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One-Pot Selective N-Formylation of Nitroarenes to Formamides Catalyzed by Core-Shell Structured Cobalt Nanoparticles

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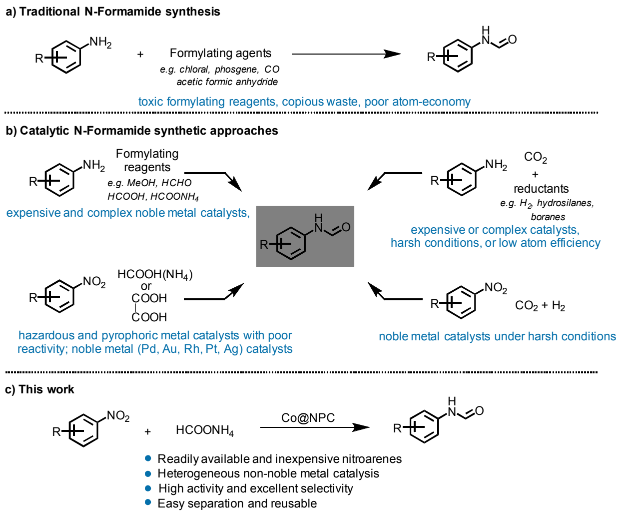
One-pot direct N-formylation of readily available nitroarenes with ammonium formate catalyzed by core-shell structured cobalt nanoparticles has been developed. A broad set of nitroarenes was successfully converted to their corresponding formamides in good to high yields with various functional groups tolerance. This heterogeneous catalyst can be easily removed from the reaction medium and can be reused for several times without significant loss in reaction efficiency.

Formamides are valuable intermediates in the synthesis of pharmaceuticals, agrochemicals, dyes, and fragrances.[1] They also serve as industrial solvents and are used as Lewis bases in catalysis.[2] In addition, the formyl group is important amine protecting groups in peptide synthesis.[3] Owing to their immense utility, the development of novel methods for the expedient synthesis of formamides continues to be an active area of research.

Traditionally, N-Formamides synthesis is typically achieved by the reaction of anilines with toxic and sensitive formylating reagents, e.g. chloral, phosgene, CO, and acetic formic anhydrides with poor atom economy and massive waste production (Scheme 1a).[4] In the past decades, transition-metal-catalyzed N-formylation of anilines to formamides has attracted considerable attention. A number of metal catalysts have been developed for N-formylation of anilines with various formylating reagents such as methanol,[5a-c] formic acid and its derivatives,[5d-g] or (para)formaldehyde.[5h-j] Remarkably, the catalytic N-formylation of anilines by using CO_2 as a carbonyl source together with varying reductants, e.g. H_2,[6] hydrosilanes,[7] or boranes,[8] in the presence of metal-based catalysts has also been demonstrated. However, expensive or complex noble metal complexes are often employed, in which relatively harsh conditions are generally required, or large amounts of by-products are produced simultaneously with low atom efficiency (Scheme 1b). Furthermore, aryl amines are most frequently used as starting materials for the synthesis of N-arylformamides among these well-developed methods, which are generally prepared from reduction of nitroarenes catalyzed by transition metals under high pressure of hydrogen.[9] As such, from both economic and environmental viewpoints, there is a strong incentive to develop an alternative inexpensive base-metal approach for highly efficient and selective synthesis of formamides from readily available and inexpensive nitroarenes.



Scheme 1. Traditional versus Proposed N-Formylation

To date, only a handful of examples catalyzed by noble metal catalysts (e.g. Pd,[10] Pt,[11] Au,[12] Rh,[13] et al) for one-pot direct N-formylation of nitroarenes to N-formamides using formic acid or its derivatives, or even CO_2/H_2 as formylating sources have been reported (Scheme 1b). However, the high cost and limited reserve on the earth of noble metal catalysts accompanying with harsh reactions significantly impede their practical applications, especially for synthesis of biologically

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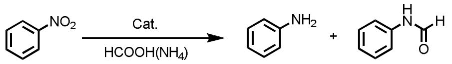
Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	Catalyst	Reductant (equiv.)	Solvent	Time (h)	Conversion (%)[b]	Selectivity (%)[b]	
						2a	**3a**
1	Co@NPC-800	HCOOH(12)	THF	24	100	5	95
2	Co@NPC-800	HCOOH(10)	THF	24	100	10	90
3	Co@NPC-800	HCOOH(8)	THF	24	68	14	86
4	Co@NPC-800	HCOOH(6)	THF	24	30	52	48
5	Co@NPC-800	HCOOH(4)	THF	24	28	66	34
6	Co@NPC-800	HCOOH(3)	THF	24	20	79	21
7	Co@NPC-800	$HCOONH_4$(10)	THF	12	100	<1	>99
8	Co@NPC-800	$HCOONH_4$(8)	THF	12	100	26	74
9	Co@NPC-800	$HCOONH_4$(6)	THF	12	100	71	29
10	Co@NPC-800	$HCOONH_4$(4)	THF	12	97	97	3
11	Co@NPC-800	$HCOONH_4$(10)	Toluene	12	100	55	45
12	Co@NPC-800	$HCOONH_4$(10)	1,4-Dioxane	12	100	13	87
13	Co@NPC-800	$HCOONH_4$(10)	CH_3CN	12	100	18	82
14	Co@NPC-800	$HCOONH_4$(10)	DMF	12	100	78	22
15	Co@NPC-800	$HCOONH_4$(10)	THF	4	100	15	85
16	Co@NPC-900	$HCOONH_4$(10)	THF	4	79	26	74
17	Co@NPC-700	$HCOONH_4$(10)	THF	4	37	35	65
18[c]	NPC-800	$HCOONH_4$(10)	THF	12	0	0	0
19[d]	–	$HCOONH_4$ (10)	THF	12	0	0	0
20	$Co(NO_3)_2.6H_2O$	$HCOONH_4$(10)	THF	12	0	0	0

[a] Reaction condtions: nitrobenzene (0.25 mmol), HCOOH or $HCOONH_4$ as formylating reagent with different equivalents with respect to nitrobenzene, catalyst (4.8 mol% of Co), solvent (2.5 mL), 120°C. [b] Conversion and selectivity were determined by GC using dodecane as an internal standard. [c] 20 mg of the NPC support instead. [d] no catalyst.

active compounds due to the toxicity of noble metals. Nonetheless, no successful one-pot direct N-formylation of nitroarenes to formamides catalyzed by heterogeneous base metals has been descried, to the best of our knowledge.

In our continuous effort to develop green catalysis for sustainable organic synthesis, we herein report a heterogeneous core-shell structured cobalt nanoparticles (NPs) catalyst for one-pot direct N-formylation of nitroarenes. The catalyst exhibits outstanding catalytic performance for formamides synthesis from the reductive N-formylation of nitroarenes with ammonium formate under mild conditions. A broad set of nitroarenes bearing with diverse functional groups could be efficiently converted to formamides in decent to high yields. In addition, the catalyst can be easily recovered for successive uses with negligible loss in activity, demonstrating strong stability. To the best of our knowledge, this is the first report of direct and selective synthesis of formamides from readily available and inexpensive nitroarenes and ammonium formate catalyzed by a heterogeneous non-noble base-metal catalyst (Scheme 1c).

The heterogeneous catalysts comprising of Co NPs as core and N,P-dual doped hierarchical porous carbon as shell derived from naturally renewable biomass, denoted as Co@NPC-T (where T represents the pyrolysis temperature), were synthesized by a facile tandem hydrothermal-pyrolysis processes as reported in our earlier work,[14] the details regarding the preparation and characterization of the catalyst Co@NPC-800 were included in the ESI. Our previous studies showed that the synergistic effect between Co NPs and N,P atoms incorporated in the carbon framework dramatically improved the catalytic performance for catalytic transfer hydrogenation of nitroarenes and the Co@NPC-800 gave the best outcome. As such, the Co@NPC-800 catalyst was initially employed for N-formylation of nitrobenzene (**1a**) as a benchmark reaction with formic acid (HCOOH) as formylating reagent to optimize the reaction conditions, and the representative results are compiled in Table 1. The reactions were performed with varying equivalent of HCOOH (with respect to **1a**) in THF at 120°C. We found that the employed amounts of HCOOH had a critical influence on both reaction activity and selectivity (entries 1-6). More excess of HCOOH resulted in higher conversion of **1a** with formation of *N*-phenylformamide (**3a**) as the major product. Particularly, complete conversion of **1a** with 95% selectivity to **3a** was achieved in the presence of 12 equivalents of HCOOH (entry 1). Similar trend for reaction efficiency and tunability in product selectivity was also observed when ammonium formate ($HCOONH_4$) was used as formylating reagent instead (entries 7-10). Comparatively, $HCOONH_4$ distinctly exhibited superior efficiency to HCOOH and exclusive selectivity to **3a** was realized when using 10 equivalents of $HCOONH_4$ within 12 h under identical conditions (entry 7).

Inspired by these findings, a set of factors including solvent, temperature, amount of catalyst loading was intensively screened. Among the solvents investigated (entries 11-14), THF showed the best catalytic performance with complete conversion and exclusive selectivity to **3a** after 12 h (entry 7). A decrease of the reaction temperature or catalyst loadings led to a lower catalytic activity and selectivity to **3a** (Table S1 & 2, Figure S2 in the ESI). Subsequently, the resultant catalysts pyrolyzed at 700 and 900°C were employed for the reaction, respectively, under otherwise identical conditions (entries 15-17). In line with our previous observations,[14] the Co@NPC-800 significantly outperformed in terms of both activity and selectivity of the desired product (entries 15-17). Moreover, the catalyst Co@NPC-800 is essential for the success of the N-formylation reaction. No reactivity was observed in the absence of catalyst or with PNC-800 or $Co(NO_3)_2$ as catalyst (entries 18-20).

Further control experiments reveal that (1) this one-pot direct N-formylation of nitroarenes undergoes successive reduction of nitro group to amine and formylation of amine to *N*-formamide; (2) HCOOH or $HCOONH_4$ serves as both a reducing and formylating reagent. We performed the reaction by adding 10 equivalents of $HCOONH_4$ batch-by-batch into the THF solution of **1a** under the standard conditions as shown in Figure 1A. 43% conversion of **1a** was exclusively reduced to aniline (**2a**) upon addition of first batch 3 equivalents of $HCOONH_4$ for 6 h, clearly indicating that $HCOONH_4$ firstly serves as a reducing reagent to facilitate reduction of nitro group. After another batch 4 equivalents of $HCOONH_4$ was added into the above reaction mixture, **1a** was further consumed but affording a mixture of **2a** and **3a** with **3a** as major product. Accordingly, the addition of rest batch 3

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equivalents led to 90% conversion of **1a** with 83% distribution of **3a**. Such observations were further confirmed by the record of the product distribution as a function of reaction time (Figure 1B, Figure S2 in the ESI). Sole formation of **2a** was observed at the early stage of the reaction; while **3a** started to form gradually with an elapse of reaction times and dominated the reaction at the late stage until exclusive formation. Meanwhile, the reduction of nitrobenzene catalysed by the Co@NPC-800 catalyst is significantly faster than N-formylation.

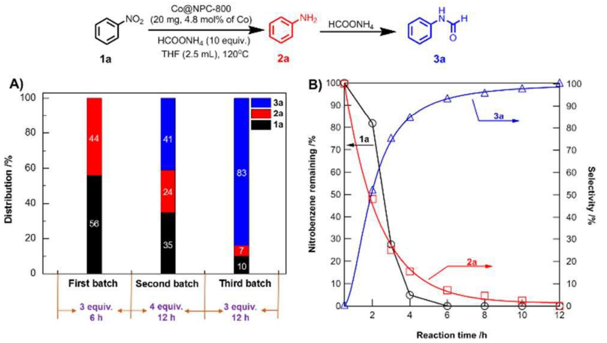
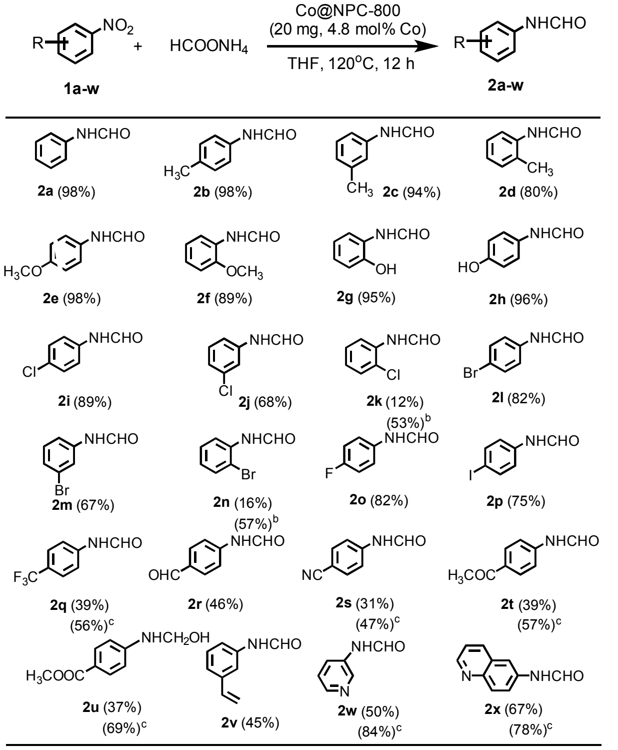


Figure 1. The product distributions for (A) with batch addition of $HCOONH_4$ and (B) as a function of reaction time for N-formylation of nitrobenzene with $HCOONH_4$ under standard conditions.

It took 4 h to fully consume **1a** while 12 h was required for complete formation of **3a**. It has been reported that the ammonium formate mediated N-formylation of anilines took place readily in acetonitrile at reflux temperature without assistant of any metal catalyst.[15] No significant difference in N-formylation reaction efficiency could be observed when **2a** was subjected to the standard conditions in the absence or presence of Co@NPC-800, indicating that there is no accelerating effect of the Co@NPC-800 catalyst in N-formylation of aniline (Scheme S1 in the ESI). Such result demonstrates the essential role of the Co@NPC-800 is to reduce nitroarenes to anilines in the whole process.

Subsequently, we investigated the substrate scope to explore the general applicability of this catalytic N-formylation protocol under the optimized conditions (Table 2). Overall, the catalyst Co@NPC-800 enabled the N-formylation of a diverse array of functionalized nitroarenes, providing the corresponding formamides in decent to high yields. Electron-donating groups substituted nitroarenes (**1a**-**h**) generally gave higher yields to their corresponding formamides than that of electron-withdrawing groups substituted ones (**1q**-**u**). Apparently, the *para*-position substituted nitroarenes regardless of the nature of substituents showed considerably poorer selectivity to the corresponding formamides albeit with complete conversion (**1d**, **1f**, **1k**, and **1n**). In these cases, anilines are favourably produced as the major products, most likely due to the steric effect. More importantly, for halogenated nitrobenzenes (**1i**-**p**), full conversion is achieved, giving decent to high yields to the respective formamides without any observation of dehalogenation processes. Gratifyingly, nitroarenes bearing readily reducible functional groups, such as aldehyde (**1r**), ketone (**1t**), nitrile **1s**), ester (**1u**), and vinyl (**1v**) were successfully formylated to the formamides and maintained the reducible groups untouched, highlighting the excellent chemoselectivity of the nanostructured core-shell cobalt NPs catalysts. In addition, heteroatom-containing nitroarenes (**1w** and **1x**) can also be efficiently formylated to their corresponding formamides, which are in particular important intermediates in the pharmaceutical industry. Notably, a considerable higher selectivity to formamide was achieved when HCOOH was used as the formylating reagent instead of $HCOONH_4$ in some cases; especially for *para*-Cl- and Br-substituted nitrobenzenes (**1k** and **1n**), more excess of HCOOH (20 equivalents) is required to achieve satisfactory results. Note that in all cases listed in Table 2, all nitroarenes were completely converted but with different selectivity to their corresponding N-formamides, as shown in Table S4 in the ESI.

Table 2. Substrate scope[a]



[a] Reaction conditions: nitroarenes (0.25 mmol), Co@NPC-800 (20 mg, 4.8 mol% of Co), $HCOONH_4$ or HCOOH (2.5 mmol), THF (2.5 mL); 120 °C, 12 h. Yields of isolated products are reported. [b] HCOOH (20 equivalents) as hydrogen donor and formylating source. [c] HCOOH (10 equivalents) as hydrogen donor and formylating source.

Durability and recyclability of a catalyst are important features for the advancement of sustainable practical processes. Upon completion of the N-formylation of nitrobenzene, the catalyst Co@NPC-800 was recollected by centrifugation, washed and dried for subsequent cycles. Noticeably, the Co@NPC-800 catalyst is highly stable and can be conveniently recycled up to five times to selectively produce *N*-phenylformamide (Figure S3 in the ESI). No noticeable changes in the core-shell nanostructure of the catalyst Co@NPC-800 can be observed after 5 cycles (Figure S4 & 5 in the ESI).

In conclusion, a novel hybrid nanocomposite comprising cobalt nanoparticles as core and N,P-dual doped porous carbon as shell is found to be a highly efficient, reusable

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heterogeneous non-noble metal catalyst for one-pot direct N-formylation of readily available nitroarenes with ammonium formate, selectively affording versatile and biologically active formamides. This study provides a green and sustainable methodology for expedient synthesis of formamides from nitro compounds under mild conditions.

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Conflicts of interest

There are no conflicts to declare.

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