Double metal cyanides as heterogeneous Lewis acid catalysts for nitrile synthesis *via* acid-nitrile exchange reaction†

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A series of transition metal-based double metal cyanides (DMCs) were studied as catalysts for the synthesis of nitriles *via* acid-nitrile exchange reaction. The best nitrile yields were obtained with $\text{Co}_3[\text{Co}(\text{CN}_6)]_2$ DMC, which proved to be a versatile, stable, reusable and highly active catalyst, exhibiting an activity comparable to that of homogeneous Lewis acid catalysts.

Nitriles are a very important type of organic compounds, found to be useful intermediates for the synthesis of amines, amides, carbonyl compounds and heterocycles. Furthermore, the $-\text{CN}$ motif is present in many useful compounds, like methyl cyanoacrylate, nitrile rubber and numerous valuable pharmaceutical products.¹ Several routes for the synthesis of nitriles have been reported, such as the Kolbe nitrile synthesis,² the Sandmeyer reaction³ and the Wittig reaction.⁴ Furthermore, more recently, nitriles have also been obtained from alcohols under oxidant-free conditions in a flow reactor.⁵ However, these synthetic procedures usually require multiple complicated steps, generate large amounts of waste, and use hazardous compounds and/or ammonia. Another common method of nitriles preparation consists in the conversion of carboxylic acids to nitriles,^{1b} usually through a reaction with ammonia at high temperature ($\sim 300^\circ\text{C}$) *via* amide formation (Ammoniation-Dehydration).⁵ A more straight-forward transformation within this group of acid to nitrile reactions is definitely the acid-nitrile exchange.⁶

Acid-nitrile exchange involves a functional exchange between the two reactants, a carboxylic acid and a sacrificial nitrile, thus representing an ammonia-free alternative to the synthesis of nitriles from carboxylic acids. To displace the acid-nitrile equilibrium, the sacrificial nitrile is normally a low boiling point

Scheme 1 Acid-nitrile exchange reactions.

nitrile used in large excess^{6g} or a short chain dinitrile,^{6h} which displaces the reaction equilibrium by cyclic amide formation. Acid-nitrile exchange proceeds without catalysts at high temperatures or in the presence of Brønsted or Lewis acids at lower temperatures (Scheme 1). However, to the best of our knowledge there are no reports of a heterogeneously catalyzed acid-nitrile exchange reaction; which would be desired for industrial applications, where catalysts recovery and reusability is an important factor.

Having obtained the best catalytic results with Lewis acid catalysts like AlCl_3 and $\text{Al}(\text{OTf})_3$,⁶ⁱ we decided to study the use of double metal cyanides (DMCs) as heterogeneous catalysts for the acid-nitrile exchange. DMCs are purely Lewis acid catalysts industrially used in the ring opening polymerization (ROP) of epoxides for obtaining polyols.⁷ Recently, several studies have focused on expanding their catalytic properties, applying them in diverse organic reactions, such as hydroamination,⁸ esterification,⁹ A^3 coupling,¹⁰ among others.¹¹ Structurally, they

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consist of two different transition metal atoms (or 2 atoms in different oxidation states of the same transition metal) bonded by a cyanide group. They can be defined by the general formula $M'_u[M''(\text{CN})_n]_v \cdot x\text{H}_2\text{O}$ (M' - M'' DMCs), where typically, M' is a divalent metal ($v = 2$) and M'' a trivalent metal ($u = 3$). This u - v combination usually leads to the DMC adopting a face center cubic structure,¹² nevertheless, the occurrence of other phases has also been observed.¹³ In the present work, the first heterogeneously catalyzed synthesis of nitriles *via* the acid-nitrile exchange reaction is reported.

A series of M' -Co DMCs based on earth-abundant transition metals were synthesized by simple mixing of aqueous solutions of a M' salt ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$, CoCl_2 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ or ZnCl_2) and a M'' cyanide salt ($\text{K}_3[\text{Co}(\text{CN})_6]$). *tert*-Butanol and PTMEG (poly(tetramethylene ether)glycol) were added as complexing and co-complexing agents, respectively. These organic additives have been found to increase the activity of DMCs in ROP and hydroamination reactions.^{8,14} ICP analyses show a $M':\text{Co}$ ratio of ~ 1.6 for all the DMC samples (Table S1), which is higher than the stoichiometric 1.5, indicating a slight excess of M' in the structure. The crystallinity of the DMC materials was studied by powder X-ray diffraction (PXRD, Fig. S1). The reflections around 15° , 17° , 24.5° and 35° 2θ proved the presence of a cubic lattice structure with space group $Fm\text{-}3m$, typical of $M'_3[\text{Co}(\text{CN})_6]_2$ -type DMCs.¹² Likewise, selected scanning electron microscopy (SEM, Fig. S2) images of Co-Co DMC reveal small crystalline nanoparticles ($< 1 \mu\text{m}$) exhibiting a cubic morphology, consistent with its crystal system. Thermogravimetric analyses (TGA, Fig. S3) revealed that the materials are stable even above 250°C , with the cyanide ligands being burnt off as $(\text{CN})_2$ between 300 and 350°C .¹⁵ This was also confirmed by *in situ* high temperature PXRD measurements. As can be seen in Figure 1, the Co-Co DMC maintains its crystalline structure (cubic phase) until $\sim 270^\circ\text{C}$. After this temperature, the pattern shows the characteristic reflections of the cubic phase of Co_3O_4 (JCPDS card No: 00-042-1467). Both PXRD and TGA analyses thus indicate that the samples can endure the temperatures (215°C) necessary for the acid-nitrile exchange, making DMCs potential heterogeneous catalysts for this process. The Fourier-transformed infrared (FTIR) spectra of the samples exhibited a blue shift in the $\nu(\text{CN})$ compared to the initial M'' cyanide salt ($\text{K}_3[\text{Co}(\text{CN})_6]$) (Fig. S4). This shift is dependent of the M' and is an indication of the formation of M' -CN-Co bridges, since the

electron donation from the CN group to both metals is known to shift the $\nu(\text{CN})$ to higher wavenumbers.¹⁶ The textural properties of the DMCs were also found to be dependent on the M' (Table S2, Fig. S5). Even though these materials give rise to a typical type I isotherm, corresponding to their microporous nature, the N_2 isotherms of the Cu-Co DMC, Co-Co DMC and Fe-Co DMC exhibit a hysteresis loop. This hints at the presence of mesopores, most likely due to intercrystal voids or by aggregation of zones with high concentration of $[\text{Co}(\text{CN})_6]^{3-}$ voids.¹⁷ The acid properties of selected samples were studied with pyridine adsorption followed by FTIR spectroscopy (Table S2, Fig. S6). While the bands at 1450 , 1490 and 1610 cm^{-1} are attributed to the presence of Lewis acid sites, the absence of bands at 1639 and 1545 cm^{-1} indicates that the DMCs contain no Brönsted acid sites and are purely Lewis acid catalysts.¹⁸

As a test reaction, the acid-nitrile exchange between 2-phenylbutyric acid (**1a**) and glutaronitrile was selected. Considering that the benzylic proton of the former is easily discerned in its ^1H NMR spectrum and that the latter aids in the shift of the reaction equilibrium by cyclic imide formation, the product analysis of this test reaction is relatively straightforward. Batch reactions were carried out with the DMC catalysts at 215°C and 165°C . The results are presented in Table 1 and Tables S3, S4. Blank experiments already give a considerable yield of 2-phenylbutyronitrile (**2a**) after 16 h reaction time (entry 1); nonetheless, the use of a catalyst is necessary to form the product in higher yields. The use of purely Lewis DMC catalysts considerably increased the yield of nitrile **2a**, as yields of $>65\%$ after 16h reaction time were obtained irrespective of the metal combination (entries 2-6). The tentative reaction mechanism has been previously studied⁶ and probably involves the activation of the nitrogen atom of the CN moiety by the Lewis acid site, forming a nitrilium ion, which in turn, is attacked by the carboxylic acid to form an *O*-acyl imideate (Scheme. 2). This intermediate undergoes Mumm rearrangement to give an imide, which in this particular case, transforms into an acyl amidine. In this step, the second nitrile moiety is activated by the Lewis acid catalyst.

Table 1 Yield (%) of 2-phenylbutyronitrile (**2a**) obtained with different catalysts in the acid-nitrile exchange reaction between 2-phenylbutyric acid (**1a**) and glutaronitrile^a

Nitrile 2a Yield (%) ^b				
Entry	Catalyst	2.5 h	5 h	16 h
1	-	12	31	52
2	Fe-Co DMC	41	51	74
3	Co-Co DMC	45	58	86
4	Ni-Co DMC	35	45	65
5	Cu-Co DMC	39	50	70
6	Zn-Co DMC	40	49	67
7	AlCl_3	50	65	90
8	Zr-BEA	42	53	81

^a Reaction conditions: 0.375 mmol of 2-phenylbutyric acid (**1a**), 6 mmol of glutaronitrile, 10 mol% of catalyst at 215°C . ^b Determined by ^1H NMR spectroscopy.

Fig. 1 PXRD patterns of Co-Co DMC during heating from 200°C to 350°C .

Scheme 2 Tentative reaction mechanism for the acid-nitrile exchange with glutaronitrile as a sacrificial nitrile.

Finally, this four-membered-ring intermediate spontaneously opens to yield the desired nitrile and the cyclic imide. The nitrile **2a** yield was found to be highly dependent on the M' . In order to derive structure-activity relations, the physicochemical properties of the DMC catalysts, namely Lewis acidity and external surface area (S_{ext}), were correlated with their catalytic activity. For the Lewis acidity, the amount of pyridine adsorbed on the Lewis acid sites (LAS) per g of DMC was plotted versus the nitrile **2a** yield (Fig. S7). No clear trend was observed, so we can infer that the acidity of the cation does not have a direct effect on its activity. Another determining factor of the differences in activity between the samples may be the S_{ext} of the DMC materials, since it is known that the pores in the DMC framework are usually too narrow ($\sim 5 \text{ \AA}$)^{8,11} to allow the diffusion of large organic molecules like the acid **1a**. In this sense, a fairly linear correlation between the yield of the nitrile **2a** after 2.5 h reaction time and the S_{ext} of the DMC catalysts was obtained (Fig. 2). Furthermore, the best yields among all the DMCs were obtained with the samples Co-Co DMC and Fe-Co DMC (Table 1, entries 2 and 3), which are the two materials with the highest S_{ext} (327 m^2/g for Co-Co DMC and 311 m^2/g for Fe-Co DMC). Remarkably the activity of the sample Co-Co DMC (86% after 16h reaction time, entry 3) is comparable to that of homogeneous Lewis acids, such as AlCl_3 (entry 7), under the same reaction conditions. Additionally, the reaction rate can be markedly accelerated by microwave irradiation. After only 0.5 h reaction time, 78% of nitrile **2a** can be obtained with Co-Co DMC as catalyst, a notable increase in comparison

Fig. 2 Linear correlation between S_{ext} and yield of nitrile (**2a**) after 2.5 h reaction time.

to the yield achieved with conventional heating under identical temperature conditions after 5 h reaction time.

As can be observed in Table 1, the sample Co-Co DMC exhibits the highest activity among all the studied DMC materials. In the light of this, we decided to employ this catalyst in further experiments to expand the substrate scope of the DMCs. The acid-nitrile exchange reaction was carried out in the presence of 10 mol% of Co-Co DMC with various carboxylic acids and the results are presented in Table S5. A comparison between entries 1-3 shows that when the phenyl substituent is further away from the $-\text{COOH}$ group, the nitrile yields are lowered. This reflects that the overall acidity of the acid is increased with the presence of a phenyl group on the α -carbon; which in turn, facilitates the activation of the nitrogen of the nitrile moiety, increasing the reaction rate. A similar effect is observed when comparing entries 4 and 5. In this case, the presence of a NO_2 substituent in the *para* position of the phenyl group results in a higher nitrile yield. This is in line with the findings of Toland and Ferstandig,^{6f} who suggested that electron withdrawing substituents accelerated the acid-nitrile exchange reaction. Remarkably, the catalyst Co-Co DMC is even able to form in respectable yields nitriles bearing quaternary centers, such as pivalonitrile (entry 6). This moiety is of particular interest as it is present in several pharmaceutical products.^{1e} This substrate scope showcases Co-Co DMC as a versatile catalyst for the synthesis of nitriles via acid-nitrile exchange.

In all these examples, one equivalent of a cyclic imide (glutarimide) is formed concomitantly with the production of the desired nitrile. While the imide can be eliminated relatively easily by flash chromatographic purification, it is interesting to investigate alternative methods to displace the equilibrium of the acid-nitrile exchange reaction. In this sense, (phenylsulfonyl)acetonitrile was studied as sacrificial nitrile. It has been reported that the use of such nitrogen donor can allow the decarboxylation of the formed carboxylic acid, constituting an alternative irreversible step towards the production of the desired nitrile.^{6j} As can be observed in Fig. S8, Co-Co DMC was able to catalyze the acid-nitrile exchange between the acid **1a** and (phenylsulfonyl)acetonitrile, forming the nitrile **2a** in substantial amounts and methyl phenyl sulfone - a lower boiling point side product, which would simplify the purification. This represents a promising result which could lead to additional studies on heterogeneously catalyzed decarboxylative acid-nitrile exchange reactions.

The heterogeneous nature of Co-Co DMC was demonstrated by a hot filtration test (Fig. S9). To this end, a sample of the product mixture was taken after 2.5 h reaction time and the catalyst was separated by filtration without cooling. This hot filtrate was left stirring for an additional 2.5 and 13.5 h. A considerably lower nitrile **2a** yield was obtained, with the small increase attributed to the catalyst-free conversion of the acid **1a**. This suggests that no active species leach from the heterogeneous catalyst, which was further proven by elemental analyses (ICP) performed after reaction (Table S1). The sample Co-Co DMC kept its activity after three consecutive reaction runs (Fig. S10), indicating that it is a stable and recyclable catalyst. Finally, Fig. S11 shows the PXRD pattern of Co-Co DMC before and after reaction. No notable

changes were observed, which demonstrates that the structure of the catalyst is preserved at the reaction temperature and after a lengthy contact time with the reactants and products. In conclusion, a series of M'-Co DMCs were studied as catalysts for the synthesis of nitriles *via* acid-nitrile exchange reaction. These materials were easily synthesized by mixing aqueous solutions of a M'Cl₂·xH₂O salt with K₃[Co(CN)₆]. The sample Co-Co DMC was found to be the most active one, showing an excellent catalytic activity in a wide range of acid-nitrile reactions with different carboxylic acids, under thermal and microwave conditions. Furthermore, the use of (phenylsulfonyl)acetonitrile as sacrificial nitrile showed potential as alternative for equilibrium displacement (decarboxylative acid-nitrile exchange). The application of DMCs as purely Lewis acid, stable and reusable catalysts represents the first report of a heterogeneously catalyzed acid-nitrile exchange reaction and can induce further studies on nitrile synthesis *via* acid-nitrile exchange and the catalytic properties of these still underexplored materials.

Conflicts of interest

There are no conflicts to declare.

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