Bottom-up synthesis of indium(0) nanoparticles and its application for the allylation of benzaldehyde. An experimental and theoretical study.

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Introduction

In recent years, the synthesis of metal nanoparticles has attracted significant attention because of their unique properties. 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. Most of the bottom-up methods require the use of indium salts and strong reducing agents such as sodium metal, zinc power, alkalides/electrides, or decomposition of organometallic complexes.[1] Regrettably, some of them provide little control over particle size and size distribution of the InNPs, and the presence of stabilizing agents is generally mandatory. Recently, we have been working on the simple, mild, and efficient synthesis of very reactive, monodisperse (4.0 ± 1.5 nm) spherical InNPs by fast reduction of indium(III) chloride with lithium powder and a catalytic amount of 4,4´-di-tert-butylbiphenyl (DTBB) in THF at room temperature, and in the absence of any anti-agglomeration additive or ligand. We explored the above mentioned InNPs-based reactive system for the allylation of a variety of aldehydes and ketones in a one-pot procedure, by adding allyl bromide over a suspension of InNPs followed by the addition of the corresponding carbonyl compound. For most of the compounds tested, the corresponding homoallylic alcohol was obtained as the major reaction product in good yields.[2]

In order to extend the scope of this indium-mediated protocol, and prompted by our interest in the search of new and useful synthetic applications of metal NPs, herein, we report a comparative study on the allylation of benzaldehyde with a series of substituted allyl bromides promoted by both InNPs and In powder, under mild reaction conditions. Additionally, computational studies have been applied in order to explain the differences in reactivity observed.

Results and discussion

As shown in Scheme 1, we initiated our studies with the indium powder and InNPs mediated allylation of benzaldehyde with four different allyl bromides, following the standard conditions previously reported for this type of reactions, in THF, working at room temperature and under N_2 atmosphere. The indium nanoparticles (InNPs) 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), using tetrahydrofuran (THF) as solvent, at room temperature and under a nitrogen atmosphere. This methodology allowed the generation of well defined, monodisperse, spherical nanoparticles with a particle size distribution of ca. 4.0±0.5 nm.
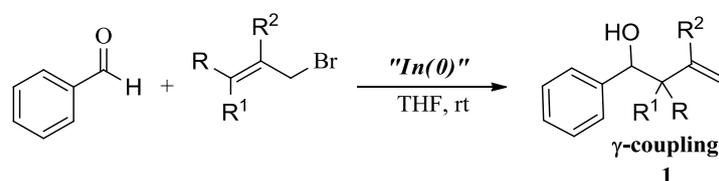
Scheme 1. *"Indium(0)"* mediated allylation of benzaldehyde

As can be seen in Table 1, the reaction of a series of allyl bromides and benzaldehyde in the presence of a suspension of In powder, gave the corresponding homoallylic alcohols **1** in poor to good yields, while the same allylation reactions promoted by InNPs, prepared *in situ* as described above, yielded the corresponding allylic alcohols almost quantitatively.

Table 1. *"Indium(0)"* mediated allylation of benzaldehyde.

Entry	R	R^1	R^2	Time (h)		Yield 1 (%)[a] In power[b]	InNPs[c]	syn : anti[d]
1	H	H	H	1	(**1a**)	74 (68)[e]	98 (86)	
2	Me	Me	H	4	(**1b**)	65[e,f]	95 (85)[g]	
3	H	H	Me	2	(**1c**)	10[e]	99	
4	H	Me	H	2	(**1d**)	58[e]	99 (87)	67 : 33

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

[b] Reaction conditions: In powder (1.0 mmol), allyl bromide (1.5 mmol), in THF as solvent (4 mL), stirred for 30 min, benzaldehyde (0.5 mmol) in THF (1 ml), at 25 °C, unless otherwise stated.

[c] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), $InCl_3$ (1.0 mmol) in THF as solvent (3 mL), allyl bromide (1.5 mmol) in THF (1 mL), stirred for 30 min, benzaldehyde (0.5 mmol) in THF (1 ml), at 25 °C, unless otherwise stated.

[d] *Syn:anti* ratio determined by ^{1}H NMR.

Under the optimized reaction conditions, the allylation of benzaldehyde with allyl bromide, mediated by granular indium (-100 mesh), gave 1-phenylbut-3-en-1-ol (**1a**) in 74% yield together with starting carbonyl compound. As expected, the same reaction mediated by InNPs, gave the homoallylic alcohol **1a** almost quantitatively (98%) in only 1 h of reaction time (Table 1, entry 1). Prenyl bromide showed to be less reactive. Assuming that an allyl-indium intermediate is formed in these carbonyl allylation reactions[3], we tested this reaction under the optimized conditions but stirring the corresponding indium reagent (InNPs suspension or In powder) with prenyl bromide for 60 min, before the addition of the carbonyl compound in order to favor the formation of this plausible intermediate. Thus, after 4 h reaction time, the γ-adduct[4] 1-phenyl-2,2-dimethylbut-3-en-1-ol (**1b**) was obtained in 65% yield in the presence of indium powder, and in 95% yield when the reaction was mediated by InNPs (Table 1, entry 2). Although the yield of the allylated product was quite similar to that obtained using allyl bromide, the reaction time was markedly longer when prenyl bromide was used as the starting allyl halide. The less reactivity observed for this substrate could be attributed to the steric hindrance caused by methyl substituents attached to the allyl moiety, which could affect, somehow, the formation of the homoallylic alcohol. Using methallyl bromide, the yield of the corresponding alcohol **1c** (1-phenyl-3-methylbut-3-en-1-ol) was markedly better by using InNPs compared to that obtained using indium powder (99% to 10%). Furthermore, in the latter reaction, a considerable amount of the starting benzaldehyde was recovered at the final reaction time (2 h) (Table 1, entry 3). The crotylation of benzaldehyde mediated by indium power gave 1-phenyl-2-methylbut-3-en-1-ol (**1d**) with moderated yield (58%) together with starting carbonyl compound, whereas in the presence of InNPs afforded the corresponding γ-coupling homoallylic alcohol **1d** almost quantitatively after 2 h. The diastereoreoselectivity observed for this reaction was slightly better than that reported previously by other authors[4] (67:33 *syn/anti*) and the *syn*-isomer was dominant (Table 1, entry 4).

These experimental observations prompted us to study in more detail the process implied in the InNPs-mediated allylation of benzaldehyde using density functional theory (DFT). The *ab initio* calculations were performed with the B3LYP[5] DFT[6] functional and the LANL2DZ basis set.

As already mentioned above, the reactivity of the allyl- and prenyl bromides was very different, both giving the corresponding homoallylic alcohol in excellent yields (98 and 95% respectively) but the allylation with prenyl bromide being notably slower. Taking this into account, and considering results reported by other authors,[7] we evaluated the potential energy surfaces (PES) for the mentioned process by considering the formation of an initial complex between benzaldehyde and the allyl-indium intermediate, a six member cyclic chair-like transition state (TS) and a final complex, as can be seen in the Scheme 2 for the preparation of **1a** as representative compound. An auxiliary bromide atom was used as ligand for the indium atom to obtain a simplified neutral model system.[7]
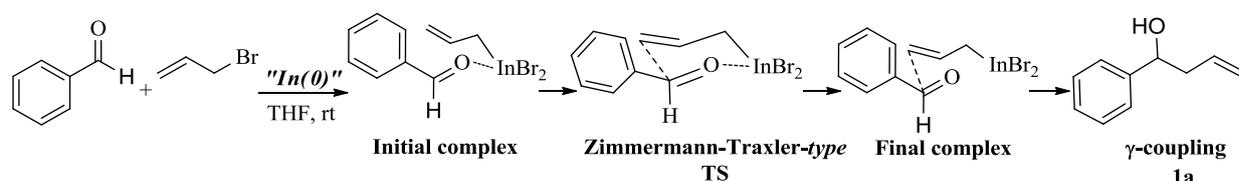
Scheme 2. Representative structures for the obtention of **1a** included in the computational analysis

As shown in Figures 1 and 2, the formation of the final complex of **1b** takes place with higher activation energy than that of **1a** (9.0 and 5.2 Kcal/mol, respectively). In addition, for product **1a** the process occurs exothermically (-5.2 Kcal/mol), while for **1b** the corresponding final complex requires +1.2 Kcal/mol. This thermochemical observation could explain the differences found in the reactivity between allyl bromide and prenyl bromide in the allylation of benzaldehyde mediated by InNPs.
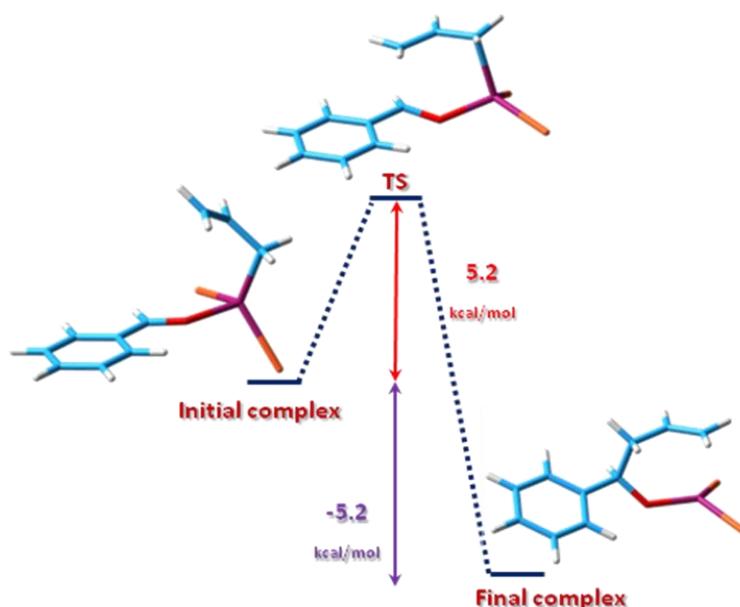

Figure 1. Gas Phase B3LYP/LANL2DZ potential energy profile for the formation of **1a**
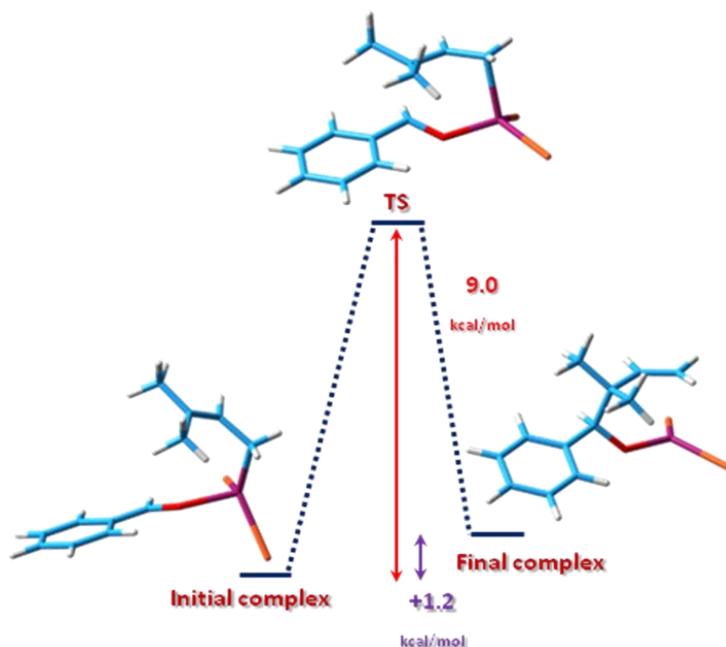
Figure 2. Gas Phase B3LYP/LANL2DZ potential energy profile for the formation of **1b**

Based on the experimental observations and the DFT studies, we propose a plausible reaction mechanism for the InNPs-mediated allylation of benzaldehyde (Scheme 3). The first step in the reaction is the formation of InNPs by electron transfer (SET) from the arene radical anion to the indium salt. After addition of the allyl bromide on InNPs suspension, it could be assumed the formation of an allyl-indium intermediate. At the end, the corresponding γ-coupling homoallylic alcohol is obtained through a Zimmerman-Traxler-type transition state,[7] by reaction of the allyl-indium intermediate with the activated carbonyl moiety, this last probably adsorbed on the InNPs surface.
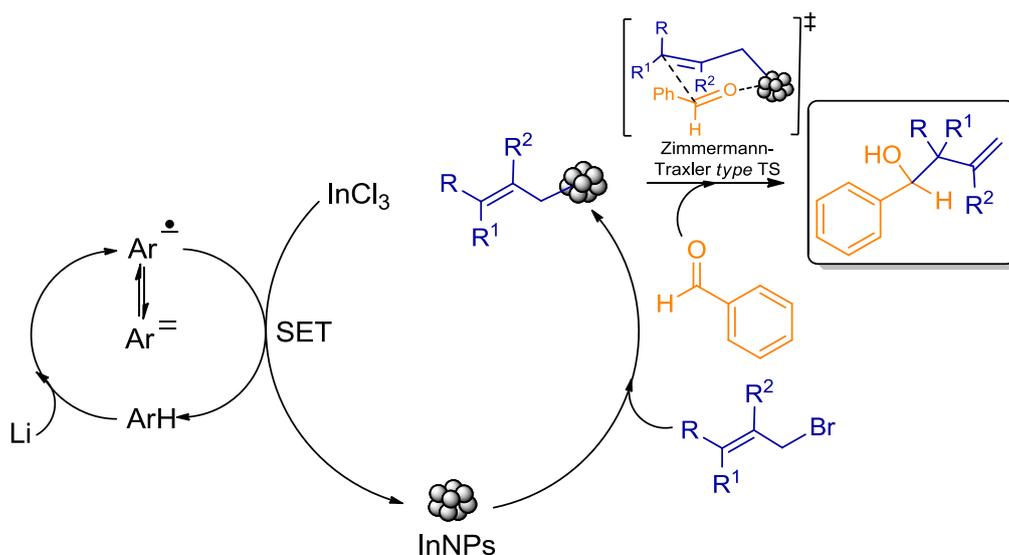
Scheme 3. General scheme of the InNPs-mediated allylation of benzaldehyde

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 for the synthesis of homoallylic alcohols from benzaldehyde using a series of substituted allyl bromides as allylating agents. As expected, InNPs demonstrated to be much more efficient than granular indium yielding the corresponding allylic alcohols almost quantitatively and at shorter reaction times. On the other hand, DFT calculations have shown to be a successful approach for studying the allylindium intermediates as well as to explain the experimental results. To conclude, based on the experimental data and DFT studies, we have proposed a possible reaction mechanism that implies the formation of γ-coupling products *via* a cyclic six-membered Zimmermann-Traxler-type transition state, and the participation of allyl-indium sesquihalides as intermediates.

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.[8] 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 and allyl compounds, included in Table 1 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.

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

A suspension of indium powder (-100 mesh, 115 mg, 1 mmol) and allyl bromide (181.3 mg, 0.128 mL, 1.5 mmol) in THF (4 mL) was stirred at room temperature under nitrogen atmosphere for 30 minutes. Subsequently, benzaldehyde (53 mg, 0.051 mL, 0.5 mmol) in THF (1 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** (68%).

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 (3 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 (1 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 (1 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** (86%).

Computational Procedure

The calculations were performed with Gaussian09.[9] The initial conformational analysis of selected compounds was performed with the semiempirical AM1 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP studies. The zero point energy corrections were made at the LANL2DZ level for the thermodynamic quantities. The exploration of the potential surface was carried out varying the selected coordinate with full optimization for the remainder degrees of freedom. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for a minimum and by

using the TS methodology for a transition state. Figures were built with the GaussView program.

Acknowledgements

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