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Selective hydration of nitriles to amides catalysed
by PCP pincer supported nickel(II) complexes†

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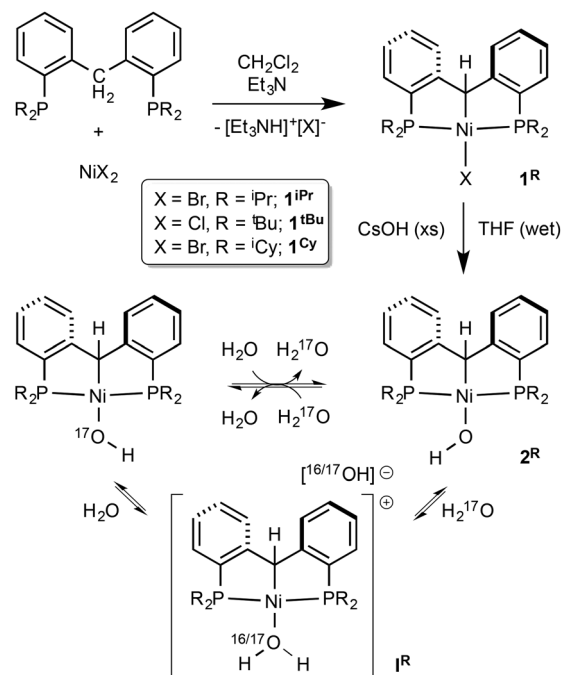
The (PCP)Ni–OH complexes 2^R ($R = {}^i\text{Pr}$, ${}^t\text{Bu}$, Cy) are effective catalyst precursors for the selective hydration of nitriles to the corresponding amides under relatively mild conditions (80 °C) and low catalyst loadings (0.05–0.5%). Substrate scope includes aliphatic, vinylic and aromatic nitriles, but substrates with protic groups poison the catalyst abruptly. The catalysts are effective because the electron rich nature of the PCP ligands and their steric bulk renders the hydroxo group labile.

While the hydration of nitriles to form organic amides may seem a rather mundane transformation, the enormous scale upon which this is done gives this reaction economic and environmental significance that few other chemical conversions have.¹ For example, hydration of acrylonitrile to give acrylamide, the monomer for polyacrylamide, produces 10^5 – 10^6 metric tonnes per annum.² The processes utilized suffer from poor selectivity, and over hydration to acrylic acid adds separation and waste disposal costs to the industry. While the use of biocatalytic routes improves selectivity,³ these processes can be more expensive to operate. Therefore, there has been interest in the development of homogeneous catalysts that selectively mediate the conversion of nitriles to amides.^{4–6} While there have been some notable successes, many of the catalysts investigated so far are based on precious metals, particularly ruthenium^{4,7} and platinum⁸ and lack suitable activity levels for enablement on the scales necessary. We describe here a family of comparatively active catalysts based on the earth abundant metal nickel, supported by electron rich PCP pincer ligands developed recently in our laboratories.⁹ To our knowledge, only one homogeneous nickel-based catalyst has been reported¹⁰ to date. Here, a Ni(0) catalyst precursor mediated the hydration of benzonitrile and

acetonitrile under rather forcing conditions (140–180 °C). Low conversions were observed (6–68% for benzonitrile, 1–10% for acetonitrile) and low turn over numbers (TON = 40–984 for benzonitrile, 17–257 for acetonitrile) were achieved.

The catalysts employed here are the Ni(II) (PCP)NiOH complexes 2^R ($R = {}^i\text{Pr}$, ${}^t\text{Bu}$, Cy) prepared as depicted in Scheme 1. The pincer ligand attachment protocol used is improved over that which we initially reported¹¹ by the inclusion of Et_3N to remove the HX produced in the C–H activation reaction between the proligands and NiX_2 . In this way, the (PCP)NiX compounds 1^R can be obtained in yields of over 90%.

These compounds were fully characterized, and the X-ray structure determinations for the chloro derivative $1^{t\text{Bu}}$ and the bromo complex 1^{Cy} are included in the ESI (Fig. S1 and S2†).



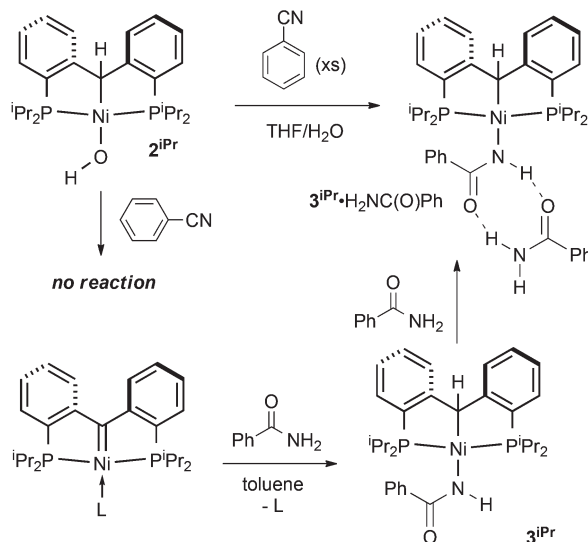
Scheme 1 Synthesis of catalysts 2^R and exchange processes associated with the hydroxo group.

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†Electronic supplementary information (ESI) available: General and detailed experimental data, thermal ellipsoid depictions of $1^{t\text{Bu}}$, 1^{Cy} , $3^{i\text{Pr}}$, $4^{i\text{Pr}}$ and $5^{i\text{Pr}}$, ^{17}O NMR spectra and catalytic speciation plots, and crystallographic data. CCDC 1039461–1039466. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4dt03902e

Conversion to the hydroxo derivatives was accomplished by treatment with an excess of CsOH in degassed, wet THF. In addition to ligand resonances, isolated hydroxo compounds 2^R exhibit characteristic signals at 4.73–4.84 ppm for the benzylic proton on the PCP ligand and triplets at –2.94 to –3.22 ppm ($^3J_{\text{HP}} \approx 5\text{--}6\text{ Hz}$) for the O–H protons in the ^1H NMR spectra. The latter resonances broaden in the presence of small amounts of water, and disappear when D_2O is added; the benzylic protons do not exchange with the deuterium in D_2O , indicating that $\text{PC}_{\text{carbene}}\text{P}$ species¹¹ are not formed *via* elimination of water from compounds 2^R . However, when ^{17}O enriched 2^{iPr} was treated with H_2O , rapid depletion of label from the Ni– ^{17}O H moiety was observed (Fig. S3†). This demonstrates that the hydroxo group in these compounds is labile under these conditions, presumably mediated by the cationic species I^R (Scheme 1) perhaps formed upon protonation of the hydroxo group. It is also conceivable that direct dissociation of the OH ligand occurs; the Ni–O bond distance of 1.978(2) Å found for 2^{iPr} ¹¹ is longer than any reported in related Ni–OH compounds^{12–17} and the C_{sp^3} anchoring group of the PCP pincer ligand should have a strong *trans* influence.¹⁸

In either case, the lability of the hydroxo group in compounds **2** in polar solvent environments suggested to us that nitriles might undergo facile hydration in the presence of a cationic species such as I^R . When 2^{iPr} was treated with an excess of benzonitrile in THF, no reaction was observed either visually or spectroscopically; however, addition of water to this solution resulted in rapid conversion of hydroxo 2^{iPr} to a new compound characterized by a broadened peak in the ^{31}P NMR spectrum at $\approx 45\text{ ppm}$, shifted downfield from that observed for 2^{iPr} at 39.3 ppm. Furthermore, slow conversion of benzonitrile to benzamide was observed over the course of several hours. The spectroscopic features of this mixture were difficult to interpret because of broadening and the presence of the various components in excess, but crystals deposited from solutions left standing for >24 hours and were subjected to diffraction analysis. In this way, the new compound was identified as the κ^1 amidate $3^{\text{iPr}}\cdot\text{H}_2\text{NC}(\text{O})\text{Ph}$ (Scheme 2). The molecular structure of this compound is shown in Fig. 1, along with selected metrical parameters. The broadness in the NMR spectra of this compound is no doubt attributable to dynamic processes involving the hydrogen bonded benzamide molecules in the product, further complicated by the presence of excess H_2O in the solutions. Amidate 3^{iPr} can be prepared free of hydrogen bonding partners by treating the known $(\text{PC}_{\text{carbene}}\text{P})\text{Ni}(\text{NC}^t\text{Bu})$ complex¹¹ with one equivalent of dry benzamide. The N–H bond adds across the Ni=C linkage to cleanly deliver 3^{iPr} ; the X-ray structure of this species has also been determined (Fig. S4†) and the numbers in parentheses in the caption for Fig. 1 indicate the distances and angles found for this species as a comparison. The lack of hydrogen bonding partners for 3^{iPr} sharpens the NMR resonances, and in the ^1H NMR spectrum a signal at 3.50 ppm may be assigned to the N–H moiety, and a sharp resonance at 45.8 ppm is observed in the ^{31}P NMR spectrum. Addition of an excess of



Scheme 2 Hydration of benzonitrile using 2^{iPr} ; catalyst resting state.

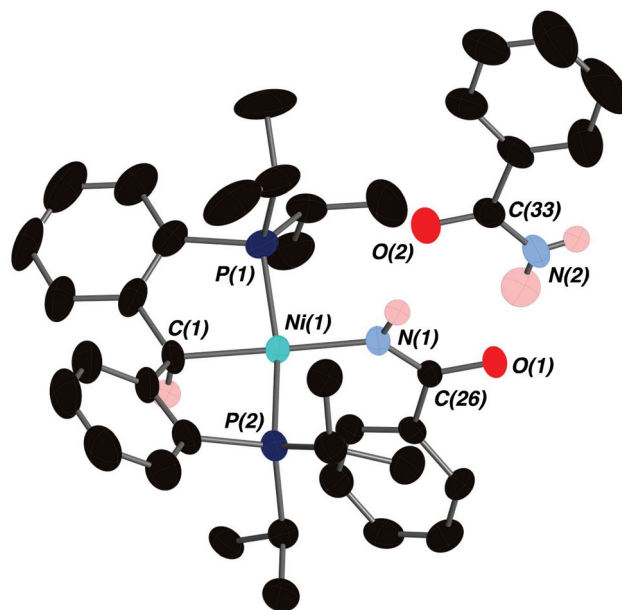


Fig. 1 Molecular structure of $3^{\text{iPr}}\cdot\text{H}_2\text{NC}(\text{O})\text{Ph}$. Most hydrogen atoms are omitted for clarity; a second molecule of benzamide H-bonded through N(2) is also not shown. Selected bond distances, non-bonded distances (Å), angles and dihedral angles ($^\circ$); numbers in square brackets are the metrical parameters for 3^{iPr} , included for comparison: Ni(1)–C(1), 1.990(4) [1.973(4)]; Ni(1)–P(1), 2.1550(12) [2.1544(10)]; Ni(1)–P(2), 2.1992(12) [2.2165(11)]; Ni(1)–N(1), 1.914(3) [1.902(3)]; N(1)–C(26), 1.308(5) [1.313(6)]; C(26)–O(1), 1.272(4) [1.232(5)]; N(1)–O(2), 3.128; O(1)–N(2), 2.870; P(1)–Ni(1)–N(1), 93.69(10) [95.01(11)]; N(1)–Ni(1)–P(2), 95.26(10) [96.94(11)]; C(1)–Ni(1)–P(1), 85.66(13) [85.77(12)]; C(1)–Ni(1)–P(2), 85.27(13) [83.62(12)]; P(1)–Ni(1)–N(1)–C(26), 120.26 [123.35]; P(2)–Ni(1)–N(1)–C(26), 73.59 [72.80].

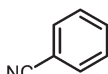
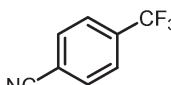
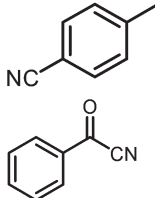
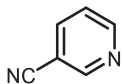
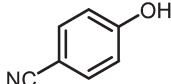
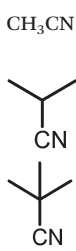



benzamide in wet THF to this sample reproduces the NMR features of $3^{\text{iPr}}\cdot\text{H}_2\text{NC}(\text{O})\text{Ph}$.

Species $3^{\text{iPr}}\cdot\text{H}_2\text{NC}(\text{O})\text{Ph}$ likely forms from a cation I^{iPr} *via* displacement of the aquo ligand by benzonitrile and nucleo-

philic attack by hydroxide on the coordinated nitrile;⁵ tautomerization of the kinetic product of this sequence would yield 3^{iPr} . This appears to be the resting state of the nickel as the reaction turns over; only $3^{\text{iPr}} \cdot \text{H}_2\text{NC(O)Ph}$ is observed as the ongoing conversion of benzonitrile to benzamide is monitored by NMR spectroscopy. The reaction is slow at room temperature, and use of THF as a solvent for larger scale catalytic runs lead to solubility problems. Through optimization, we found that iso-propanol-water mixtures, spiked with a small amount of d^8 -THF for NMR spectroscopic purposes, was the best medium for the reaction; running the reactions at a temperature of 80 °C gave convenient rates.

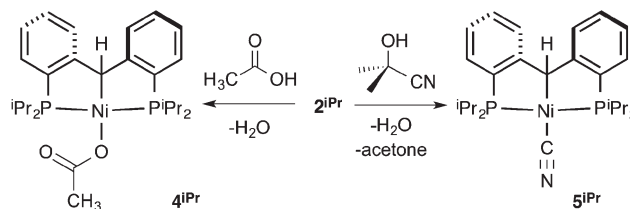
A study of the catalyst precursor and substrate scope for nitrile hydration was conducted using these standard con-

Table 1 Catalyst and substrate scope for the hydration of nitriles using nickel hydroxo compounds 2^{R}

Substrate	Entry	Cat (%)	Time (h)	Yield (%)	TON
	1a	2^{iPr} , 0.1	9	95 ^a	950
	1b	2^{Cy} , 0.1	6.5	99 ^a	990
	1c	2^{tBu} , 0.1	3	99 ^a	990
	1d	2^{tBu} , 0.05	10	88	1750
	2	2^{tBu} , 0.5	1	100	200
	3	2^{tBu} , 0.5	6	98 ^a	196
	4	2^{tBu} , 0.5	0.5	100	200
	5a	2^{iPr} , 0.5	1	95 ^a	950
	5b	2^{tBu} , 0.5	0.5	99 ^a	990
	5c	2^{tBu} , 0.05	6	88	2000 ^c
	6	2^{tBu} , 0.5	24	0	—
	7a	2^{iPr} , 0.1	2	47	470
	7b	2^{iPr} , 0.5	2	92 ^a	200
	7c	2^{tBu} , 0.5	1	32	64
	8a	2^{iPr} , 0.5	3	99 ^a	200
	8b	2^{tBu} , 1	4	95 ^a	190
		9a	2^{iPr} , 0.5	6	95 ^a
9b		2^{tBu} , 1	8	95 ^a	95
	10a	2^{iPr} , 0.5	0.5	50 ^b	100
	10b	2^{tBu} , 0.5	1	45 ^b	90
	11a	2^{iPr} , 0.2	3	99 ^a	500
	11b	2^{tBu} , 0.1	6	100	1000
	12	2^{iPr} , 0.5	—	0	—

^a Isolated Yield ^b Full conversion observed but low selectivity.

^c Maximum achieved TON.



Scheme 3 Catalyst poisoning processes with protic impurities.

ditions (Table 1). A comparison of the three catalyst precursors 2^{R} for the hydration of benzonitrile showed that the catalyst with the di-*tert*-butyl phosphine was more active than the isopropyl or cyclohexyl substituted catalyst precursors (Table 1, entries 1a–d, Fig. S5†) for this substrate. Indeed, 2^{tBu} was the most active catalyst for all aryl nitriles examined (entries 2–5). When 2^{Cy} was employed, it exhibited average performance and so was not examined in any further detail. For aliphatic nitriles, however, 2^{iPr} was competitive, perhaps somewhat superior, in terms of performance (entries 7–9). In the case of acetonitrile (entry 7), at lower catalyst loadings of 2^{iPr} , the reaction stopped at $\approx 50\%$ conversion; this was due to the conversion of the catalyst to the κ^1 acetate complex 4^{iPr} (Scheme 3). Formation of 4^{iPr} was ascribed to the presence of traces of acetic acid in the substrate feed, rather than over hydration of the acetamide product, since higher catalyst loadings resulted in full conversion, and prolonged exposure of pure acetamide to catalytic conditions did not produce acetic acid or 4^{iPr} . Compound 4^{iPr} was separately synthesized from 2^{iPr} and acetic acid and fully characterized, including *via* X-ray crystallography (Fig. S6†).

Unfortunately, acrylonitrile underwent competitive reactions involving the C=C double bond (entry 10), and only 45–50% conversion to acrylamide was observed. The main side reaction involved addition of iso-propanol to the double bond, followed by hydration of the amide. However, when methylacrylonitrile was subjected to catalytic conditions, selective conversion to the amide was observed (entry 11). Substrates with more acidic protic groups (entries 6 and 12) were not tolerated, since these species led to immediate catalyst poisoning. In the case of the acetone cyanohydrin substrate, treatment of the catalyst precursor 2^{iPr} with even one equivalent results in rapid conversion to the cyano complex 5^{iPr} (Scheme 3) which was isolated and characterized by X-ray crystallography (Fig. S7†) and spectroscopic methods. Details on the path by which 5^{iPr} forms are not available, but could involve either formation of the alkoxide followed by β -cyano elimination, or (more likely) *via* direct reaction of 2^{iPr} with hydrogen cyanide, which is present in equilibrium with the cyanohydrin in water.⁵

Conclusions

Despite these limitations, the catalysts 2^{R} can be regarded as being comparatively quite active and robust when evaluated against other homogeneous systems.⁵ Furthermore, the use of

an earth abundant metal is an attractive feature of this chemistry, and the catalysts disclosed here are more active than any nickel-based catalysts systems reported to date. The detailed mechanism by which these catalysts turnover is currently under investigation, focusing on how the resting state of the catalyst, of $3^{\text{iPr}}\text{-H}_2\text{NC(O)Ph}$, releases product. For example, it is not clear if the catalytic cycle is completed by regeneration of the hydroxo complex 2^{iPr} , or if a cationic nitrile adduct akin to 1^{iPr} (Scheme 1) arises directly from $3^{\text{iPr}}\text{-H}_2\text{NC(O)Ph}$ without formation of 2^{iPr} .

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