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DFT Studies on the Allylation of Styrene Oxide Catalyzed by Indium Nanoparticles (InNPs) †

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Abstract: Allyl-indium species are known to smoothly react with electrophiles as epoxides. The intrinsic tension of these cyclic systems makes them very reactive starting materials, giving access to more complex products through regioselective ring-opening. In this work, indium nanoparticles (InNPs) have been prepared by fast reduction of indium(III) chloride with lithium sand and a catalytic amount of 4,4′-di-tert-butylbiphenyl. InNPs, were employed as catalysts for the ring-opening allylation reaction of styrene oxide with allyl or prenylbromide. All the possible reaction paths for the formation of the different alcohols were modeled applying DFT calculations, achieving good correlation between the experimental and computational results.

Keywords: indium nanoparticles; epoxides; allylation; DFT methods

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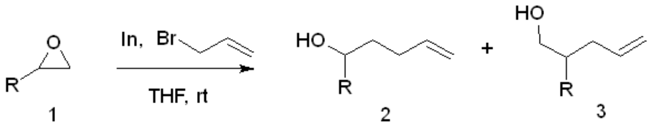
1. Introduction

Epoxides are extremely interesting electrophiles in terms of their properties and reactivity. They are part of many natural products as well as numerous compounds of biological importance. In organic synthesis, organometallic compounds provide a source of nucleophilic carbon centers that can react with electrophiles to form new carbon-carbon bonds. In particular, allyl-indium species react with various electrophiles, such as carbonyl compounds, to generate homoallylic alcohols [1]. Epoxides present great reactivity due to the intrinsic tension of the cyclic system and can react with organometallic compounds, giving rise to the formation of ring-opening products to give molecules larger and more complex. For this reason, the general aspects of epoxide synthesis and ring-opening reactions have been extensively reviewed [2].

The allylation of different epoxides with indium metal has been reported [3]. Yadav et al. [3a] described a novel and highly efficient protocol for the allylation of terminal epoxides using metallic indium and allyl bromide in THF, to obtain the corresponding bishomoallylic alcohols (Scheme 1).



Scheme 1. Regioselective allylation of epoxides with indium metal.

In our research group we have been working on the development of methodologies based on the use of metal nanoparticle catalysts (MNPs). The epoxidation of a variety of olefins has recently been reported with good to excellent yields and high selectivity using a new heterogeneous catalyst system composed of cobalt nanoparticles (CoNPs) supported on MgO with *tert*-butyl hydroperoxide (TBHP) as oxidant [4].

Based on the aforementioned, we studied the allylation reaction of styrene oxide, with different allyl bromides, catalyzed by InNPs under different reaction conditions. With the aim to explain the experimental observations, we performed a computationally study applying DFT methods with the Gaussian09 software [5]. Based on the experimental and computational results, we proposed a reaction mechanism for the allylation reaction of styrene oxide catalyzed by InNPs.

2. Methods

2.1. 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. All starting materials were of the best available grade (Aldrich, Merck) and were used without further purification. Preparative plate chromatography was performed with Macherey-Nagel silica gel P/UV254 with $CaSO_4$ for thin layer chromatography with fluorecense indicator. Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm).

2.2. Instrumentation and Analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as the solvent. Mass spectra (EI) were obtained at 70 eV on an Agilent 7890B gas chromatograph coupled with an Agilent 5977A mass selective detector (MSD) (Agilent, Santa Clara, CA, USA), equipped with HP-5MS capillary column (30 m × 0.25 mm inner diameter, 0.25 m film thickness).

2.3. Reaction between Styrene Oxide and Allyl Bromide Catalized by InNPs

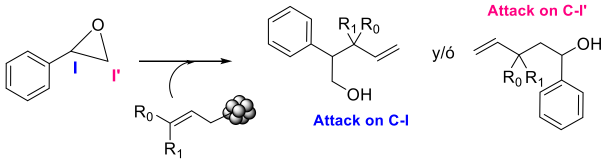
The InNPs catalyst was prepared following the procedure previously reported in our group [1]. On 0.66 mmol of InNPs generated in-situ, 1 mmol of allyl bromide dissolved in 1 mL of ACN was added. For the Grignard-type reaction, the solution was allowed to react for 1 h with continuous stirring. After this time, 0.33 mmol of styrene oxide dissolved in 1 mL of ACN were added and the reaction was heated under ACN reflux for 48 h. At this time the reaction was finished by adding 2 mL of 1M HCl and was elaborated by multiple extraction with dichloromethane. The organic phase was dried over anhydrous $MgSO_4$, filtered and analyzed by GC-MS. For the Barbier-type reaction, once the InNPs have been generated, the allyl bromide and styrene oxide were added at the same time. In both cases, other conditions were analyzed, we worked at THF reflux and with ACN and THF at room temperature.

2.4. Computational Procedure

The conformational analysis for the structures was performed with the functional PM6. The geometries of the most stable structures were refined with the B3LYP functional and the LANL2DZ pseudopotential [6]. The characterization of the stationary points was verified with a complete optimization of the minima (or transition states) by the absence of (or the presence of a single) negative frequencies. The figures were built by using the Avogadro software [8].

3. Results and Discussion

Based on a scientific work published in our research group [1], we have carried out a study of the reaction and the mechanism of the allylation of styrene oxide catalyzed by InNPs with allyl and prenyl bromide. According to bibliographical references, it is assumed the formation of allyl-In species [9], which react with the epoxide to give the corresponding alcohols. This epoxide allowed us to carry out a regiochemical study of the process, since the nucleophilic attack can occur on the carbon atom attached to the aromatic ring (C-I) or on the less substituted carbon atom (C-I′) (Scheme 2).



Scheme 2. nucleophilic attack on the epoxide.

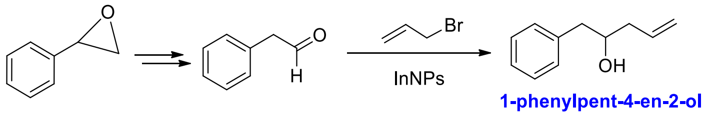
3.1. Experimental Study

3.1.1. Grignard-Type Reaction between Styrene Oxide and Allyl Bromide Catalyzed by InNPs

Then 48 h, the reaction performed in THF at room temperature showed the formation of the by-products: 2-chloro-1-phenylethanol and 1-phenylethane-1,2-diol, in a ratio: 45–55%, respectively. The reaction in ACN at room temperature showed the same by-products, in a ratio: 30–70%, respectively. The first could arise from the opening of the epoxide after attack by the chloride ion (from lithium chloride) and the second, would be generated after the attack by the hydroxyl ion (from lithium hydroxide). These by-products would indicate that the allylation was not favored under these reaction conditions [10].

In view of the aforementioned results, to favoring the allylation reaction, we carried out the same reactions at the reflux of THF and ACN. At the end of these reactions, an allyl alcohol was observed as the only product. It is worth mentioning that, then 5 h of reaction, phenylacetaldehyde was observed by CG-EM.

Yadav et al. [3a], informed an erroneous assignment in the ^{1}H-NMR spectrum of the aforementioned alcohol, which according to the authors would be 1-phenylpent-4-en-1-ol, came from the allyl attack on the carbon atom C-I′ (Scheme 2). Hirashita et al. [9] reviewed the Yadav et al. published results, finding doubtful the signal assignment at 2.75 ppm, and re-assigned it as the benzyl protons of the 1-phenylpent-4-en-2-ol, this alcohol came from to the direct allylation of phenylacetaldehyde. Phenylacetaldehyde is quickly formed (we detected it in both reactions) as a consequence of the benzylic C-O bond opening of the epoxide under the reaction conditions, and gives rise to the formation of the aforementioned homoallylic alcohol after carbonyl allylation [1] (Scheme 3).



Scheme 3. opening of the epoxide and allylation of phenylacetaldehyde with allyl bromide.

Taking into account that in their works, Ranú [10] and Hirashita [9] suggested that the allyl-indium species formed under the reaction conditions would have Lewis acid characteristics, favoring the formation of the aldehyde from the epoxide, it was considered to reduce the ratio of the allylating species in the reaction. We were using an allyl bromide:InCl3:epoxide ratio of 1.5:1:0.33 (mmol), and so we ran a reaction with an allyl bromide:InCl3:epoxide ratio of 1:0.66: 0.33 (mmol), at reflux of ACN, which gave as the only product 1-phenylpent-4-en-2-ol, the homoallylic alcohol from the allylation of phenylacetaldehyde.

As a new experimental approach and based on the work published by Oh et al. [3b], we decided to change the order of the addition of the reagents, and work under Barbier conditions.

3.1.2. Barbier-Type Reaction between Styrene Oxide and Allyl Bromide Catalyzed by InNPs

We carried out the reaction at reflux of ACN and after 48 h, the homoallylic alcohol 1-phenylpent-4-en-2-ol was the only reaction product.

3.1.3. Grignard-Type Reaction between Styrene Oxide and Prenyl Bromide Catalyzed by InNPs

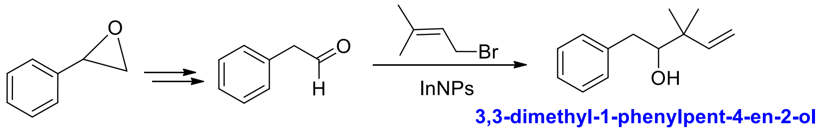
Oh et al. [3b] carried out a selectivity study as a function of the allyl bromide employed as allylating specie and vinyl epoxide, achieving the highest selectivity towards the expected alcohol, when using prenyl bromide. Based on that, we consider this new experimental approach since it is known that prenyl bromide is less reactive than the allyl bromide towards carbonyl allylations [1].

Under reflux of ACN, after 48 h, the reaction did not give the expected alcohols, but two products were observed, 2-chloro-1-phenylethanol (80%) and an oxidized allylic by-product.

3.1.4. Barbier-Type Reaction between Styrene Oxide and Prenyl Bromide Catalyzed by InNPs

When we carried out the reaction under reflux of THF, after 24 h, the starting epoxide was recovered. At reflux of ACN, after 22 h, phenylacetaldehyde was detected, and at finished it, after 48 h, 2-chloro-1-phenylethanol and 3,3-dimethyl-1-phenylpent-4-en-2-ol, the homoallylic alcohol from the carbonyl prenylation (Scheme 4), were the main products observed (90 and 10% respectively).

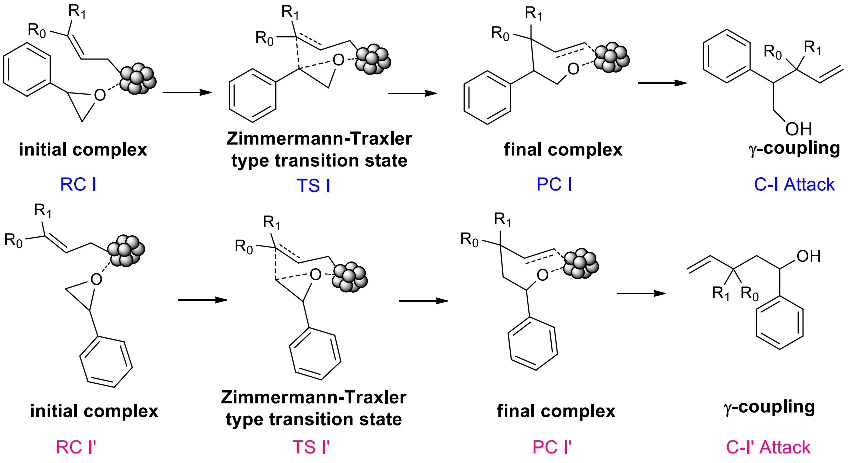
We worked in ACN at 50 °C, and although in this case, no formation of the phenylacetaldehyde was observed, 2-chloro-1-phenylethanol was the main product obtained.



Scheme 4. opening of the epoxide and allylation of phenylacetaldehyde with prenyl bromide.

3.2. Computational Study

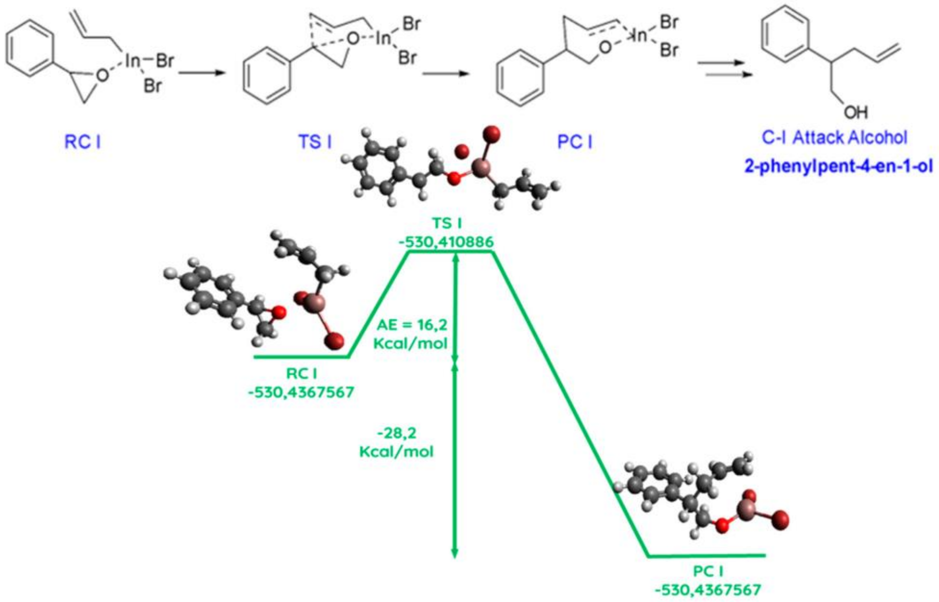
To start with computational modeling studies, following the proposed mechanism for the allylation of carbonyls compounds published by our research group [1], as can be seen from Scheme 5, we considered that at first, the epoxide is adsorbed on the surface of the InNPs of the allyl-In specie, to give the initial complex (reactive complex—RC). Then, a cyclic Zimmerman-Traxler type transition state (TS) is formed, and the π electrons of the allylic system, attack one of the carbon atoms of the epoxide, giving rise to a new C-C bond through a γ-coupling. By the adding of diluted HCl, the double bond of the alkene is regenerated, giving rise to the final product (product complex—PC). Since the epoxide is not symmetric, we can obtain two alcohols from the allylic attack on each of the carbon atoms (C-I and C-I’) of the oxo-cyclic system.



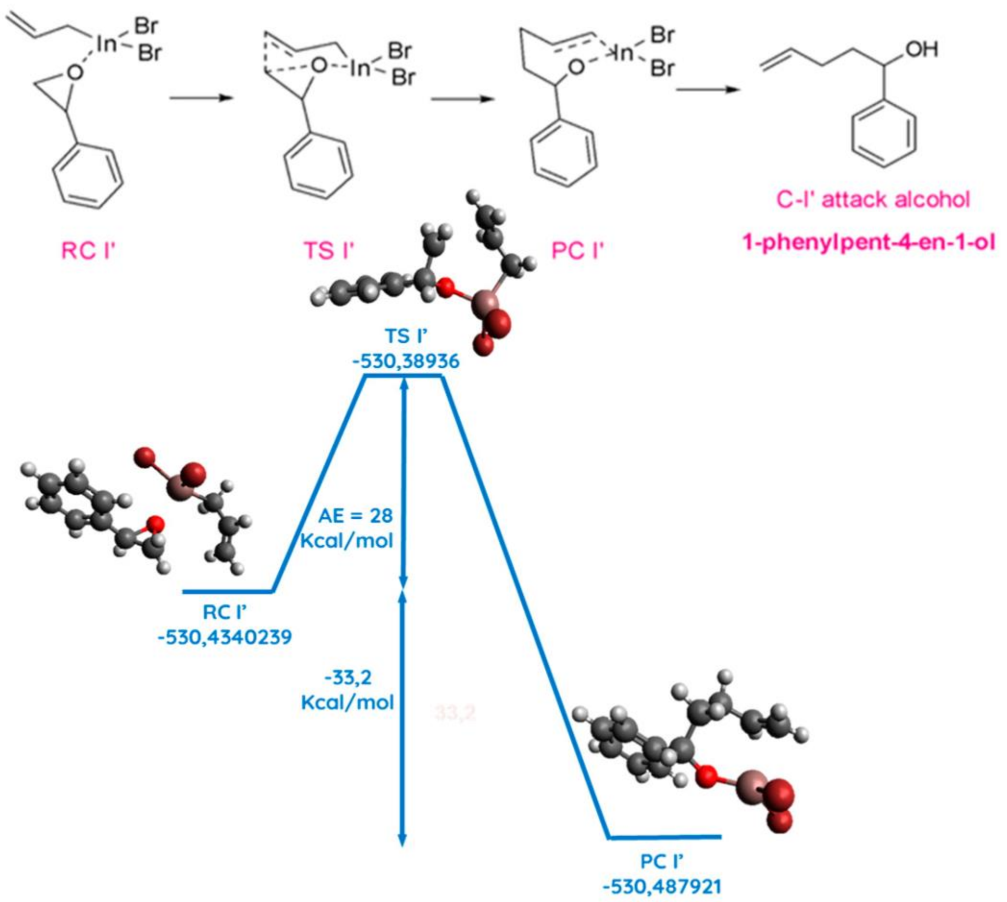
Scheme 5. mechanism of formation of both alcohols.

We report below the theoretical results obtained from computational calculations, for the direct allylation on each carbon atom at the oxo-cyclic structure of styrene oxide, C-I (Scheme 6) and C-I′ (Scheme 7). To simplify the reactive allylic species, an auxiliary bromide atom was used, as a ligand, to obtain a neutral allylic-indium specie.

As can be seen in Schemes 6 and 7, from a thermochemical point of view the formation of both alcohols would be feasible, since they are exothermic processes (28.2 and 33.2 kcal/mol, respectively). However, if we perform a kinetic analysis, the formation of both products would be ruled out, due to the high activation barriers, 28 kcal/mol for 1-phenylpent-4-en-1-ol and 16.2 kcal/mol for 2-phenylpent-4-en-1-ol.



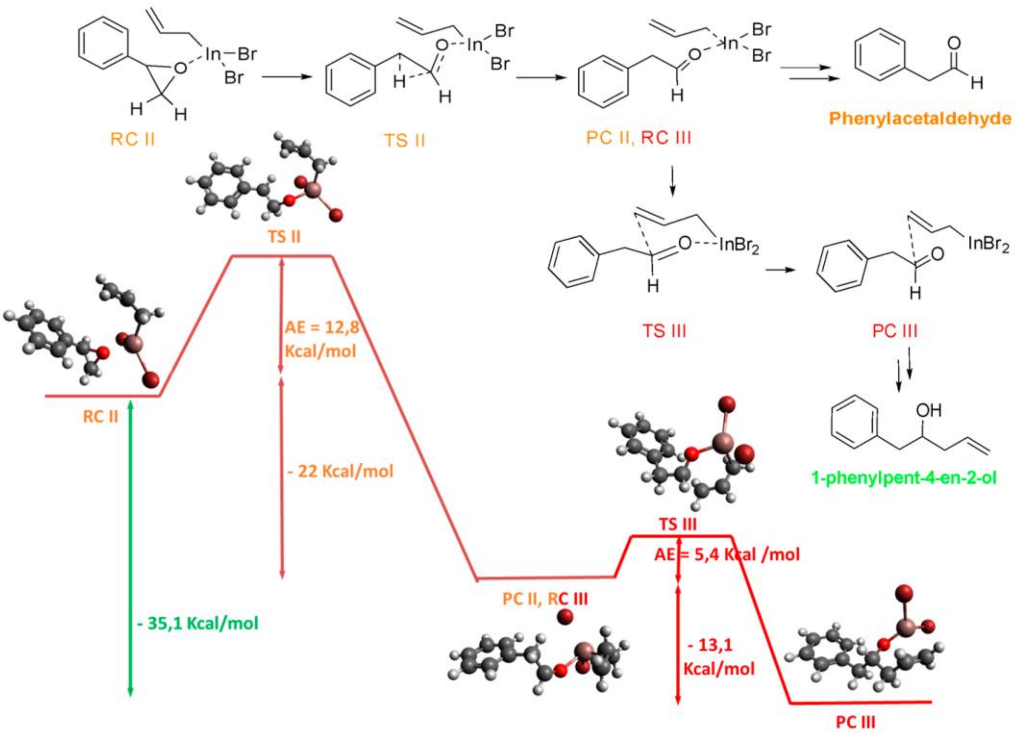
Scheme 6. Representative structures (**top**) and Potential Energy Profile (kcal/mol) at B3LYP/LanL2DZ level for the formation of 2-phenylpent-4-en-1-ol (**bottom**).



Scheme 7. Representative structures (**top**) and Potential Energy Profile (kcal/mol) at B3LYP/LanL2DZ level for the formation of 1-phenylpent-4-en-1-ol (**bottom**).

On the other hand, as can be seen from Scheme 8, based on the experimental observations, we computationally modeled the formation of phenylacetaldehyde and its subsequent allylation. The oxo-cyclic opening promoted by the allyl-indium species, to give the aldehyde, required 12.8 kcal/mol, a lower barrier than those discussed above. Furthermore, the formation of phenylacetaldehyde, was thermodynamically highly favored, since 22 kcal/mol ware released in the process. InNPS-catalyzed carbonyl allylation, is a chemically and energetically very favorable process, demonstrated by the low activation barrier (5.4 kcal/mol) and the observed exothermicity (−13.1 kcal/mol).

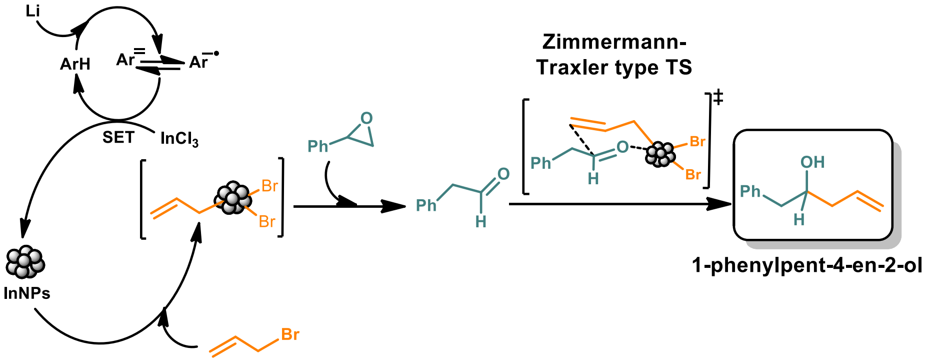
From these results, we can say that the calculation methodology used was a good approximation for these processes, since it would allow us, both kinetic and thermodynamic point of view, to show that the epoxide prefer to give rise to phenylacetaldehyde, and this aldehyde would be very easily allylated, in agreement with the experimental results.



Scheme 8. Representative structures (**top**) and Potential Energy Profile (kcal/mol) at B3LYP/LanL2DZ level for the formation of phenylacetaldehyde and its allylation reaction to give 1-phenylpent-4-en-2-ol (**bottom**).

3.3. Proposed Mechanism

Based on the stoichiometry of the reaction, the experimental observations, and DFT studies, we propose a plausible reaction mechanism for the studied transformation. As can be seen from Scheme 9, the InNPs would be getted from the indium salt by the action of the reducing system, then, the addition of allyl bromide could lead to the formation of an allyl-indium intermediate, which by reaction with the epoxide would give the phenylacetaldehyde. This activated carbonyl compound could give rise to the corresponding homoallylic alcohol through a Zimmerman-Traxler type transition state.



Scheme 9. Proposed reaction mechanism for the reaction between styrene oxide and allyl bromide catalized by InNPs.

4. Conclusions

In(0) nanoparticles have been evaluated as catalysts for the allylation of styrene oxide with allyl and prenyl bromide at different reaction conditions. In most of the reactions, we observed the formation of phenylacetaldehyde by the opening of the benzylic C-O bond of the epoxide. The allylation of this aldehyde would give rise to 1-phenylpent-4-en-

2-ol, as the final product of the reaction. Through a theoretical study with DFT methods, we modeled the complete process, achieving a very good agreement between the experimental and computational results. Besides, we have proposed a possible reaction mechanism that would explain the oxo-cyclic opening to give the aldehyde, as well the allylation of the phenylacetaldehyde to give rise the homollylic alcohol under the studied reaction conditions.

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Conflicts of Interest: The authors declare no conflict of interest.

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