

Communication

Indium-Catalyzed Cycloisomerization of 1,6-Cyclohexenylalkynes

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Abstract: Efficient four- and five-step routes to access functionalized bicyclo[3.2.1]oct-2-ene and bicyclo[3.3.1]nonadiene via indium-mediated cycloisomerization of 1,6-enynes has been developed. This atom-economical catalytic process was optimized and relied on the efficiency of InCl_3 leading to the preparation of functionalized bicyclic adducts in up to 99% isolated yield. The cyclization occurred on two different processes (5-*exo* versus 6-*endo* pathway) and were influenced by the substitution of the alkynyl moiety. The *exo* process was favored for non-substituted alkynes whereas the *endo* pathway was generally observed for substituted alkynes. Then, the presence of electron-withdrawing groups on the aryl substituted alkyne increased the ratio of the *exo* isomer. DFT calculations were performed on stability of intermediates and corroborated the intervention of InCl_3 .

Keywords: indium; cycloisomerization reaction; 1,6-enyne; catalysis; atom economy



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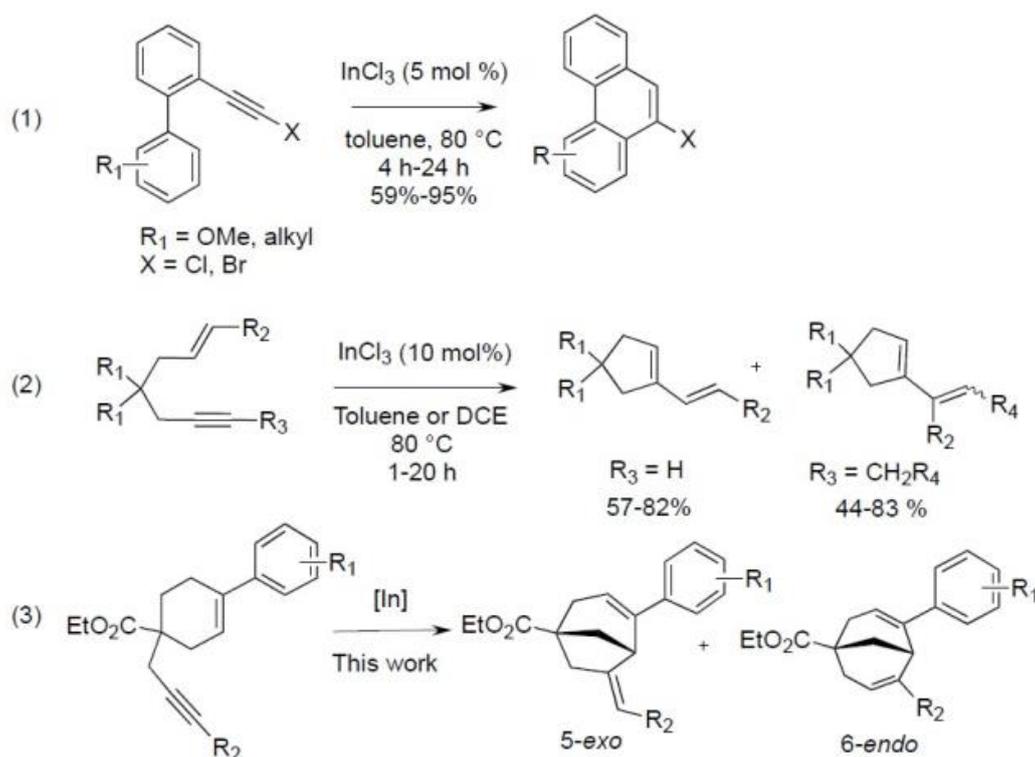


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1. Introduction

Indium was discovered in 1863 by Reich and Richter of the Freiberg School of Mines in Germany [1]. It is a fairly rare metal, its presence in the earth's crust is estimated at about 0.05 parts per million. Indium comes mainly from by-products of zinc mining (95%), and to a lesser extent, from tin, lead and copper ores. Used from the 1950s in the preparation of semiconductors, it is then used in the form of indium phosphite in the development of light-emitting diodes (LEDs). In the 21st century, its application in the form of indium oxide in high-tech industries such as liquid crystal displays (LCDs) has led to a sustained growth in world demand for indium. Its use in organic synthesis in the form of salts (halides or acid derivatives) has been growing for three decades and the pronounced Lewis acid character of indium has pushed organic chemists to study its reactivity with an additional financial interest since its price is attractive compared to other noble salts [2–6]. The first examples of indium-catalyzed intramolecular hydroarylation reactions of alkynes were reported by Fürstner's group from *o*-alkyne biaryl derivatives leading to halophenanthrene derivatives in yields ranging from 59% to 95% (Scheme 1, (1)) [7]. Chatani's group studied in 2006 the rearrangement of 1,6-enynes in the presence of indium trichloride as catalyst leading to the formation of 1-vinylcyclo-alkene derivatives (1,3-diene) or 1-allylcyclo-alkene derivatives (diene-1,4) depending on the substitution of the alkyne (Scheme 1, (2)) [8]. These pioneered works were followed by other studies such as the one from Gandon's team on the intramolecular hydroarylation cyclization reactions of ω -alkynyl-arenes derivatives [9] and from Corey's group on the cascade synthesis of complex polycyclic molecules from the polyenyne derivative [10]. The high reactivity of indium salts could also generate a double activation as shown by Nakamura's group in the case of the β -ketoester substrate containing the acetylene function [11–13]. We have also investigated the use of indium

trichloride in alkyne activation for carbocyclization reactions by describing an efficient synthesis of *exo*-methylene α -disubstituted cyclopentane derivatives [14–16] and following our continuous work on gold catalysis [17–21], we wondered if we could promote cycloisomerization processes on cyclohexenylalkynes [22] in the presence of indium salts. These bicyclic derivatives are key building blocks and represent privileged scaffolds for biologically active molecules and natural products [23–28]. We wish therefore to describe our results in the presence of InCl_3 catalyst and a critical comparison with our previous results with gold complexes.



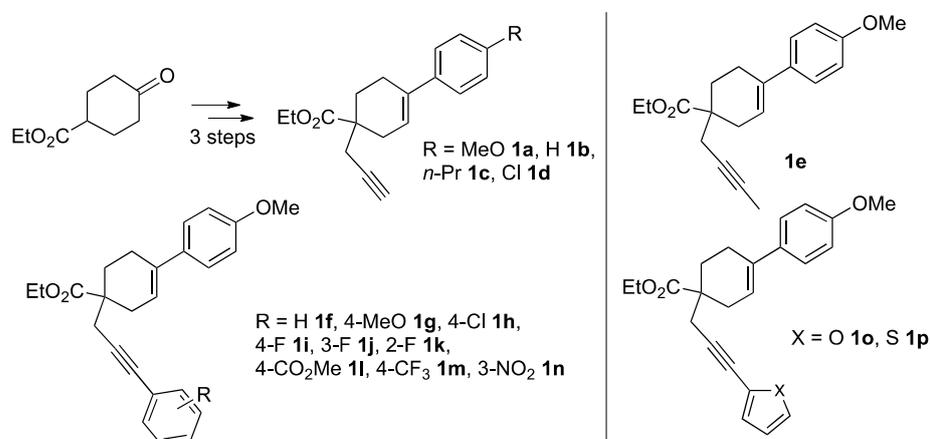
Scheme 1. In-catalyzed hydroarylation and cycloisomerization reactions.

2. Results

At the outset of our study, we prepared several functionalized 1,6-enynes, starting from ethyl 4-cyclohexanone-carboxylate according to a straightforward three-step route implying a triflate formation, a Suzuki–Miyaura coupling and a propargylation (Scheme 2). We prepared non-substituted alkynes **1a–d** as well as substituted ones such as Me-substituted **1e**, and Ar-substituted **1f–1p**, the latter being obtained via classical Sonogashira cross-coupling reactions on **1a** [22].

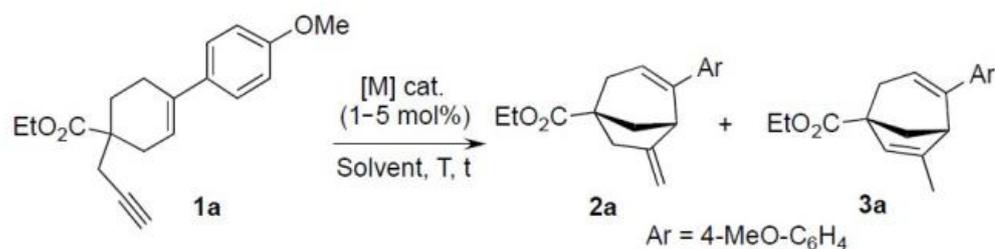
Based on our gold-catalyzed experience, we have recently studied the cycloisomerization reactions of the known ethyl 4-oxocyclohexane carboxylate **1a** and showed that the use of gold catalysts allowed the formation of bicyclo[3.2.1]oct-2-ene **2a** as well as the isomerized **3a** in various ratio depending on the gold catalyst (Table 1, entries 1–3) [22]. The reaction allowed the formation of **2a** in 81% conversion after 1 h with 2 mol % catalyst, but **3a** was observed in high ratio (Entry 1). In toluene, the reaction was similar and led to **2a**:**3a** in 53:47 ratio (Entry 2). The use of a NHC-type gold catalyst IPrAuNTf_2 gave selectively the desired cycloisomerized adduct **2a** in 90% yield with a lower catalyst loading (Entry 3). Disappointingly, the same reaction conditions in the presence of commercially available InCl_3 salt did not promote the cyclization (Entry 4). Increasing the temperature and the catalyst loading to 5 mol %, according to Chatani’s work [8], was very positive as the desired adduct **2a** was isolated in 90% yield and in an excellent 99:1 ratio (Entry 5). Noteworthy that no conversion was observed at room temperature in the presence of

5 mol % indium. When the reaction was conducted in DCE at 40 °C, a lower yield was observed, because of some degradation (Entry 6). Moreover the isomerization process was competitive and the **3a:2a** ratio increased to 15:85.



Scheme 2. Structures of prepared 1,6-enynes.

Table 1. Au and In-catalyzed cycloisomerization reaction of ethyl 4-oxocyclohexane carboxylate.



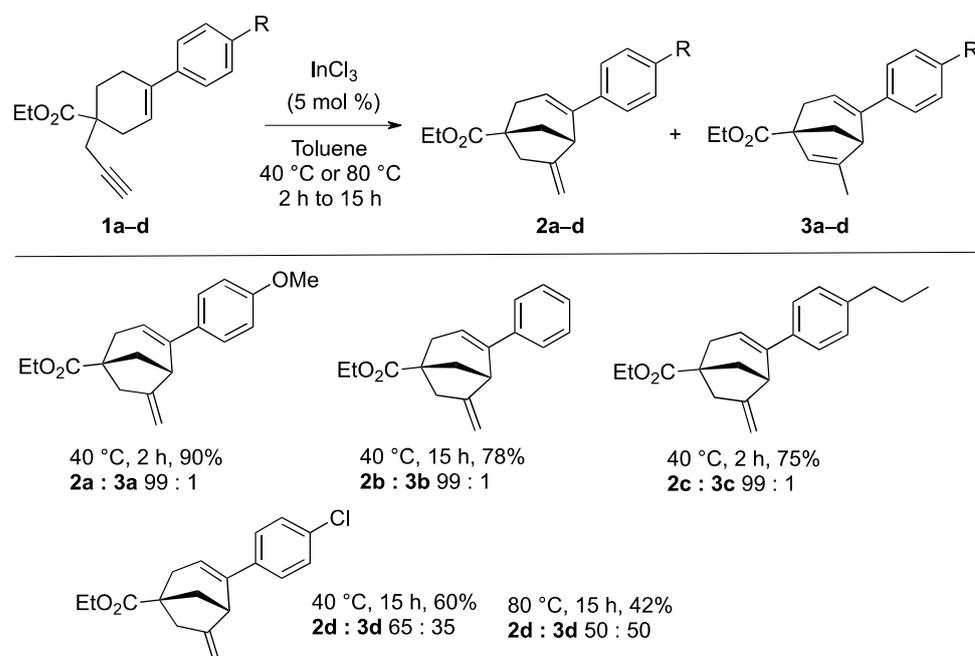
Entry	[M] (x mol %)	Solvent	T (°C)	t (h)	2a:3a Ratio (%) ¹	Yield ² (Conv) (%)
1	(PPh ₃)AuNTf ₂ (2)	DCM	rt	1	45:55	60 (81)
2	(PPh ₃)AuNTf ₂ (2)	toluene	rt	0.5	53:47	50 (100)
3	IPrAuNTf ₂ (1)	toluene	rt	0.75	99:1	90 (100)
4	InCl ₃ (1)	toluene	rt	2	/	/ (0)
5	InCl ₃ (5)	toluene	40	1	99:1	90 (96)
6	InCl ₃ (5)	DCE	40	0.33	85:15	60 (100)
7	Bi(OTf) ₃ (5)	toluene	40	1	80:20	35 (40)

¹ Determined on ¹H NMR of crude mixture. ² Isolated yield.

Comparatively, the use of another similar Lewis acid such as bismuth [29] led to the desired bicyclo[3.2.1]oct-2-ene but in a lower yield and selectivity compared to the results with indium (Entry 7 versus entry 5). We anticipated that Bi(OTf)₃ would promote the isomerization of the *exo*-double bond, which was demonstrated by submitting **2a** to 5 mol % of Bi(OTf)₃. Indeed when bismuth triflate was added to the *exo* derivative **2a**, the isomerization of the double bond was observed very quickly, in 30 min. The ratio of *exo* derivative **2a** to *exo* isomerized derivative **2b** is 40/60 and was observed similarly in both solvents, DCE and toluene (Entries 6, 7) [30]. The isomerization of the *exo*-double bond may therefore be explained by a Brønsted acid catalyzed process (TfOH or HCl) as already observed in the literature for other polycyclic structures [31–33]. The origin of such acids would come from partial hydrolysis of the catalyst InCl₃ and Bi(OTf)₃ in the presence of traces of water.

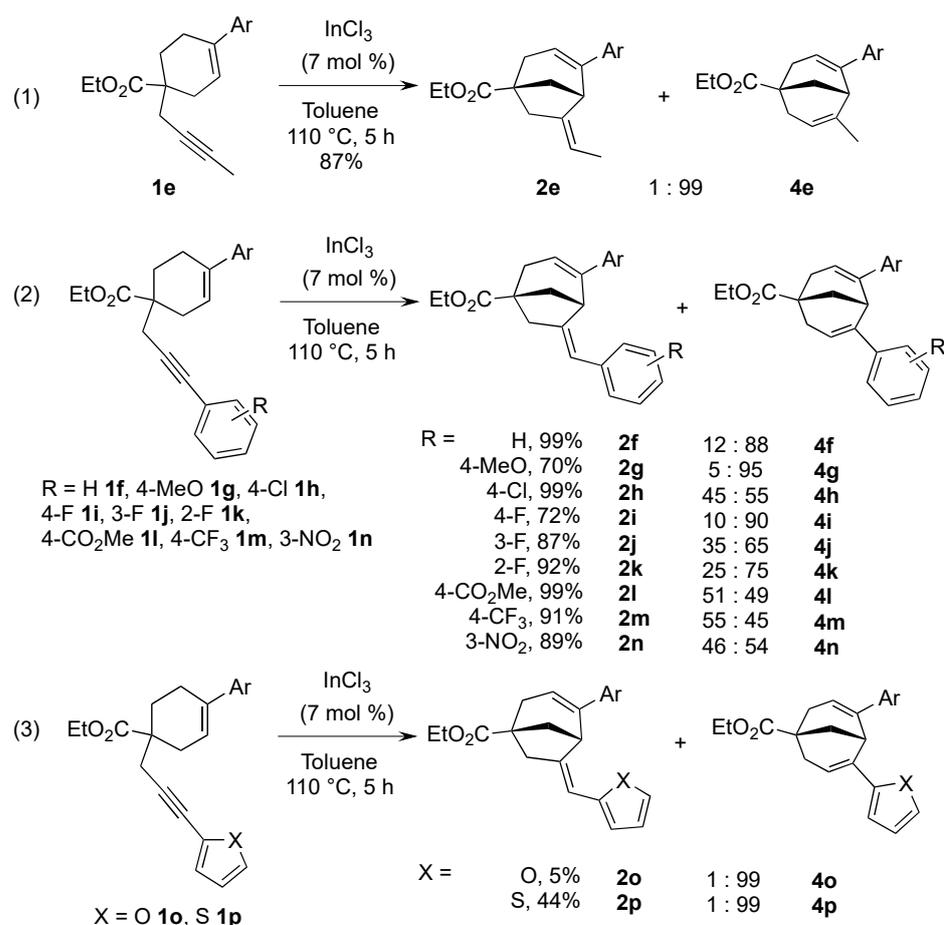
We selected the optimized conditions employing InCl₃ in toluene at 40 °C, and studied the scope and limitations with a wide range of functionalized enynes (Scheme 3). In the case of propargyl enyne derivatives **1a–d**, complete conversions were observed in 2 h

up to 15 h with temperatures of 40 °C and 80 °C. The cycloisomerization reaction was particularly efficient with the derivatives possessing the 4-methoxy-phenyl **1a**, the phenyl **1b** and the 4-*n*-propylphenyl **1c** groups (75–90% yields). Excellent 5-*exo* isomer selectivity was also observed. With the chlorinated derivative **1d**, the reaction led to the products **2d** and **3d** in a lower yield of 60% at 50 °C and a 65:35 mixture of the *exo* isomer and its *exo* isomerized counterpart. A higher temperature (80 °C) resulted in a worse yield of 42%, due to degradation. The isomerization of the double bond was also observed in a higher proportion.



Scheme 3. In-catalyzed cycloisomerization of ethyl 4-oxocyclohexane carboxylate derivatives **1a–d**.

In the case of substituted alkynes **1e–p** (Scheme 4), the reactions were more sluggish and we had to increase the temperature to 110 °C and the catalyst loading to 7 mol %. The reaction outcomes allowed the formation of 2 isomers, **2** and **4**, resulting from 5-*exo* and 6-*endo* cyclization processes respectively. In most cases, the *endo* derivative was determined as the major isomer, but the competition with the formation of the *exo* adduct could be important in some cases. The cycloisomerization reaction of the methyl-substituted enyne **1e** led to the *endo* derivative **4e** as the major adduct in 87% isolated yield (Scheme 4, (1)). The *endo/exo* ratio was still high for 4-MeO- and 4-F-functionalized derivatives **4g** and **4i** respectively, but slowly decreased for phenyl, 4-Cl- as well as 3-F- or 2-F-functionalized adducts (Scheme 4, (2)). In the case of enynes bearing electron-withdrawing groups such as **1l–n**, the preference towards a cyclization mode was reduced and the *endo/exo* ratios were closed to 50:50. The reactions were nevertheless very efficient as the mixture of *endo/exo* isomers were isolated in good to excellent yields (89–99%). In contrast, for the heterocyclic derivatives **1o–p**, the yields were much lower, 44% for the 2-thiophenyl derivative **4p** and only 5% for the 2-furanyl **4o** (Scheme 4, (3)). Additional tests were performed, decreasing the reaction temperature to 40 °C and 80 °C but without significant improvement. Degradation products, which could not be identified were isolated at 110 °C in the case of the 2-thiophenyl.



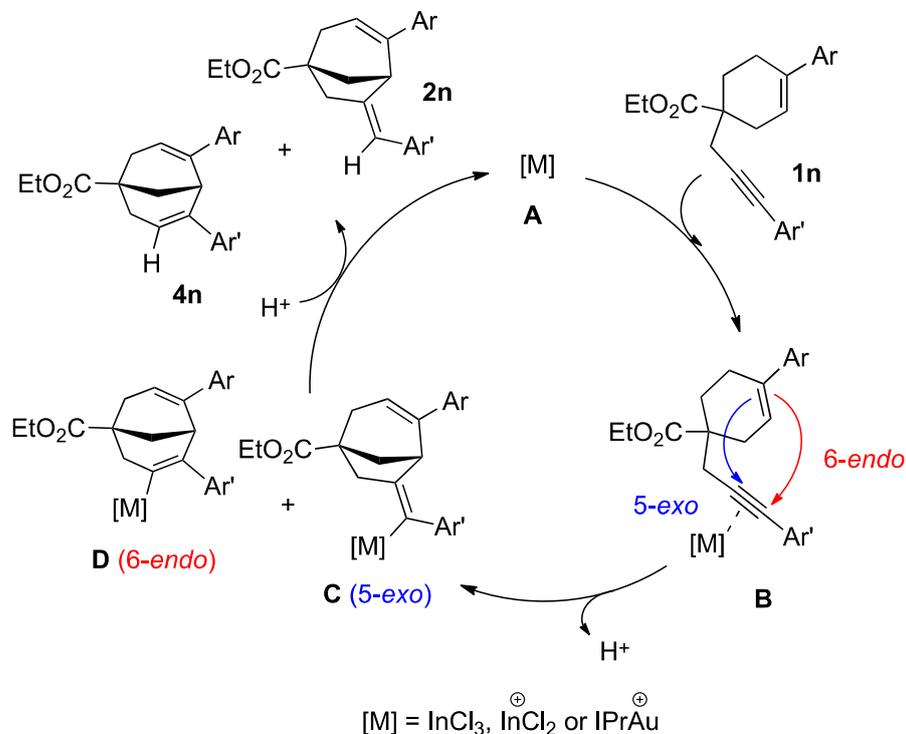
Scheme 4. In-catalyzed cycloisomerization of substituted derivatives **1e–p** (Ar = 4-MeOC₆H₄).

The selectivity towards “5-*exo*” and “6-*endo*” cyclized product was then compared between the indium and gold catalytic systems. In the case of **1e**, **1f**, **1g** as well as for the F-substituted enynes **1i–k** or the heterocyclic adducts **1o–p**, similar results were observed having *endo:exo* ratio equal or very similar. A significant difference in percentage was observed in the case of the 3-NO₂-substituted derivative as the use of IPrAuNTf₂ allowed the formation of **4n** in 70% selectivity (**2n:4n** = 30:70). As **2n** and **4n** were easily separated, the interest of indium salt was thus to allow the formation of the *exo* derivative in a better ratio. The case of **1l** and **1m** also showed significant difference in selectivity. According to the same trend, the percentage of the *exo* isomers were significantly increased with indium catalyst, as **2l** and **2m** were isolated in a 85:15 (**2l:4l**) and 65:35 (**2m:4m**) respectively in the presence of gold.

These unexpected results on the selectivity induced by In or Au prompted us to perform DFT calculations with the Gaussian 16 suite of programs (Revision A.03) [34] on the intermediates related to *endo* and *exo* isomer and we chose the 3-NO₂ adduct for this study. Mechanistically [35–37], the π activation of the alkyne, would lead to intermediate **B** and then the nucleophilic addition of alkenyl group would proceed according to a 5-*exo* or 6-*endo* pathway (Scheme 5). The resulting vinyl metal intermediates **C** and **D** would then give **2n** or **4n** by protodemetalation. The difference between indium and gold may be evaluated by considering the stability of intermediates **C** and **D**.

Following the seminal work from Gandon [9] and Yu [38–40] with indium and gallium salts, In and Au intermediates **C** and **D** were optimized with the dispersion corrected B3LYP-D3 exchange-correlation functional [41–45] and the results are collected in Table 2. The effective-core potential of Hay and Wadt with a double- ξ valence basis set (LANL2DZ) was used to describe In and Au [46] and the other atoms were described by the 6–31g(d,p) basis set. We used the PCM implicit solvation model to take into account the solvation

effects of toluene. Computing vibrational frequencies and summing electronic and thermal free energies led to the reported Gibbs free energies. Indium was considered as InCl_3 or InCl_2 as previously advocated [9,35–37].



Scheme 5. Mechanistic rationale.

Table 2. DFT calculations.

Entry	Experimental <i>endo:exo</i> Ratio (%)	[M]	<i>endo</i>	<i>exo</i>	Theoretical <i>endo:exo</i> Ratio (%)
1	54:46	InCl_3			43:57
2	54:46	InCl_2			96:4
3	70:30	IPrAu			99:1

In the case of the InCl_3 intermediate, the theoretical stability of the *exo* vinylmetal intermediate (entry 1) was found to be slightly higher than the *endo* one. It was in good

agreement with the experimental analysis of the reactivity of **1n**. The reaction of **1n** led to an *endo:exo* mixture in a 54:46 ratio (Scheme 4, (2)). The InCl_2 intermediates did not allow any relevant correlation with the experimental results (Table 2, entry 2). We also analyzed the stability of the vinyl gold complexes, and the *exo* intermediate was also found to be the more stable one (Table 2, entry 3), in a higher ratio, experimentally and theoretically. This difference between indium and gold could be explained considering the higher Lewis acid properties of gold compared to indium, inducing a higher polarization of the triple bond. We verified this statement on our substrate by comparing the partial charges (using the MKUFF method for Au and in alkyne complexes, see Supporting Information) between **B-In** and **B-Au** intermediates. In the case of π -gold complex, the polarization of alkynyl carbons was found to be 0.175 and -0.305 (0.48 difference), whereas the carbons were found to be charged -0.209 and -0.056 (0.153 difference), which therefore explains the difference in selectivity. Therefore the experimental values were in agreements with the theoretical data.

In conclusion, we have extended the methodology of the indium-catalyzed reactions by studying the cycloisomerization of cyclohexenylalkynes leading to functionalized bicyclo[3.2.1]oct-2-ene and bicyclo[3.3.1]nonadiene. The scope and limitations study showed that the cyclizations occurred according to an *exo* process in the case of non-substituted alkynes whereas the *endo* isomers were generally obtained for substituted alkynes. The presence of electron-donating and electron-withdrawing groups on the aryl substituted alkyne influenced the cyclization outcome, increasing the ratio of the *exo* isomer for electron-deficient groups. DFT calculations confirmed the prevalence of InCl_3 -based intermediates and showed good correlations with the experimental data. This methodology is therefore complementary to the one developed in the presence of gold. Further studies will focus on potential asymmetric versions of this atom economical process and on the applications of such skeletons.

Supplementary Materials: Supplementary materials present the synthesis of bicyclic adducts **2**, **3** and **4**, as well as the DFT calculations. The following are available online at <https://www.mdpi.com/article/10.3390/catal11050546/s1>.

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

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