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Hemilability Driven Water Activation: A Ni(II) Catalyst for Base-Free Hydration of Nitriles to Amides

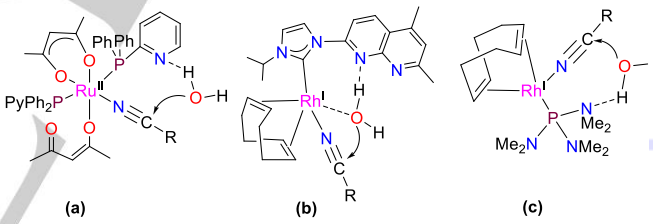
Kuldeep Singh, Abir Sarbajna, Indranil Dutta, Pragati Pandey and Jitendra K. Bera*[a]

Abstract: A Ni(II) complex **1** containing pyridyl- and hydroxy-functionalized N-heterocyclic carbenes (NHC) is synthesized and its catalytic utility for selective nitrile hydration to amide under base-free condition is evaluated. The title compound exploits hemilabile pyridyl unit to interact with a catalytically relevant water molecule *via* hydrogen-bonding and promote nucleophilic water attack to the nitrile. A wide variety of nitriles are hydrated to the corresponding amides including pharmaceutical drugs Rufinamide, Rifater and Piracetam. Synthetically challenging α-hydroxyamides are accessed from cyanohydrins under neutral conditions. Related catalysts that lack the pyridyl unit (**2** and **4**) are not active whereas those containing both the pyridyl and the hydroxy or only the pyridyl pendant (**1** and **3**) show substantial activity. A linkage isomer **1'** where hydroxy group is bound to the metal instead of the pyridyl was isolated under different crystallization conditions insinuating ligand hemilabile behavior. pK_a measurements reveal accessible pyridyl unit under catalytic conditions. Kinetic studies support a ligand-promoted nucleophilic water addition to a metal-bound nitrile. This work reports a Ni based catalyst that exhibits functional hemilability for hydration chemistry.

Introduction

Nitrile hydration is a highly convenient and a desired route for amide synthesis.[1] It prevails over the limitation of poor atom economy and avoids the use or generation of toxic chemicals associated typically with traditional amide synthesis techniques.[2] Most hydration catalysts involve precious second and third row transition metals.[3] There is a pressing demand to develop 3d metal-based catalysts for obvious reasons- lower down the production cost, reduce the environmental impact and eliminate the metal ion toxicity.[4] Although catalysts involving earth abundant 3d metals are known for nitrile hydration reaction,[5] only a few Ni compounds are reported under both homogeneous and heterogeneous conditions.[6] However, they exhibit limited substrate scope, require additives and, in most cases, are not molecularly well defined.[7]

Several metalloenzymes are credited to hydrate a host of substrates.[8] One such enzyme is *carboxypeptidase* where a divalent Zn and a glutamate carboxylate act in unison to promote nucleophilic water attack to a peptide bond.[9] Inspired by the design strategies of natural systems, several synthetic catalysts have been developed. These '*metal-ligand cooperative catalysts*' operate on the principle that a heteroatom present in the ligand backbone polarizes a water molecule *via* hydrogen-bonding interactions and promote hydration reaction.[10] Oshiki, Takai and co-workers demonstrated that the pyridyl unit of Ph_2Ppy ligand enhances nitrile hydration activity of the catalyst *cis*-Ru(acac)$_2$(Ph_2Ppy)$_2$ (acac = acetylacetonate, Ph_2Ppy = diphenyl-2-pyridylphosphine) (Scheme 1a).[11] We earlier exploited double hydrogen-bonding interactions of 1,8-naphthyridine with a water molecule to hydrate organonitriles efficiently and selectively using the catalyst [Rh(COD)(PIN)Br] (PIN = 1-isopropyl-3-(5,7-dimethyl-1,8-naphthyrid-2-yl)imidazol-2-ylidene, COD = 1,5-cyclooctadiene) at room temperature (Scheme 1b).[12] Cadeirno group has made remarkable progress in recent years using homogeneous ruthenium/rhodium catalysts containing pyridyl-phosphines, aminoaryl-phosphines, thiazolyl-phosphines, 1,3,5-triaza-7-phosphaadamantane (PTA), amino-phosphines (Scheme 1c) and related auxiliary ligands.[13]



Scheme 1. Water activation strategies for nitrile hydration.

All these catalysts employ a heteroatom in the ligand backbone to direct water attack to the nitrile carbon. Catalyst featuring a *free* basic unit attached to the ligand architecture presents several problems. Protic impurities may diminish the water activating ability of the catalyst. The possibility of a stable dimer formation *via* coordination of the donor group to the metal from a second molecule compromises catalyst activity. Bulky ancillary ligands are usually employed to impede aggregation though it has detrimental consequences for sterically hindered substrates. Further, building such catalysts imposes a significant synthetic challenge. A likely solution is to use a hemilabile basic group for water activation.[14] The hemilability would allow the passage of a water molecule to the vicinity of the metal and the basic group would engage the water molecule *via* hydrogen-bonding interaction promoting its nucleophilic attack to the nitrile (Scheme 2). Besides water activation, such hemilability might improve the selectivity, the reversibility and hence the overall turnover values.[15]

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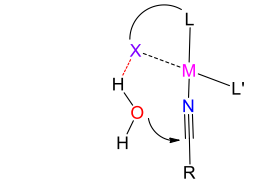


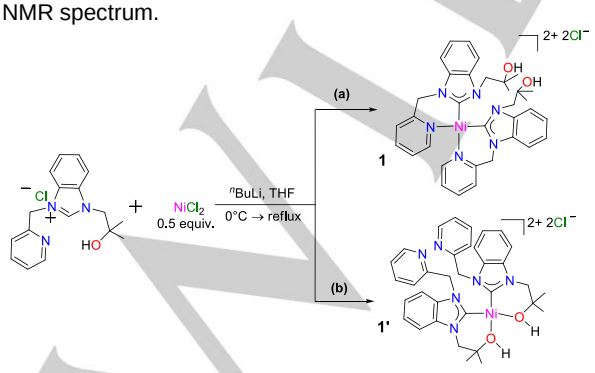
Scheme 2. Hemilabile ligand-promoted nitrile hydration reaction.

We herein report a Ni(II) catalyst bearing functionalized N-heterocyclic carbene (NHC) ligands, which exploits hemilabile pyridyl groups to catalyze nitrile hydration reactions without additives or base. A wide range of nitriles is hydrated efficiently and selectivity to the corresponding amides including several pharmaceutical drugs. Synthetically challenging α-hydroxyamides are accessed under base-free conditions. Control experiments demonstrate the significance of the activity-enhancing hemilabile pyridyl group. The accessibility of the pyridyl unit under catalytic conditions is corroborated by pK_a experiments. Kinetic studies support a ligand-promoted nucleophilic water reaction with a metal-bound nitrile. Hemilability driven nitrile hydration to amide by a Ni based catalyst is reported in this work.

Results and Discussion

Synthesis of Hemilabile Catalyst

Reaction between a pyridyl and hydroxy functionalized NHC-ligand precursor **[L^{1}H]Cl** and $NiCl_2$ (2:1 molar ratio) in presence of excess ^{n}BuLi in THF provided the dicationic compound **1** in 85% yield (Scheme 3). Molecular structure of **1** depicts two NHC ligands bound to nickel *via* carbene carbons in *cis* arrangement and the remaining sites in the square planar geometry are occupied by pyridine nitrogens (Figure 1). The Ni1−C7 and Ni1−C26 bond distances are 1.847(7) and 1.845(6) Å whereas the corresponding values for Ni1−N1 and Ni1−N4 are 1.943(5) and 1.950(5) Å respectively. The relatively longer Ni−N distances reflect the *trans* effect of the carbene carbons. The *cis* angles around the metal range from 87.7(3) to 93.0(3)° revealing a slightly distorted environment from a perfect square planar structure. The carbene carbon appears at δ 173.3 ppm in the ^{13}C NMR spectrum.



Scheme 3. Synthesis of **1** or **1'** depending upon different crystallization conditions: (a) methanol/diethyl ether, rt; (b) acetonitrile/methanol/diethyl ether, −20°C.

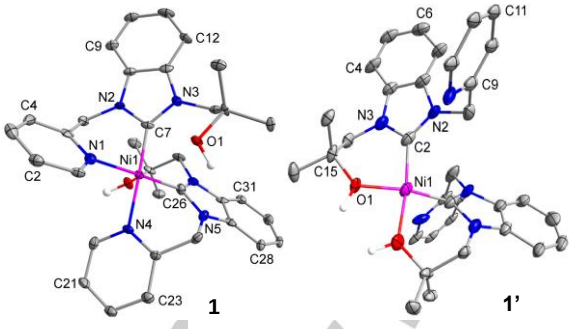


Figure 1. Molecular structures (40% probability thermal ellipsoids) of **1** (left) and **1'** (right) with important atoms labeled. Hydrogen atoms except the hydroxy group are omitted for the sake of clarity.

Compound **1** was obtained when crystallized from a methanol solution layered with diethyl ether. Interestingly, a linkage isomer **1'** was isolated from an acetonitrile/methanol (1:1) mixture layered with diethyl ether at −20°C (Scheme 3). X-ray structure reveals a chelate structure similar to that of **1** but here the hydroxy groups are bound to the metal instead of pyridines (Figure 1). Isolation of two isomers under different crystallization conditions hints at hemilabile nature of the ligand.

Catalysis

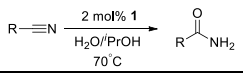
Nitrile Hydration

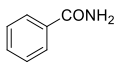
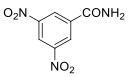
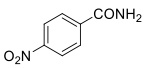
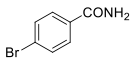
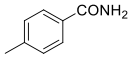
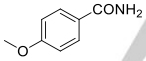
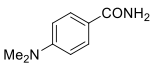
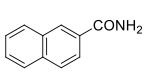
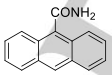
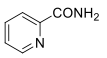
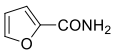
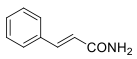
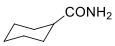
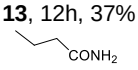
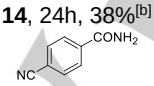
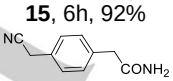
Catalyst **1** was evaluated for the hydration of benzonitrile at 2 mol% catalyst loading in H_2O/^{i}PrOH (1:3 *v/v*) at 70°C. After 6 h, 91% amide conversion was observed (Table S2). No over-hydrated acid/ester or any other side products were detected during the course of the reaction. Addition of 10 mol% ^{t}BuOK marginally improved the amide formation (97%, Table S2). Solvent optimization was done over a range of combinations including H_2O/THF, H_2O/MeOH, H_2O/EtOH, H_2O/DMSO, H_2O/acetone, H_2O/1,4-dioxane. Significant conversion could be achieved only for H_2O/MeOH combination (68%, Table S2). Notably, catalyst **1** was active when pure water was used as solvent. However, a higher temperature (100°C) and a longer reaction time (24 h) were needed to achieve good conversion (82%, Table S2). Lowering the catalyst loading or temperature had a detrimental effect on the reaction rate (Table S2). Hence, all subsequent reactions were carried out at the standard conditions: 2 mol% catalyst loading in H_2O/^{i}PrOH (1:3 *v/v*) at 70°C. Compound **1'** showed very similar hydration activity under identical reaction conditions.

Substrate scope for catalyst **1** was evaluated using different organonitriles under optimized conditions (Table 1). Electron deficient nitriles such as 3,5-dinitrobenzonitrile, 4-nitrobenzonitrile and 4-bromobenzonitrile were converted to the corresponding amides in high yields (Table 1, entries 2-4). Presence of electron donating group had an adverse effect on the yields. 4-methylbenzamide and 4-methoxybenzamide were isolated from the corresponding nitriles in 72% and 65% yields respectively (entries 5, 6). Only 15% 4-(dimethylamino)benzamide was obtained after 24 h for entry 7. Increasing the steric bulk from 2-naphthalenecarbonitrile to 9-anthracenecarbonitrile drastically decreased the product

formation from 88% to <10% (entries 8, 9). Catalyst **1** was successfully employed to obtain *o*-substituted pyridyl amide (82%) from the corresponding nitrile (entry 10). An excellent yield (97%) was also obtained for heterocyclic 2-furonitrile (entry 11) proving that the presence of a donor site on the substrate did not impede the catalytic effectiveness of **1**. A range of aliphatic nitriles were also tested. Cinnamonitrile showed 62% conversion to its corresponding amide (entry 12). Diphenylacetonitrile showed moderate conversion (37%) presumably because of increased steric crowding at nitrile position (entry 13). Aliphatic cyclohexanecarbonitrile was converted to cyclohexanecarboxamide in moderate yield 38% (entry 14). Industrially important acrylamide was synthesized in high yield of 92% without any over oxidized product (entry 15). For butyronitrile, the reaction took 12 h to show 52% yield (entry 16). Aromatic and aliphatic dintriles were also included as substrates and selective amidation of only one functional group was achieved (entries 17, 18).

Table 1. Catalytic hydration of nitriles by **1**[a]

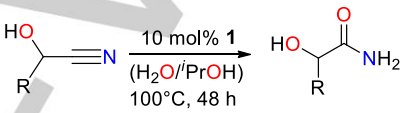


		
1, 6h, 91%	**2**, 2h, 99%	**3**, 2h, 99%
		
4, 6h, 94%	**5**, 24h, 72%	**6**, 24h, 65%
		
7, 24h, 15%[b]	**8**, 6h, 88%	**9**, 24h, <10%[b]
		
10, 6h, 82%	**11**, 6h, 97%	**12**, 12h, 62%
		
13, 12h, 37%	**14**, 24h, 38%[b]	**15**, 6h, 92%
		
16, 12h, 52%	**17**, 6h, 72%	**18**, 6h, 45%

[a] Organic nitrile (1 mmol) and distilled water (1 mL) were sequentially added to a 3 mL ^{i}PrOH solution of the catalyst **1** (0.02 mmol) and the reaction mixture was heated at 70ºC. Yields are calculated based on isolated products after work-up. [b] GC yields are reported relative to mesitylene as an internal standard.

Cyanohydrin Hydration

Hydration of cyanohydrins is synthetically challenging as it rapidly decomposes in solution to produce ketones and HCN.[16] Tyler and co-workers, using catalysts [$RuCl_2(\eta^6$-*p*-cymene){$P(NMe_2)_3$}] and [$RuCl_2(\eta^6$-*p*-cymene)(PMe_2OH)], demonstrated catalyst deactivation by generated cyanide.[17] A practical solution for hydrating cyanohydrins is to design catalyst which operates under neutral conditions and has high catalytic activity to disrupt the equilibrium of the cyanohydrin/ketone-HCN reaction. The ability of the catalyst **1** to hydrate nitrile under base-free conditions prompted us to check its effectiveness for the hydration of typical cyanohydrins (Scheme 4). Only 22% amide was obtained from mandelonitrile after 6 h in presence of 2 mol% **1**. The yield substantially increased to 68% after 48 h at 100°C when catalyst loading was adjusted to 10 mol%. The reaction was extended to 4-methoxymandelonitrile (52%) and 4-chloromandelonitrile (70%) to produce corresponding α–hydroxyamides in modest yields.



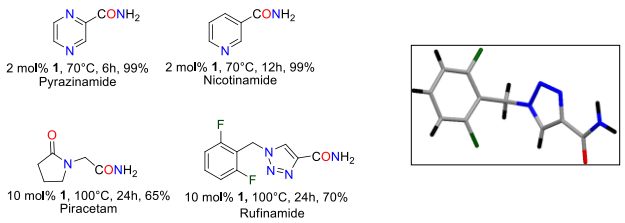
R = C_6H_5 (68%), 4-C_6H_4OMe (52%), 4-C_6H_4Cl (70%)

Scheme 4. Synthesis of α–hydroxyamides.

Bioactive Amides

Once an optimum number of substrates were tested for hydration, the scope of catalyst **1** was expanded to synthesize commercial pharmaceuticals (Scheme 5). Pyrazinamide (commercially sold as Rifater®), a widely recommended drug during short-course treatment of pulmonary tuberculosis,[18] was synthesized from pyrazinecarbonitrile in quantitative yield. Nicotinamide has anti-inflammatory actions and benefits patients with inflammatory skin conditions.[19] Quantitative yields of nicotinamide were achieved using catalyst **1**. 2-(2-oxopyrrolidin-1-yl)acetonitrile under catalytic conditions produced 2-(2-oxopyrrolidin-1-yl)acetamide, also known as Piracetam, a nootropic agent which improves the function of neurotransmitters *via* muscarinic cholinergic receptors.[20]

The catalytic utility of **1** was further exploited for the synthesis of Rufinamide, an antiepileptic drug. Rufinamide (marketed as Inovelon® in Europe) is prescribed as an adjunctive seizure medicine for children and for adults with Lennox-Gastaut syndrome.[21] The nitrile precursor was synthesized from commercially available 2-(bromomethyl)-1,3-difluorobenzene and 2-chloroacrylonitrile (Scheme S1).[22] Subsequent hydration by 10 mol% **1** at 100°C in 24 h produces the target drug molecule in 70% yield. At room temperature, product crystallizes out of the reaction mixture that was filtered off and purified by column chromatography. The isolated compound was characterized by NMR spectroscopy and X-ray crystallography (Scheme 5, inset). Energy dispersive X-ray (EDX) analysis experiments confirmed no Ni incorporation in the product (Figure S8).

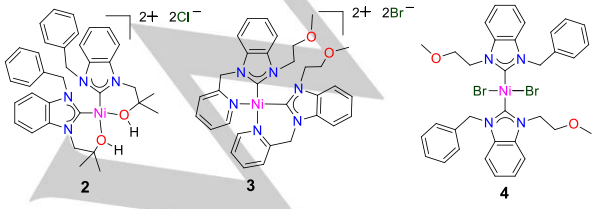


Scheme 5. Synthesis of pharmaceutical drugs by **1**. X-ray structure of Rufinamide is depicted inset.

Mechanistic Investigation

Control Experiments

In order to recognize the key role played by the hemilabile units, several related catalysts were synthesized and their catalytic activities were examined. First, a ligand precursor **[L^{2}H]Br** that is devoid of the pyridyl unit but contains the hydroxy side group was synthesized. Reaction between **[L^{2}H]Br**, excess ^{n}BuLi and $NiCl_2$ (0.5 equivalents) in THF provided complex **2** in 72% yield. The molecular structure of **2** shows a *cis* arrangement of two carbene ligands and the two remaining sites in the square planar geometry are occupied by the hydroxy groups (Scheme 6; Figure S2 for X-ray structure). Under optimized conditions, **2** gave less than 10% benzamide in 6 h that could be increased to 30% in the presence of catalytic amount of ^{t}BuOK (10 mol%). This experiment strongly suggests that the hemilabile pyridyl unit is indispensable for the hydration activity. Subsequently, a new ligand **[L^{3}H]Br** was synthesized which bears the pyridyl group but the hydroxy appendage was masked. Molecular structure of **3** revealed a dicationic structure analogous to **1** (Scheme 6; Figure S3 for X-ray structure). Under standard conditions, **3** afforded benzamide in 85% yield (*vs* 91% for catalyst **1**). This indicates that the absence of hydroxy appendages does not impede the hydration activity significantly. The peripheral alcohol groups in **1** may enhance the catalyst solubility in aqueous-alcohol binary mixture and consequently afford marginally better yield. Finally, a Ni complex **4**, devoid of both the pyridyl and the hydroxy side group, was synthesized (Scheme 6; Figure S4 for X-ray structure). The molecular structure of **4** shows two monodentate NHCs bound to the metal centre in *trans* geometry along with two bromides. Catalyst **4** gave less than 5% amide formation under catalytic conditions. In summary, catalysts that lack the pyridyl component (**2** and **4**) are not active whereas those containing both the pyridyl and the hydroxy or only the pyridyl pendant (**1** and **3**) show substantial activity. Systematic tuning of the ligands reveals that a hemilabile pyridyl unit is essential for the hydration activity.



Scheme 6. Catalysts **2**, **3** and **4**.

Hemilability and pK_a

A working hypothesis for the catalyst activity involves decoordination of the pyridyl unit from the metal center under catalytic conditions to pave the way for an incoming water and then polarizes it by hydrogen-bonding interaction. To establish ligand hemilability, pK_a measurement of the putative unbound pyridyl unit was attempted. Complex **3** was chosen since it is devoid of protic hydroxy groups. When 1:2 (*m/m*) mixture of **3** and TfOH in acetonitrile/water at room temperature was titrated against a standard 0.01 M NaOH solution, a gradual increase in pH was observed. This implies that the pyridine ring is bound to the metal and hence not accessible for protonation. Interestingly, when the same mixture was stirred at 70ºC for 1 h and then titrated against NaOH, a sigmoidal curve was observed from which pK_a of 2.51 was estimated (Figure 2a). In a separate experiment, an 1:1 (*m/m*) mixture of **[L^{3}H]Br** and TfOH in acetonitrile/water mixture at room temperature when titrated against a standard NaOH solution gave pK_a of 2.99 attributed to the pyridynium hydrogen (Figure 2b). The closeness of the pK_a values of **[L^{3}H]Br** and **3** suggests that the pyridyl unit in the latter complex is accessible under the reaction conditions.

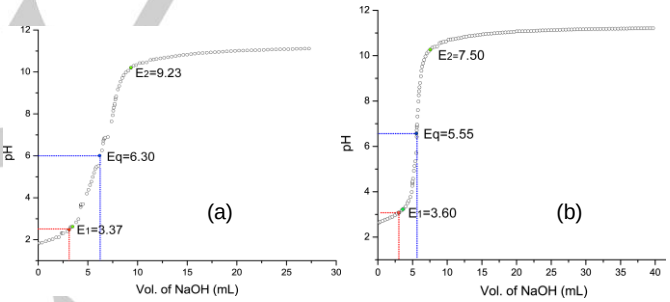


Figure 2. Titration curves obtained by titrating a) 1:2 (*m/m*) of **3** and TfOH in acetonitrile/water 3:1 (*v/v*) at 70ºC for 1 h against 0.01 M NaOH; b) 1:1 (*m/m*) of **[L^{3}H]Br** and TfOH in acetonitrile/water 3:1 (*v/v*) against 0.01 M NaOH.

Kinetic Studies

Kinetic experiments were performed to gain insight on the hydration mechanism. Kinetic Isotope Effect (KIE) was determined by carrying out nitrile hydration of benzonitrile with H_2O and D_2O, and a k_H/k_D value of 1.38 ± 0.21 was obtained (Figure 3a). This observation is consistent with other nitrile hydration catalysts.[23] The effect of temperature on the rate of the reaction of **1** with 4-nitrobenzonitrile was evaluated. The activation parameters were determined from ln(*k*/T) versus 1/T plot which is linear over the temperature range studied (333–353 K) (Figure 3b). The estimated entropy of activation ($\Delta S^{\ddagger}$) is −33.39 ± 0.56 cal mol^{-1} K^{-1}, and the enthalpy of activation ($\Delta H^{\ddagger}$) is 11.35 ± 0.77 kcal mol^{-1}. Such high negative $\Delta S^{\ddagger}$ value is indicative of an organized transition state involving both substrates (water and nitrile) and the catalyst.

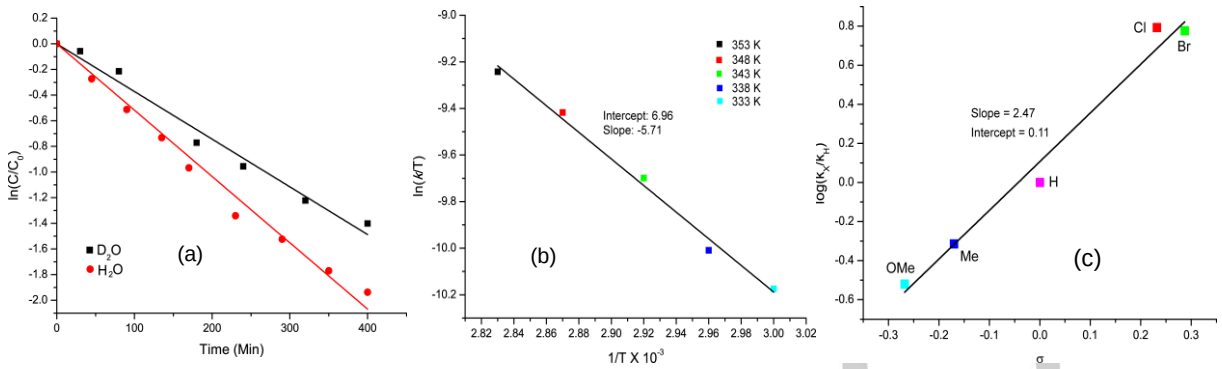


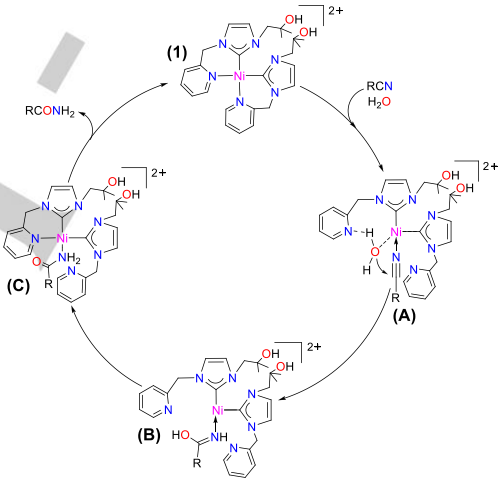
Figure 3. a) Reaction rates for amide formation in H_2O and D_2O; b) Arrhenius plot for hydration of 4-nitrobenzonitrile catalyzed by **1** over 333−353 K; c) Hammett plot for competitive hydration of benzonitrile and *p*-substituted derivatives catalyzed by **1** at 343 K.

The relationship between the relative rates and the Hammett parameter for the hydration of *p*-substituted benzonitrile by **1** was also examined. For *p*-substituted benzonitriles, their hydration reactivity follows the trend: *p*-Br >*p*-Cl >*p*-H >*p*-Me >*p*-OMe. The relative rates ($\log(k_X/k_H)$) were plotted against the substituent constant (σ) yielding a fairly good linear relationship. From the slope of the Hammett plot, ρ = +2.47 ± 0.19 was determined (Figure 3c). A positive ρ value suggests that the reaction should be favored by electron deficient substrates, which is in complete agreement with the experiments (*vide supra*). Further, it suggests a transition state in the rate-determining step (rds) in which negative charge is developed at α-carbon atom adjacent to the phenyl ring.[24] However, a linearity could not be achieved when $\log(k_X/k_H)$ was plotted against standard σ^- values.[25] This implies that the negative charge developed at α-carbon in the transition state is of lesser extent and hence a nucleophilic water attack to the metal-bound nitrile is more likely over a hydroxide (*vide infra*).

Proposed Mechanism

A hemilability driven water addition mechanism is proposed for nitrile hydration to amide (Scheme 7). The pyridyl units being *trans* to the carbene centers (long Ni-N distances, *vide supra*) are detached from the metal to allow the approach of a water molecule and a substrate nitrile towards the metal centre forming **A**. pK_a measurements indicated accessibility of the pyridyl group under catalytic conditions. Hydrogen-bonding interaction with one of the pyridyl nitrogen atom polarizes the water molecule. Such interaction also aids in bringing a catalytically relevant water molecule from the bulk solvent to the vicinity of the metal center.[9b, 12] Subsequent ligand-promoted nucleophilic water attack leads to the formation of an iminol intermediate **B**. This is followed by a rapid tautomerization to yield the amide coordinated intermediate **C**. Finally amide is released and catalyst **1** is regenerated completing the cycle.

An alternative pathway is water proton abstraction by the pyridyl nitrogen and simultaneous hydroxide attack to the nitrile carbon (Scheme S2).[12, 26] However, the pK_a values reveal that the pyridyl nitrogen is not sufficiently basic to abstract water hydrogen.[27] The absence of primary KIE also does not support a water dissociation mechanism. Furthermore, a linear Hammett plot was obtained with σ parameters of the substrates but not with σ^- values. Thus, kinetic experiments do not support a hydroxide attack. For hydration reaction that is carried out in neutral conditions, direct water addition to the nitrile carbon appears to be favored over a hydroxide attack.[28]



Scheme 7. Proposed mechanism for nitrile hydration (for clarity, benzimidazole is replaced with imidazole).

Conclusions

A Ni(II) catalyst bearing NHC-derived hemilabile ligands is reported. It hydrates a wide range of organonitriles to the corresponding amides, including several amide-based pharmaceuticals. Cyanohydrins, which are otherwise destroyed in basic medium, are hydrated by this catalyst. Control experiments reveal the activity-enhancing roles for the hemilabile pyridyl group. pK_a measurements validate ligand hemilability under catalytic conditions. Kinetic studies suggest a ligand-promoted nucleophilic water addition to the nitrile carbon. Hemilability driven nitrile hydration by a 3d-metal complex opens up new avenues for further development of water-activation catalysts.

Experimental Section

General Procedures. All reactions were carried out under nitrogen atmosphere with the use of standard Schlenk–line techniques unless stated otherwise. Glasswares were flame–dried under vacuum prior to use. ^{1}H, ^{13}C and ^{19}F NMR spectra were obtained on JEOL JNM–LA 500 MHz and JEOL JNM–LA 400 MHz spectrometers. Chemical shift values were referenced to the residual signals of the deuterated solvents. ESI–MS were recorded on a Waters Micro mass Quattro Micro triple–quadruple mass spectrometer. Elemental analyses were performed on a Thermoquest EA1110 CHNS/O analyzer. The crystallized compound was washed several times with dry diethyl ether, powdered and dried in vacuum for at least 48 h prior to elemental analyses. GC–MS experiment was performed on an Agilent 7890A GC and 5975C MS system. EDX experiment was performed on a JEOL EDS-LA *6510* analyzer. Potentiometric titration was carried out at 25ºC using Metrohm 794 Basic Titrino instrument connected to a Metrohm AG 9101 Herisau pH glass-electrode and a ground-joint diaphragm. Prior to the experiment, the standardization was carried out with aqueous buffer solutions at pH 4.00 and 7.00. The ionic-strength of the medium was maintained at I = 0.1 M $NaNO_3$.

Materials. Solvents were dried by conventional methods, distilled under nitrogen and deoxygenated prior to use. Anhydrous $NiCl_2$ and organonitriles were purchased from Sigma-Aldrich. ^{n}BuLi was bought from Acros Organics.

X-ray data collections and refinement. Single crystal X–ray structural studies were performed on a CCD Bruker SMART APEX diffractometer equipped with an Oxford Instruments low–temperature attachment. Data were collected at 100(2) K using graphite–monochromated Mo–Kα radiation (λ_α = 0.71073 Å). The frames were indexed, integrated and scaled using SMART and SAINT software package,[29] and the data were corrected for absorption using the SADABS program.[30] The structures were solved and refined using SHELX 2014 suite of programs.[31] The hydrogens of the O–H groups in complex **1**, **1'** and **2** were located in the difference Fourier map and were refined with restraints. All other hydrogen atoms were included in the final stages of the refinement and were refined with a typical riding model. All non–hydrogen atoms were refined with anisotropic thermal parameters. The "SQUEEZE" option in the PLATON program was used to remove any disordered solvent molecule, if present from the overall intensity data.[32] Crystallographic data and pertinent refinement parameters for compounds are summarized in Table S1 in the Supporting Information. The crystallographic figures used in this manuscript have been generated using Diamond 3.1e software.[33] CCDC 1457346, 1479483-1479487, 1539691 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of **[L^{1}H]Cl**. Benzimidazole (1.00 g, 8.46 mmol) and isobutylene oxide (0.7 mL, excess) were taken in a pressure tube and were heated at 50ºC for 6 h in neat condition. This was followed by the addition of neutralized picolyl chloride (1.19 g, 9.31 mmol) in 5 mL THF. The resulting solution was refluxed for another 24 h. A pink precipitate appeared which was filtered, subsequently washed with diethyl ether and finally dried in vacuum. Yield: 2.42 g (90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (s, 1H, Im), 8.49 (d, J = 5.15 Hz, 1H, Py), 7.76 (d, J = 8.60 Hz, 1H, Py), 7.72-7.69 (m, 2H, Py), 7.61 (d, J = 7.45, 1H, Ph), 7.59-7.55 (m, 1H, Ph), 7.53-7.47 (m, 1H, Ph), 7.25-7.22 (m, 1H, Ph), 5.86 (s, 2H, $PyCH_2$), 4.67 (s, 2H, CH_2), 4.23 (s, 1H, OH), 1.29 (s, 6H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C_{Py}), 149.9 (C_{Py}), 144.6 (C_{Im}), 137.8 (C_{Py}), 132.5 (C_{Ph}), 131.1 (C_{Ph}), 127.0 (C_{Ph}), 126.9 (C_{Ph}), 124.1 (C_{Py}), 123.3 (C_{Py}), 114.2 (C_{Ph}), 113.3 (C_{Ph}), 69.6 (C_{CH2}), 56.5 (C_{COH}), 52.8 (C_{CH2Py}), 27.5 (C_{CH3}), 27.3 (C_{CH3}); ESI-MS (CH_3CN): *m/z* 282.1606 [M-Cl]$^+$; Anal. Calcd for $C_{17}H_{20}N_3Cl_1O_1$: C, 64.33; H, 6.36; N, 13.25. Found: C, 64.12; H, 6.11; N, 12.99.

Synthesis of **1**. In a flame dried Schlenk flask **[L^{1}H]Cl** (220 mg, 0.70 mmol) was dissolved in 15 mL THF and cooled to 0°C. ^{n}BuLi (1.75 mmol, 1.6 M in hexane, 2.5 equivalents) was added to this solution followed by addition of anhydrous $NiCl_2$ (44 mg, 0.35 mmol, 0.5 equivalents). The mixture was allowed to attain room temperature and then refluxed for 24 h. The solution was cooled and the solvent was evaporated under reduced pressure. The crude solid obtained was redissolved in 15 mL methanol and the orange mixture was filtered through a small pad of celite. The solution was concentrated under reduced pressure, and 15 mL diethyl ether was added to induce precipitation. The supernatant solution was discarded by cannula filtration, and the precipitate was further washed with diethyl ether (3x10 mL). Finally, the precipitate was dried under vacuum to afford **1** as a yellow solid. Crystals suitable for X-ray diffraction were grown by layering diethyl ether over a concentrated methanolic solution of **1** inside an 8 mm o.d. vacuum−sealed glass tube. Yield: 412 mg (85%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 4.56 Hz, 1H, Py), 8.04 (d, J = 8.24 Hz, 1H, Py), 7.87 (t, J = 7.80 Hz, 1H, Py), 7.80 (d, J = 8.24 Hz, 1H, Ph), 7.65-7.60 (m, 3H, Ph), 7.37-7.34 (m, 1H, Py), 5.91 (s, 2H, CH_2py), 4.53 (s, 2H, CH_2), 2.01 (s, 1H, OH), 1.28 (s, 6H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) 173.3 (C_{Im}), 154.2 (C_{Py}), 151.7 (C_{Py}), 148.8 (C_{Py}), 140.3 (C_{Ph}), 137.0 (C_{Ph}), 132.3 (C_{Py}), 126.0 (C_{Py}), 111.2 (C_{Ph}), 109.8 (C_{Ph}), 69.0 (C_{CH2}), 55.9 (C_{COH}), 54.8 (C_{CH2Py}), 25.1 (C_{CH3}), 24.4 (C_{CH3}); ESI-MS (CH_3CN): *m/z*: 310.1205 [M-2Cl]$^{2+}$; Anal. Calcd for $C_{34}H_{38}N_6O_2Cl_2Ni_1$: C, 59.12; H, 5.55; N, 12.17. Found: C, 58.95; H, 5.37; N, 11.99. Compound **1'** was crystallized from a 1:1 mixture of CH_3CN/CH_3OH layered with Et_2O solution at -20°C. Spectroscopic details of **1'** are identical to **1**.

Synthesis of **[L^{2}H]Br**. Benzimidazole (1.00 g, 8.46 mmol) and isobutylene oxide (0.7 mL, excess) were taken in a pressure tube and were heated at 50ºC for 6 h in neat condition. This was followed by the addition of benzyl bromide (1.59 g, 9.31 mmol) in 5 mL THF. The resulting solution was refluxed for another 24 h. A white precipitate appeared which was filtered subsequently washed with diethyl ether and finally dried in vacuum. Yield: 2.50 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H, Im), 7.89 (d, J = 7.80 Hz, 1H, Ph), 7.57-7.46 (m, 5H, Phen), 7.36-7.31 (m, 3H, Ph), 5.84 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 4.18 (s, 1H, OH), 1.26 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2 (C_{Im}), 133.0 (C_{Ph}), 132.2 (C_{Ph}), 131.2 (C_{Ph}) 127.1 (C_{Phen}), 126.8 (C_{Phen}), 124.2 (C_{Phen}), 123.3 (C_{Phen}), 114.3 (C_{Ph}), 113.2 (C_{Ph}), 79.9 (C_{OH}), 69.6 (C_{CH2}), 52.8 (C_{CH2}), 27.5 (C_{CH3}), 27.3 (C_{CH3}).

Synthesis of **2**. In a flame dried Schlenk flask **[L^{2}H]Br** (252 mg, 0.70 mmol) was dissolved in 15 mL THF and cooled to 0°C. ^{n}BuLi (1.75 mmol, 1.6 M in hexane, 2.5 equivalents) was added to this solution followed by addition of anhydrous $NiCl_2$ (44 mg, 0.35 mmol, 0.5 equivalents). The mixture was allowed to attain room temperature and then refluxed for 36 h. The solution was cooled and the solvent was evaporated under reduced pressure. The crude solid obtained was redissolved in 15 mL dichloromethane and the yellow mixture was filtered through a small pad of celite. The solution was concentrated under reduced pressure, and 15 mL petroleum ether was added to induce precipitation. The supernatant solution was discarded by cannula filtration, and the precipitate was further washed with petroleum ether (3x10 mL). Finally, the precipitate was dried under vacuum to afford **2** as a yellow solid. Crystals suitable for X-ray diffraction were grown by layering petroleum ether over a concentrated dichloromethane solution of **2** inside an 8 mm o.d. vacuum-sealed glass tube. Yield: 311 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.78 (m, 2H, Ph), 7.57-7.44 (m, 5H, Phen), 7.40-7.32 (m, 2H, Ph), 5.84 (s, 2H, CH_2), 4.80 (s, 2H, CH_2), 4.82 (s, 1H, OH), 1.28 (s, 6H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (C_{Im}), 137.2 (C_{Ph}), 129.1 (C_{Ph}), 128.2 (C_{Ph}), 127.9 (C_{Phen}), 126.7 (C_{Phen}), 125.0 (C_{Phen}), 118.9 (C_{Phen}), 110.9 (C_{Ph}), 110.6 (C_{Ph}), 71.9 (C_{COH}), 68.7 (C_{CH2}), 52.4 (C_{CH2}), 26.5 (C_{CH3}) 26.3 (C_{CH3}).

Synthesis of **[L^{3}H]Br**. Benzimidazole (1.00 g, 8.46 mmol), picolyl chloride (1.19 g, 9.31 mmol), and KOH (1.04 g, 18.62 mmol, 2.2 equivalents) were dissolved in 15 mL THF and heated at reflux for 6 h. The resulting mixture was cooled to room temperature, and solvent was evaporated under vacuum. Water was added to the residue and extracted three times with 30 mL of dichloromethane. After washing with water, the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and volatiles were removed under reduced pressure. Yellow solid 1-benzyl-1*H*-benzimidazole was formed. Subsequently, 1-benzyl-1*H*-benzimidazole, 2-bromoethyl methyl ether (0.87 mL, 9.31 mmol, 1.1 equivalents) and 5 mL dry THF were taken in a pressure tube and refluxed for 24 h. Obtained white precipitate was filtered and washed with diethyl ether. Finally, the precipitate was dried under vacuum to afford **[L^{3}H]Br**. Yield: 2.42 g (82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.35 (s, 1H, Im), 8.48 (d, *J* = 4.05 Hz, 1H, Py), 7.88 (d, = 8.00 Hz, 2H, Ph), 7.78 (d, *J* = 8.60 Hz, 1H, Py), 7.74-7.70 (m, 1H, Py), 7.59-7.53 (m, 2H, Ph), 7.25-7.22 (m, 1H, Py), 6.00 (s, 2H, CH_2), 4.78 (t, *J* = 4.85 Hz, 2H, CH_2), 3.94 (t, *J* = 4.85 Hz, 2H, CH_2), 3.35 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5 (C_{Py}), 149.7 (C_{Im}), 143.2 (C_{Py}), 137.8 (C_{Py}), 132.1 (C_{Ph}), 131.6 (C_{Ph}), 127.1 (C_{Py}), 127.1 (C_{Py}), 124.1 (C_{Ph}), 124.0 (C_{Ph}), 114.3 (C_{Ph}), 113.8 (C_{Ph}), 70.2 ($C_{CH2OCH3}$), 59.3 (C_{OCH3}), 52.6 (C_{CH2Py}), 48.0 ($C_{CH2CH2OCH3}$); Anal. Calcd for $C_{16}H_{18}N_3O_1Br_1$: C, 55.32; H, 5.23; N, 12.10. Found: C, 55.14; H, 4.97; N, 11.84.

Synthesis of **3**. In a flame dried Schlenk flask **[L^{3}H]Br** (174 mg, 0.50 mmol) was dissolved in 15 mL THF and cooled to 0°C. ^{n}BuLi (0.75 mmol, 1.6 M in hexane, 1.5 equivalents) was added to this solution followed by addition of $Ni(COD)_2$ (69 mg, 0.25 mmol, 0.5 equivalents). The mixture was allowed to attain room temperature and then refluxed for 36 h. The volatiles were evaporated and crude solid was again dissolved in 15 mL dichloromethane and the red mixture was filtered through a small pad of celite. The filtrate was concentrated and 15 mL of hexane was added with stirring to induce precipitation. The supernatant solution was discarded by cannula filtration, and the precipitate was further washed with petroleum ether (3x10 mL). Finally, the precipitate was dried under vacuum to afford **3** as a red solid. Crystals suitable for X-ray diffraction were grown by layering diethyl ether over a concentrated methanol solution of **3** inside an 8 mm o.d. vacuum−sealed glass tube. Yield: 319 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.56 Hz, 1H, Py), 7.59-7.56 (m, 1H, Py), 7.18-7.14 (m, 2H, Py), 7.11-7.04 (m, 2H, Ph), 7.00-6.92 (m, 2H, Ph), 5.19 (s, 2H, $PyCH_2$), 4.10 (t, *J* = 5.48 Hz, 2H, CH_2O), 3.70 (t, *J* = 5.48 Hz, 2H, CH_2), 3.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (C_{Im}), 154.5 (C_{Py}), 149.5 (C_{Py}), 137.1 (C_{Py}), 130.0 (C_{Ph}), 129.3 (C_{Ph}), 122.7 (C_{Py}), 121.8 (C_{Py}), 121.6 (C_{Ph}), 121.4 (C_{Ph}), 108.6 (C_{Ph}), 108.5 (C_{Ph}), 70.6 ($C_{CH2OCH3}$), 59.1 (C_{OCH3}), 47.0 (C_{CH2Py}), 41.5 ($C_{CH2CH2OCH3}$); Anal. Calcd for $C_{32}H_{34}N_6Ni_1O_2Br_2$: C, 51.20; H, 4.57; N, 11.20. Found: C, 50.94; H, 4.29, N, 10.95.

Synthesis of **[L^{4}H]Br**. Benzimidazole (1.00 g, 8.46 mmol), benzyl bromide (1.11 mL, 9.31 mmol, 1.1 equivalents) and KOH (1.04 g, 18.62 mmol, 2.2 equivalents) were dissolved in 15 mL THF and refluxed for 6 h. The resulting mixture was cooled to room temperature, and solvent was evaporated under vacuum. Water was added to the residue and extracted three times with 30 mL of dichloromethane. After washing with water, the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and volatiles were removed under reduced pressure. Yellow solid 1-benzyl-1*H*-benzimidazole was formed. Subsequently, 1-benzyl-1*H*-benzimidazole, 2-bromoethyl methyl ether (0.87 mL, 9.31 mmol, 1.1 equivalents) and 5 mL dry THF were taken in a pressure tube and heated at reflux for 24 h. Obtained white precipitate was filtered and washed with diethyl ether. Finally, the precipitate was dried under vacuum to afford **[L^{4}H]Br**. Yield: 2.50 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H, Im), 7.81 (d, *J* = 7.80 Hz, 1H, Ph), 7.56-7.47 (m, 5H, Phen), 7.33-7.30 (m, 3H, Ph), 5.84 (s, 2H, CH_2), 4.82 (t, *J* = 4.56 Hz, 2H, CH_2), 3.93 (t, *J* = 5.04 Hz, 2H, CH_2), 3.32 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C_{Im}), 132.7 (C_{Phen}), 132.3 (C_{Ph}), 131.1 (C_{Ph}), 129.5 (C_{Phen}), 129.3 (C_{Phen}), 128.4 (C_{Phen}), 127.2 (C_{Ph}), 114.2 (C_{Ph}), 113.5 (C_{Ph}), 70.2 ($C_{CH2OCH3}$), 59.2 (C_{OCH3}), 51.6 ($C_{CH2Phen}$), 48.0 ($C_{CH2CH2OMe}$); Anal. Calcd for $C_{17}H_{19}N_2O_1Br_1$: C, 58.95; H, 5.53; N, 8.09. Found: C, 58.72; H, 5.29; N, 7.84.

Synthesis of **4**. In a flame dried Schlenk flask **[L^{4}H]Br** (242 mg, 0.70 mmol) was dissolved in 15 mL THF and cooled to 0°C. ^{n}BuLi (1.05 mmol, 1.6 M in hexane, 1.5 equivalents) was added to this solution followed by addition of anhydrous $NiCl_2$ (45 mg, 0.35 mmol, 0.5 equivalents). The mixture was allowed to attain room temperature and then refluxed for 36 h. The volatiles were evaporated and crude solid was redissolved in 15 mL dichloromethane and the yellow mixture was filtered through a small pad of celite. The filtrate was concentrated and 15 mL of hexane was added with stirring to induce precipitation. The supernatant solution was discarded by cannula filtration, and the precipitate was further washed with petroleum ether (3×10 mL). Finally, the precipitate was dried under vacuum to afford **4** as a yellow solid. Crystals suitable for X-ray diffraction were grown by layering petroleum ether over a concentrated dichloromethane solution of **4** inside an 8 mm o.d. vacuum−sealed glass tube. Yield: 429 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.32-7.29 (m, 5H, Phen), 7.11-6.96 (m, 3H, Ph), 6.84 (d, *J* = 7.76 Hz, 1H, Ph), 5.06 (s, 2H, CH_2), 4.09 (t, *J* = 5.52 Hz, 2H, CH_2), 3.70 (t, *J* = 5.52 Hz, 2H, CH_2), 3.33 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (C_{Im}), 136.4 (C_{Phen}), 130.0 (C_{Ph}), 128.8 (C_{Ph}), 127.7 (C_{Phen}), 127.6 (C_{Phen}), 121.4 (C_{Phen}), 121.3 (C_{Ph}), 108.5 (C_{Ph}), 108.3 (C_{Ph}), 70.7 ($C_{CH2OCH3}$), 59.0 (C_{OCH3}), 45.0 ($C_{CH2Phen}$), 41.4 ($C_{CH2CH2OCH3}$); Anal. Calcd for $C_{34}H_{38}Br_2N_4O_2Ni_1$: C, 54.39; H, 5.11; N, 7.47. Found: C, 54.11; H, 4.91; N, 7.25.

Nitrile Hydration. An oven dried Schlenk tube was charged with compound **1** (0.02 mmol), nitrile (1 mmol) and ^{i}PrOH/H_2O (4mL, 3:1 *v/v*). The tube was placed in a pre-heated oil bath at 70°C with stirring for the specified time. After the reaction was over, the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to give desired amide. Yields are calculated based on isolated products. GC yields are reported in presence of internal standard mesitylene (for selected entries) in the manuscript.

Hydration of cyanohydrins. An oven dried Schlenk tube was charged with compound **1** (0.1 mmol), cyanohydrin (1 mmol) and ^{i}PrOH/H_2O (4 mL, 3:1 *v/v*). The tube was placed in a pre-heated oil bath at 100°C with stirring for 48 h. After the reaction was over, the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH) to give desired α–hydroxyamide. Yields are calculated based on isolated products.

Kinetic Isotope Effect Studies. An oven dried Schlenk tube was charged with compound **1** (0.02 mmol), benzonitrile (1 mmol), internal standard mesitylene (0.5 mmol) and ^{i}PrOD-d_8/D_2O (3:1 *v/v*). The tube was placed in a pre-heated oil bath at 70°C with stirring. After stipulated time intervals, small aliquots of 0.2 mL were taken out with a hypodermic needle. KIE was calculated to be the ratios for the two reaction rates.

Arrhenius Plot. An oven dried Schlenk tube was charged with compound **1** (0.02 mmol), benzonitrile (1 mmol), internal standard mesitylene (0.5 mmol) and ^{i}PrOH/H_2O (3:1 *v/v*). The tube was placed in a

pre-heated oil bath with stirring and after stipulated time intervals, small aliquots of 0.2 mL were taken out with a hypodermic needle. The activation parameters were determined from the ln(*k*/T) versus 1/T plot which is linear over the temperature range studied (333–353 K).

Hammett plot. An oven dried Schlenk tube was charged with compound **1** (0.02 mmol), benzonitrile (1 mmol), *p*-substituted benzonitriles (1 mmol), internal standard mesitylene (0.5 mmol) and ^{i}PrOH/H_2O (3:1 *v/v*). The tube was placed in a pre-heated oil bath at 70°C with stirring and after stipulated time intervals, small aliquots of 0.2 mL were taken out with a hypodermic needle. Reactivity towards hydration reaction follows the sequence *p*-Br >*p*-Cl >*p*-H >*p*-Me >*p*-OMe. The relative rates ($\log(k_X/k_H)$) were plotted against the substituent constant (σ) yielding a fairly good linear relationship. From the slope of the Hammett plot, a positive ρ value was determined.

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Keywords: Water Activation • Cooperative Catalysis • Hemilability • 3d-Metal Catalysis • Amide Synthesis

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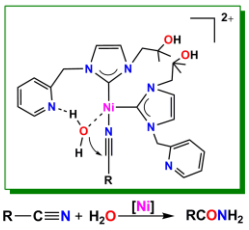
FULL PAPER

Water Addition: A hemilabile pyridyl unit on a Ni catalyst bearing functionalized NHC ligands, guides a water molecule to the metal, polarizes it through hydrogen-bonding interaction and promotes nucleophilic attack to the nitrile carbon for nitrile hydration to amide under base-free condition.

Functional Hemilability for Nitrile Hydration



- 3d-metal
- Base-free conditions
- Easy access to amide-based drugs

*Kuldeep Singh, Abir Sarbajna, Indranil Dutta, Pragati Pandey and Jitendra K. Bera**

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Hemilability Driven Water Activation: A Ni(II) Catalyst for Base-Free Hydration of Nitriles to Amides