

Efficient nickel catalyst for coupling of acetonitrile with aldehydes†

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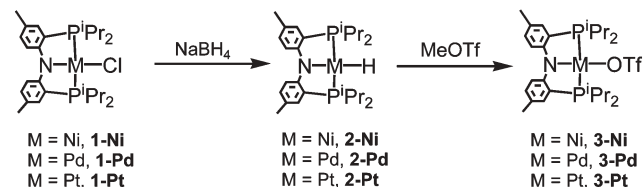
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A Ni complex of a diarylamido-based PNP ligand is an efficient and robust catalyst for coupling of acetonitrile with aldehydes.

Coupling of carbon-based nucleophiles with the carbonyl electrophiles is one of the most widely used strategies for carbon–carbon bond formation. Utilization of α -deprotonated nitriles as nucleophiles is an attractive method for the synthesis of β -cyanoalcohols, useful building blocks in synthesis.^{1–5} However, the scope of nitrile-derived nucleophiles is usually limited to those arising from nitriles with enhanced C–H acidity, such as α -arylnitriles and α -acylnitriles.^{1,2} Catalytic utilization of the less acidic simple alkylnitriles has been problematic. A strong base that would be required for direct deprotonation¹ may not be compatible with pendant functional groups and may render the process less economical. Shibasaki *et al.* recently explored coordination to a Lewis acidic transition metal complex as a way to activate acetonitrile towards deprotonation by a mild base.³ The screening of several candidate Ru, Cu, and Pd complexes yielded [CpRu(PPh₃)(NCMe)₂]PF₆ as the catalyst of choice. Other recent approaches include the use of CuOBU¹ and a strong neutral base proazaphosphatane as catalysts.^{4,5}

Our group has been exploring the transition metal chemistry of the diarylamido-based PNP pincer ligands.^{6,7} These ligands are an excellent fit for group 10 metals where they form extremely robust (PNP)MX (M = Ni, Pd, Pt) square planar compounds (Scheme 1).⁸ Compounds **3** were synthesized by adaptation of the previously reported methods. Amido is a weak *trans*-influence ligand and this should be reflected in strong binding of 2-electron donors (L or X[−]) in a position *trans* to N. For example, the Pd–Cl bond in (PNP)PdCl (**1-Pd**)⁸ is *ca.* 0.06–0.12 Å shorter than in related (PCP)PdCl complexes where Cl is *trans* to a strong *trans*-influence aryl donor.⁹ We surmised that a cationic [(PNP)M]⁺ fragment should behave as a potent Lewis acid. Strong binding of a substrate in the fourth coordination site of a square planar complex would not prohibit ligand exchange because ligand exchange in square planar d⁸ 16-electron complexes occurs

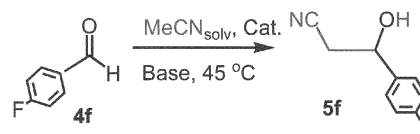


Scheme 1

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preferentially *via* associative pathways.¹⁰ Coupling of acetonitrile with aldehydes seemed a suitable test application because it is viewed as challenging even in its racemic version.^{3–5} The utility of metal complexes of neutral tridentate ligands such as the “pybox” family as Lewis acid catalysts has been firmly established.¹¹ The explorations of the catalytic applications of anionic pincer ligands (primarily of the PCP type) have been focused elsewhere.¹²

We have surveyed (Table 1) three compounds bearing the PNP ligand (**3-Ni**, **3-Pd**, and **3-Pt**) as catalysts for coupling of *p*-fluorobenzaldehyde (**4a**) with acetonitrile. For all three cases, we have found that triflate in **3** is easily displaced by MeCN upon dissolution in acetonitrile and so a truly three-coordinate precursor [(PNP)M]⁺ is not necessary. We chose *p*-fluorobenzaldehyde (**4a**) as our test substrate because of the convenience of the ¹⁹F NMR spectroscopic probe and because the *p*-F substituent is “average” (*e.g.*, similar to H) in terms of its electronic effect.¹³



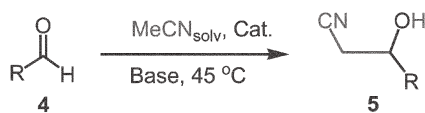
Scheme 2

Table 1 Effect of different Lewis acids, bases, temperature and additives on the coupling of CH₃CN with 4-fluorobenzaldehyde^a

#	Catalyst	T/°C	Base/mol%	Time	Yield
1	None ^b	60	100 DBU ^c	18 h	13%
2	None	60	100 DBU	18 h	10%
3	None	45	100 ^d DBUH ⁺	24 h	0%
4	None	45	100 ^d DBUH ⁺ + 100 DBU	24 h	0%
5	5% 3-Ni	60	100 DBU	18 h	81%
6	5% 3-Ni ^b	60	100 DBU	18 h	81%
7	5% 3-Pd	50	100 DBU	22 h	11%
8 ^e	5% 3-Pd + 5% NaBAR ^f ₄	45	100 DBU	14 h	7%
9	5% 3-Pt	50	100 DBU	22 h	7%
10 ^e	5% 3-Pt + 5% NaBAR ^f ₄	45	100 DBU	14 h	5%
11	5% 3-Ni	50	10 DBU	22 h	55%
12	5% 3-Ni	50	20 DBU	22 h	65%
13	5% 3-Ni	50	50 DBU	22 h	75%
14	5% 3-Ni	50	100 DBU	22 h	90%
15	5% 3-Ni	50	200 DBU	22 h	95%
16	5% 3-Ni	50	100 NEt ₃	22 h	0%
17	5% 3-Ni	45	100 proton sponge	24 h	0%
18	5% 3-Ni	45	100 DBU	24 h	88%
19 ^d	5% 3-Ni + 5% NaBAR ^f ₄	45	100 DBU	24 h	90%

^a Reaction was carried out with 0.20 mmol of aldehyde in 0.5 mL of CH₃CN (9.6 mmol). Yield calculated *in situ* using ¹⁹F NMR (single runs). ^b 4A molecular sieves. ^c 1,8-Diazabicyclo[5.4.0]undecene.

^d Triflate counterion. ^e Ar = 3,5-(CF₃)₂C₆H₃.



Scheme 3

The following conclusions can be made from the results presented in Table 1:

- 1) Compounds **3-Pd** and **3-Pt** are not competent as catalysts.
- 2) Addition of molecular sieves is not necessary.
- 3) The choice of DBU as base is crucial. Larger concentration of DBU enhances the rate.
- 4) 45–50 °C is the optimal temperature range.
- 5) Addition of Na[B(C₆H₃(CF₃)₂)₄] has no effect on the reaction.
- 6) The reaction is not merely catalyzed by the Brønsted acids or bases and **3-Ni** is critical for selective catalysis. DBU catalyzes a slow and unselective “background” reaction (see ESI†).

The study was then extended to a number of other aldehydes using **3-Ni** as the catalyst (Table 2). We find that in general electron-poor and “average” aromatic aldehydes react at > 90% conversion in < 24 h to give the desired β-cyanoalcohols with little or no side products. The more reactive aldehydes are converted to the products in high yield even at 22 °C. The electron-rich aldehydes (bearing Me and *p*-MeO substituents) reacted more slowly. On the other hand, steric factors appear to play at most a limited role in the reactivity of aromatic

Table 2 Coupling of CH₃CN with various aldehydes catalyzed by **3-Ni**

#	Aldehyde, R =	DBU/mol%	T/°C	Time/h	Yield (%) ^b
1	<i>p</i> -MeC ₆ H ₄ (1a)	100	45	24	75
2	<i>p</i> -MeC ₆ H ₄ - (1a)	100	45	24	70 ^c
3	<i>p</i> -MeC ₆ H ₄ - (1a)	5	45	39	35
4	<i>p</i> -MeOC ₆ H ₄ (1b)	100	45	24	40
5	<i>p</i> -MeOC ₆ H ₄ (1b)	5	45	39	25
6	<i>p</i> -MeOC ₆ H ₄ (1b)	100	45	24	42 ^e
7	2,4-Cl ₂ C ₆ H ₄ (1c)	100	45	24	>95
8	2,4-Cl ₂ C ₆ H ₄ (1c)	100	RT	24	95 ^c
9	2,4-Cl ₂ C ₆ H ₄ (1c)	5	45	16	>95
10	<i>o</i> -MeC ₆ H ₄ (1d)	100	45	24	90
11	<i>o</i> -MeC ₆ H ₄ (1d)	5	45	47	66
12	Ph (1e)	100	45	24	76
13	Ph (1e)	5	45	47	80
14	<i>p</i> -FC ₆ H ₄ (1f)	100	45	24	88
15	<i>p</i> -FC ₆ H ₄ (1f)	5	45	39	75
16	<i>p</i> -FC ₆ H ₄ (1f)	100	45	22	90 ^d
17	<i>p</i> -CF ₃ C ₆ H ₄ (1g)	100	45	24	>95
18	<i>p</i> -CF ₃ C ₆ H ₄ (1g)	5	45	23	>95
19	2-furyl (1h)	100	45	24	>95
20	2-furyl (1h)	100	RT	24	89 ^c
21	2-furyl (1h)	5	45	23	>95
22	<i>n</i> -C ₇ H ₁₆ (1i)	100	45	24	traces
23	(<i>E</i>)-PhCHCH (1j)	5	45	42	46
24	(<i>E</i>)-PhCHCH (1j)	100	45	42	73
25	<i>p</i> -MeO ₂ CC ₆ H ₄ (1k)	100	RT	16	95
26	2,6-Cl ₂ C ₆ H ₄ (1l)	100	45	23	95
27	2,6-Me ₂ C ₆ H ₄ (1m)	100	45	72	52
28	Isopropyl (1n)	100	45	72	90

^a Reaction was carried out on a 0.20 mmol scale of aldehyde with 5% (^{Me}PNP^{i-Pr})NiOTf in 0.5 mL CH₃CN (9.6 mmol) unless noted otherwise. ^b NMR yield (single runs) calculated using 1,4-dioxane as an internal integration standard. ^c Isolated yield. ^d CH₃CN “off the shelf”. ^e Reaction was performed with 5% (^{Me}PNP^{i-Pr})NiOTf and 5% NaBAR₄.

aldehydes – 2,6-dichlorobenzaldehyde is one of the most reactive ones, while *o*-tolualdehyde was in fact more reactive than *p*-tolualdehyde. An alkenyl aldehyde, (*E*)-cinnamaldehyde, exhibited reactivity comparable to that of *p*-tolualdehyde. Acetone and cyclohexenone were unreactive, as was 1-octanal. However, *i*-butyraldehyde produced the corresponding β-cyanoalcohol in a 90% yield, albeit rather slowly. The reason behind the higher reactivity of *i*-butyraldehyde compared with 1-octanal is not clear at this time. In all reactions except entries 23 and 24 (8% and 10% side-products), the amount of side-products (see ESI†) was 3% or less.

For some substrates, the reaction did not go to completion even after extended periods of time. We found that the increase in the yield of **5** can be achieved by decreasing the volume of CH₃CN used (Table 3), albeit at a cost of the increase in the amount of side-product (see ESI†).

Initially we used acetonitrile that was rigorously dried by distillation from CaH₂. The components used in this reaction were stored in a glovebox over molecular sieves for reasons of convenience (and/or out of habit). However, utilization of the “off the shelf” acetonitrile as is did not result in an experimentally significant change in conversion (Table 2, entry 16). As well, for several reactions the components were combined in the air without apparent detriment. **3-Ni** is stable in the air.

We performed a series of kinetic experiments¹⁴ in an attempt to elucidate the mechanism of the catalysis using *p*-FC₆H₄CHO as a convenient reporter (*via* its ¹⁹F NMR resonance) substrate. In contrast to [CpRu(PPh₃)(NCMe)₂]PF₆ as catalyst, the isotope effect was found to be close to unity (*k*(CH₃CN)/*k*(CD₃CN) = 1.13(9)). We undertook a study of the initial rates as a function of the concentrations of the relevant components. The rate of the aldehyde consumption was found to be first order in [Ni], and of order 0.46(10) in DBU. The rate dependence on [*p*-FC₆H₄CHO] appeared to be negligible within the experimental error.¹⁵ It seems to us appropriate to remark, however, that the same kinetics may not necessarily apply to all substrates and conditions.

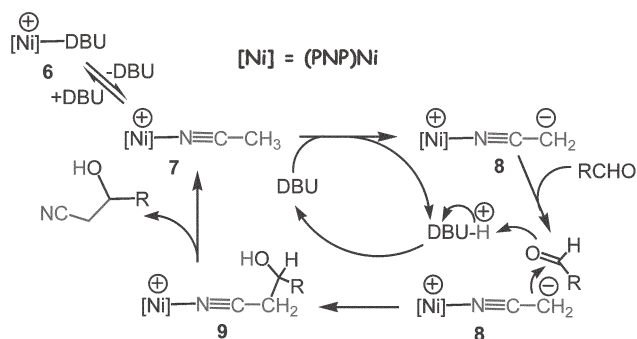
Although we cannot definitively rule out all other mechanistic possibilities, we tentatively propose a mechanism (Scheme 4) related to that delineated by Shibasaki *et al.*³ The only species observed by ³¹P NMR at the outset of the catalytic reaction (and the major component at the end of the reaction) is the complex **6**.

The exchange between **6** and **7** is slow on the NMR timescale as evinced by the observation of two distinct ³¹P NMR resonances in

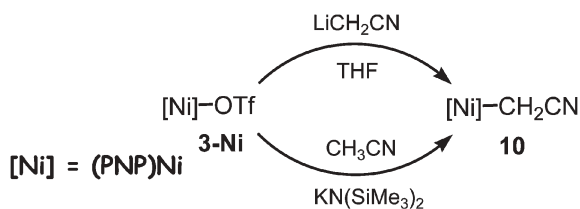
Table 3 Coupling of CH₃CN with selected aldehydes in a smaller volume of CH₃CN catalyzed by **3-Ni**^a

#	Aldehyde, R =	3-Ni	Conversion (%) ^{b,c}	Product (%) ^{b,d}	Yield ^{b,e}
1	<i>p</i> -MeC ₆ H ₄ (1a)	5%	95	90	5%
2	<i>p</i> -MeOC ₆ H ₄ (1b)	5%	70	68	<3%
3	<i>p</i> -MeOC ₆ H ₄ (1b)	10%	82	70	12%
4	<i>o</i> -MeC ₆ H ₄ (1d)	5%	>95	92	6%
5	Ph (1e)	5%	>95	90	6%
6	<i>p</i> -FC ₆ H ₄ (1f)	5%	>95	89	9%
7	(<i>E</i>)-PhCHCH (1j)	10%	94	75	19%
8	2,6-Me ₂ C ₆ H ₄ (1m)	10%	>95	80	15%

^a 0.20 mmol aldehyde in 0.1 mL CH₃CN with 0.20 mmol of DBU at 45 °C for 24 h. ^b Yields measured by NMR versus the internal integration standard (1,4-dioxane). ^c As 100% - fraction of starting aldehyde. ^d NMR yield of **5**. ^e NMR yield of the side product(s) (see ESI).



Scheme 4



Scheme 5

an independently prepared mixture of **6** and **7**. Thus the concentration of **7** in the catalytic mixture can only be very small. It seems reasonable at this juncture to propose that the displacement of DBU by MeCN is the rate-limiting step or at least a large contributor to the rate limiting step by way of pre-equilibrium. This is consistent with the observed isotope effect of near-unity and with the effective lack of dependence of the rate on the concentration of [*p*-FC₆H₄CHO]. The partial order in [DBU] is more difficult to rationalize. In the proposed mechanism DBU impedes the formation of **7**, but is necessary for the deprotonation of **7**. It is possible that these two contributions are responsible for the *apparent* partial positive order in [DBU].

Compound **8** would thus be a key catalytic intermediate. However, attempts at its independent preparation resulted (Scheme 5) only in the formation of the C-bound isomer **10** (coupling to two ³¹P nuclei is exhibited by both the ¹³C and the ¹H nuclei of the Ni-CH₂ moiety). **10** does not catalyze the title reaction, does not react with (DBU)H⁺, is not formed in a separate reaction between **7** and DBU, and is not observed in the catalytically active reaction mixtures. Perhaps the isomer **8** is stabilized in some way in the reaction mixture *via* hydrogen bonding with (DBU)H⁺. It is also possible that the reaction of **8** with an aldehyde is much faster than the isomerization to **10**.¹⁶

In contrast to the Ru catalyst,³ we do not observe unselective decomposition of **3-Ni** in the catalytic mixture. Experiments with low catalyst loading (Table 4) show that high turnover numbers can be achieved, although at low Ni loading and high DBU concentration the unselective background reaction becomes competitive. Catalysis by **3-Ni** does not require additives such as NaPF₆ or molecular sieves which were critical for the performance of [CpRu(PPh₃)(NCMe₂)PF₆].³

Table 4 Coupling of CH₃CN with 2-furaldehyde catalyzed by **3-Ni** at low loading

#	T/°C	DBU	Time/h	3-Ni	Yield ^a	TON
1	45	5%	23	0.1%	36%	360
2	45	100%	23	0.1%	61%	610
3	45	100%	48	0.5%	81% ^b	162

^a NMR yield of **5** (single runs). ^b Conversion is 100%, 19% side products (see ESI).

In summary, we report a robust and easy to handle catalyst for coupling of aldehydes with acetonitrile. The catalysis proceeds under mild conditions and is applicable to a broad spectrum of aldehydes. While pincer complexes of Pd have been applied to a number of processes such as the Heck reaction,¹² pincer complexes of Ni have not found as much application so far despite the fact that Ni is cheap and environmentally benign. The present work thus represents a surprisingly rare example of catalytic utilization of a pincer-ligated Ni complex.

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- See Electronic Supplementary Information for details.
- Interestingly, Shibasaki *et al.*³ reported that the rate of the reaction was also of zeroth order in aldehyde, but first order in DBU and partial order in the metal catalyst.
- We thank one of the referees for this insightful suggestion.