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On the Nature of Organoindium Intermediates: the Formation of Readily Isolable Difluoropropargylindium Reagents and their Regioselectivity Towards Electrophilic Substitutions

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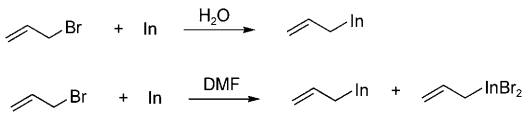
Abstract: The structure and reactivity of intermediate propargylindium complexes have been investigated. Their reaction with electrophiles produced a difluoroalkyne or -allene, depending on the nature of the electrophiles. A mechanism based on the Curtin–Hammett principle was invoked to explain this phenomenon. A newly proposed mechanism on the formation of indium(III) complexes, through the intermediacy of indium(I) species, could help to explain the reaction of indium with 1,1,1-difluorobromo-2-alkynes in the presence of aldehydes.

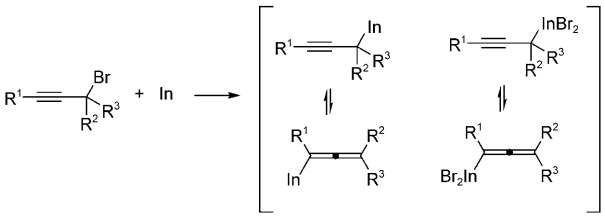
Keywords: allenyls · Curtin–Hammett principle · indium · NMR spectroscopy · propargyls

Introduction

During the last two decades, the use of indium in organic synthesis has increased to the extent that nowadays this element is regarded as an important tool in the arsenal of environmentally friendly, metal-mediated organic reactions.[1–4] The interaction of allylic or propargylic halides with indium metal—through metal–halogen exchange/insertion or transmetalation—and subsequent addition to carbonyl compounds, olefins, imines, or alkynes has been actively pursued, but the mechanism of these reactions has eluded many investigators due to the fleeting nature of the organoindium intermediates.[5,6] Early on, it was suggested that a reactive indium intermediate might possess a sesquihalide $[In_2R_3X_3]$ structure.[7] In 1999, Chan proposed the intermediacy of an indium(I) complex in a Barbier-type reaction of indium metal with allyl bromide in aqueous media, ruling out both the presence and participation of bromine or the indium surface (Scheme 1).[8] In the reaction of propargyl bromide with indium in THF, Chan and co-workers proposed the intermediacy of both indium(I) and indium(III) species, based on NMR evidence (Scheme 2).[9] However, NMR alone could not determine if one or two bromine atoms were present in the indium(III) complex. According to the authors, the competition for predominance by either In^{I} or In^{III} species in an allenyl–propargyl metaloprotic rearrangement depended on steric factors and the solvent system utilized.[9] In aqueous media, only an organoindium(I) discrete species was observed. Although an allenylindium is favored at equilibrium, methyl substitution shifts the equilibrium toward propargylindium(I) and -indium(III) species. In all cases, the products of their reaction with aldehydes have the regioselectivity expected from an S_E2' pathway. Loh's approach to the subject consisted in examining the indium-mediated reaction of trialkylsilyl propargyl bromide with aldehydes in an effort to tune the regioselectivity toward the synthesis of allenic alcohols or homopropargylic alcohols.[10] Chan's earlier report produced allenic alcohols with moderate to good



Scheme 1. Allylindium complexes proposed by Chan et al.



Scheme 2. Propargylindium complex proposed by Chan et al.

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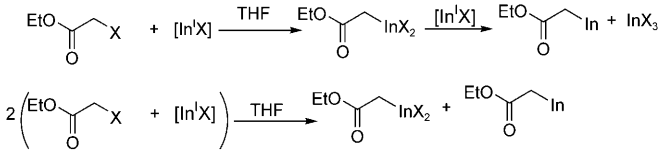
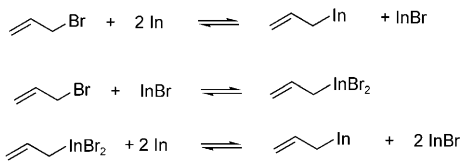
regiocontrol; Loh utilized a combination of solvent (THF or THF/water), the steric and chelation effects of the silicon group on the γ-carbon, and a combination of indium(0) and indium(III), to obtain either allenic alcohols or homopropargylic alcohols with high regioselectivities. As in Chan's mechanistic analysis, Loh also invoked a S_E2' pathway to explain the regiochemical outcome of his experiments, but he did not comment on the nature of his indium complex(es). In other developments, Lee used a palladium-catalyzed cross-coupling reaction mediated by In^0 to exclusively synthesize aryl-substituted allenes starting from propargyl bromides.[11] The existence of organoindium(I) and -indium(III) transient intermediates was also postulated by Baba and coworkers in their indium(0)-mediated Reformatsky-type reaction of bromoacetates with ketones(Scheme 3)).[6,12] The



Scheme 3. Formation of low-valent indium species in the Reformatsky reaction.

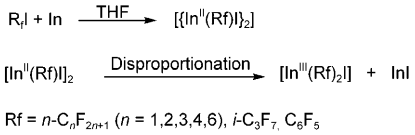
interconversion of indium(I) to indium(III) complexes has been proposed when an ionic liquid was used as solvent (Scheme 4).[13] In addition to an indium(I) mechanism, in-



Scheme 4. Allylindium complexes formation mechanism in ionic liquids.

dium(II) species have also been reported to be products of reaction of indium with perfluorinatedalkyl halide; these indium(II) species exist in the form of dimers, and they tend to disproportionate to indium(III) species and [In^IX] (Scheme 5).[14]

From the reports summarized above, it is apparent that the nature, mechanism of formation, and regiochemistry of indium-mediated propargylation or allenylation are still the subject of debate. This is due partially to the fact that organoindium complexes are transient and short-lived intermediates, and that indium-mediated reactions could only be

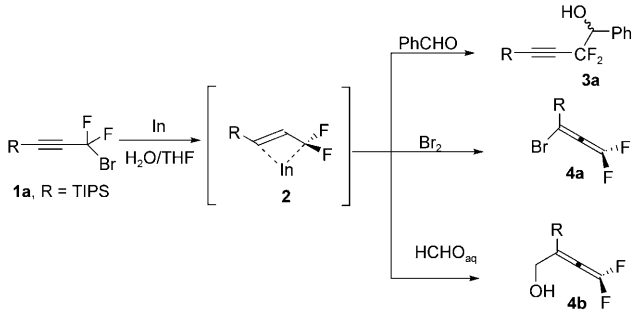


Scheme 5. Mechanism invoking indium(II) species.

monitored by ^1H NMR spectroscopy. We surmised that the substitution of CH_2 by CF_2 in a propargyl system not only would stabilize a nascent organoindium complex without introducing unwanted steric modifications due to fluorine's small size, but also it would facilitate the study of their reactions by ^{19}F NMR spectroscopy without interference of solvent or reagents. We now report the results of our investigations on the mechanism of formation of organofluoroindium reagents and their regioselectivity toward electrophiles.

Results and Discussion

Synthesis and identification of difluoropropargylindium complexes: For some time now we have been interested in the reaction of indium with difluorobromopropargyl substrates as a way to incorporate fluorine selectively in organic molecules. Our earlier work on the reaction of difluoropropargyl bromide **1a** (R = TIPS = triisopropylsilyl) with indium in predominantly aqueous media, after extraction with diethyl ether, produced a stable crude complex, loosely represented as **2** (Scheme 6).[15] This crude organoindium reagent **2** yielded allenylic product **3** or propargylic product **4** depending on the nature of the electrophile (E^+) used (Scheme 6).[15,16]



Scheme 6. Initial postulate on the nature of organofluoroindium species.

With the purpose of elucidating the structure of the indium complex **2**, a 1:1 mixture of **1a** and indium metal in predominantly aqueous media was sonicated at 5–10 °C (bath) and monitored by ^{19}F NMR spectroscopy. Two slowly increasing resonance signals, centered at $\delta = -89$ ppm, were detected after 0.5 h, and all the starting material was consumed after 5–6 h (Figure 1a). Clearly, the ^{19}F NMR spectrum of crude indium complex **2** has two peaks, which means it contains at least two indium species. To get pure indium complexes for further analysis, we isolated each indium species using SiO_2 flash chromatography, resulting in two fractions, their ^{19}F and ^{13}C NMR spectra are shown in Figure 1. We found that DMSO stabilized the indium complexes to give white solids. These solids could be kept at room temperature for several weeks without decomposition, and stored for months in the refrigerator. Satisfactory carbon and hydrogen analyses were also obtained. Their

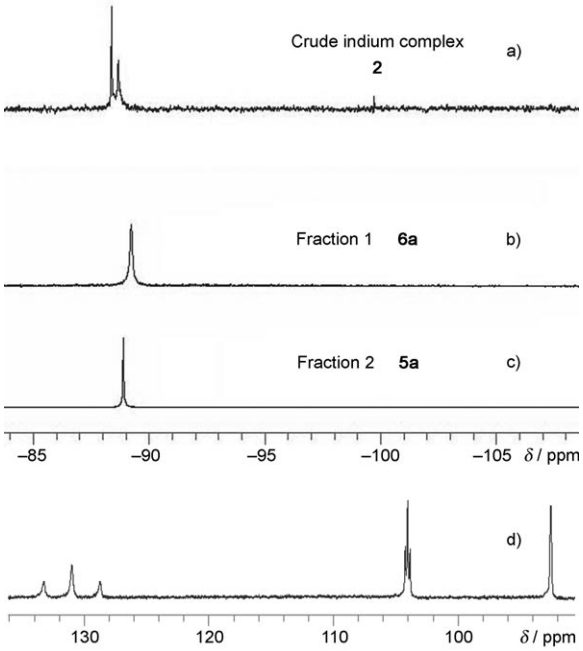
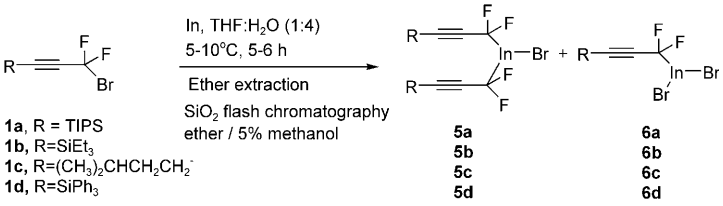


Figure 1. NMR of indium complexes. a) ^{19}F NMR spectrum of crude indium complex **2**; b) ^{19}F NMR spectrum of the first fraction **6a**; c) ^{19}F NMR spectrum of the second fraction **5a**; d) ^{13}C NMR spectrum of **6a** (only three carbon atoms in propargyl system are shown).

^{19}F NMR chemical shifts ($\delta = -88.8$ and -89.1 ppm) and ^{13}C NMR signals seemed to support a propargyl structure. If present, an allenyl indium complex would have shown a large downfield shift for the central sp carbon (around $\delta =$ 200 ppm in ^{13}C NMR spectrum). In addition, IR showed a strong signal at 2172 cm^{-1}; this is further evidence supporting the propargylic nature of the complex. Based on that information, the structures of those indium complexes were assigned as **5a** and **6a** (Scheme 7).



Scheme 7. Preparation and separation of crude difluoropropargylindium complex.

Since attempts to obtain suitable single crystals of **5a** or **6a** failed, we prepared a number of organoindium complexes (Scheme 7). To our satisfaction, the triphenylsilyl-substituted indium complex **5d** crystallized by slow evaporation of a saturated solution in mixture of DMSO and dichloromethane at room temperature. Its structure was determined by single-crystal X-ray techniques.[17] The other physical properties (melting points and UV absorption) of the indium complexes were also examined (see Supporting Information). The indium complexes also exhibit very strong UV absorption, generally their λ_{max} are around 250–300 nm, and their ε_{max} are around 5000 dm^3 mol^{-1} cm^{-1}.

Reaction of difluoropropargylindium(III) complexes with electrophiles: The reaction of indium complex **5a** and **6a** with relatively reactive electrophiles like CHOCOOH (glyoxylic acid) and NCS (*N*-chlorosuccinimide) was first considered. Because both starting material and product contain fluorine, it should be relatively easy to follow the reaction process by ^{19}F NMR spectroscopy. Both difluoropropargylindium complexes **5** and **6** react with reactive electrophiles (CHOCOOH, NCS, and bromine) to give difluoroallene (Figures 2 and 3). This kind of reaction is usually completed in less than 0.5 h at 0–5 °C; the [InRBr$_2$]-type indium complex **6** is slightly more reactive than [InR$_2$Br]-type indium complex **5**. This may be due to steric effects. The reaction of alkyl-substituted propargylindium complexes **5c** and **6c** with glyoxylic acid and NCS also gave the corresponding allenyl product **4** (see Supporting Information).

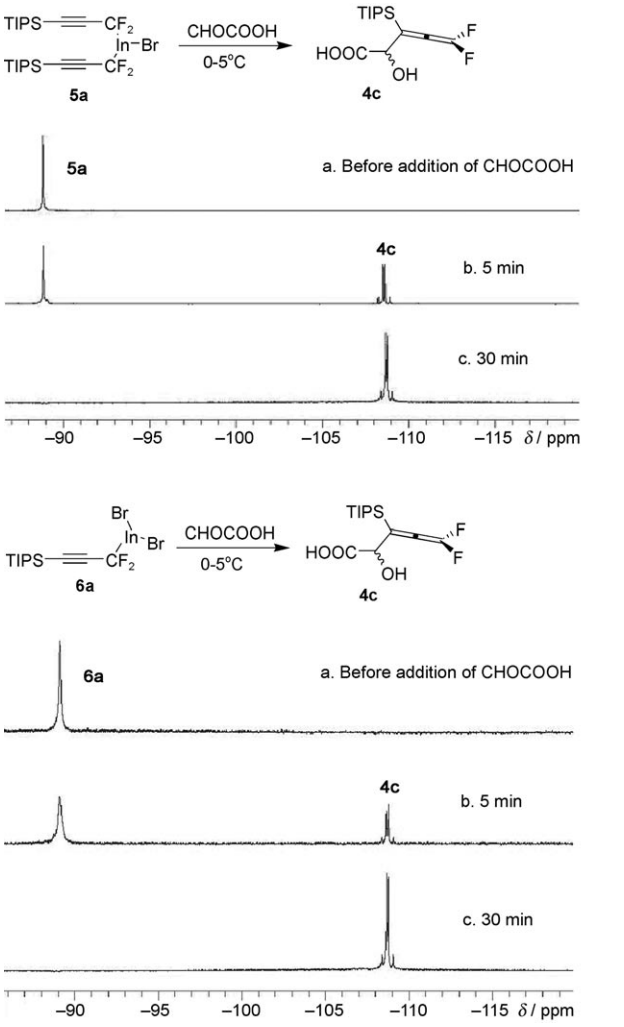


Figure 2. Reaction of indium(III) complexes with glyoxylic acid monitored by ^{19}F NMR spectroscopy.

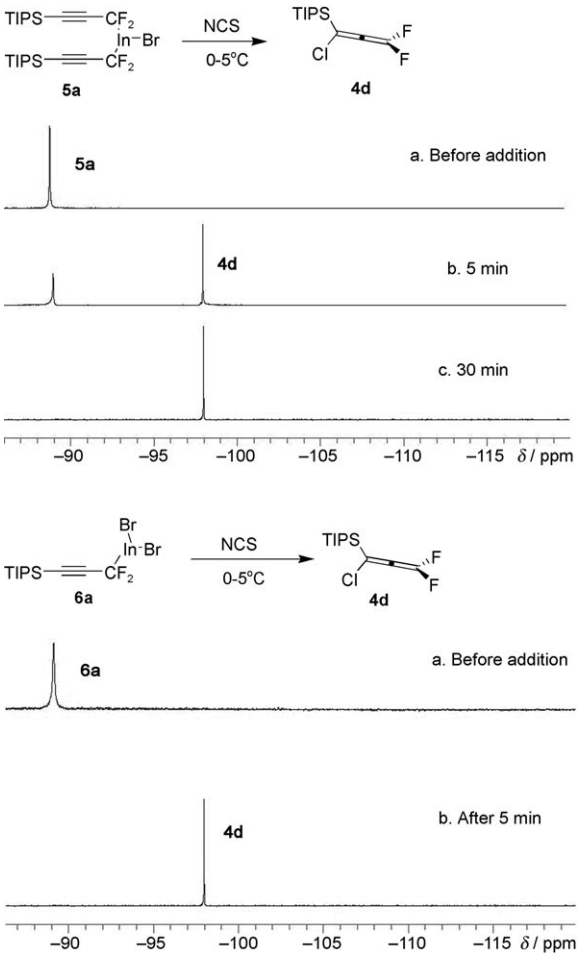


Figure 3. Reaction of indium(III) complexes with NCS monitored by ^{19}F NMR spectroscopy.

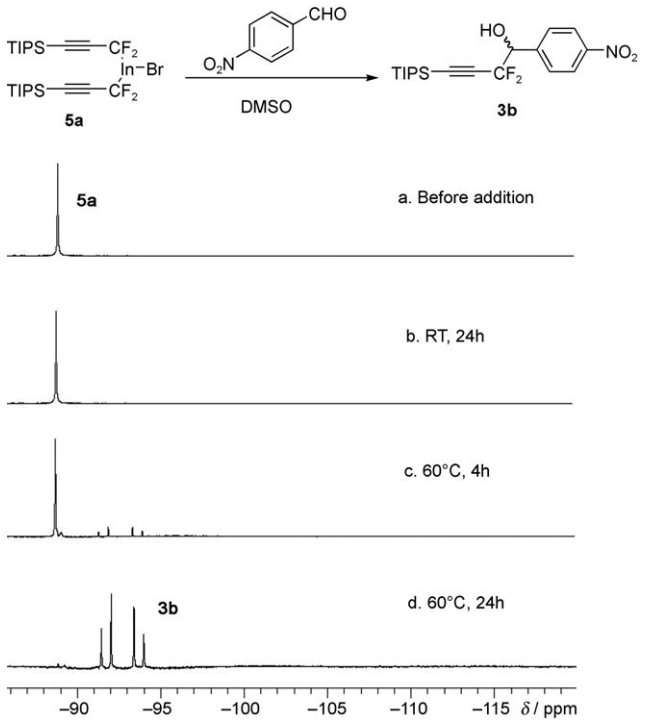
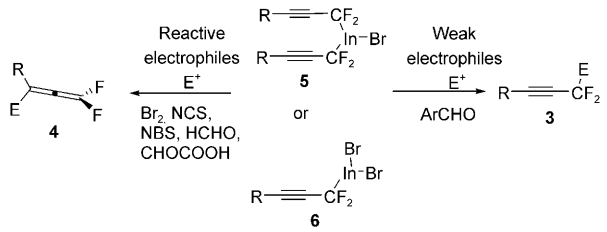


Figure 4. Reaction of **5** with *p*-nitrobenzaldehyde monitored by ^{19}F NMR spectroscopy.

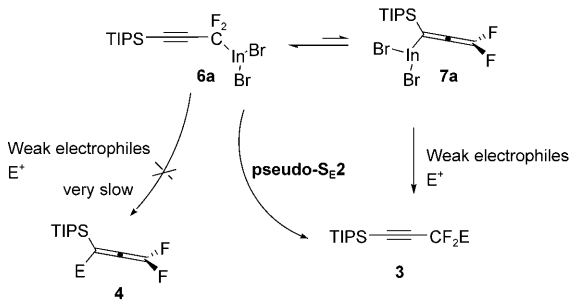


Scheme 8. Reaction pattern of propargyl indium complexes with electrophiles.

We also investigated the reaction of indium complex **5** and **6** with relatively unreactive electrophiles like aromatic aldehydes. In contrast to the reactive electrophiles, such electrophiles (e.g., benzaldehyde, *p*-nitrobenzaldehyde) give only the propargyl product **3**; this reaction usually proceeds very slowly at room temperature and needs more than one day to complete even at high temperatures (Figure 4).

From the above results, we can conclude the following: 1) difluoropropargylindium complexes **5** and **6** (Scheme 8) have similar regioselectivity towards electrophiles; 2) reaction of **5** and **6** with reactive electrophiles give allenyl products **4**; on the other hand reaction of **5** and **6** with relative unreactive electrophiles yields propargyl products **3** (Scheme 8).

The reaction of propargylindium(III) with reactive electrophiles to give difluoroallene through a S_E2' path can be explained invoking an extension of electronic effects through the triple bond. On the other hand, the reaction with weak electrophiles that furnishes the difluoropropargyl isomer could be explained using the Curtin–Hammett principle.[18] This principle states that, for a reaction that has a pair of reactive intermediates or reactants that interconvert rapidly, each going irreversibly to a different product, the product ratio will depend only on the difference in the free energy of the transition state going to each product ($\Delta\Delta G$), and not on the equilibrium constant between the intermediates. Taking indium complex **6a** as an example, we proposed that there is an equilibrium between propargylindium(III) **6a** and its allenylic isomer **7a** (Scheme 9). The interconver-



Scheme 9. Pseudo-S_E2 reaction of **6a** with weak electrophiles.

sion of propargyl metal species and allenyl metal species has been well documented in literature.[19–21] A potential energy diagram for reaction of **6a** with weak electrophiles is shown in the Supporting Information. In this case, the energy of activation for the reaction of indium complex with electrophiles may be greater than the equilibrium of the two indium complexes **6a** and **7a**. When the electrophile is weak or unreactive, the reaction of **6a** with this electrophile to give difluoroallene **4** is very slow; **6a** may isomerize to **7a** and then **7a** react with weak electrophile to give propargyl product **3**. Because the overall reaction goes from a propargyl starting material to a propargyl product, we may call this reaction a pseudo-S_E2 reaction (Scheme 9).

Formation of propargylindium(III) complexes 5 and 6: The indium complexes **5** and **6** were capable of reacting with electrophiles yielding allenes **3** or alkynes **4**. However, this result does not necessarily imply that other reactive indium species cannot be formed during the reaction; it only means that the indium(III) complexes **5** and **6** are thermally stable, isolable, and capable of reacting with electrophiles. Indium-(III) complexes **5** and **6** may be just final products of the reaction of indium with propargyl bromide **1**, and perhaps there could be other short-lived transient indium species produced during the reaction.

To investigate if there was any intermediate indium species produced during the reaction, we monitored the reaction of **1c** with indium using ^{19}F NMR spectroscopy. The results are shown in Figure 5.

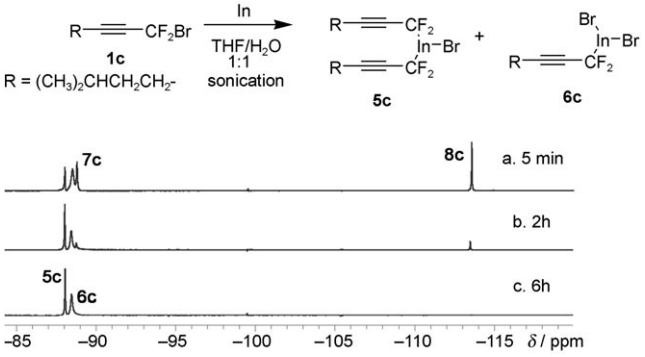
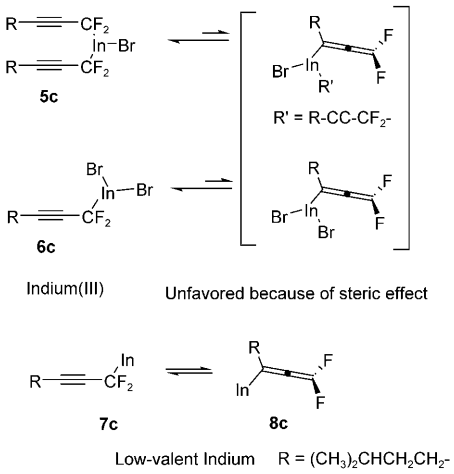


Figure 5. Monitor of the indium complex formation form **1c** by ^{19}F NMR spectroscopy.

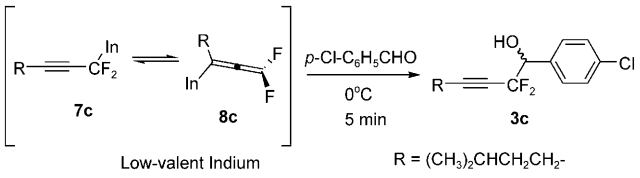
According to the results shown in Figure 5, after 6 h, two propargylindium(III) complexes **5c** and **6c** were the dominant species after 6 h (Figure 5c). However, at the very beginning of the reaction, we observed another pair of signals ($\delta = -88$ and -112 ppm, Figure 5a), the intensities of which decreased with time and disappeared after 6 h (Figure 5c). These intermediates could be low-valence indium complexes composed of a mixture of propargylic (-88 ppm) and allenylic (-112 ppm) species. This is in contrast with indium-(III) complexes that are propargylic in nature due to the steric effects (Scheme 10). The low-valence indium complexes could be indium(I) or indium(II) complexes. Indeed, indium(II) complexes have been reported as intermediates (Scheme 5),[14] but we believe that the formation of indium(II) is unlikely in our case, because a [In^{II}RBr]-type complex would be paramagnetic, a property that would have been readily apparent in our NMR experiments. We also conducted EPR experiments on the intermediate indium complex, and found no signs of the presence of paramagnetic species. Thus, the low-valence indium complex peaks were regarded as indium(I) complexes.



Scheme 10. Equilibrium between propargylindium and allenylindium complexes.

We then checked the reactivity of these low-valence indium(I) complexes. These are much more reactive than the corresponding indium(III) complexes. For example, when *p*-chlorobenzaldehyde was added to the indium complexes shown in Figure 5a, after only 5 min at room temperature, the two low-valence indium complexes had disappeared, and the signal corresponding to propargyl alcohol **3c** had formed. On the other hand, the signals corresponding to indium(III) **5c** and **6c** remained unchanged even after 24 h.[22] The reaction of a low-valence indium complex with aldehyde also yields propargyl product **3c** (Scheme 11); this could be explained by the Curtin–Hammett principle in a similar way as the reaction of indium(III) complexes **5** and **6** with aldehyde.

Since we observed the existence of low-valence indium complexes, one important question remains: do these complexes convert to more stable indium(III) complexes or do they decompose gradually? To answer this question, we followed the progress of the reaction by ^{19}F NMR spectroscopy



Scheme 11. Reactivity of low-valence indium species with aldehyde.

just after all the starting material **1c** had been consumed. For this purpose, we added an internal standard and sealed the NMR tube. We did observe a signal increase corresponding to the indium(III) complexes (**5c**+**6c**) with a concomitant decrease in the intensity of the signals corresponding to indium(I) complexes; this result is shown in Figure 6. This phenomenon was confirmed by repeated experiments.[22]

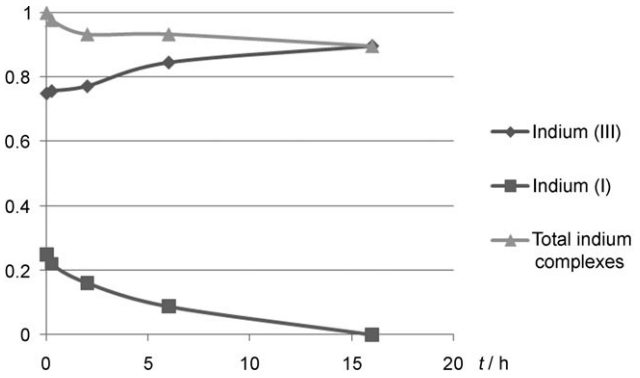
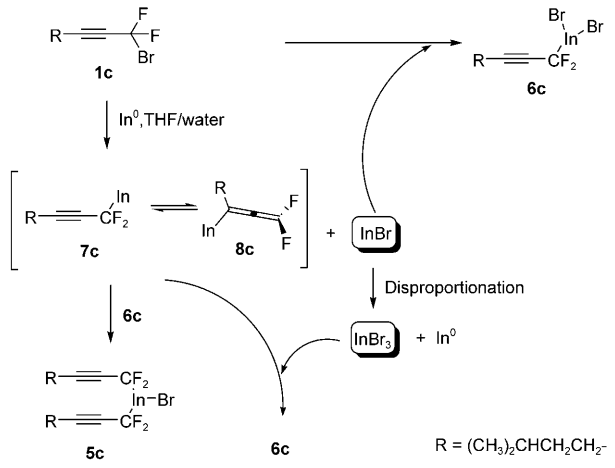


Figure 6. Increase of indium(III) complex intensity.

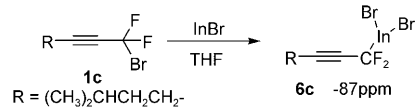
How could an indium(I) complex convert to indium(III) species? Although it is known that indium(I) species tend to disproportionate to indium(III) and indium(0),[23] in our case the indium(I) species contains no bromide, and hence it could not disproportionate to propargylindium(III) bromide **5** or **6**. To explain the conversion of low-valence indium to indium(III) species, we have proposed a new mechanism (Scheme 12). First, difluoropropargyl bromide **1c** reacts with indium to give an equilibrating mixture of propargyl and allenyl indium(I) (**7c** and **8c**) and $In^{I}Br$ (see also Scheme 3). Difluoropropargyl bromide **1c** could react with the InBr produced to give propargylindium(III) dibromide **6c**; InBr also could disproportionate to $InBr_3$ and In^0.[24] Because the indium(I) species is quite reactive (we can see it from its fast reaction with aldehyde), the indium(I) complex would



Scheme 12. Mechanism for indium(III) complex formation.

react with $InBr_3$ to give propargylindium(III) dibromide **6c**. This step is reasonable because it is similar to the reaction of lithium reagents with $InCl_3$ or $InBr_3$, which is a common way to make organoindium(III) complex.[25,26] Similarly, complexes **7c** or **8c** also could react with propargylindium(III) dibromide **6c** to give bis(difluoropropargyl)indium(III) bromide **5c**.

We were able to prepare complex **6c** through an independent route, by reacting **1c** with InBr in THF. This is another support for our mechanism (Scheme 13).



Scheme 13. Synthesis of complex **6c** from InBr.

The in situ generation of an indium complex in the presence of aldehyde: Unlike Grignard reagents many metal complexes cannot be prepared in preformed fashion due to their low thermal stability; the easiest way to overcome the stability problem of a metal complex is its genesis in the presence of electrophiles. So it is very common for the metal complex to be generated in situ and then react with electrophiles in real time before it undergoes decomposition. Our group has reported several indium- or magnesium-mediated Barbier type reactions of **1** with aldehyde, imine, and other electrophiles.[15,27–29] From the above discussion, the formation of indium(III) complexes may involve the intermediacy of low-valence indium(I) complexes. Since a low-valence indium(I) complex is much more reactive than corresponding indium(III) complex, the indium-mediated Barbier-type reaction of **1** in the presence of an electrophile like an aldehyde may proceed through a different mechanism compared to the reaction of preformed indium(III) complex with aldehydes. To elucidate this question, we examined the reaction of **1c** with indium in the presence of an aldehydes (mole ratio of **1c**/indium/aldehyde = 1:1:1); the reaction proceeded smoothly at 0–5 °C, and after 2–3 h all the starting material **1c** had disappeared leaving behind two new signals in ^{19}F NMR spectrum (Figure 7a), one of which corresponded to product **3c**, the other signal belonged to indium complex **6c** (by comparison with the isolated indium complex **6c**, Figure 7b). This phenomenon can be explained easily by the mechanism shown in Scheme 14, similar to Scheme 12. First, difluoropropargyl bromide **1c** reacts with indium to give an equilibrating mixture of propargyl- and allenylindium(I) (**7c** and **8c**) and $In^{I}Br$. Difluoropropargyl bromide **1c** could then react with InBr formed to give propargylindium(III) dibromide **6c**; InBr also could disproportionate to $InBr_3$ and In^0.[24] However, in this case the reaction took place in the presence of an aldehyde, which we knew was very reactive to indium(I) complex (Scheme 11). Hence, the indium(I) species **7c** and **8c** are no longer able to react with $InBr_3$ or **6c** to give propargylindium(III) dibromide **5c** as they did in

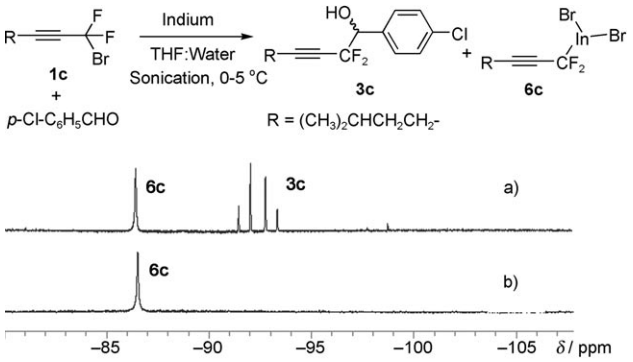
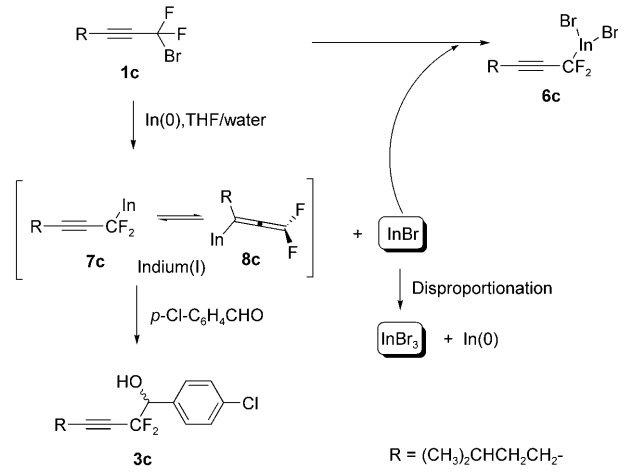


Figure 7. Reaction of **1c** and indium in the presence of aldehyde. a) ^{19}F NMR spectrum of reaction mixture after 3 h. b) ^{19}F NMR spectrum of isolated **6c**.



Scheme 14. Plausible mechanism for the reaction of **1c** and indium in the presence of *p*-chlorobenzaldehyde.

the absence of aldehyde (Scheme 12). Therefore in the end, we obtained **6c** and **3c** as major products.

Conclusion

The structure and reactivity of the difluoropropargyl indium complex has been investigated. Their reaction with electrophiles produced a difluoroalkyne or -allene, depending on the nature of the electrophiles. We have invoked a mechanism based on the Curtin–Hammett principle to explain this phenomenon. And we also have postulated a mechanism for the formation of indium(III) complexes through the intermediacy of indium(I) species, which can also explain the reaction of indium with **1** in the presence of aldehydes.

Experimental Section

General procedure for monitoring of reaction by ^{19}F NMR: The monitoring of reactions was conducted in a NMR tube with screw cap. Before reaction, the NMR tube was flushed with argon. A sealed capillary filled with [D_6]benzene was used to facilitate lock and shimming when non-deuterated solvent was used. Variable-temperature control (Varian Inova 500) was used to control temperature of reaction during ^{19}F NMR experiment. The percentage yield was obtained using α,α,α-trifluoromethylbenzene as internal reference.

For the experimental data for the synthesis and characterization of the compounds described here, see the Supporting Information.

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