Homogeneous Catalysis

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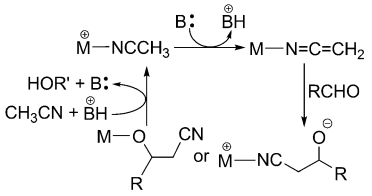
A Robust Nickel Catalyst for Cyanomethylation of Aldehydes: Activation of Acetonitrile under Base-Free Conditions**

*Sumit Chakraborty, Yogi J. Patel, Jeanette A. Krause, and Hairong Guan**

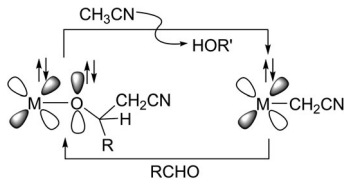
Nucleophilic addition of α-cyano carbanions to carbonyl substrates is a synthetically important process as it provides easy access to a large variety of pharmaceutically important compounds through the resultant β-hydroxy nitriles.[1] This method is straightforward and avoids the use of highly toxic cyanide salts (for the ring-opening of epoxides), but is often limited to activated nitriles (e.g., α-arylnitriles, pK_a values of ca. 22 in DMSO) with increased acidity of the α-CH protons.[2] Utilization of unactivated simple alkylnitriles, such as acetonitrile (pK_a = 31.3 in DMSO), is challenging as it generally requires a strong base to generate the desired carbanions.[3] The employed reaction conditions are incompatible with base-sensitive substrates, and in some cases, lead to the loss of the hydroxy group by dehydration.[2a–c,3a] For cyanomethylation of carbonyl substrates in particular, efforts have been made to circumvent the deprotonation of acetonitrile by catalytically activating Me_3SiCH_2CN using a base,[4] fluoride,[5] or N-heterocyclic carbene (NHC).[6]

Transition-metal catalysis has offered an alternative solution to cyanomethylation of carbonyl substrates, in which a relatively weak base can be used to deprotonate acetonitrile. The working hypothesis (Scheme 1) is that



Scheme 1. Activation of CH_3CN by a Lewis-acidic metal center.

a Lewis-acidic metal center would lower the pK_a value of acetonitrile substantially once it is coordinated. Guided by this hypothesis, Shibasaki and co-workers have identified $[CpRu(PPh_3)(CH_3CN)_2]PF_6$ (Cp = cyclopentadienyl) as an effective catalyst for the coupling of aldehydes and acetonitrile in the presence of DBU (DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene) as the base.[7] Ozerov et al. have developed a catalytic system involving a cationic nickel complex supported by a diarylamido-based PNP pincer ligand.[8] They have proposed a mechanism similar to the one depicted in Scheme 1 (B: = DBU). We surmised that cyanomethylation of aldehydes could be catalyzed by a transition-metal complex without an added base. The key is to synthesize a cyanomethyl complex which is sufficiently nucleophilic to attack aldehydes (Scheme 2). Although the pK_a value of a secondary alcohol is



Scheme 2. Activation of CH_3CN by the relief of dπ–pπ repulsion.

expected to be lower than that of a typical alkylnitrile,[9] the activation of CH_3CN could be driven by the relief of dπ–pπ repulsion between an occupied metal d orbital and the oxygen lone pair.[10] Conceivably, the catalytic reactions can also be initiated by an appropriate metal alkoxide or hydroxide. It is interesting to note that cyanomethylation of aldehydes has been reported to be catalyzed by 10 mol% of CuO*t*Bu[5d,11] or 1 mol% of $[\{Rh(OCH_3)(cod)\}_2]/PCy_3$ (cod = 1,5-cyclooctadiene),[12] although a Lewis-acidic metal center (Cu^I or Rh^{III}) has been suggested to be responsible for the observed catalytic activity. Herein we report an inexpensive, air- and moisture-stable nickel cyanomethyl complex capable of catalyzing the coupling of aldehydes and acetonitrile without adding any base or additive. The catalytic turnover numbers (TONs up to 82000) are the highest ever for such a transformation. A preliminary mechanistic study is consistent with the mode of activation of acetonitrile as outlined in Scheme 2.

We have recently reported catalytic reduction of aldehydes and CO_2 promoted by square-planar nickel hydride complexes bearing a bis(phosphinite)-based pincer ligand, and have highlighted the importance of Ni–H hydricity enhanced by the strongly *trans*-influencing pincer ligand.[13] We therefore anticipated that a nickel cyanomethyl complex with the same ligand system should result in a nucleophilic CH_2CN moiety. After reacting with an aldehyde, the filled–filled repulsion between nickel and oxygen orbitals in the resultant nickel alkoxide species is expected for the square-planar geometry, thereby facilitating the activation of acetonitrile. To begin our study we treated Zargarian's nickel complex (**1**)[14] with $LiCH_2CN$ [Eq. (1); THF = tetrahydro-

[*] Dr. S. Chakraborty, Y. J. Patel, Dr. J. A. Krause, Prof. H. Guan
Department of Chemistry, University of Cincinnati
P. O. Box 210172, Cincinnati, OH 45221-0172 (USA)
E-mail: hairong.guan@uc.edu
Homepage: http://homepages.uc.edu/~guanhg/index.html

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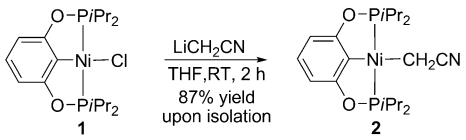


(1)

furan]. The obtained product **2** was found to be air- and moisture-stable in both solid state and solution (toluene). The most characteristic resonance in the ^{1}H NMR spectrum of **2** in [D$_8$]THF is a triplet centered at $\delta = 0.78$ ppm ($^3J_{P\text{-}H} = 9.2$ Hz),[15] thus suggesting that **2** is a C-bound cyanomethyl complex. The methylene carbon resonance of **2** (in CD_2Cl_2) was observed at $\delta = -23.91$ ppm as a triplet ($^2J_{P\text{-}C} = 13.0$ Hz), thus confirming the coordination mode of the CH_2CN ligand. The IR spectrum of **2** (in CH_2Cl_2) revealed a strong band at $\nu = 2185$ cm^{-1}, which falls in the range for ν(C≡N) of a C-bound cyanomethyl complex.[16] The structure of **2** was further established by X-ray crystallography (Figure 1).[17] The Ni-

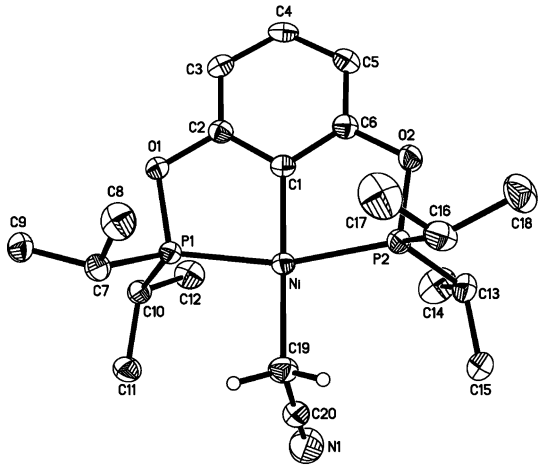
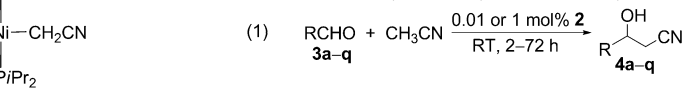


Figure 1. Molecular structure of **2**. Thermal ellipsoids shown at the 50% probability level. Hydrogen atoms except those on the cyanomethyl ligand are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Ni–C1 1.9101(18), Ni–C19 2.0123(19), C19–C20 1.438(3), C20–N1 1.149(3); Ni-C19-C20 110.39(14), C19-C20-N1 178.0(2), C1-Ni-C19 177.69(8).

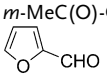
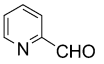
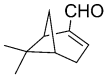
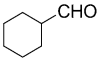
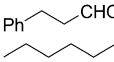
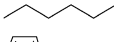
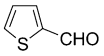
CH_2CN bond distance was found to be 2.0123(19) Å, which is longer than the one reported by Ritleng, Chetcuti, and co-workers for their [Cp(NHC)Ni(CH_2CN)] complex [1.961(2) Å],[16b] but comparable to Jones' [Ni(dippe)-(CH_2CN)Cl] (dippe = 1,2-bis(diisopropylphosphino)ethane) complex [2.0135(14) Å].[16d] The elongation of the Ni–C bond in **2** is likely due to the strong *trans* influence of the pincer aromatic ring.

With the nickel cyanomethyl complex in hand, we decided to test its catalytic activity by adding 1 mol% of **2** (with respect to aldehyde) into a 0.77 M solution of PhCHO in acetonitrile. At room temperature, the reaction was complete within 6 hours, thus providing the β-hydroxy nitrile product **4a** (Table 1) quantitatively, as judged by NMR spectroscopy. When the catalyst loading was reduced to 0.01 mol% and the concentration of PhCHO was increased to approximately 3.1 M (entry 2),[18] a quantitative conversion was achieved

Table 1: Cyanomethylation of aldehydes catalyzed by **2**.[a]



(2)

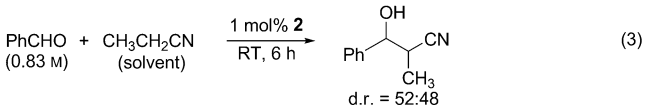
Entry	**2** (mol%)	RCHO	*t* [h]	Yield [%][b]
1	1	PhCHO (**3a**)	6	91
2	0.01	PhCHO (**3a**)	72	83[c]
3	1	*p*-$CF_3C_6H_4CHO$ (**3b**)	2	93
4	0.01	*p*-$CF_3C_6H_4CHO$ (**3b**)	36	90[c]
5	1	*p*-$NO_2C_6H_4CHO$ (**3c**)	2	88
6	1	*o*-FC_6H_4CHO (**3d**)	4	95
7	1	*m*-FC_6H_4CHO (**3e**)	4	89
8	1	*p*-FC_6H_4CHO (**3f**)	4	85
9	1	*p*-MeOC(O)-C_6H_4CHO (**3g**)	4	84
10	1	*p*-$MeOC_6H_4CHO$ (**3h**)	48	77
11	1	*o*-MeC_6H_4CHO (**3i**)	36	71
12	1	*m*-MeC(O)-C_6H_4CHO (**3j**)	8	79
13	1	 (**3k**)	4	87
14	1	 (**3l**)	4	90
15	1	 (**3m**)	24	73
16	1	 (**3n**)	8	95
17	1	 (**3o**)	12	88
18	1	 (**3p**)	12	86
19	1	 (**3q**)	2	90

[a] Unless noted otherwise, 25 μmol of **2** and 2.5 mmol of RCHO were mixed in 3 mL of CH_3CN. All reactions were monitored by ^{1}H NMR spectroscopy to ensure quantitative conversion of RCHO. [b] Yield of isolated product. [c] 6.8 μmol of **2** and 68 mmol of RCHO were mixed in 15 mL of CH_3CN.

within 72 hours with a TON of 10000. This catalytic system is remarkably active and robust as the catalyst loading can be further reduced close to the ppm level. We found that stirring the mixture consisting of 138 mL of PhCHO (1.36 mol), 150 mL of CH_3CN (2.87 mol), and only 3.0 mg of **2** (5 ppm catalyst loading) for 72 hours produced **4a** with 41% of PhCHO converted, thus giving a TON of 82000 and a turnover frequency of 1139 h^{-1}. It should be mentioned that both PhCHO and CH_3CN were used without drying and degassing. Control experiments showed no reaction in the absence of **2** and no inhibition with added mercury (150 equiv with respect to **2**).

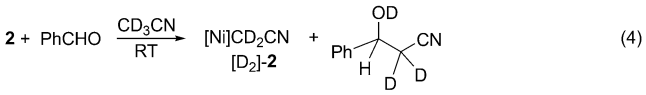
Next, we examined the scope of this cyanomethylation reaction with other aldehydes, and typically we used 1 mol% of **2** for the catalytic studies. As shown in Table 1, the catalytic system is amenable to a wide variety of aldehydes including substituted benzaldehydes (entries 3–12), as well as hetero-aromatic (entries 13, 14, and 19), α,β-unsaturated (entry 15), and aliphatic aldehydes (entries 16–18). In general, benzaldehydes bearing an electron-withdrawing group (entries 3–9) react faster than PhCHO, which in turn reacts faster than those bearing an electron-donating group (entries 10 and 11). Simple ketones such as acetophenone are unreactive under our catalytic conditions, and in fact for *m*-acetylbenzaldehyde

(entry 12), cyanomethylation takes place exclusively at the aldehyde functionality. For the α,β-unsaturated substrate **3m**, only the 1,2-product was obtained. Dehydration of β-hydroxy nitrile products, self-aldol condensation of aldehydes (for **3n–p**), and transesterification of **3g** (or **4g**) are potential side reactions which usually occur under basic conditions. Gratifyingly, none of those were observed in our studies. For CH_3CH_2CN, which contains even less acidic α-CH protons ($pK_a = 32.5$ in DMSO), its coupling with PhCHO can also be effectively catalyzed by **2** [Eq. (3)], albeit with low diastereoselectivity.



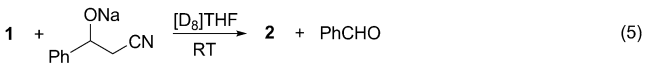
(3)

To probe the mechanism for the cyanomethylation process, we first monitored the catalytic reaction of PhCHO in CD_3CN (with 10 mol% of **2**) by NMR spectroscopy. Throughout the catalysis, the only observed nickel species was [D_2]-**2**. The incorporation of deuterium into the nickel complex is, as confirmed in a separate experiment, due to rapid H/D exchange between **2** and CD_3CN. If indeed the mechanism in Scheme 2 is operating, the insertion of PhCHO into the Ni–C bond of **2** should be the rate-determining step. As anticipated, the stoichiometric reaction between **2** and PhCHO in CD_3CN [Eq. (4)] yielded [D_2]-**2** and the deuterium-labeled **4a** without the observation of the proposed



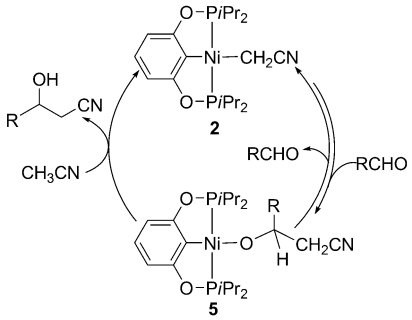
(4)

nickel alkoxide intermediate. Replacing the NMR solvent with [D_8]THF, however, showed no aldehyde insertion. We suspected that the insertion step might be reversible. Consistent with this hypothesis, the reaction of **1** and the sodium alkoxide derived from **4a** afforded **2** and PhCHO [Eq. (5)].

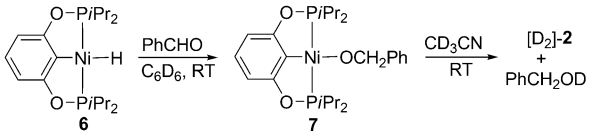


(5)

In view of the above-mentioned NMR results, we propose a catalytic cycle (Scheme 3) for the cyanomethylation reactions. The insertion of an aldehyde into **2** to generate **5** is kinetically feasible but thermodynamically uphill (as confirmed by the NMR studies described above). However, the unfavorable equilibrium is shifted by the deprotonation of CH_3CN with **5**. To mimic the step regenerating the catalyst **2**, we prepared the nickel benzyloxide **7** (in C_6D_6) in situ from the hydride **6** and PhCHO according to our previously reported procedure.[13a] Evaporating C_6D_6 and subsequent treatment of the residue with CD_3CN led to an immediate formation of [D_2]-**2** and $PhCH_2OD$ (Scheme 4). Given the fact that $PhCH_2O^-$ itself is not basic enough to deprotonate CH_3CN,[19] the observed reactivity probably arises from dπ–



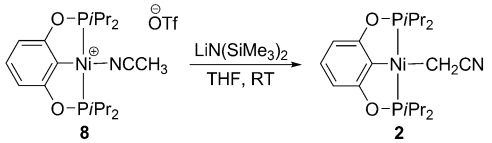
Scheme 3. Proposed catalytic cycle.



Scheme 4. Deprotonation of acetonitrile by a nickel alkoxide species.

pπ repulsion between nickel and oxygen centers, which disappears upon the formation of **2**. Further study using 1 mol% of **6** for the coupling of PhCHO and CH_3CN showed similar catalytic activity to complex **2**, thus suggesting the possibility of entering the catalytic cycle through a nickel hydride or alkoxide species. As a control experiment, we dissolved **6** in CD_3CN and did not observe the formation of [D_2]-**2**, thus confirming that the cyanomethyl catalyst must be produced by the route shown in Scheme 4.

The group of Naota has shown that ruthenium cyanomethyl complexes undergo interconversion between C-bound and N-bound isomers through sliding the metal along the cyanomethyl ligand skeleton.[16a] Ritleng, Chetcuti, and coworkers have proposed a similar isomerization process which converts [Cp(NHC)Ni–N=C=CH_2] to [Cp(NHC)Ni–CH_2C≡N].[16b,c] Thus, our catalytic system may involve rate-limiting isomerization of **2** to the N-bound isomer, which converges with the steps proposed for Lewis acid catalysis (Scheme 1).[7,8,11,12] Attempts to generate the N-bound nickel cyanomethyl complex by deprotonating the cationic acetonitrile complex **8**[14b,20] were unsuccessful [Eq. (6)]. Analogous to the observations for other nickel systems,[8,16b,c] only the C-bound isomer **2** formed. Nevertheless, the N-bound isomer is not likely to be involved in our catalytic system. We noticed that catalytic cyanomethylation of PhCHO was very sensitive to the change of phosphorus substituents on the nickel pincer catalysts. For example, replacing the *i*Pr groups in **2** with more bulky *t*Bu groups completely shut down the catalysis. Steric alterations near the nickel center are likely to have little effect on the C-to-N isomerization across the linear C–C≡N moiety as well as the electrophilic attack on the remote carbon end of [Ni]–N=C=CH_2. In contrast, steric environment around nickel is expected to strongly influence the insertion of PhCHO into the Ni–C bond of **2**. More definitive evidence arguing against rate-limiting C-to-N isomerization came from the experiments measuring half-lives of PhCHO during catalytic cyanomethylation reactions. When the catalyst concentration



8 2 (6)

was kept constant, tripling [PhCHO] did not change the half-life of the aldehyde. This result is consistent with the mechanism shown in Scheme 3, where the overall reaction is first-order in PhCHO.

In conclusion, we have shown an incredibly robust nickel catalyst for the cyanomethylation of aldehydes under base-free conditions with unprecedentedly high turnover numbers and frequencies. Mechanistic studies have suggested reversible insertion of aldehydes into a C-bound cyanomethyl complex and subsequent activation of acetonitrile with the resulting nickel alkoxide intermediate. We have ascribed the thermodynamic driving force for the latter step to the relief of dπ–pπ repulsion present in the nickel alkoxide species. Further mechanistic studies and the development of an asymmetric variant of cyanomethylation reaction are currently in progress.

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Keywords: aldol reaction · C–H bond activation · nickel · phosphane ligands · synthetic methods

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[18] The adjustment of [PhCHO] was purely for the convenience of setting up the reaction without using too much CH_3CN to dilute the catalyst concentration. For more details, see the Supporting Information.

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