS.

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1. Introduction

Nitriles are key motif in the structure of numerous useful compounds [1,2], such as pharmaceuticals, bioactive natural products, and functional materials. In addition, they also serve as versatile building blocks in organic synthesis. Nitriles are commonly prepared [3-5] using the Sandmeyer reaction, the Rosenmund-von Braun reactions, cyanation of aryl or alkyl halides, oxidization of primary amines, Koble's nitrile synthesis, and others. However, the (super)stoichiometric quantities of undesired by-products which are inevitably produced in these methods may be wasteful, unsustainable and environmentally deleterious. In past decades, the Ru-catalyzed acceptorless dehydrogenation of primary amines aroused great interests among the chemists. In this transformation the primary amine is directly dehydrogenated twice to the nitrile with hydrogen gas (a clean fuel) as the sole by-product. Accordingly, it represents the cleanest, atom-economical and environmentally friendly route for nitrile synthesis and meets the requirement of green and sustainable chemistry.

However, the strong nucleophilic character of the amines and the low reactivity of the β -hydride elimination from amino and/ or amido complexes, make amine acceptorless dehydrogenation to nitrile be a challenging problem [6]. To date, only a few of suc-

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cessful examples have been reported. The original work was reported by Szymczak's groups with a ruthenium complex bearing an amide-derived NNN-type ligand as a catalyst (Fig. 1a) [6a,6b]. This seminal work highlighted thepositive effect of the ligand on this reaction. Later on, several other type ligands, such as nitrogen heterocycle carbenes (NHC) [6c], naphthyridinyl pyrazoles [6d] have been developed for this reaction (Fig. 1b–c). Nevertheless, these systems still suffer from low reaction efficiency, limited substrate scope, moderate selectivity and low TON. To address these problems and meet the the requirement of the green and sustainable chemistry, we endeavoured to develop a more efficient and high selective catalyst system for acceptorless dehydrogenation of primary amines to nitriles.

In recent years, our group has developed N-heterocyclic carbene-nitrogen-phosphine ligands (CNPP and CNP) [7a,7b], and the high catalytic performance of their ruthenium complexes has been proven in the cross-coupling dehydrogenation of primary alcohols cross-esters to form [7c], the acceptorless dehydrogenation of alcohols to acids [7d] and the acceptorless dehydrogenation of diols with amines to N-substituted lactams [7e]. The excellent performance can be attributed to the anchoring effect of the NHC moiety and coordination hemilability of the P and N atoms, as well as the facial coordination mode adopted in the Ru-CNP complexes. Encouraged by these achievements, we speculated that such type of ligands would address the problems associated with the dehydrogenation of primary amines to nitriles.





JOURNAL OF CATALYSIS X. Nie et al.



Fig. 1. Ruthenium catalyzed acceptorless dehydrogenation of amines to nitriles.

On the other hand, the bimetallic complexes show generally to be highly efficient catalysts for a wide range of chemical transformations, such as olefin hydroformylation [8], the C–H acetoxylation [9a], dihydroalkoxylation of alkynes [9b], alkyne polymerization, cyclopropanation reaction [10] and others [11,12]. By constraining two metal centers in close proximity to each other, a cooperative action might arise and enhance greatly the reactivity compared with their anologeous monometallic complexes [13]. However, such a synergistic effect has never been investigated in amine dehydrogenation reaction. In this regard, we originally synthesized a series of dual CNP ligands with different linkers and envisioned they could bring two ruthenium centers into relative proximity that may allow for interaction of both ruthenium atoms with the same amine molecule to achieve the diruthenium synergistic catalysis for the acceptorless dehydrogenation of amines. Herein, we report the first successful example of bimetallic catalyst system for acceptorless dehydrogenation of primary amines. This bimetallic protocol enabled a variety of aliphatic and aromatic primary amines to be converted into corresponding nitriles in excellent yields. In most cases, the nitriles were obtained in quantitative yields, not only reducing the wasteful byproducts but also obviating the need for chromatographic purification, which comply with the principle of green chemistry.

2. Results and discussion

2.1. Catalyst preparation characterization

To assess the relationship between catalyst activity and the chain length of linker, we designed and synthesized four ligands $R(CNP)_2$ [R = $-(CH_2)_n$ (n = 1, 2, 4) (**L2-L4**) and R = o-xylyl (**L5**)]. The linkers $-(CH_2)_n$ - and o-xylyl can be readily installed by reacting the imidazole with $Cl(CH_2)_nCl$ or $o-(ClCH_2)_2C_6H_4$, then followed by an analogous synthetic route to that of the CNP ligand (**L1**) to afford the desired ligands **L2-L5**. All these ligands **L1-L5** are fully characterized with both NMR and mass spectra, and the structures of **L3** and **L5** were further identified by single-crystal X-ray diffraction [SI, Fig. S1].[14]

Then, the corresponding **Ru-Ln** (n = 1–5) complexes were prepared by reacting the corresponding ligand Ln with [Ru(η^{6} -C₆H₆) Cl₂]₂ in MeOH (Scheme 1). The ³¹P{¹H}NMR resonances of the coordinated phosphines appeared at around 43.5 ppm (SI, Fig. S2).



Scheme 1. Synthesis of complexes Ru-Ln.

Notably, the characteristic peak of proton in carbene carbon at 9.45 ppm still exists in ¹H NMR spectrum, showing that the NHC did not coordinate with Ru center (SI, Fig. S2). In addition, the upfield shift of the proton of CH=N in the 1H NMR spectrum revealed the nitrogen coordination with the ruthenium. Combined with HRMS results, the structure of ruthenium complex bearing **L1** was attributed as a mononuclear cationic [RuCl(κ^2 -NP)(η^6 -C₆H₆)][PF₆][CI] (**Ru-L1**) and that bearing **L2-L5** were attributed as dicationic diruthenium complexes [(η^6 -C₆H₆)ClRu(κ^2 -NPRNP- κ^2)RuCl (η^6 -C₆H₆)][PF₆]₂[CI]₂ (**Ru-Ln**).

2.2. Catalytic activity measurement

The catalytic activities of these complexes for the acceptorless dehydrogenation of primary amines to nitriles were examined by using 1.0 mol% **Ru-L1** and 0.5 mol% **Ru-Ln** (n = 2-5) (Table 1, entry 1–5), respectively. The reaction proceeded at 100 °C for 24 h, open to a N₂ atmosphere, with Cs₂CO₃ as the base, and N,N-dimethylformamide (DMF) as the solvent. As expected, all the four bimetallic complexes showed enhanced activities relative to their analogous monometallic complex (entry 1, L1). In addition, the yield [15] of the nitrile **1** increased gradually with increasing car-

Table 1

Acceptorless Dehydrogenation of Amines to Nitriles.^a



Entry	Variation of conditions	Conv [%]	Selectivity [%]	Yield(%)b
1 ^a	Ru-L1	46.9	91.4	42.7
2 ^c	Ru-L2	56.1	92.7	52.0
3°	Ru-L3	77.3	92.7	71.4
4 ^c	Ru-L4	87.4	90.6	79.2
5 ^c	Ru-L5	93.0	93.4	86.9
6 ^d	Ru-L5	100	97.2	97.2
7	Add 300 eq Hg	100	96.4	96.4
8	Without ligand	0.8	100	0.8
9	Without base	100	27.9	27.9
10	Closed system	1.3	100	1.3

(a) Reaction conditions: benzylamine (1.0 mmol), Cs_2CO_3 (1.0 mmol), **Ru-L1** (0.01 mmol), DMF (2 mL), 100 °C for 24 h with N₂ balloon. (b) Yields were determined by GC-MS. (c) **Ru-Ln** (0.005 mmol). (d) **Ru-L5** (0.01 mmol), 24 h.

bon chain length of the linker (entry 2–4, L2-L4), and the –(CH₂)₄– appeared to be the most favourable to cause the desired bimetallic cooperative effect. Encouragingly, such a positive effect was further enhanced by replacement of the flexible four-carbon linker with a semirigid linkage o-(CH₂)₂C₆H₄ (entry 4 and 5, 79.2% yield for L4 and 86.9% for L5). Thus, the highest catalyst activity was obtained with complex **Ru-L5**. It was found that even if the catalyst loading was decreased to 0.2 mol%, **Ru-L5** still gave a yield of 86.7% with prolonging reaction time to 72 h, thus affording a high TON of 856. To the best of our knowledge, this is the highest TON among the reported acceptorless dehydrogenation of amines to nitriles (SI, Table S1). Using the increased catalyst loading of 1 mol% led to a very clean and quantitative conversion of amine to nitrile within 24 h.

To further understand the difference between the systems **Ru-L1** and **Ru-L5**, a series of experiments were conducted with the same **Ru** loading to compare the conversion and selectivity of the reaction by monitoring the reaction profile of the **Ru-L1** and **Ru-L5** system (see SI for detail, Pages S15-S17). As can be seen from Fig. 2, the yield of nitrile obtained with **Ru-L5** system at any given time after 6 h is significantly higher than that obtained with **Ru-L1** system. These results further comfirmed that the catalytic capability of the active species in the bimetallic system is higher than that in the monometallic system.

All these results demonstrated that the bimetallic complexes **Ru-L5** is a very efficient and robust catalyst in this reaction. Notably, the reaction was higher yielding in polar aprotic DMF or dimethyl acetamide (DMA) than in nonpolar solvents such as toluene, o-xylene, mestitylene, chlorobenzene, fluobenzene etc (Fig. 3). This may be due to the enhanced solubility of cationic **Ru-L5** and Cs₂CO₃ in DMF/DMA (SI, Fig. S4). From environmental considerations, the usage of DMF or DMA as the reaction solvent instead of the commonly used toluene would be advantageous, since toluene presents a number of chronic toxicity hazards.

Then several experiments were carried out to gain more information about our catalyst system (Table 1, entry 7–10). Firstly, mercury poisoning experimental results revealed the homogeneous nature of the catalytic system (entry 7). Subsequently, the experiments in the absence of either **L5** or base resulted in a significant decrease in yield, demonstrating their vital roles for the reaction (entry 8 and 9). The reaction did not proceed well in a closed system, and only 1.3% yield of **1** was detected (entry 10). Finally,





Journal of Catalysis 391 (2020) 378-385

Fig. 3. Comparison of different solvents. Reagents and conditions: amine (1.0 mmol), Cs_2CO_3 (1.0 mmol), Ru-L5 (0.01 mmol), solvent (2 mL), 100 °C for 24 h with N₂ balloon. Yields were determined by GC-MS.

the H_2 evolution experiment (SI, Page S12), measured by the drainage method, showed about releasing 1.9 equiv. of H_2 during the reaction, which is fully in line with the stoichiometry of the reaction [6d].

2.3. Substrates scope for acceptorless dehydrogenation reaction

With the optimal conditions in hands (detail see SI. Tables S2-S9), the scope of amines was investigated. As shown in Table 2, the dehydrogenation reaction was proven to be rather general regardless of the electronic and steric factors of the substrates. A variety of aryl or alkyl nitriles 1-44 could be generated from their corresponding amines in high yields and a gram scale reaction were also efficient (1, detail see SI, Page S11). The catalytic system was highly compatible with various functional groups. For example, all of the substituted benzylamines bearing Me, MeO, EtO, ^tBu, Ph, NH₂, CF₃ and halogen were dehydrogenated to their benzonitriles in excellent yields. Notably, in comparison with the previously reported system, the present protocol showed outstanding reactivity with an extended substrate scope. For example, low yields of 58% and 22% were reported for *m*-NH₂ and *m*-Cl substituted benzylamines [6a], while high yields of 95.3% (14) and 75.4% (16) were achieved in our system. Furthermore, the bromo-substituted benzylamines of which the acceptorless dehydrogenation to nitrile has never been demonstrated in the literature were also tolerated under the reaction condition and afforded the corresponding nitriles in the excellent yields of 89.4-93.0% (10, 17, 24). The multisubstituted aryl nitriles 26-29 could be formed in higher than 96% yields, In particularly, even the sterically demanding (2,6-dimethylphenyl)methanamine underwent the reaction very well, affording the product 26 in 98.8% yield. Furthermore, 1-naphthalenemethanamine and 3,4-(methylene dioxy)benzyl-amine were almost quantitatively converted into corresponding nitriles 30 and 31. The catalytic system is also suitable to the synthesis of heterocyclic nitriles. The primary amines containing heterocyclic motifs, such as pyridine, thiophen, furan and indole, could be converted to the corresponding nitriles 32-35 in good yields. Interestingly, p-



Table 2

Substrates scope of the reaction.^a



(a) Reaction conditions: amine (1.0 mmol), Cs2CO3 (1eq), Ru-L5 (1 mol %), DMF (2 mL), 100 oC for 24-36 h with N2 balloon. (b) Yields were determined by GC-MS and isolated yields were reported in parentheses. (c) Closed system under argon atmosphere. (d) gram scale reaction. amine (10.0 mmol), Cs2CO3 (0.5eq), Ru-L5 (0.5 mol %), DMF (2 mL), 100 oC for 5 days with N2 balloon, (e) 60 oC for 48 h.

xylylenediamine was dehydrogenated into **36** in 87.8% yield with one CH_2NH_2 group being transformed into a cyano group and another one to primary amide group. But the exact reason for this transformation is not clearly understood at this stage, we preliminarily suspect that amide was obtained by the interaction between nitrile formed by dehydrogenation of primary amine and DMF (SI, Pages S24-S25). The alkyl amines were also viable substrates and successfully converted to nitriles (**37–43**) in 85– 99% yields. Alkyl dinitriles, such as **40** could be obtained from their corresponding diamines in excellent yield of 95.4%. Again, the sterically hindered adamantan-1-ylmethanamine could react smoothly and afforded the product **43** in 85.4% yield. Notably, indoline, a cyclic secondary amine was converted to indole **44** in 96.7% yield, possibly via a dehydrogenation followed by a tautomerization process.

As aforementioned, the dehydrogenation of the primary amines did not work well in a closed system, which might be ascribed to the generated H₂. Whereas the (3-nitrophenyl) methanamine hydrochloride could react smoothly both under N2 balloon condition and in a closed system to give the product 46 in 86.8% and 83.7% yields, respectively (Scheme 2, eqs 2 and 3). In sharp contrast with previously reported Ru/pyrazole [6d], $[Ru(C_6H_6)Cl_2]_2/HMTA$ [6f] and RuCl_{3 n}H₂O [6g] systems, in which the NO₂-substituted benzylamine was converted into nitrile with the nitro group being remained (Scheme 2, Eq. 1), in our system the nitro group was reduced into the $-NH_2$ group by the generated H_2 , indicating that **Ru-L5** complex also has the potential hydrogenation ability. Indeed, the hydrogenation reaction of 3nitrobenzonitrile with a H₂ balloon under the otherwise identical condition to the dehydrogenation reaction could produce 46, albeit in relatively low yield (Scheme 2, Eq. 4). We also found that the 4-vinyl benzylamine was converted to the nitrile with the vinyl group being reduced to ethyl group. This result further evidences that the Ru-CNP complexes own dehydrogenation and hydrogenation properties.

To further clarify the nature of the present system, several experiments were conducted. Firstly, the competing reactions [16,17] between PhCH₂NH₂ and PhCH₂ND₂, as well as PhCH₂NH₂ and PhCD₂NH₂, disclosed a kinetic isotopic effect (KIE) of 1.51 and 1.03, respectively (SI, Scheme S3). This result suggested that neither the N-H nor the C-H bond cleavage was the rate-determining step. We suspect that the coordination of Ru center with H atom (Scheme 5A–B and E–F) was the rate-determining step because the low electron density of hydrogen atom in C–H bond of the substrate molecule leads to weak coordination to Ru center. Especially, the fact that these substrates bearing the electron-withdrawing groups give the relatively lower yields than those bearing electron-donating groups probably is a reasonable evidence.

Then, a Hammett plot, which can give the information about the reaction sensitivity towards the substituents, was constructed with benzylamines substituted by Me, MeO, NH₂, Cl, Br, F and CF₃ in meta-position and para-position, respectively. In both cases, the negative slopes of $\rho = -0.34$ and -0.42 were given in the Hammett



Scheme 2. Investigation of dehydrogenation and hydrogenation ability of Ru-L5 system. Reagents and conditions: amine (1.0 mmol), Cs_2CO_3 (1 eq), Ru-L5 (1 mol %), DMF (2 mL), 100 °C for 24 h. Yields were determined by GC-MS.

plot (SI, Fig. S5). Compared to the ρ value of -1.22 in Bera group system [6d], the more placid negative slope in our system clearly indicated that our system is less sensitive to the electronic nature of substituents. This should be the reason why our system is well suitable for the wide substrate scope.

To clarify the bimetallic synergistic effect in the reaction process, in-situ NMR spectroscopic studies were performed to monitor the structure transformation of complexes in Ru-L1 and Ru-L5 system. For **Ru-L1** system, upon addition of 20 equiv of Cs₂CO₃, the disappearance of the carbene C–H resonance (9.45 ppm) in ¹H NMR (SI, Fig. S6, a) and the signal at 43.5 ppm (II) in ³¹P NMR (Fig. 4a) indicated that the NHC in L1 coordinated to Ru with the assistance of base. At the same time, three new species in ³¹P NMR were present in downfield at 55.6 ppm (III), 78.5 ppm and 80.5 ppm, respectively (Fig. 4a and Scheme 3). When the reaction time was extended, the peak at 55.6 ppm gradually diminishes and two species at 78.5 ppm and 80.5 ppm become more prominent. In addition, ¹H NMR monitoring of the solution showed the signal of free benzene which dissociated from the coordinated η^6 -C₆H₆ with ruthenium (Fig. 4c). Furthermore, the addition of LiCl caused the increase of peak intensity at 80.5 ppm (Fig. 4d), which evidences two species at 78.5 ppm and 80.5 ppm build up an equilibrium in solution. Hence, it is reasonable to attribute the peak at



Fig. 4. NMR spectra of Ru-L1 and Ru-L5 system.



Scheme 3. The possible active species in Ru-L1 system.

55.6 ppm to complex **III**, 78.5 ppm to complex **IV** and 80.5 ppm to complex **V** (Scheme 3 and SI, Scheme S4). It is also in good agreement with the fact that the coordination of more chlorides with Ru center would cause the downfield shift of the coordinated P atom [18].

For Ru-L5 (Fig. 4b), in the early stage, each of the two halves of L5 coordinated independently with ruthenium in a similar manner to that of L1. But in the late stage, these analogous species (Scheme 4, VI, VII and VIII) with Ru-L1 gradually disappeared, several new species (Fig. 4b) appeared in the upfield region in ³¹P NMR. Especially, a singlet at 11 ppm emerged as the major species, which evidences a symmetric structure. In addition, the highresolution mass spectrometry (HRMS) analysis of the solution (Scheme 4 and SI, Scheme S5) showed a peak at m/z = 1177.0705. So we tentatively assign this as a bimetallic Ru species, formulated as $Ru_2(L5)Cl_2(u-Cl)$ (IX) or $Ru_2(L5)(u-Cl)_3$ (X) (Scheme 4). The linkage of ligand L5 forces the two Ru center closer to each other and forms a symmetric chloro-bridged bimetallic complex. This structure should be relevant with its higher catalytic activity than Ru-L1 system. Notably, only a low nitrile yield of 30% was detected at the beginning 12 h and the major metal species $[(\eta^6-C_6H_6)RuCl(\kappa^2-CNP-(o-xylyl)-\kappa^2-CNP)RuCl(\eta^6-C_6H_6)](PF_6)_2$

(VI) was detected in situ NMR during this time. The result indicated that complex VI was less active for this reaction. However, after the catalytic system was pretreated without benzylic amine under the standard condition for 12 h, the complex VI was gradually converted into species IX or X (Fig. 4, b and Scheme 4). Subsequently, benzylic amine was added to this system and reacted for 12 h. In this case the dehydrogenation proceeded about 1.7 times faster than nonpretreated system and the yieldof nitrile increased up to 50%. These results indicated the IX or X might be the more reactive species.

The **Ru-H** species are believed to be the key intermediate for the dehydrogenation of benzylic amine [6,19]. After the benzylic amine (10 equiv) was added, the in-situ ¹H NMR studies on the **Ru-L1** system (Fig. 5a) showed that two doublets at -10.34 and -10.25 ppm with $J_{HP} = 118.9$ Hz and 113.4 Hz, respectively. The large coupling constant suggested that the hydride and phosphorus atom were mutually located in the *trans* position. However, the peaks of Ru-H appeared at $\delta -10.19$ ppm ($J_{HP} = 25.4$ Hz) and $\delta -12.64$ ppm ($J_{HP} = 15.0$ Hz) for **Ru-L5** system. The small coupling constants indicated that the hydride located in the *cis* position of the phosphorus atom (Fig. 5, b). Combining with HRMS data, we assumed that **Ru-L5** finally form a chloro-bridged bimetallic species, in which the hydride was located in the *cis*-position of phosphorus atom in the catalytic cycling.

On the basis of above results and literature reports, a plausible bimetallic mechanism for the dehydrogenation of benzylic amine



Scheme 4. The possible bimetallic species in Ru-L5 system.



Fig. 5. ^1H NMR evidence for the formation of Ru-H species in Ru-L1 and Ru-L5 system.



Scheme 5. Proposed mechanistic cycle of primary amine dehydrogenation.

has been proposed in Scheme 5. Firstly, the benzylic amine associates with one Ru center of the in-situ generated Cl bridged bimetallic species IX or X and forms the amido species A with the assistance of base. Subsequently, another ruthenium abstracts a benzylic hydrogen atom via a six-membered ring transitional state (Scheme 5, B) to give an imine-bound species C. This is not only thermodynamically more favorable than the four-membered ring involved in the monometallic **Ru-L1** system (Scheme 5, **B'**), but the coordination space in Ru-L5 in this manner also benefits to accomodate the bulkier substrates (19-28, 43 in Table 2). The fact that no free imine is detected with in-situ NMR spectrum (SI, Fig. S15) supports that species \mathbf{C} preferentially undergoes H₂ elimination via another six-membered ring T.S. D, with concomitant generation of an imido species F. And then F goes through a similar pathway as **B** to **C** to afford a nitrile-bound intermediate G, upon which a new benzylic amine substrate replaces the product nitrile to give **H**. Finally, the second H₂ is eliminated to regenerate the active species A.

3. Conclusions

In summary, a series of new N-Heterocyclic carbene-nitrogenphosphine ligands **R(CNP)**₂ have been synthesized and characterized. These novel ligands enable us to develop a highly efficient bimetallic catalyst system (**Ru-L5**) for the acceptorless dehydrogenation of primary amines to nitriles. It exhibits enhanced catalytic reactivity compared with its analogous monometallic counterpart. The present system displays much broader substrate scope and functional group compatibility than other known acceptorless amine dehydrogenation systems. The excellent catalytic performance can be attributed to a bimetallic synergistic effect, in which one Ru center combines with nitrogen atom of the amine, and the another abstracts the C—H proton of the benzylic amine via a six-membered ring transition state. This is more thermodynamically favourable than the four-membered ring involved in the monometallic **Ru-L1** system.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2020.09.005.

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