Mild chemical synthesis of Indium(0) Nanoparticles. Characterization and application in allylations of carbonyl compounds.

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Introduction

In recent years, the synthesis of metal nanoparticles (NPs) has attracted significant attention because of their unique physical and chemical properties. Among these size-dependent properties, melting point, conductivity, magnetism, specific heat, UV-visible absorption and catalytic activity are of interest for a wide range of applications, including catalysis, electronics, optics, magnetism, lubricants, clinical diagnosis [1]. On the other hand, although the specific role of metal NPs as catalysts in diverse chemical reactions is not always easy to ascertain, they have demonstrated to exhibit unique catalytic properties, which are supposed to be strongly related to their high surface area and the possibility of charge distribution in electron transfer reactions [2]. Besides, it is known that the reactivity, reproducibility and the stereochemistry outcome of many metal NPs-mediated reactions are commonly affected by the method of preparation, the source of the metal, the reaction conditions, and the use of additives such as stabilizing agents [3]. With regard to indium metal particles, they have shown to be superconducting, active for surface plasmon resonance, useful components in low-melting solders and solid-state lubricants, and have been applied in electronics, bio-nanotechnology, nanoxerography, and also have been widely used as catalyst in a variety of organic reactions. Since indium reagents are stable to air and moisture become easier to handle and more environmentally friendly than other organometallic compounds. On the other hand, they are excellent bases but poor nucleophiles and therefore they tolerate a wide range of functional groups [4]. In spite of this, although many strategies for the preparation of noble- and transition-metal nanoparticles have been published, the synthesis of indium nanoparticles (InNPs) has been scarcely reported. Some top-down methods involve dispersion of bulk indium in paraffin oil [5], ultrasound irradiation [6], thermal evaporation combined with aerosol technology [7], sputter deposition of indium foil [8], or solvated metal atom dispersion followed by digestive ripening of indium shot [1]. Regrettably, most of these methods provide little control over particle size and size distribution, and require the use of specific and/or sophisticated laboratory equipment. Moreover, particles less than 10 nm are obtained

by applying very high temperatures and/or high vacuum, and the use of amine or phosphine ligands to passivate the InNPs' surface. On the other hand, the bottom-up methods generally involve the reduction of indium salts by strong reducing agents, among them, sodium metal in high boiling solvents [9], sodium borohydride in ionic liquids (IL) at high temperatures [10], or the same reducing agent at room temperature in the presence of a stabilizing compound [11], or by a two-step phase-transfer reaction at high temperature in the presence of a surfactant [12]. Most of these methods produce particles with average sizes in the range of 10-100 nm in diameter. Recently, InNPs less than 10 nm were prepared *via* reduction of indium salts by using different reducing agents such as lithium borohydride in amine solvents [13], electrochemical reduction in IL [14] or by a thermal decomposition of organometallic complexes [15]. It is noteworthy that with all of these methodologies it is mandatory the presence of stabilizing agents like octylamine, polyvynilpirrolidone or triethylphosphine, and in some cases, size control is achieved by inducing InNPs growth on small gold clusters.

On the other hand, the reducing systems based on the use of alkali-metals in combination with arenes in aprotic media, with the arene acting as electron carrier have received much attention. Some of us have been working on the preparation of transition metal nanoparticles by fast reduction of the corresponding metal chlorides with lithium and a catalytic amount of an arene [naphthalene, 4,4´-di-*tert*-butylbiphenyl (DTBB)] as electron carrier. These transition-metal NPs have been utilized for various important organic transformations in our laboratories, mainly for reduction [16] and coupling reactions [17]. The above mentioned transition-metal NPs were prepared under mild reaction conditions, in tetrahydrofuran (THF) as the solvent and at room temperature, from the corresponding commercially available metal chlorides. This methodology allowed the obtention of very reactive, monodisperse spherical nickel(0), iron(0), copper(0), manganese(0), cobalt(0) and titanium(0) nanoparticles with an average size near 3.0±1.5 nm, which efficiently promoted a wide variety of useful organic synthetic transformations.

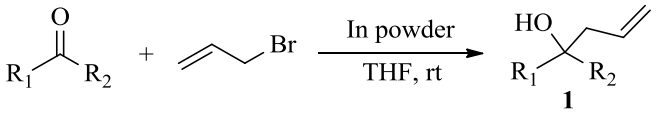
Herein, we report, a one-pot, one-step, simple, mild, and efficient synthesis of very reactive, monodisperse (4.0 ± 0.5 nm) spherical indium(0) nanoparticles, using indium(III) chloride in the presence of lithium powder and a catalytic amount of DTBB in THF at room temperature, and in the absence of any anti-agglomeration additive or ligand. The InNPs were characterized by transmission electron microscopy (TEM) and UV-Visible spectroscopy. Focusing on one of the most studied indium-mediated transformations of organic compounds [18,19], and prompted by our interest in the search of new and useful synthetic applications of metal NPs, we decided to explore the performance of our InNP-based reactive system in the allylation of a variety of

aldehydes and ketones To the best of our knowledge, this is the first report describing the use of naked InNPs in a synthetic organic transformation.

Results and discussion

Indium powder-mediated allylation of carbonyl compouns

As can be seen in Table 1, at first, and following the stoichiometry previously reported for this type of reactions, we investigated the indium powder-mediated allylation reaction of three different carbonyl compounds with allyl bromide. As shown in Scheme 1, the reaction of a series of aldehydes and ketones with a suspension of In powder in THF, at room temperature and under N_2 atmosphere, gave the corresponding homoallylic alcohols **1** in poor to good yields.



Scheme 1. Indium powder mediated allylation of carbonyl compounds

Table 1. Indium powder-mediated allylation of carbonyl compounds.[a]

Entry	R_1	R_2	Time (h)	**1** Yield (%)[b]
1	Ph	H	3	82[c,d] (**1a**)
2	Ph	CH_3	24	63[d] (**1b**)
3	-$(CH_2)_5$-		24	36[d] (**1c**)

[a] Reaction conditions: carbonyl compound (0.5 mmol), allyl bromide (1.5 mmol), In powder (1.0 mmol), in THF as the solvent (4 mL), at 25 ºC.
[b] Quantified by GC analysis using internal standard method.
[c] Together with reduced starting carbonyl compound (10%).
[d] Together with unreacted starting carbonyl compound.

Under the above conditions, benzaldehyde gave 1-phenylbut-3-en-1-ol (**1a**) in good yields in 3 h at room temperature along with 10% of the direct reduction product. Only a little amount of the starting carbonyl compound was detected at the final reaction time (Table 1, entry 1). As expected, ketones shown to be less reactive, 20 h reaction time was needed to obtain 2-phenylpent-4-en-2-ol (**1b**) in 63% yield, and 1-allylcyclohexanol (**1c**) in only 36% yield. Furthermore, a considerable amount of starting ketone was recovered at the final reaction time in both cases (Table 1, entries 2 and 3).

With these results in hand, we decided to study the performance of the InNPs-mediated allylations of a series of aldehydes and ketones.

Synthesis and characterization of InNPs

The indium nanoparticles were generated in situ by reduction of commercially available $InCl_3$ with an excess of lithium sand (3.5:1 M ratio relative to the corresponding indium trichloride) and a catalytic amount of DTBB (10 mol% referred to the indium salt). The reactions were performed using tetrahydrofuran (THF) as the solvent, at room temperature and under a nitrogen atmosphere. Droplets of the InNPs suspension obtained were analyzed by transmission electron microscopy (TEM) showing well defined, monodisperse, spherical nanoparticles with a particle size distribution of ca. 4.0±0.5 nm (Figure 1). The sizes were determined for 100 nanoparticles selected at random.

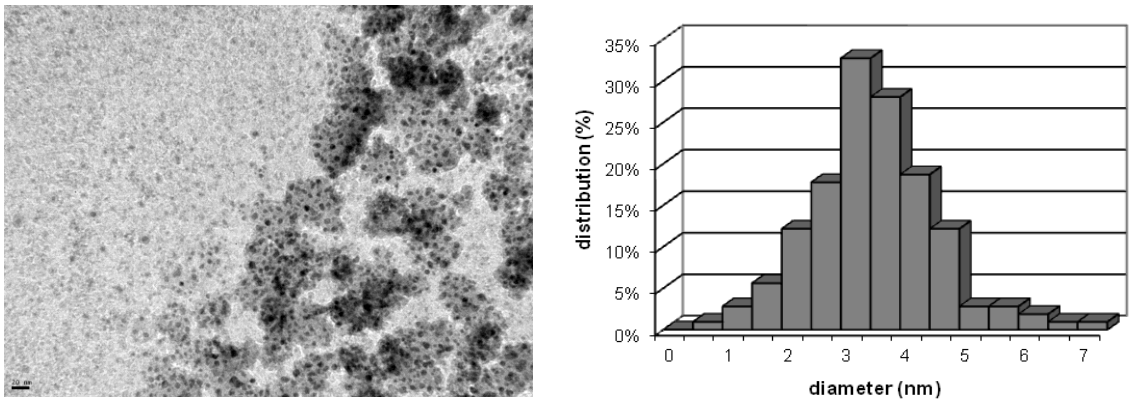


Figure 1. TEM micrograph and size distribution of the InNPs

The UV absorption spectra is shown in Figure 2. The sample was obtained by evaporating the THF (20 mbar) and redispersing the InNPs in dichloromethane (DCM). The spectrum shows the typical band of surface plasmon resonance at 260 nm, indicating the formation of indium(0) NPs of less than 50 nm in size [9].

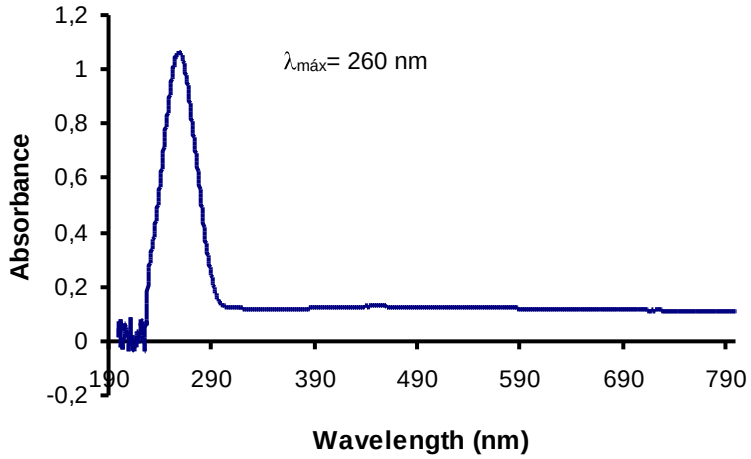
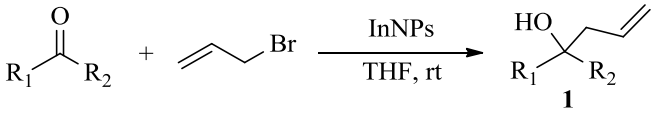


Figure 2. UV absorption spectra of InNPs dispersed in DCM

Table 2 shows the results obtained in the allylation of carbonyl compounds promoted by InNPs prepared in situ as described above. As shown in Scheme 2, the reaction of a series of aldehydes and ketones with the InNPs suspension, at room temperature and under a N_2 atmosphere, gave the corresponding homoallylic alcohol **1** in good to excellent yields.



Scheme 2. Indium NPs mediated allylation of carbonyl compounds

Under the same reaction conditions as those used in Table 1, the reactions performed with the InNPs, gave higher yields of the homoallylic alcohol products **1a**, **1b** and **1c**. Benzaldehyde was used as model substrate in order to optimize the reaction conditions for aldehyde allylation. Thus, we observed a total conversion into the corresponding alcohol **1a** in shorter reaction time (1 h) than using indium powder (Table 2, entry 1). On the other hand, cyclohexanone was used as model substrate in order to optimize the reaction conditions for ketone allylations. After 20 h of reaction time, the yield of the homoallylic alcohol **1c** was markedly improved compared to that obtained using indium powder (36% to 76%), and the formation of the corresponding α-allyl ketone as by-product was detected (Table 2, entry 2). We assumed that the formation of this by-product might proceed through the alkylation of the ketone enolate generated by the excess of lithium metal. To confirm this assumption we reproduced the same reaction conditions but in the absence of the indium salt. Thus, the starting ketone was recovered in a 60% yield together with the α-allyl ketone product (ca. 40%) (Table 2, entry 3).

It is assumed that an allyl-indium intermediate is formed in these carbonyl allylation reactions [20], thus, in order to favor the formation of this plausible intermediate, we tested the allylation of cyclohexanone under the optimized conditions but stirring the InNPs suspension with the allyl bromide for 1 h, before the addition of the carbonyl compound. Under these conditions, cyclohexanone gave the corresponding product **1c** in excellent yield (Table 2, entry 4). Under the same reaction conditions, acetophenone, after 20 h, led to the homoallylic alcohol **1b** in 67% yield (Table 2, entry 5). Taking into account the excellent result obtained with cyclohexanone, we then tested the allylation reaction of (-)-mentone, which proceeded with very low conversion (*ca.* 12%) of the starting cyclic ketone (Table 2, entry 6). The lack of reactivity observed for this substrate could be attributed to the steric hindrance caused by the *iso*-propyl

substituent attached to the α-position of the carbonyl group, which could make it difficult the approach of the allyl-indium intermediate to the electrophilic center. Finally, allylation of 3-pentanone resulted in a 30% conversion of the starting material after 24 h (Table 2, entry 7).

Table 2. Indium NPs mediated allylation of carbonyl compounds.[a]

Entry	R_1	R_2	Time (h)	Yield (%)[b]
1	Ph	H	1	98 (84) (**1a**)
2	$-(CH_2)_5-$		20	76[c,d] (**1c**)
3[e]	$-(CH_2)_5-$		20	---[f]
4[g]	$-(CH_2)_5-$		20	96 (**1c**)
5[g]	Ph	CH_3	20	67[c] (**1b**)
6[g]	$-CH_2CH(CH_3)(CH_2)_2CH(CH(CH_3)_2)-$		22	12[c] (**1d**)
7[g]	CH_3CH_2	CH_3CH_2	24	30[c] (**1e**)
8	$(CH_3)_2C=CH(CH_2)_2CH(CH_3)CH_2$	H	1	95 (91) (**1**f)
9	$PhCH_2$	H	3	97 (**1g**)

[a] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), $InCl_3$ (1.0 mmol) in THF as the solvent (2 mL), allyl bromide (1.5 mmol) in THF (2 mL), stirred for 30 min, carbonyl compound (0.5 mmol) in THF (2 ml), at 25 ºC, unless otherwise stated.

[b] Quantified by GC analysis using internal standard method. Isolated yield after column chromatography shown in parentheses.

[c] Together with starting substrate.

[d] Together with α-allylketone (9%).

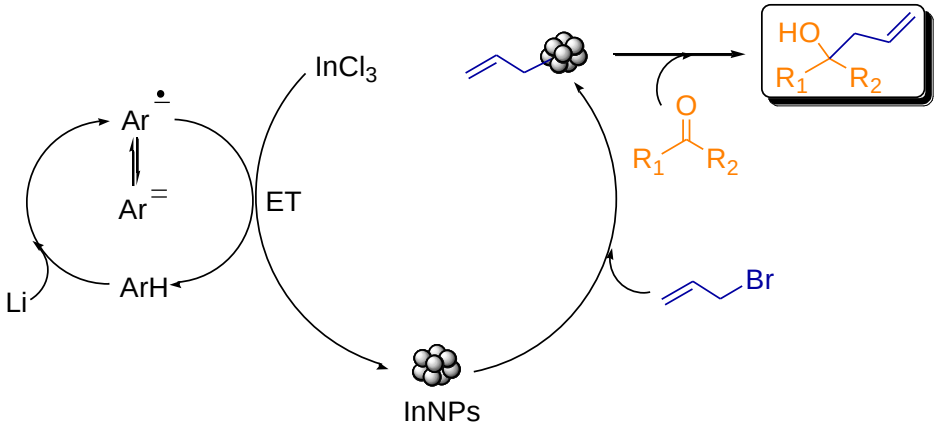
[e] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), in THF as the solvent (2 mL), allyl bromide (1.5 mmol) in THF (2 mL), carbonyl compound (0.5 mmol) in THF (2 ml), at 25 ºC.

[f] Starting substrate (60%) together with α-allylketone (40%).

[g] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), $InCl_3$ (1.0 mmol) in THF as the solvent (2 mL), allyl bromide (1.5 mmol) in THF (2 mL), stirred for 60 min, carbonyl compound (0.5 mmol) in THF (2 ml), at 25 ºC.

With the aim to study the compatibility of the allylation system with the presence of reducible functional groups in the starting carbonyl compounds, we tested the allylation of an unsaturated aldehyde as (-)-citronellal. The reaction led to the alcohol product **1f** as a ca. 1:1 mixture of both possible diastereoisomers in almost quantitative yield (Table 2, entry 8) and with the carbon-carbon double bond remaining intact. Finally, phenylacetaldehyde, after 3 h of reaction time gave the homoallylic alcohol **1g** in a 97% yield (Table 2, entry 9).

The Scheme 3 shows the plausible reaction pathway involved in the InNPs-mediated allylation of carbonyl compounds. The first step in the reaction would be the formation of InNPs by electron transfer (ET) from the arene radical anion to the indium salt. The addition of allyl bromide to the InNPs suspension, could led to the formation of an allyl-indium intermediate [19], which would gave the homoallylic alcohol by reaction with the corresponding carbonyl compound.



Scheme 3. Proposed reaction pathway for the InNPs-mediated allylation of carbonyl compounds

Conclusions

We have developed a simple and convenient methodology for the synthesis of very reactive, well defined, monodisperse, spherical InNPs with a particle size distribution of ca. 4.0±0.5 nm, through the SET reduction of indium(III) chloride in the presence of lithium sand and a catalytic amount of DTBB, under mild conditions and in the absence of any anti-agglomeration additive or ligand. These *in situ* prepared InNPs have demonstrated to be efficient in the synthesis of homoallylic alcohols from carbonyl compounds, using allylbromide as allylating agent. To the best of our knowledge, this is the first organic functional group transformation based on the use of *in situ* prepared indium nanoparticles. We are now studying the allylation of other carbonyl systems in order to extend the scope of this methodology.

Experimental Section

General

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents used were treated prior to use by standard methods. [21] All starting

materials were of the best available grade (Aldrich, Merck) and were used without further purification. Column chromatography was performed with Merck silica gel 60 (0.040-0.063 mm, 240-400 mesh). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm). All the starting carbonyl compounds, included in Tables 1 and 2, were purchased from commercial sources (Aldrich, Fluka, Merck), and used as received.

Instrumentation and analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a GC Shimadzu (GC-14B) with a flame ionization detector equipped with a HP-5MS column (30 m × 0.25 mm × 0.25 μm) using nitrogen as carrier gas. Indium nanoparticles were characterized by Transmission Electron Microscopy (TEM), in a JEOL 100CX2 operated at an acceleration voltage of 100 kV. The UV-Visible absorption spectrum was measured by a Jasco V-630 Bio spectrophotometer.

Representative procedure for the allylation of carbonyl compounds promoted by InNPs. Synthesis of homoallylic alcohol **1a**

A mixture of lithium powder (24.5 mg, 3.5 mmol), DTBB (26.7 mg, 0.1 mmol) and $InCl_3$ (221 mg, 1.0 mmol) in THF (2 mL) was stirred at room temperature under nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, indicating the formation of the indium nanoparticles (InNPs). Then allyl bromide (181.3 mg, 0.128 mL, 1.5 mmol) in THF (2 mL) was added by syringe, and the suspension was stirred for 30 minutes. Subsequently, benzaldehyde (53 mg, 0.051 mL, 0.5 mmol) in THF (2 mL) was added by syringe. After total conversion of the starting material (TLC, GC), the resulting suspension was diluted with diethyl ether (10 mL) and treated with 10% HCl and water. The combined extracts were dried over anhydrous Na_2SO_4, and evaporated (20 mbar). The resulting residue was purified by flash column chromatography (silica gel, hexane-ethyl acetate) to give the corresponding homoallylic alcohol **1a** (84%).

Representative procedure for the allylation of carbonyl compounds promoted by InNPs. Synthesis of homoallylic alcohol **1c**

A mixture of lithium powder (24.5 mg, 3.5 mmol), DTBB (26.7 mg, 0.1 mmol) and $InCl_3$ (221 mg, 1.0 mmol) in THF (2 mL) was stirred at room temperature under nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, indicating the formation of the indium nanoparticles (InNPs). Then allyl bromide (181.3 mg, 0.128 mL, 1.5 mmol) in THF (2 mL) was added by syringe, and the suspension was stirred for 45 minutes. Subsequently, cyclohexanone (48 mg, 0.049 mL, 0.5 mmol) in THF (2 mL) was added by syringe. When no further progress in the reaction (TLC, GC), the suspension was diluted with diethyl ether (10 mL) and treated with 10% HCl and water. The combined extracts were dried over anhydrous Na_2SO_4, and the corresponding homoallylic alcohol **1c** was quantified by GC (96%).

Acknowledgements

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