Reactivity and selectivity of the InNPs mediated allylation of carbonyl compounds: a DFT study.

Leandro Fortunato, Lucía Rossi, Gabriel Radivoy and Viviana Dorn*

Instituto de Química del Sur (INQUISUR-CONICET), Depto. de Química, Universidad Nacional del Sur, Av. Alem 1253, B8000CPB Bahía Blanca, Argentina.

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Introduction

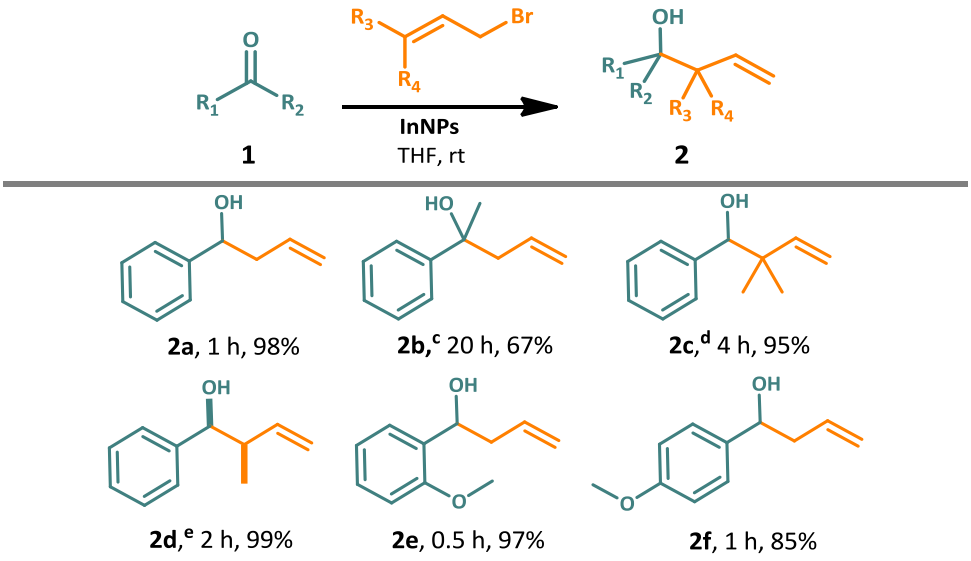
Metal-mediated allylation of carbonyl compounds with allyl bromides is an interesting and convenient method to form C-C bond and to obtain homoallylic alcohols, which are significant building blocks in organic synthesis. Besides the reactivity, the diastereoselectivity in the addition of an allyl-metal 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, in our group, we have synthesized indium nanoparticles (InNPs) of 4.0 ± 0.5 nm, 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. The catalytic efficiency of these InNPs was evaluated by the allylation reaction of carbonyl compounds, giving excellent yields of the corresponding homoallylic alcohols. 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.[2] In order to extend the scope of this indium-mediated allylating methodology, we employ different *ortho*-substituted carbonyl compounds and crotyl bromide as allylating agent to study their effect over the diastereoselectivity in this C-C bond formation. Additionally, and in order to give an explanation to the reactivity and the *syn-anti* selectivity observed from the experimental results, computational studies have been applied by the Gaussian09 program.

Results and Discussion

As it was mentioned, the InNPs were in situ generated and we choose benzaldehyde as model substrate to optimize the stoichiometry and reaction time for the allylation reaction. The best results were obtained by using $InCl_3$ (1.0 mmol) with an excess of lithium sand (3.5 mmol) in the presence of DTBB (0.1 mmol) as electron carrier, THF (2 mL) as the solvent, with allyl bromide (1.5 mmol dissolved in 1 ml THF) and benzaldehyde (0.5 mmol dissolved in 1 ml THF) at room temperature and under a nitrogen atmosphere obtaining the alcohol homoallylic 1-phenylbut-3-en-1-ol (**2a**) in 98% yield. Under the optimized conditions, the allylation of acetophenone led to 2-phenylpent-4-en-2-ol (**2b**) in 67% yield after 20 h. Besides, we investigated the allylation reaction of benzaldehyde by using different allylating agents, thus, crotylation of benzaldehyde gave 1-phenyl-2-methylbut-3-en-1-ol (**2d**) almost quantitatively after 2 h. The diasterereoselectivity observed for this reaction (67:33 *syn/anti*) was slightly

better than that previously reported by other authors for bulk indium mediated crotylations,[3] being the *syn*-isomer dominant. Prenyl bromide showed to be less reactive, so it was necessary to stirr the InNPs suspension with the prenyl bromide for 60 min prior to the addition of benzaldehyde. Thus, after 4 h reaction time, the γ-adduct 1-phenyl-2,2-dimethylbut-3-en-1-ol (**2c**) was obtained in 95% yield. The less reactivity observed could be attributed to the steric hindrance caused by methyl substituents attached to the allyl moiety, which could affect the formation of the homoallylic alcohol.

Table 1. InNPs mediated allylation of carbonyl compounds.[a,b]



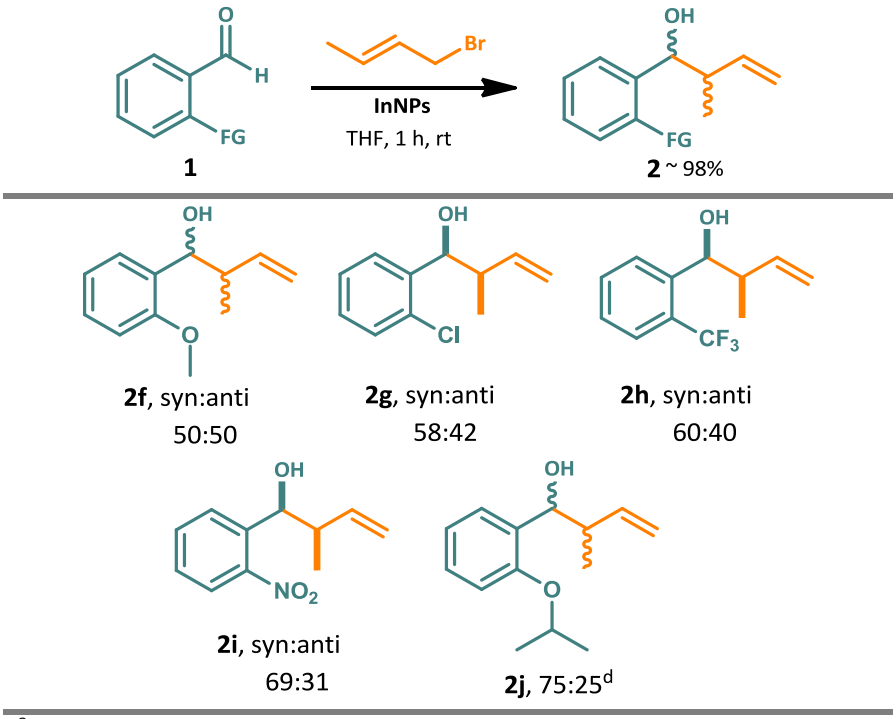
[a] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), $InCl_3$ (1.0 mmol) in THF (2 mL), allyl bromide (1.5 mmol) in THF (1 mL), stirred for 30 min, carbonyl compound (0.5 mmol) in THF (1 ml), at 25 ºC. [b] Quantified by GC analysis using internal standard method. [c] Together with unreacted carbonyl compound. [d] Reaction performed by stirring the allyl bromide for 60 min. [e] *syn*:*anti,* 67:33 determined by ^{1}H NMR.

Besides we evaluated the effect of the substituted-position on the reactivity, thus, *ortho*- and *para*-methoxy benzaldehyde gave the corresponding alcohols in excellent to good yields. Thus, *o*-methoxy- gave 1-(2-methoxyphenyl)-3-buten-1-ol (**2e**) (97%, 30 min) and *p*-methoxy- gave 1-(4-methoxyphenyl)-3-buten-1-ol (**2f**) in 85% yield after 1 h reaction time. All these results are shown in Table 1.

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. (Table 2). Thus, *o*-methoxy- and *o*-chlorobenzaldehyde gave 1-(2-methoxyphenyl)-2-methyl-3-buten-1-ol (**2f**) (syn:anti 50:50) and 1-(2-chlorophenyl)-2-methyl-3-buten-1-ol (**2g**) (syn:anti 58:42), respectively. Also, *ortho*-benzaldehydes bearing strongly electron-withdrawing groups such as

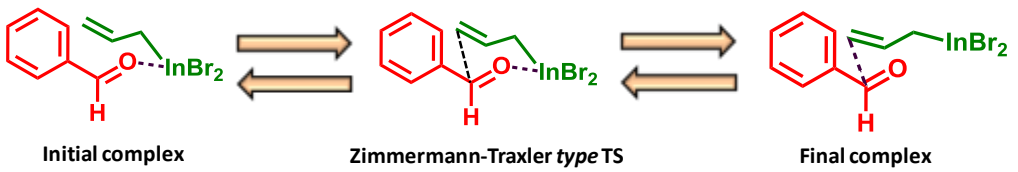
trifluoromethyl or nitro, gave the corresponding 1-(2-(trifluoromethyl)phenyl)-2-methyl-3-buten-1-ol (**2h**) and 1-(2-nitrophenyl)-2-methyl-3-buten-1-ol (**2i**) with a *syn:anti* relation of 60:40 and 69:31, respectively. It should be mentioned that *ortho*-propoxybenzaldehyde yield the expected homoallylic alcohol with a 75:25 diastereoselectivity determined by ^{1}H-RMN. While we suppose that the *syn*-diastereomer would be the major product, this could not be determined yet.

Table 2. InNPs mediated allylation of *ortho*-substituted benzaldehydes with crotyl bromide.[a,b,c]



[a] Reaction conditions: Li (3.5 mmol), DTBB (0.1 mmol), $InCl_3$ (1.0 mmol) in THF (2 mL), crotyl bromide (1.5 mmol) in THF (1 mL), stirred for 30 min, carbonyl compound (0.5 mmol) in THF (1 ml), at 25 ºC, 1 h reaction time. [b] Quantified by GC analysis using internal standard method. [c] *Syn*:*anti* relation determined by ^{1}H NMR. [d] Stereoisomers undefined yet.

With the aim to explain and understand these experimental results, we performed a computational analysis using DFT[4] methods with the Gaussian09 program.[5] The initial conformational analysis was performed using the semiempirical PM3 method, then we work with the B3LYP[6] 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 **2a** as representative compound. An auxiliary bromide atom was used as ligand for the indium atom to obtain a simplified neutral model system.[7]



Scheme 1. Representative structures for **2a** utilized in the computational analysis.

Regarding the reactivity, as already mentioned above, the allylation of benzaldehyde with allyl bromide gave 98% of **2a** after 1 h reaction time, while the allylation of acetophenone, after 20 h, gave **2b** in 67% yield. The computational modeling showed a very good agreement with the experimental results, thus, the activation energy (Ea) for the first process (exothermic in 3.4 kcal/mol) was 6.9 kcal/mol, while the Ea for the allylation of acetophenone was 10.2 kcal/mol, being an endothermic process (+0.94 kcal/mol) (Figure 1).

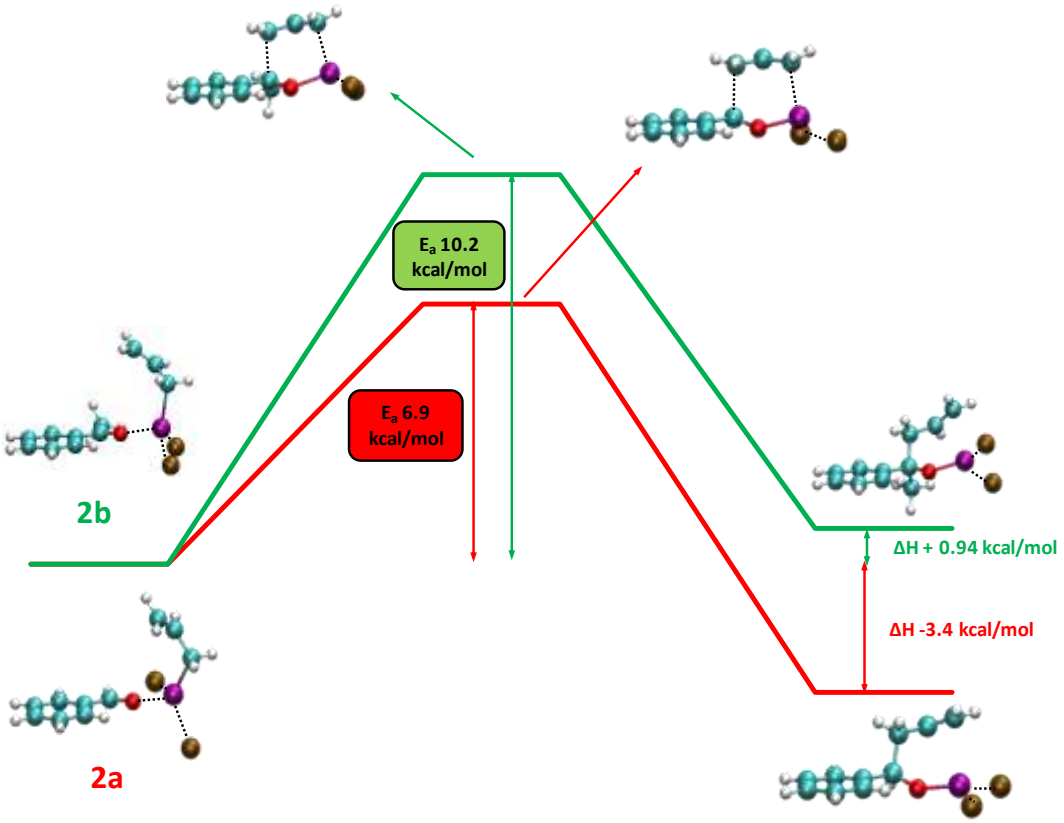


Figure 1. B3LYP/6-31+G*LanL2DZ(In)/PCM(THF) potential energy profiles (kcal/mol) for the formation of **2a** (red line) and **2b** (green line).

On another hand, reactivity of the allyl- and prenyl bromides was very different, both giving the corresponding homoallylic alcohol in excellent yields (98 and 95%) but the allylation with prenyl bromide being notably slower, 1h *vs* 4 h reaction time respectively. As shown in Figure 2 the formation of the final complex of **2c** takes place with higher Ea that **2a** (11.4 and 6.9 kcal/mol, respectively). In addition, for **2a** the process occurs exothermically (-3.4 Kcal/mol), while for **2c** the corresponding final complex requires +3.6 kcal/mol. These energetic

observations would correspond to steric hindrance by methyl group of prenyl bromide in **2c** and could explain the difference found in the reactivity with **2a**.

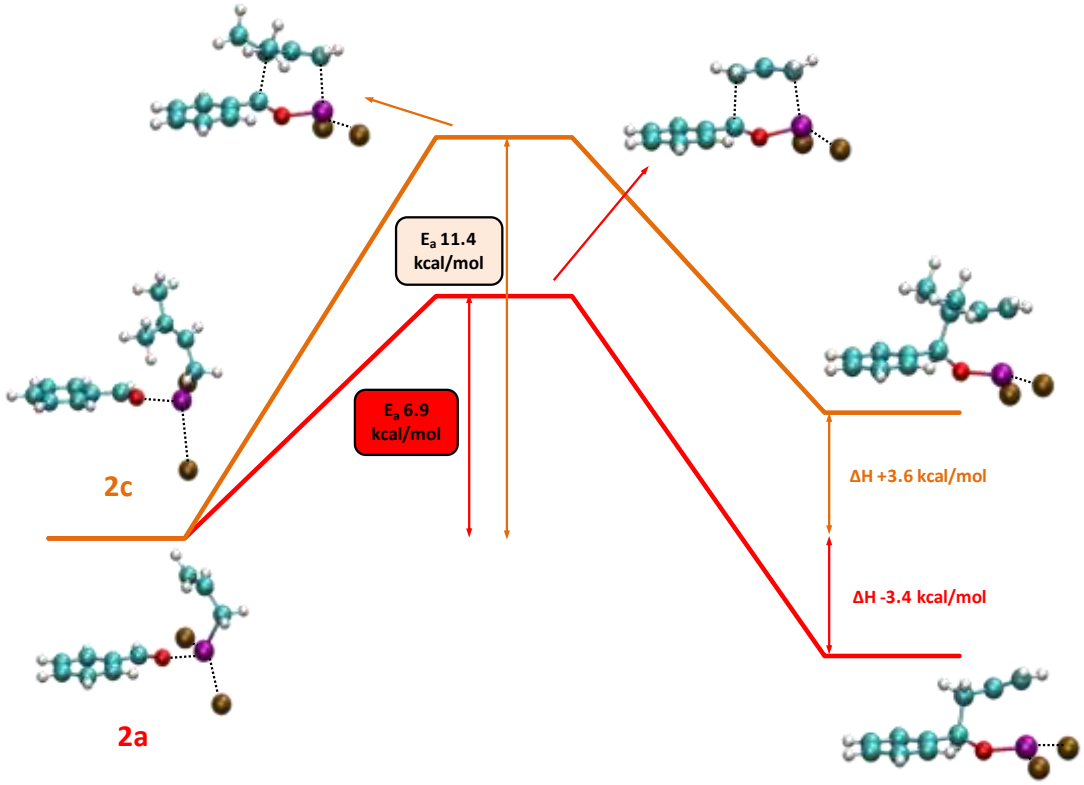


Figure 2. B3LYP/6-31+G*LanL2DZ(In)/PCM(THF) potential energy profiles (kcal/mol) for the formation of **2a** (red line) and **2c** (orange line).

Besides, the allylation of *ortho*-methoxy benzaldehyde showed to be faster than *para*-methoxy benzaldehyde, and we found that the Eas for **2e** and **2f** were 8.5 and 9.6 kcal/mol respectively, moreover, the first process was exothermic while the second was slightly endothermic (-1.7 *vs* +0.3 kcal/mol respectively).

Relative the selectivity, when we employed crotyl bromide as allylating agent and benzaldehyde, a mixture of diastereomer alcohols (**2d**) were obtained, with a higher proportion of *syn* regarding to *anti* (67:33). The computational analysis was agreed with these results, being the Eas 8.0 and 9.6 kcal/mol respectively (Figure 3).

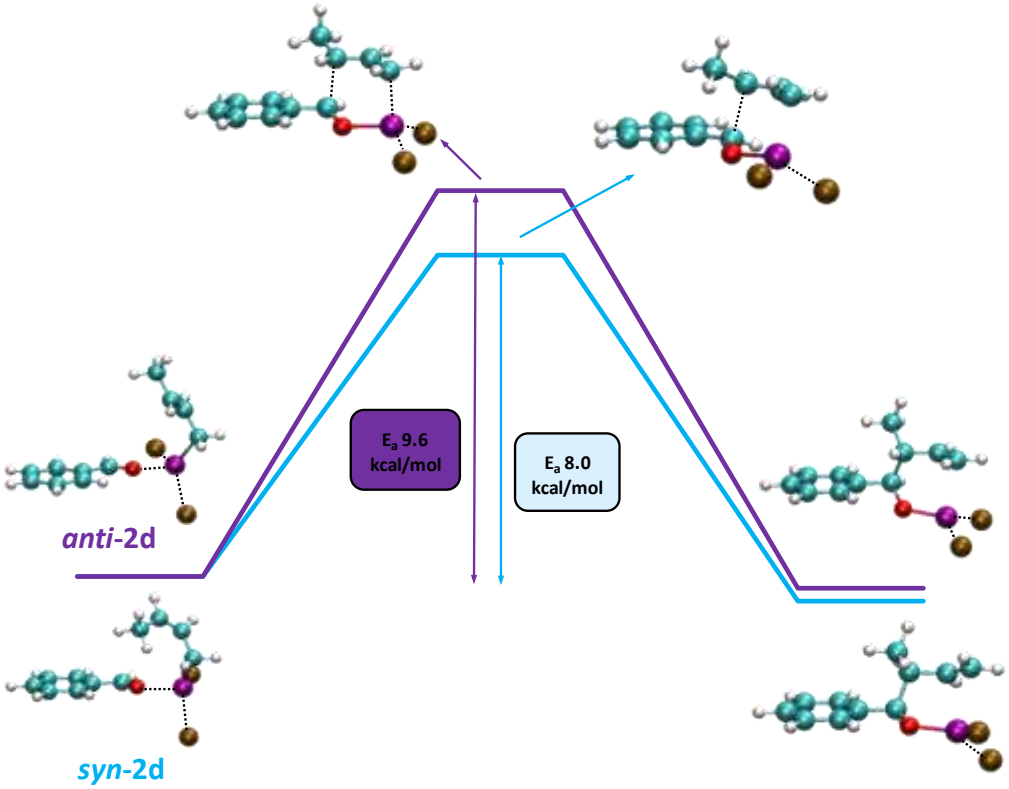


Figure 3. B3LYP/6-31+G*LanL2DZ(In)/PCM(THF) potential energy profiles (kcal/mol) for the formation of *syn*- (light blue line) and *anti*- (violet line) **2d** diastereomers.

Besides, we studied the *syn:anti* selectivity for the crotylation of *ortho*-substituted benzaldehydes, thus, for *ortho*-OMe derivative (**2f**) a obtained relation *syn:anti* of 50:50, and the computational modeling showed very similar Eas, 12 and 11 kcal/mol respectively, while the process were endothermic (+3.5 *vs* +1.5 kcal/mol respectively). *Ortho*-Cl derivative (**2g**) showed a *syn:anti* diastereoisomers relation of 58:42, and the computational modeling indicates that 8.1 kcal/mol are required to give the *anti* diastereomer while only 5.7 kcal/mol for the *syn* product; moreover, the *anti*-process is less exothermic than the *syn*-process (-2.7 *vs* -4.0 kcal/mol respectively). For *ortho*-CF_3 derivative (**2h**) the relation *syn:anti* was 60:40, and the computational modeling was agreed with these results, being the Eas 5.7 and 8.0 kcal/mol respectively, while the process were both exothermic (-4.3 and -4.0 kcal/mol respectively). *Ortho*-NO_2 derivative (**2i**) showed a *syn:anti* diastereoisomers relation of 69:31, in agreed with the computational results, that indicates that 4.8 kcal/mol are required to give the *anti* diastereomer while only 2.6 kcal/mol for the *syn* product, and the process were exothermic (-7.7 (*syn*) *vs* -7.5 (*anti*) kcal/mol). On another hand, as can be seen from Figure 4, the TS geometries of the *syn-anti* diastereomers of **2f** and **2i** derivatives showed remarkable interactions, thus, an stabilizing interaction between the *H*-C atom and *O*-Me atom for the *anti*-**2f** could increased the proportion of this diastereomer in the mixture (50:50). Moreover, a destabilizing interaction between the *O*=C atom and *O*-NO atom was observed for the *anti*-**2i**, that could reduced the proportion of this diastereomer in the mixture (69:31).

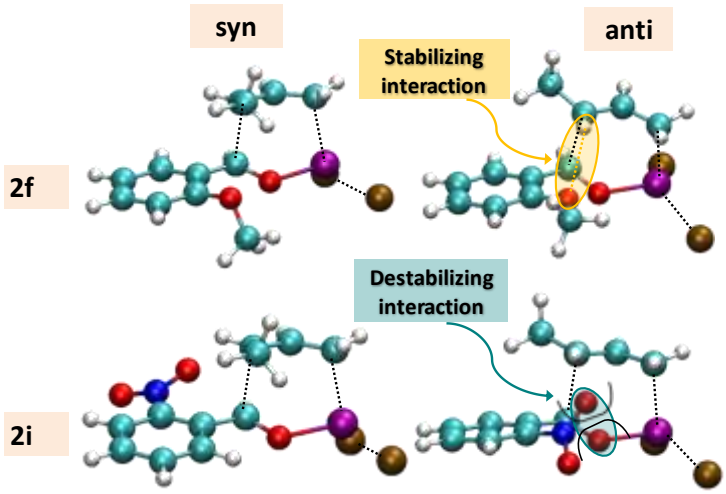
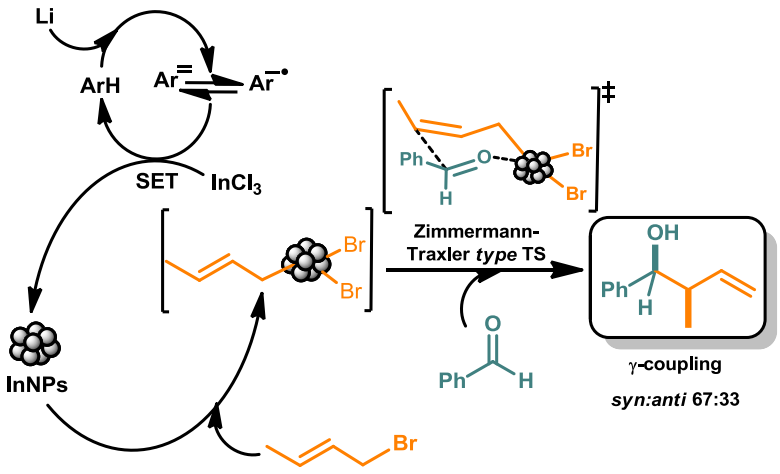


Figure 4. B3LYP/6-31+G*LanL2DZ(In)/PCM(THF) *syn-anti* TS geometries for **2f** and **2i**.

With the aim to extent the scope of the diastereolectivity for the InNPs-mediated crotylations, we synthesized *ortho*-propoxy benzaldehyde and obtained a diastereoisomeric relation of **2j** 75:25 (by ^{1}H-RMN), but we could not distinguish each other yet. We are now making additional RMN experiments and computational calculations to elucidate the major diastereomer in the mixture.

Although the exact mechanistic pathway is difficult to ascertain, based on the stoichiometry of the reaction, our experimental observations and DFT studies, we propose a plausible reaction pathway for the studied transformation. As can be seen from Scheme 2, the first step in the reaction would be the formation of InNPs by electron transfer (SET) from the arene radical anion to the indium salt. The addition of the allyl bromide to the InNPs suspension, could led to the formation of an allyl indium(III) intermediate, which by reaction with the activated carbonyl compound (probably adsorbed to the InNPs surface) could led to the corresponding γ-coupling homoallylic alcohol through a Zimmerman-Traxler *type* transition state.



Scheme 2. Proposed reaction pathway for the InNPs-mediated allylation of carbonyl compounds.

Conclusion

The *in situ* prepared InNPs have demonstrated to be efficient for the synthesis of homoallylic alcohols almost quantitatively and at shorter reaction times. Besides the methodology allowed us to study experimentally the *syn-anti* selectivity of the reaction and DFT calculations have shown to be a successful approach for studying the allylindium intermediates as well as to explain the experimental results. 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.

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References

[1] Hirashita,T., Kamei, T., Satake, M., Horie, T., Shimizu, H., Araki, S. *Org. Biomol. Chem.* **2003**, *1*, 3799-3803.

[2] Dorn, V., Chopa. A., Radivoy, G. *RSC Advances*, **2016**, *6*, 23798-23803.

[3] Haddad, T. D., Hirayama, L. C., Singaram, B. *J. Org. Chem.,* **2010**, *75*, 642.

[4] Kohn, W.; Sham, I. J. *Phys. Rev.* **1965**, *140*, A1133–A1138.

[5] Gaussian 09, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.

[6] a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789; b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100; c) Miehlich, E.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.

[7] a) Bowyer, W. J.; Singaram, B.; Sessler, A. M. *Tetrahedron,* **2011**, *67*, 7449 and references therein; b) Dam, J. H.; Fristrup, P.; Madsen, R. *J. Org. Chem.,* **2008**, *73*, 3228.