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Direct Reductive Amination of Aldehydes Catalyzed by Carbon Nanotube/Gold Nanohybrids

Rahul Kumar,^[a, b] Edmond Gravel,^[a] Agnès Hagège,^[c, d] Haiyan Li,^[e] Deepti Verma,^[b] Irishi N. N. Namboothiri,^{*[b]} and Eric Doris^{*[a]}

Amines constitute a key scaffold of numerous biologically active compounds and are versatile intermediates in several organic transformations.^[1] However, in spite of their significance, there are only a limited number of methods for their synthesis,^[2] including the one-pot reductive amination of carbonyl compounds.^[3] In contrast to indirect methods, which involve the isolation of an unstable imine intermediate,^[4] direct reductive amination constitutes a more efficient and straightforward route.^[5] Classically, various boron^[6] and tin^[7] complexes have been used for this transformation, but they suffer from low selectivity (over-alkylation), require harsh conditions (acidic), and only afford the products in moderate yields, along with toxic by-products. More recently, the combination of noble metals (e.g., Rh, Ir, and Ru) and H₂ gas has been reported to efficiently promote direct reductive amination.[5d, 8] Other procedures involve hydride sources, such as isopropanol,^[9] Hanztsch esters,^[10] formates,^[11] and silanes.^[12] Indeed, silanes are mild hydride donors that are able to reduce imines in combination with Lewis or Brønsted acids, but they have not yet been shown to be effective in combination with gold nanoparticles.

Although metallic gold has traditionally been regarded as a poor catalytic species, its activity is dramatically enhanced upon downsizing it to nanometer-sized particles (AuNPs).^[13]

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[a]	R. Kumar, Dr. E. Gravel, Dr. E. Doris CFA. iBiTerS
	Service de Chimie Bioorganique et de Marquage
	91191 Gif-sur-Yvette (France)
	Fax: (+ 33) 169-08-79-91
	E-mail: eric.doris@cea.tr
[b]	R. Kumar, Dr. D. Verma, Prof. Dr. I. N. N. Namboothiri
	Indian Institute of Technology
	Bombay, Mumbai 400 076 (India)
	E-mail: irishi@chem.iitb.ac.in
[c]	Dr. A. Hagège
	CEA, iBEB
	Service de Biochimie et de Toxicologie Nucléaire
	30207 Bagnols-sur-Cèze (France)
[d]	Dr. A. Hagège
	CEA, IBEB
	CNRS-UMR 7205 13108 Saint Paul-les-Durance (France)
[0]	
[e]	State Key Laboratory of Physical Chemistry for
	Solid Surfaces and National Engineering Laboratory for
	Green Chemical Productions of Alcohols, Ethers, and Esters
	Department of Chemistry
	College of Chemistry and Chemical Engineering
	Xiamen University
	xiamen 361005 (P.K. China)
	Supporting information for this article is available on the WWW under
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Nanoscale gold has found multiple applications in fine-chemical synthesis, including in selective hydrogenation, carboncarbon bond formation, and oxidation reactions.^[14] We have recently contributed to the field of reactions that are catalyzed by carbon nanotube (CNT)-supported nanogold by reporting efficient systems for the oxidations of silanes^[15] and alcohols.^[16] Compared to other supports, CNTs offer several advantages, including chemical, thermal, and mechanical stability, inertness (i.e., little-to-no interactions with the catalyzed organic transformation), high surface area, and chemically tunable topography.^[17] Moreover, CNTs are electronically active and can contribute to the stabilization of transient higher oxidation states of the metal atoms. Herein, we report our investigations on the direct reductive amination of aldehydes catalyzed by our gold/carbon-nanotube nanohybrid (AuCNT, Figure 1).



Figure 1. Schematic representation of the AuCNTs assembly.

The AuCNT catalyst was prepared according to a literature procedure.^[15] Briefly, amphiphilic nitrilotriacetic diyne (DANTA) self-assembled on the surface of the carbon nanotubes (Figure 1), thereby giving rise to hemi-micelles with a nanor-ing-type structure that were further stabilized by UV photopo-lymerization of the diyne motif that was incorporated into the lipophilic chain. Thereafter, the second cationic PDADMAC layer was deposited before a solution of freshly prepared colloidal gold nanoparticles was added to the doubly coated CNTs.

TEM analysis showed a dense and uniform coating of monodisperse AuNPs on the CNTs (Figure 2). Statistical diameter measurements indicated a mean particle diameter of about



Figure 2. TEM image of the AuCNT catalyst; inset shows a 300% magnification of the area indicated by the black rectangle.

3 nm (see the Supporting Information, Figure S14). The AuCNT catalyst was suspended in water and the gold content in the aqueous suspension of the nanohybrid was determined to be 4 mm by inductively coupled plasma mass spectrometry (ICP-MS).

Our studies started with the one-pot condensation of benzaldehyde (1 equiv) with aniline (1 equiv) in the presence of a silane hydride source (1.5 equiv) and a catalytic amount of AuCNT (0.2 mol%). To avoid hydrolysis of the transient imine (which is formed in situ), water was depleted from the catalyst by repeated precipitation and resuspension in dry THF. Initially, two silanes (i.e., Et₃SiH and Cl₃SiH; Table 1, entries 1 and 2) were initially screened, albeit without success as no conversion was detected. Then, diphenylsilane was tested as the hydride source (Table 1, entry 3), which promoted the expected reductive amination reaction in 89% yield after 7 h. These promising results prompted us to screen a few more conditions and further improvement was achieved by using PhMe₂SiH, which permitted access to amine 3a in 96% yield after just 3.5 h (Table 1, entry 4). Next, we investigated the influence of different solvent systems and found that, under similar conditions, CH₂Cl₂, MeOH, and toluene (Table 1, entries 5, 6, and 7) were less effective, because the quantitative conversion of the substrates required prolonged reaction times. Thus, PhMe₂SiH and THF were selected to further investigate the direct reductive amination process.

Upon increasing the catalyst loading to 0.4 mol%, amine **3 a** was formed in quantitative yield and the reaction time was shortened to 1 h (Table 1, entry 8). The reductive amination was still operative with only 0.004 mol% of the AuCNTs (Table 1, entry 9) and, under these conditions, remarkable values of the turnover number (TON = 21250) and turnover frequency (TOF = 1328 h⁻¹) were calculated. If the kinetic values



[a] Conditions: Benzaldehyde (0.1 mmol), aniline (0.1 mmol), silane (0.15 mmol), AuCNTs (50 μ L of a 4 mm suspension in THF, 0.2 mol%), solvent (1 mL), RT. [b] Yield of isolated product. [c] No reaction. [d] The products were formed as a complex mixture. [e] The reaction was performed with 0.4 mol% of the catalyst. [f] The reaction performed with 0.004 mol% of the catalyst. [g] The reaction performed without a catalyst. [h] None of the desired product was obtained; only the imine was isolated. [i] The reaction was performed without the silane.

were to be calculated by only taking into account the surface gold atoms (those in contact with the medium, as calculated by using the method reported by Djéga-Mariadassou and co-workers)^[18] and not the actual Au loading (total gold content), more-flattering TOF and TON values would be obtained (TON = 70833, TOF = 4426 h⁻¹). Notably, no reaction was observed in the absence of either the AuCNT catalyst (Table 1, entry 10) or the silane (Table 1, entry 11).

With the optimized reaction conditions in hand, we examined the scope of our catalytic AuCNTs/PhMe₂SiH system in the direct reductive amination of aldehydes. We started by studying the effect of substituents on the aromatic ring of the benzaldehyde substrate. Whereas aldehydes that contained parahalogenated aromatic rings (Table 2, entries 2 and 3) provided the corresponding secondary amines (3b and 3c) in almostquantitative yields (97-98%) within 1.5-2 h, the introduction of an electron-withdrawing NO₂ group (Table 2, entry 4) led to a slightly lower yield (91%) and required an extended reaction time (5 h). In the case of aldehydes that contained electron-donating groups (Table 2, entries 5 and 6), the reactions also proceeded smoothly; meta-tolualdehyde led to amine 3e in 95% yield within 1.5 h and para-methoxybenzaldehyde provided amine 3 f in 96% yield after 3 h. Bulkier 2-naphthaldehyde (Table 2, entry 7) was also converted into the desired secondary amine (3g) in high yield (88%) within 3 h. Under our optimized conditions, the conversion of 2-thiophenecarboxaldehyde into the corresponding amine (3 h) was easily performed (93%, 4.5 h; Table 2, entry 8), as well as that of cinnamaldehyde to yield compound 3i (86%, 4h; Table 2, entry 9). The reaction of aliphatic phenyl acetaldehyde with para-toluidine (Table 2, entry 10) was more sluggish and required more time

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Table 2	. Scope of the	e reaction. ^[a]	A	$2NT (0.4 mol^{9})$		
	R ¹ Cł 1	HO + R ² NH ₂ 2	Pł	$rac{1}{100}$		
Entry	R ¹	R ²	t [h]	Product	3	Yield ^[b] [%]
1	Ph	Ph	1		3a	99
2	4-BrPh	Ph	1.5	Br	3 b	98
3	4-FPh	Ph	2	F	3c	97
4	4-NO₂Ph	Ph	5	O ₂ N H	3 d	91
5	3-MePh	Ph	1.5	Me	3e	96
6	4-OMePh	Ph	3	MeO	3 f	95
7	2-naphthyl	Ph	3		3 g	88
8	2-thienyl	Ph	4.5	N N N	3 h	93
9	PhCH=CH	Ph	4	N N	3i	86
10	PhCH ₂	4-MePh	6	N Me	3 j	81
11	Ph	4-MePh	2	N H	3 k	95
12	Ph	4-BrPh	2	N H Br	31	88
13	Ph	1-naphthyl	4		3 m	85
14	Ph	PhCH ₂ CH ₂	24		3n	_[c]

(6 h), although the corresponding amine (**3 j**) was produced in satisfactory (81 %) yield.

The influence of the amine counterpart on the reaction outcome was also investigated. Thus, benzaldehyde was reacted with various amines. Electronrich toluidine (Table 2, entry 11) and electron-deficient *para*-bromoaniline (Table 2, entry 12) both afforded the corresponding amines in good yields (95 and 88%, respectively) after only 2 h of reaction. Moreover, naphthylamine (Table 2, entry 13) afforded amine **3m** in 85% yield within 4 h. Disappointingly, the reactions of benzaldehyde with primary aliphatic amines (phenethylamine and benzylamine; Table 2, entries 14 and 15) failed because the process stopped at the intermediate imine stage.

The recyclability of the catalyst was assessed by using benzaldehyde and aniline as the starting substrates. The AuCNT system was recovered by centrifugation and could be reused in five consecutive runs without any significant loss of activity (Table 3). TEM analysis of the AuCNT catalyst that was recovered after the fifth cycle showed no significant alteration of the hybrid morphology, except for some bare areas on the surface of the nanotubes (see the Supporting Information, Figure S15).

To demonstrate the role of the catalyst, the reaction of benzaldehyde with aniline was performed by using 0.2 mol% of AuCNT and stopped after 2 h, at which point 35% conversion was observed (as confirmed by ¹H NMR spectroscopy). Then, the catalyst was removed by simple filtration and the AuCNT-free mixture was stirred overnight. However, no further evolution of the reaction was detected, thus confirming the heterogeneous nature of the catalyst.

A putative mechanism for this transformation is shown in Scheme 1. The supported gold catalyst likely plays a dual role, that is, as a soft Lewis acid (thus allowing imine condensation) and as a "hydride source" (thus allowing imine reduction). By analogy with other noble metals, it is likely that phenyldimethylsilane undergoes oxidative insertion of the Si–H bond on the surface of the gold nanoparticles,^[19] which produces an activated silane that is capable of reducing the transient imine. Reduction takes place simultaneously with silylation of the nitrogen atom. However, owing to the facile hydrolysis of the latter species, we were not successful in isolating the postulated N-silylated intermediate.

In summary, we have reported a highly efficient process for the reductive amination of aldehydes by using a CNT/gold nanohybrid catalyst and phenyldimethylsilane. This report is the first on the use of a carbon nanotube-supported gold catalyst for reductive amination reactions. The AuCNT-promoted process compares favorably with previously described methods in terms of yields, mild conditions, catalyst loading, and recyclability.^[3-12]

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(0.15 mmol), AuCNTs (100 μ L of a 4 mm suspension in THF, 0.4 mol%), THF (1 mL), RT, 1 h. [b] Yield of isolated product.



Scheme 1. Proposed mechanism for the AuCNT-catalyzed reductive amination reaction.

Experimental Section

General procedure for the reductive amination of aldehydes

Under a N_2 atmosphere, PhMe₂SiH (0.15 mmol) and AuCNTs (100 μ L of a 4 mm suspension in THF, 0.4 mol%) were added to a stirring solution of aldehyde **1** (0.1 mmol) and amine **2** (0.1 mmol) in THF (1 mL). The reaction mixture was stirred until the starting material had been completely consumed (by TLC). After completion of the reaction, the catalyst was removed by filtration and the mixture was concentrated under vacuum. The crude residue was directly subjected to column chromatography on silica gel (cyclohexane/EtOAc, 96:4) to afford secondary amine **3**.

Recycling experiment

Under a N_2 atmosphere, $PhMe_2SiH$ (0.15 mmol) and AuCNTs (100 μL suspension in THF, 0.4 mol%) were added to a stirring solu-

tion of benzaldehyde (**1a**, 0.1 mmol) and aniline (**2a**, 0.1 mmol) in THF (1 mL). The reaction mixture was stirred until the starting material had been completely consumed (by TLC). After completion of the reaction, the catalyst was recovered by centrifugation and reused without further purification.

TON and TOF experiments

Under a N_2 atmosphere, PhMe₂SiH (0.15 mmol) and AuCNTs (10 μ L suspension in THF, 0.004 mol%) were added to a stirring solution of benzaldehyde (1 a, 1 mmol) and aniline (2 a, 1 mmol) in THF (2 mL). The re-

action mixture was stirred for 16 h at RT. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The crude residue was directly subjected to column chromatography on silica gel (cyclohexane/EtOAc, 96:4) to afford compound **3a** in 85% yield.

TON for compound $\mathbf{3a} = \mathsf{mmol} \mathsf{ product}/\mathsf{mmol} \mathsf{ catalyst}$

= 0.85/0.00004= 21 250 TOF for compound **3** a= TON/time = 21 250/16 = 1328 h⁻¹

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Keywords: gold • heterogeneous catalysis • nanoparticles • nanotubes • silanes

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- Direct Reductive Amination of Aldehydes Catalyzed by Carbon Nanotube/Gold Nanohybrids

R-CHO+H2N-R' PhMe2SiH

Gold digger: The direct reductive amination of aldehydes catalyzed by gold/ carbon-nanotube nanohybrids with a silane as a hydride source is reported.