APPLICATIONS OF COMPUTATIONAL AND NMR METHODOLOGIES TO THE STUDY OF HOMOALLYLIC ALCOHOLS DIASTEREOMERS

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ABSTRACT

Through the reducing system $InCl_3$-Li-DTBB(cat.) in THF at room temperature and in the absence of any additives or anti-caking ligand we have synthesized indium nanoparticles (InNPs) of about 4 nm. The catalyst was employed in the allylation of carbonyl compounds, giving excellent yields of the corresponding homoallylic alcohols. We have established that the reaction products come from a γ-coupling, via a six members cyclic transition state, type Zimmerman-Traxler.[1] Relative the selectivity, the allylation with crotyl bromide of *ortho* substituted benzaldehydes (e.g. *o*-NO_2, *o*-OMe, *o*-Cl, *o*-CF_3) showed *syn* selectivity. With the aim to improve the mentioned selectivity, we synthetized *o*-^{i}PrO-benzaldehyde, and evaluated the reaction with crotyl bromide and InNPs. The homoallylic alcohol 1-(2-isopropoxyphenyl)-2-methylbut-3-en-1-ol was obtained almost quantitatively after 1h as a mixture of the *syn*- and *anti*- isomers. The relationship observed by ^{1}H-RMN was 75:25, but we did not know if the *syn*-isomer was the dominant because the product has not been reported in the scientific literature. Based on this, and in order to determinate which ones 1H-NMR signals corresponding to each isomer, we started computational theoretical and NMR studies.

The initial conformational analysis was performed using the semiempirical PM3 method, then we work with the B3LYP functional, applying the 6-31+G* basis set and the solvent effect (chloroform) was evaluated with the PCM model as implemented in Gaussian09. So, we found thirteen low-energy conformations for the *syn*-diastereomer and six low-energy conformations for the *anti*-diastereomer.

On the other hand, we have carried out NMR experiments such as 1H, 13C, HSQC, to assign the signals of each diastereomer; and experiments such as NOESY, selective NOE, JRes, homo- and hetero-nuclear *J*-coupled and *J*-decoupling, to be able to measure coupling constants and establish the structure of each diastereomer.

Keywords: Indium nanoparticles, DFT, NMR.

INTRODUCTION

In the last years we have been working in the indium-mediated allylation of carbonyl compounds with allyl bromides as an interesting and convenient method to obtain homoallylic alcohols, significant building blocks in organic synthesis. Besides the reactivity, the diastereoselectivity in the addition of an allyl-metal to a carbonyl compound is a fundamental parameter to consider, and could be explained by steric and stereoelectronic or chelating effects.[1] In this sense, previously we report[2] a series of reactions of carbonyl compounds and allylic bromides mediated by indium nanoparticles (InNPs) of 4.0 ± 0.5 nm. The reagents were selected rationally in order to complete an appropriate mechanistic knowledge of the system. Substituted allyl bromides allowed us to establish that the reaction products come from a γ-coupling, via a six-membered cyclic transition state, type Zimmerman-Traxler. On another hand, in order to assess the *syn*-*anti* selectivity of the InNPs-mediated allylation of carbonyl compounds, we investigated the reaction of a series of *ortho*-substituted benzaldehydes bearing either electron-donating or electron-withdrawing groups with crotyl bromide. The reaction led to the corresponding alcohols in excellent yields, in rather short reaction times and giving *syn*-diastereomers as the major products. In this sense, *ortho*-propoxybenzaldehyde yield the expected product with a 75:25 diastereoselectivity determined by ^{1}H-RMN. Considering that the homoallylic alcohol 1-(2-isopropoxyphenyl)-2-methylbut-3-en-1-ol was not reported in the scientific literature, we apply different DFT and NMR methodologies that could allow us to assign each diastereomer, the discussion about these topics is included below.

METHODS

General

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. 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).

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.

Synthesis of *o*-isopropoxybenzaldehyde (**1**)

A mixture of K_2CO_3 (2.8 g, 20 mmol) and salicylaldehyde (1.22 g, 1.4 ml, 10 mmol) in anhydrous DMF (10 mL) was stirred at room temperature under nitrogen atmosphere. The reaction mixture changed to yellow. Then isopropyl bromide (6.4 mL, 10 mmol) was added drop to drop by syringe, and the suspension was stirred for 2 days. Then, the resulting suspension was diluted with dichloromethane (30 mL) and treated with NaOH 2M 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 aldehyde (1.6g, 98%).

Synthesis of 1-(2-isopropoxyphenyl)-2-methylbut-3-en-1-ol (**2**)

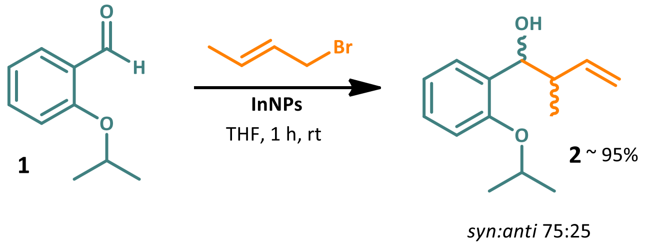
A mixture of lithium powder (24.5 mg, 3.5 mmol), DTBB (26.7 mg, 0.1 mmol) and $InCl_3$ (221 mg, 1.0 mmol) in THF (2 mL) was stirred at room temperature under nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, indicating the formation of the indium nanoparticles (InNPs). Then crotyl bromide (202.5 mg, 0.150 µL, 1.5 mmol) in THF (2 mL) was added by syringe, and the suspension was stirred for 30 minutes. Subsequently, *o*-isopropoxybenzaldehyde (54 mg, 0.33 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 (95%).

Computational Procedure

The calculations were performed with the Gaussian09 program.[3] The initial conformational analysis of selected compounds was performed with the semiempirical PM6 method. The geometry of the most stable conformer thus obtained was used as starting point for the B3LYP studies. Zero-point energy were computed at the 6-31+G* level for all atoms and LanL2DZ for indium. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for the minimums and by using the QST2 or QST3 methodologies for the transition state. The energies in solution were obtained within the Tomasi's polarized continuum model (PCM) as implemented in Gaussian09. The figures were built with the VMD program.

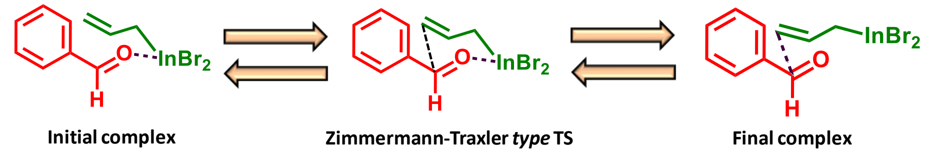
RESULTS AND DISCUSSIONS

The reaction between *ortho*-propoxybenzaldehyde (**1**) and crotyl bromide catalyzed by the InNPs, in THF as solvent and then 1 h of reaction time, led to the corresponding homoallylic alcohol (**2**) in excellent yields with a 75:25 diastereoselectivity determined by ^{1}H-RMN.



InNPs mediated allylation of *ortho*-isopropoxybenzaldehyde with crotyl bromide

As we have been doing, we performed a computational analysis using DFT[4] methods with the Gaussian09 program. The initial conformational analysis was performed using the semiempirical PM3 method, then we work with the B3LYP[5] functional, applying the LanL2DZ pseudopotential for the indium and the 6-31+G* basis set for all the other atoms and the solvent effect was evaluated with the PCM model. To simplify the reactive system and considering results reported by other authors, we evaluated the potential energy surfaces (PES) for the mentioned process by considering the formation of an initial complex between the carbonyl compound and the allyl-indium intermediate, a six-member cyclic chair-like transition state (TS) and a final complex, as can be seen in Scheme 1 for a representative compound. An auxiliary bromide atom was used as ligand for the indium atom to obtain a simplified neutral model system.[6]



Scheme 1. Representative structures applied in the computational analysis.

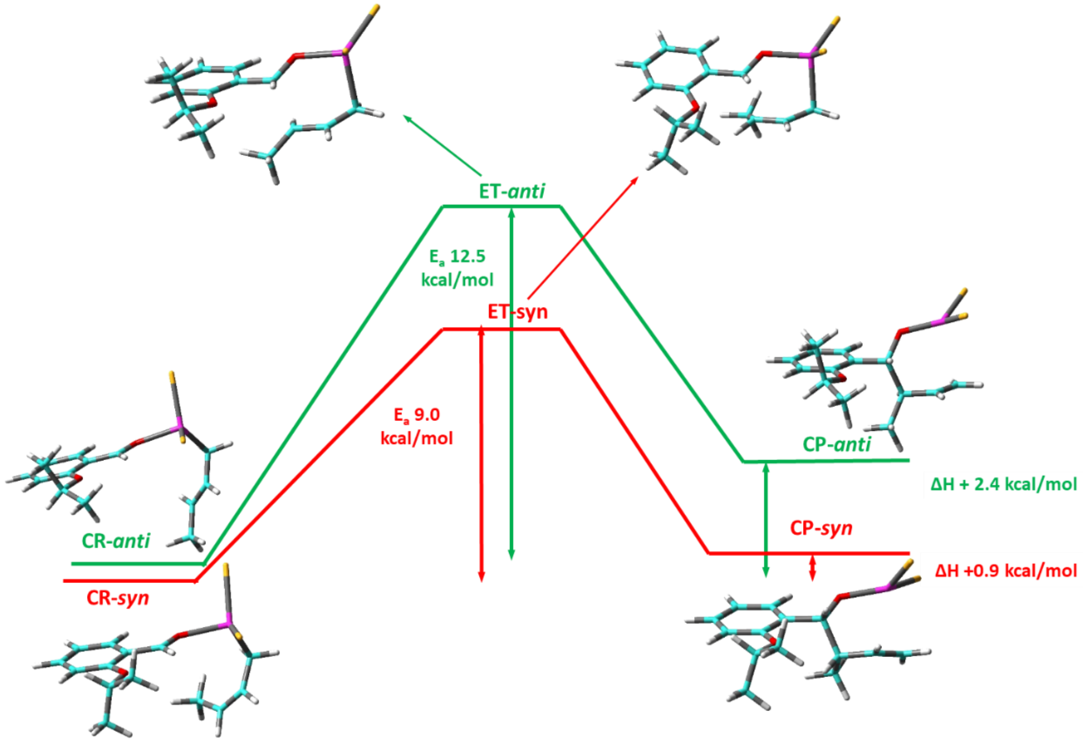


Figure 1. B3LYP/6-31+G*LanL2DZ(In)/PCM(THF) potential energy profiles (kcal/mol) for the formation of **CP-*syn*** (red line) and **CP-*anti*** (green line).

As we mentioned previously, for the crotylation of o-propoxybenzaldehyde, a mixture of diastereomer alcohols (**2**) were obtained, with a higher proportion of *syn* regarding to *anti* (75:25). The computational analysis was agreed with these results, being the Eas 9.0 and

12.5 kcal/mol respectively, besides, while both processes were endothermic, the first process was much less endothermic (+0.9 kcal/mol) than the second (+2.4 kcal/mol) (Figure 1). Then, we carry out a more specific conformational inspection of the diastereomers of the product, the homoallylic alcohol **2.** At first, we obtain a lot of initial conformers by changing three dihedral angles 1, 2 and 3 (Figure 2) at the same time, and we optimized them using the semiempirical PM3 method. Then we work with the B3LYP functional, applying the 6-31+G* basis set and we found thirteen low-energy conformations for the *syn*-diastereomer and six low-energy conformations for the *anti*-diastereomer, of which five *syn*-diastereomers (Figure 3) and two *anti*-diastereomers (Figure 4), would structurally match with the data that we obtained from the different NOE's experiments.

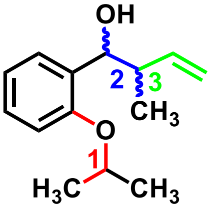


Figure 2. Homoallylic alcohol **2**

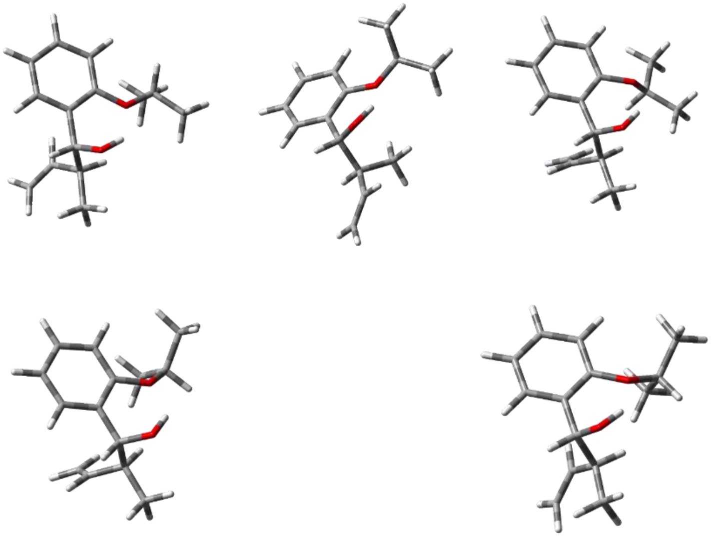


Figure 3. The five low-energy conformations for the *syn*-diastereomer of **2**

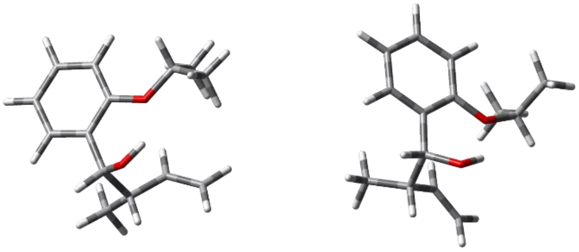


Figure 4. The two low-energy conformations for the *anti*-diastereomer of **2**

With regard to the NMR analysis, from the signal **A** of the ^{1}H-NMR of the mixture of diastereomers of **2**, we obtained the *syn*:*anti* relationship 75:25.

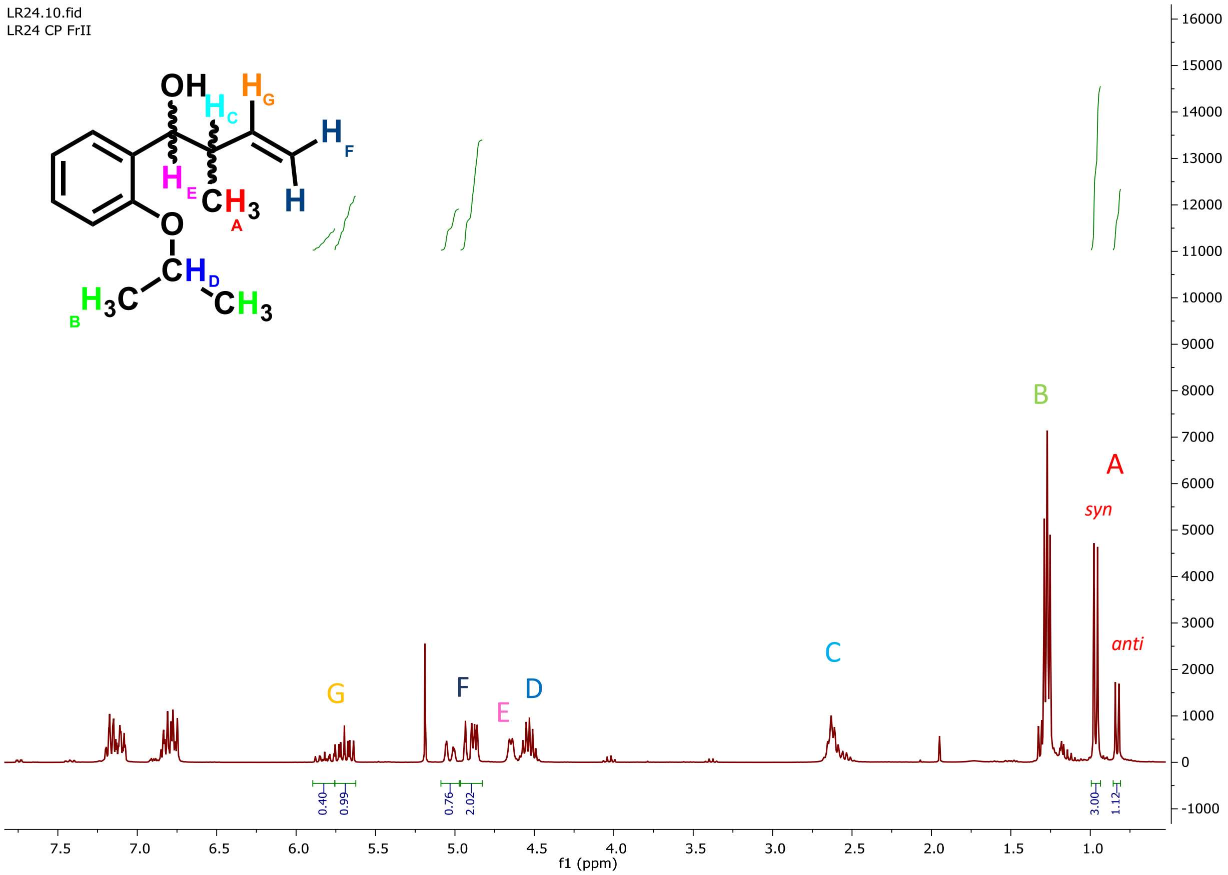


Figure 5. ^{1}H-NMR of diastereomers mixture of **2**

It is known that the coupling constant (*J*) values are extremely useful for the conformational analysis of organic compounds, since the homonuclear scalar couplings $^{3}J_{HH}$ values are directly related to the dihedral angles through the Karplus equation. Considering the *J*-based methodology reported by Riccio *et. al.*[7] applied to the determination of the relative configuration of two vicinal methines, we found intermediate values of $^{3}J_{H(E)H(C):}$ 6.7 Hz (*syn*-diastereomer) and 7.3 Hz (*anti*-diastereomer), these values are related to two possible orientations *gauche* or *anti* for H_E and H_C respectively. Likewise, the heteronuclear scalar couplings $^{2}J_{CH}$ values, are particularly useful when the carbon bears an electronegative substituent like an oxygen; in this case, this $^{2}J_{CH}$ value, can be related to the dihedral angle between the proton (H_C) and the oxygen (OH) bound to the carbon. We found large values of $^{2}J_{C(E)H(C):}$ 128.7 Hz (*syn*-diastereomer) and 124.5 Hz (*anti*-diastereomer), these values are related to a *gauche* orientation for H_E and OH respectively. That observations are in agreement to the structures found through the computational calculations (Figures 3 and 4).

Regarding to the nuclear Overhauser effect (NOE), from a series of selective NOE experiment, we could observe a series of NOE effect for the *syn*-diastereomer between H_E-H_G; H_C-H_F; H_A-H_E; H_C-H_A and for the *anti*-diastereomer between H_A-H_D; H_C-H_A. In the case of the syn isomer, these observations would be in agreement with two of the *syn*-conformers of Figure 3.

CONCLUSIONS

The *in situ* prepared InNPs have demonstrated to be efficient for the synthesis of a novel homoallylic alcohols. Both, the DFT and NMR methodologies applied, allowed us to study the *syn-anti* selectivity of the reaction, and have shown to be a successful approach for assignment of the diastereomers. We are currently performing computational NMR calculations of chemical shift using the GIAO method, in order to ensure the assignment of diastereomers.

Acknowledgements

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