Communication

Double Dehydrogenation of Primary Amines to Nitriles by a Ruthenium Complex Featuring Pyrazole Functionality

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Double Dehydrogenation of Primary Amines to Nitriles by a Ruthenium Complex Featuring Pyrazole Functionality

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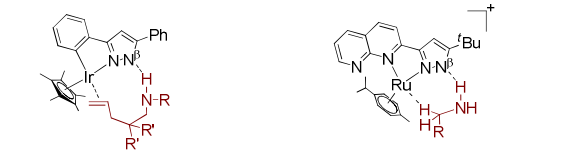
Supporting Information Placeholder

ABSTRACT: A ruthenium(II) complex bearing naphthyridine-functionalized pyrazole ligand catalyzes oxidant-free and acceptorless selective double dehydrogenation of primary amines to nitriles at moderate temperature. The role of the proton responsive entity on the ligand scaffold is demonstrated by control experiments including the use of a N-methylated pyrazole analogue. DFT calculations reveal intricate hydride and proton transfers to achieve the overall elimination of two H_2 equivalents.

Nitrile is an important functionality in organic synthesis. Natural products, bio-active molecules, and industrially relevant compounds have abundant presence of nitriles.[1] Common methodologies for nitrile syntheses include Sandmeyer reaction, ammoxidation, oxidation using hypervalent iodine-based compounds and transition metal catalyzed oxidations, among others.[2,3] However, these conventional methods often suffer from limited reactivity, poor atom economy, harsh reaction conditions and narrow functional group tolerance.

An alternative nitrile synthesis protocol involves transition metal catalyzed double dehydrogenation of primary amines. Brookhart reported an Ir pincer catalyst for amine dehydrogenation in the presence of stoichiometric hydrogen acceptor.[4] Other known catalysts are either low yielding[5] or require exogenous additives under harsh conditions.[6] Further, competition between second dehydrogenation and transamination pathway invariably leads to the loss of selectivity.[7] We are aware of only one report from Szymczak group who employed a NNN-Ru(II) hydride complex for oxidant-free and acceptorless selective conversion of primary amines to nitriles.[8] An inner-sphere mechanism involving proton transfer from a coordinated amine (or imine) to Ru-hydride followed by H_2 release was proposed.[9] Although alcohols are readily dehydrogenated by numerous bifunctional catalysts,[9,10] ligand-promoted amine dehydrogenation remains a difficult task to accomplish. The higher nucleophilic character of the amines and energetically unfavorable β-H elimination step are the principal challenges to be overcome for amine dehydrogenation.[11] Designing a bifunctional catalyst for amine activation is reliant on the basicity of the proton responsive unit.[12] Kuwata and Ikariya have exploited metal-ligand cooperation strategy utilizing metal/pyrazole systems for bifunctional substrate activation.[13] An intramolecular hydroamination reaction proceeds via nucleophilic attack of the amine to an iridium-coordinated olefin promoted by a pyrazolato ligand through secondary interactions (Scheme 1a).[13c,e] This prompted us to incorporate a β-protic pyrazole moiety on a naphthyridine scaffold. A ruthenium complex containing a naphthyridine-pyrazole ligand was synthesized that was found to be an excellent catalyst for selective dehydrogenation of various primary amines to nitriles, without requiring oxidant or acceptor. The essential role of the β-protic center is demonstrated by using an analogous N-methylated pyrazole complex. In contrast to direct amine deprotonation (Scheme 1b) that one may initially envision, DFT calculations suggest that N^{β} facilitates intricate proton/hydride transfer in the catalytic double dehydrogenation pathway.

Scheme 1. β-Protic Pyrazole for Amine Activation.



A pyrazole unit was attached to 1,8-naphthyridine (NP) scaffold by a multistep synthesis starting from 2-aminonicotinaldehyde (Scheme S1). Treatment of pzH-NP (L^1) with $[Ru(p\text{-cymene})Cl_2]_2$ (2:1 molar ratio) in 2-propanol afforded $[Ru(p\text{-cymene})(L^1)(Cl)]Cl$ (**1**) in 81% yield. The molecular structure of **1** is shown in Figure 1. The pyrazole NH shows interaction with the counter anion chloride (N4H4A···Cl2 = 2.123 Å) implying the Brønsted acidic nature of the pyrazole proton.[13d] ESI–MS revealed a signal at *m/z* 523.1200 for $[\mathbf{1}\text{–Cl}]^+$ (Figure S7). The pyrazole hydrogen appears downfield at δ 10.19 ppm.

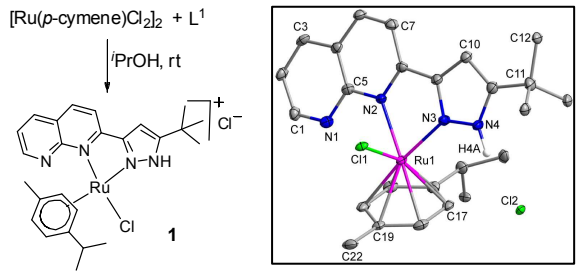


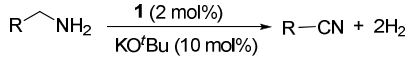
Figure 1. Synthesis of **1**. Molecular structure of **1** is depicted in the inset.

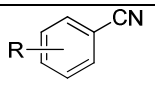
Initial attempt towards acceptorless dehydrogenation of *p*-methylbenzylamine (*p*-MBA) using 2 mol% catalyst **1** in the presence of 10 mol% KO^{t}Bu at 70°C afforded *p*-methylbenzonitrile exclusively in 89% yield after 24 h (Table 1). A slow stream of nitrogen gas was allowed to pass through the reaction vessel to drive away the produced hydrogen gas.[8] Performing the reaction in a sealed tube (closed system) led to a substantial reduction in the yield (42%). The reaction was hindered in the absence of base (Table S2). Optimization studies showed that KO^{t}Bu and toluene were the best combinations among a variety of bases and solvents. The reaction temperature was maintained at 70°C to achieve optimized yields. The homogeneity of the reaction medium was confirmed by mercury addition experiments.[14]

Substrate scope for various amines was examined under optimized reaction conditions (Table 1). Benzylamine and its electron rich derivatives afforded the corresponding nitriles (84-92%, entries 1-3) in excellent yields. Electron deficient benzylamines gave slightly lower yields (72-80%, entries 4-6). Position of substituent (*o*- or *p*-) on the aromatic ring did not show any significant effect on the product formation (entries 7-8). Dehydrogenation of 2-phenethylamine afforded moderate yield of 2-phenylacetonitrile (42%, entry 9), an important precursor for pharmaceuticals.[1c] For *p*-substituted phenethylamines, electron-donating methoxy group gave relatively higher yield (49%, entry 10) than an electron withdrawing nitro derivative (37%, entry 11). Heterocyclic amines afforded the corresponding nitriles in good to moderate yields (52-76%, entries 12-14). The scope of **1** was further extended for aliphatic amines. Long chained amines afforded the corresponding nitriles in excellent yields (87-93%, entries 15, 16). Oleylamine gave oleonitrile in 76% yield (entry 17) where the double bond remained unaffected. Cyclohexanecarbonitrile (81%, entry 18) and butyronitrile (65%, entry 19) were also obtained from their amine derivatives. Aliphatic diamines were employed to access the corresponding dinitriles (54-72%, entries 20-22). *p*-Aminobenzylamine was converted to *p*-aminobenzonitrile (85%, entry 23) keeping the aromatic amino group intact, which demonstrates chemoselectivity of **1**. Oxidative dehydrogenation of secondary amines affords a mixture of products that include imine, aldehyde and alcohol.[3j-m] Catalyst **1**, to our delight, afforded the selective imine products for dibenzylamine and bis(4-methylbenzyl)amine (53-57%, entries 24, 25). Heterocyclic amine indoline was converted to indole in high yield (88%, entry 26).

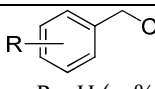
Since imine or imine derivatives were not detected during primary amine dehydrogenation, it can be safely assumed that a second dehydrogenation of short-lived aldimine intermediate is preferred over a competitive transamination reaction (Scheme S8, Figure S25). Conversion of primary amines to nitriles is accompanied by the release of two molecules of hydrogen, which was identified by GC (thermal detector) and quantified on a gas buret set up (Figures S21-23). Styrene hydrogenation to ethylbenzene in the presence of Wilkinson catalyst further confirmed molecular hydrogen as the by-product.[15,16]

Table 1. Amine Dehydrogenation Catalyzed by 1.[a,b]

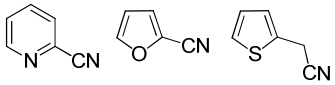




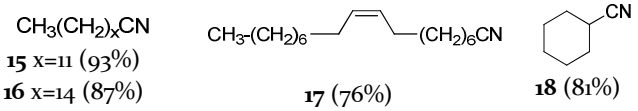
1 R = H (84%)
2 R = 4–OCH_3 (92%)
3 R = 4–CH_3 (89%)
4 R = 4–Cl (80%)
5 R = 4–NO_2 (78%)
6 R = 3,5–NO_2 (72%)
7 R = 2–CN (76%)
8 R = 4–CN (77%)



9 R = H (42%)
10 R = 4–OCH_3 (49%)
11 R = 4–NO_2 (37%)



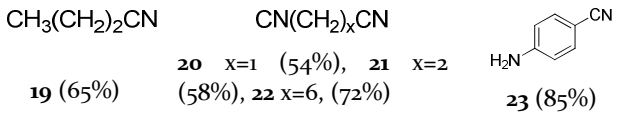
12 (73%) **13** (76%) **14** (52%)



15 x=11 (93%)
16 x=14 (87%)

17 (76%)

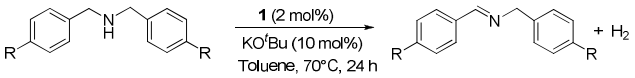
18 (81%)



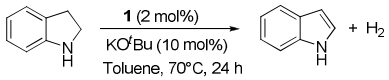
19 (65%)

20 x=1 (54%), **21** x=2 (58%), **22** x=6, (72%)

23 (85%)



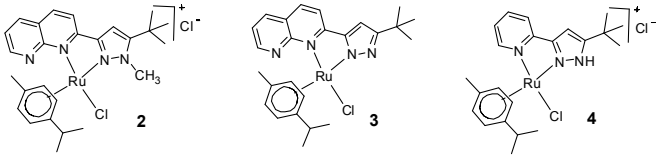
24 R = H (53%), **25** R = CH_3 (57%)



26 (88 %)

[a]Reaction conditions: 0.5 mmol amine, **1** (2 mol%), KO^{t}Bu (10 mol%), toluene, 70°C, 24 h. [b]Yields are determined by GC–MS using dodecane as internal standard.

Scheme 2. Modified Catalysts and Their Activities for *p*-MBA Dehydrogenation.



Additive: KO^{t}Bu
Yield: 19%

Additive: $TlPF_6$
Yield: 84%

Additive: KO^{t}Bu
Yield: 61%

Catalyst **1** was designed to exploit proton responsive β-NH for dehydrogenation. To verify its participation, the performance of an analogous N-methyl complex [Ru(*p*-cymene)(L^2)(Cl)]Cl (**2**) was examined.[17] Complex **2** showed

poor activity (19% *p*-methylbenzonitrile) (Scheme 2) for the model reaction strongly suggesting the vital role of the β-NH in the dehydrogenation process. To further check the involvement of the pyrazolato complex in the catalytic pathway, a neutral complex **3** was synthesized by the treatment of **1** with Et_3N in benzene.[17] Under base-free condition, and in the presence of 5 mol% $TlPF_6$, catalyst **3** showed comparable activity (84% vs 89% for **1**).[18] The pyrazolato form of **1**, therefore, is most likely the active catalyst. An analogous pyridine complex [Ru(*p*-cymene)(L^3)(Cl)]Cl (**4**) was also synthesized.[17] Even with increased catalyst loading (5 mol%), **4** showed reduced activity compared to **1** (61% vs 89%). Hence, we pursued the amine dehydrogenation reactions with **1**.[19]

The initial rate of the dehydrogenative oxidation reaction was monitored (up to ~10-15% conversion) to determine the reaction order with respect to amine. Increasing the concentration of *p*-MBA results in an increase in rate with a linear dependency, up to a certain point, after which increase in [*p*-MBA] shows zero-order dependency (Figure S26). The observed saturation kinetics implies a pre-equilibrium step, and the overall reaction is driven forward in the presence of excess amine.[9]

The effect of temperature on the reaction rate was studied, and activation parameters were determined from ln(*k*/T) vs 1/*T* plots (Figure S27-28). A high negative $\Delta S^{\ddagger}$ value (–20.03 ± 0.56 cal mol^{-1} K^{-1}) is indicative of an organized and associative transition state involving substrates and the catalyst. The Gibbs energy of activation ($\Delta G^{\ddagger}$) was estimated to be 26.2 kcal/mol at reaction temperature. Further, a Hammett plot was constructed using electronically disparate amine derivatives (Figure S29). A plot of the relative rates ($\log(K_X/K_H)$) against the substituent constant σ yielded a fairly good linear relationship following the reactivity trend *p*-OMe>*p*-CH_3 >*p*-H >*p*-Cl >*p*-NO_2. An observed negative ρ value of –1.22 suggests that the reaction should be favored by electron rich substrates, which is in agreement with substrate activities (Table 1).[20] However, when $\log(K_X/K_H)$ was plotted against standard σ^+ values, linearity could not be obtained.[20a,b] These observations indicate that the turnover limiting transition state of the reaction has a partial positive charge deployment over the entire system which points to a concerted mechanism.

Comparing the reaction rate of $PhCH_2NH_2$ in toluene and $PhCD_2NH_2$ in toluene-d_8 showed a kinetic isotope effect (KIE) of k_{C-H}/k_{C-D} = 1.52 ± 0.04 (Figure S30). When $PhCD_2ND_2$ was used as a substrate, the rate of reaction was 3.91 ± 0.02 times slower than with $PhCH_2NH_2$ and 2.57 ± 0.03 times than with $PhCD_2NH_2$. These data indicate that cleavage of the N–H bond during the hydrogen elimination has a transition state with more direct influence on the overall rate than cleavage of the C-H bond.

To further obtain insight about the reaction mechanism, a DFT study (B97D3-BJ/def2-TZVP, IEF-PCM(SMD)) was carried out for substrate *p*-MBA. Computed reaction pathway is shown in Figure 2 (see Scheme S9 for complete cycle). Given the experimentally used activation method for **1** (KO^tBu), and comparable activity of **3**/$TlPF_6$ as well, it is plausible to assume the species available in solution prior to enter the catalytic cycle to be the dechlorinated (at Ru) and deprotonated (N^{β}) cationic complex **I**, which exergonically can bind one (**II**, ΔG = –20.5 kcal/mol, Table S7) and even two (**III**, ΔG = –26.7 kcal/mol) molecules of *p*-MBA, with **III** defining the lowest point in the catalytic cycle (TDI 1). A direct amine deprotonation by N^{β} was attempted but a relevant intermediate within a realistic energy span could not be obtained. Instead, one of the amine molecules rearranges from N– to C–H type coordination (**IV**) to ruthenium, which necessitates the dissociation of the second amine.[21] The ruthenium centre receives the hydride to form **VI** with an activation barrier of 27.1 kcal/mol. The protonated aldimine then transfers a proton to a molecule of *p*-MBA through the involvement of pyrazolato β-N (**VII**) to give **IX**. Computing a pathway from **VI** to **IX** without involving a second amine either results in energy barriers far too high to make such a pathway realistic or the appropriate transition states could not be localized. In principle, the first dehydrogenative pathway could involve proton transfer to the N^{β} of the ligand backbone and H_2 could be eliminated from **XIX** (Scheme S10). However, the Gibbs free energy of the corresponding transition state (**XX**, 41.0 kcal/mol) is way too high (67.7 kcal/mol relative to **III**) to be overcome.[22] Instead, the first dehydrogenation occurs from **XII** via ammonium-mediated protonation of the Ru-H moiety (TS **XIII**, 4.0 kcal/mol; overall barrier height relative to **III** = 30.7 kcal/mol, TDTS 1). As the reaction is conducted in an open flask, liberated H_2 is driven away from the system resulting in complex **III**, which can be considered as the starting point for the second dehydrogenation. The imine hydrogen and carbon-bound hydrogen of the *cis*-aldimine[23] are transferred to an amine molecule and Ru (**XIV**), respectively, through a concerted transition state (**XV**, 11.1 kcal/mol, TDTS 2) generating the nitrile with an activation barrier of 28.0 kcal/mol.

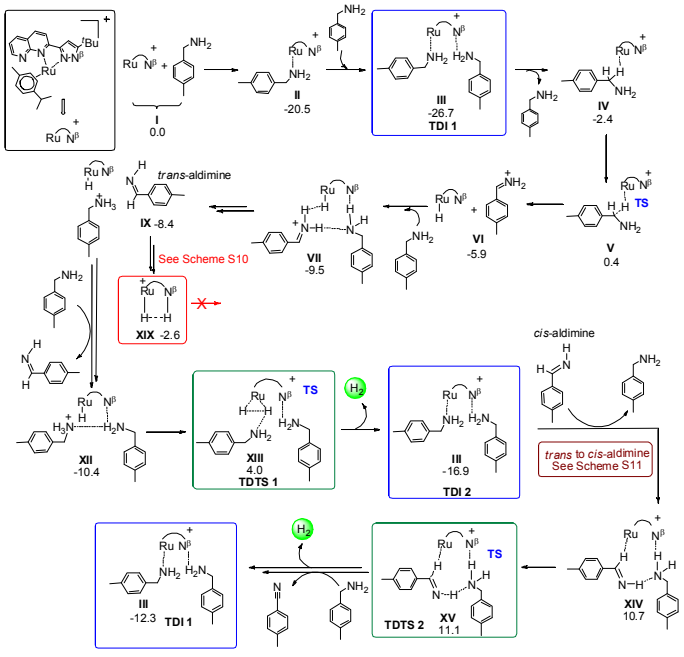


Figure 2. Computed reaction mechanism showing double dehydrogenation of *p*-MBA. For full cycle, see Scheme S9. Gibbs free energy values are in kcal/mol.

In conclusion, we herein report a cooperative Ru/pyrazole system for selective dehydrogenation of a wide range of primary and secondary amines to nitriles and imines, respectively, at a moderate temperature, without requiring oxidant or hydrogen acceptor. Catalyst **1** exhibits wider substrate scope, operates under milder reaction condition and displays

higher activity compared to other known systems. The poor yield obtained for a related N-methylated pyrazole complex confirms the vital role of the protic ligand in the dehydrogenation reaction. Kinetic isotope studies suggest that N–H bond cleavage during the hydrogen elimination has a direct influence on the overall rate. DFT calculations reveal intricate hydride and proton transfer aided by the pyrazolato β-N. Insights gained in this work should pave the way to develop new generation dehydrogenation catalysts based on proton responsive pyrazole ligands.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, catalysis reactions, kinetic plots, supporting schemes and figures, available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interests.

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(14) The addition of Hg(0) (~ 600 equiv) didn't affect the production of p-methylbenzonitrile. See, (a) Crabtree, R. H. *Chem. Rev.* **2012**, *112*, 1536–1554. (b) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317–341.

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(16) The catalytic reaction was conducted in a flask that was connected to a second flask containing equimolar styrene and a catalytic amount of $RhCl(PPh_3)_3$ in benzene (Scheme S7). Detection of

ethylbenzene in the second flask after the completion of the reaction demonstrates that hydrogen gas is generated during the ADD of amine (Figure S24).

(17) See ESI for detailed synthesis and X-ray characterization of **2**, **3** and **4**.

(18) The use of $TlPF_6$ was warranted to remove the chloride from metal coordination sphere, without which the conversion was only 14%.

(19) The rationale to use naphthyridine-functionalized ligand was to introduce a free N atom on the ligand architecture, situated close to the metal center, to promote hydration reaction. We envisaged that the product nitrile could be subsequently hydrated to the amide by the same catalyst utilizing naphthyridine-N_8 via a tandem dehydrogenation-hydration. See ESI for details.

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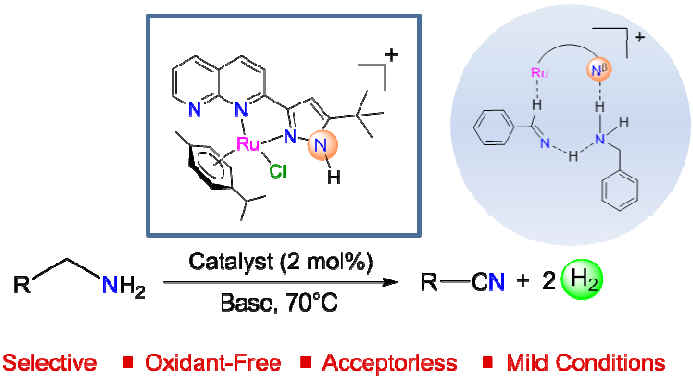
(21) While the formation of **III** is inevitable energetically at this stage of the reaction, one of the two amines of **III** must dissociate to create the necessary spatial requirements needed to travel to transition state **V** from **IV**.

(22) Even when tunneling corrections are applied, barrier height is 53.2 kcal/mol.

(23) Computed pathway for barrier-less *trans*- to *cis*–aldimine is shown in Scheme S11.

TOC


Catalyst (2 mol%)
Basc, 70°C
R—CN + 2 H2
Selective
Oxidant-Free
Acceptorless
Mild Conditions