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dihydropyridines and related substrates using gold nanoparticles

Direct and co-catalytic oxidative aromatization of 1,4-

supported on carbon nanotubes[†]

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A heterogeneous catalyst was assembled by stabilization of gold nanoparticles on carbon nanotubes. The resulting nanohybrid was used in the catalytic aerobic oxidation of 1,4-dihydropyridines. The system proved very efficient on the investigated substrates either directly or in the presence of a quinone co-catalyst.

Pyridines have found applications in various domains such as in the synthesis of drugs,¹ herbicides,² or insecticides.³ In addition, the pyridine scaffold plays a central role in living systems since nicotinamide adenine dinucleotide (NAD⁺/NADH) and nicotinamide adenine dinucleotide phosphate (NADP⁺/NADPH) are key pyridine-incorporating cofactors involved in oxido-reduction processes.⁴ Among the various methods developed for the synthesis of pyridine derivatives,⁵ the oxidation of Hantzsch 1,4-dihydropyridines is likely one of the most straightforward approaches. The Hantzsch pyridine synthesis is a multi-component process which involves an aldehyde, two equivalents of a β -keto ester, and a nitrogen atom source. The initial condensation affords a dihydropyridine intermediate which can be oxidized, in a second step, into the corresponding pyridine. This reaction was reported for the first time in 1881 by Arthur Hantzsch.⁶ Numerous reagents have been reported to promote the second step-oxidative aromatization reaction and include, for example, copper bromide,⁷ ferric chloride,⁸ palladium on carbon,⁹ manganese dioxide,¹⁰ and *tert*-butylhydroperoxide.¹¹

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However, the oxidation of dihydropyridines is not always easy when substrates bear sensitive functional groups and there is still the quest for mild and general protocols. Also, some of the reported procedures lead to the formation of by-products which can be difficult to remove from the reaction mixture. Therefore, the development of milder, sustainable, and more effective methods for the oxidative aromatization of 1,4dihydropyridines is sound. In the present article, we report the assembly and use of a recyclable CNT-supported gold catalyst for the selective and mild aerobic oxidation of 1,4dihydropyridines and related substrates (Figure 1).



Figure 1 Overview of the catalytic assembly and catalyzed oxidation processes studied in the present work.

The CNT-gold catalyst was assembled using a layer-by-layer approach according to a previously reported procedure from our group.¹² Our strategy relied on the use of specific amphiphiles which are made of a nitrilotriacetate polar head and a C_{25} -diacetylene lipophylic chain. This amphiphile can spontaneously self-assemble in water on the CNT to yield hemi-micellar structures having lipophylic chains in interaction with the CNT and polar heads oriented towards the aqueous medium. This primary layer provides a dense anionic covering

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of the nanotube that is not dependent on the presence of the carboxylic defects on the CNT surface, unlike most strategies classically designed for the decoration of carbon nanotubes.¹³ The diacetylene motif of the amphiphiles also allowed further stabilization of the supramolecular assembly through a polymerization process triggered by UV irradiation at 254 nm. After photopolymerization the coating becomes robust and withstands ethanol washings which is not the case of the nonpolymerized equivalent. The negatively charged CNT surface is then used for the deposition of the second layer composed of a cationic polymer (polydiallyldimethyl ammonium chloride) which is immobilized through electrostatic interactions. This polymer provides a tridimensional network that is capable of accommodating and stabilizing pre-formed gold nanoparticles¹⁴ that are finally added to the multilayered nanotube to afford the AuCNT nanohybrid catalyst. The above procedure led to carbon nanotubes uniformly covered with gold nanoparticles of ca. 3 nm of diameter, as visualized by transmission electron microscopy (Figure 1 and Figure S3).



 a Reaction conditions: dihydropyridine **1** (0.1 mmol), AuCNT (0.5 mol%), CHCl₃/H₂O (3:1, 2 mL), O₂. b Isolated yields. c under air. d In methanol (2 mL). e AuCNT (1 mol%).

Gold concentration of the aqueous suspension was assessed by ICP-MS ([Au] = 3.4 mM), and the metallic nature of gold evidenced by X-ray photoelectron spectrometry (XPS, Figure S4). The presence of the metallic species on the CNT surface was further evidenced by energy dispersive X-ray analysis (EDX, Figure S5) and thermogravimetric analysis (TGA, Figure S6) which revealed that the nanohybrid had a gold content of *ca*. 25 wt%.

With the CNT-gold nanohybrid in hands, we next looked at its performances in the catalytic oxidation of various 1,4dihydropyridines. Standard oxidation reaction conditions were set using 1,4-dihydropyridine 1a as model substrate in the presence of 0.5 mol% of the catalyst, in CHCl₃/H₂O under air. Under these conditions, 97% of pyridine 2a was produced in 24 h (Table 1, Entry 1). Changing the air atmosphere for pure oxygen permitted to increase the reaction rate as pyridine 2a was obtained in nearly quantitative yield (99% conversion) in only 11 h (Entry 1). It was thus decided to perform the ensuing experiments under an oxygen atmosphere. To assess the scope of the process, the conversion of several other 2,3,5,6tetrasubstituted dihydropyridines into the corresponding pyridines was studied (Entries 2-5). Diketone derivative 1b (Entry 2), di-allylester derivative 1c (Entry 3), and DHP 1d bearing ethyl groups in positions 2 and 6 (Entry 4) were all converted into the corresponding pyridines (2b, 2c, and 2d, respectively) in excellent yields under the action of the AuCNT hybrid. The oxidation of unsymmetrical bicyclic compound 1e (Entry 5) was quantitative after 36 h of reaction but required the use of 1 mol% of the catalyst.

Although efficient on 1,4-dihydropyridines that are not substituted at the 4-position, the direct AuCNT-catalyzed oxidation failed on the phenyl-substituted 1,4-dihydropyridine **1f** (Entry 6), even with extra catalyst loading (*e.g.* 1 mol%). Nevertheless, we conceived that the use of a quinone co-catalyst could help to achieve the expected transformation, since redox-active quinones are known oxidants of 1,4-DHPs.¹⁵ Thus, the combination of a quinone co-catalyst together with AuCNT could provide the answer to the observed inertness of some of the 1,4-DHP-substrates. The quinone unit would catalyze the aromatization reaction of 4-substituted 1,4-DHPs while the supported gold particles achieve the *in situ* reoxidation of the released hydroquinone, hence completing the catalytic cycle (Scheme 1).¹⁶



Scheme 1 Proposed strategy for the co-catalytic oxidative aromatization of 1,4-dihydropyridines.

Various quinone derivatives (Figure 2) were screened in the co-catalytic oxidative aromatization of 1,4-DHP **1f** under oxygen atmosphere. Thus, 1,4-DHP **1f** was reacted with 1 mol% of AuCNT in $CHCl_3/H_2O$ and in the presence of 20 mol% of a co-catalyst (either **3**, **4**, or **5**). While the use of gallacetophenone (3) or 4-*tert*-butylcatechol (4) as co-catalysts

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provided only poor to moderate yields of the aromatized pyridine **2f** after 36 h of reaction (*ca.* 5% and 40% yield, respectively), the use of 2,5-dichloro-1,4-benzoquinone (**5**) gratifyingly afforded the expected pyridine **2f** in 78% yield (Table 2, Entry 1). A blank experiment conducted under the same conditions (20 mol% of **5**) but in the absence of AuCNT led only to 14% conversion of **1f** into **2f**. This result highlights the cooperative contribution of the two co-catalysts that synergistically catalyzed the oxidative aromatization reaction.











^a Reaction conditions: dihydropyridine 1 (0.1 mmol), AuCNT (1 mol%), 5 (20 mol%), CHCl₃/H₂O (3:1, 2 mL), O₂. ^b Isolated yields.

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Additional examples of 4-substituted dihydropyridines were studied using the co-catalytic system (Table 2, Entries 2-5). Dihydropyridines substituted by various aromatic groups at the 4-position were successfully oxidized to the corresponding pyridines in satisfactory to good yields (from 45 to 84%). It appeared that compounds bearing electron-rich aromatics at the 4-position (Entries 2) seemed to react more readily than substrates incorporating electron withdrawing groups (Entry 3). The reaction worked equally well on the DHP 1i which is substituted with an aliphatic methyl group (Entry 4) but was more sluggish on furanyl derivative 1j whose pyridine counterpart 2j was produced in 45 % yield (Entry 5). It is to be noted that reaction times were in general higher in the case of 4-substituted DHPs compared to their non-substituted counterparts. Yet, our AuCNT system compares favorably with a previously reported polymer-supported platinum catalyst which required a co-factor for non-substituted (at the 4position) DHP substrates.¹⁷

Recyclability of the AuCNT nanohybrid was evaluated over five consecutive oxidation reactions of **1a** using the same batch of the catalyst which was recovered by simple centrifugation after each cycle. The catalytic activity remained the same throughout the experiment as the pyridine derivative **2a** was obtained in each case in nearly quantitative yields (Table 3). TEM analysis after the fifth run showed no significant alteration of the nanohybrid catalyst.



Conclusions

A heterogeneous catalyst was assembled by stabilization of gold nanoparticles on carbon nanotubes *via* a layer-by-layer approach. The resulting nanohybrid was used in the catalytic aerobic oxidation of 1,4-dihydropyridines under very mild conditions (room temperature, atmospheric pressure). The gold-CNT assembly proved very efficient on its own for the oxidation of 2,3,5,6-tetrasubstituted dihydropyridines and was also active, in combination with a quinone co-catalyst, for the oxidation of 2,3,4,5,6-pentasubstituted dihydropyridines. The

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heterogeneous nature of the catalyst enabled its recycling and reuse with no loss of activity.

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