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Nature of the intermediates formed during indium mediated allylation under Barbier conditions. Spectroscopic and experimental data on allylindium species

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1. Introduction

Over the past twenty years, indium mediated allylations (IMA) have proven to be a powerful tool for the formation of C–C bonds.[1–3] IMAs offer many advantages over Grignard reagents and other traditional organometallic compounds. First, the reactions often proceed with remarkably high regio-, enantio-, and diastereoselectivity. Second, the indium reactions can be performed in water, obviating the need for dry, flammable solvents. Therefore, indium reagents address the demands of Green chemistry by being safer and more environmentally friendly than the alternatives. Third, because organoindium compounds are excellent nucleophiles but poor bases, they tolerate a wide range of functional groups. At the same time, IMAs have proven useful in allylations of a wide variety of electrophiles. Fourth, the reactions proceed under mild conditions, usually by stirring at room temperature. Finally, few side reactions complicate the reactions, and overall yields are typically high.[1–3]

Although organoindium compounds have long been known and well characterized,[4–9] allylindium compounds are more reactive and, until recently, very few had been well characterized. Araki et al. established the importance of indium mediated allylations for synthetic applications some twenty years ago.[10,11] Shortly thereafter, Chan and his students demonstrated that the reactions can be carried out in water,[12] dramatically increasing the value of IMAs. Since then, the importance of allylindium compounds to synthetic

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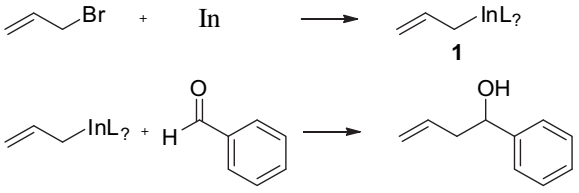
chemists has mushroomed, as demonstrated by the frequent appearance of reviews.[1–3,13–17]

Typically, the reaction proceeds by stirring an allyl halide, indium powder, and an electrophile in a solvent, resulting in allylation of the electrophile. For example, Scheme 1 illustrates the allylation of benzaldehyde to form the homoallylic alcohol. However, this simple example belies the scope of the reaction. Variations in the electrophile and the allyl halide have broadened the synthetic scope of IMAs, which have been applied to the synthesis of a wide range of compounds including carbohydrates, natural products, drugs, heterocycles, and others.[13,14]



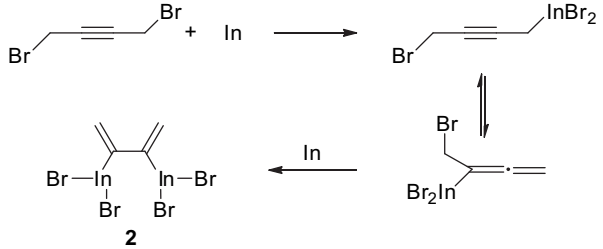
Scheme 1.

IMAs are often regio- and stereoselective, and many authors have made clever use of their selectivity, both to control product geometry and to explore the mechanism of the second step of the reaction (Scheme 1).[18–20] In some cases, the stereoselectivity is extraordinarily high.[21–25] In recent developments, indium has served to catalyze allylations.[26–29]

It is well established that the first step is reaction of the allyl halide with indium to produce an allylindium intermediate, **1** (Scheme 1).[30,31] In the second step, this intermediate then goes on to react with the electrophile. Because of the importance of IMAs, the structure of the organoindium intermediate(s) has been the subject of many studies over the past twenty years, and recent developments are especially significant. However, there still exists conflicting ideas in the literature regarding the nature of the allylindium intermediates, and this article reviews the accumulated experimental evidence for these intermediates. Although there have been many excellent reviews on the synthetic applications of IMA, to our knowledge, this is the first review to focus on the organoindium intermediates in IMA.

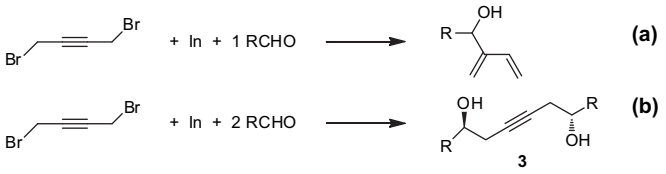
2. Two illustrations of the importance of knowing the intermediates' structure

In an illustration of the power of knowing the structure of the organoindium intermediate, in 2003 Miao et al.[32] investigated the reaction of 1,4-dibromobutyne with In in THF-d_8. After reaction overnight, the butyne was fully consumed, and two singlets at 6.33 and 5.56 ppm appeared in the ^{1}H NMR spectrum. ^{13}C NMR showed peaks at 164.4 (a methylene C by DEPT) and 130.8 ppm (with no attached H). By ESI-MS, a cluster of peaks was attributable to $[C_4H_4In_2Br_5]$. These data combined with COSY, HSQC, and HMBC experiments are all consistent with 2,3-butadienyldiindium tetrabromide, **2**, as the intermediate (Scheme 2).

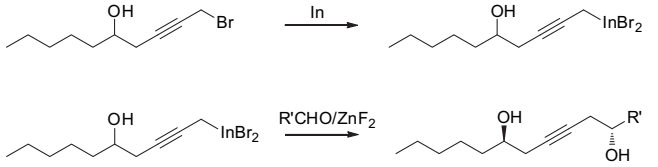


Scheme 2.

By knowing the structure of this intermediate, a complex reaction scheme was elucidated. In the reaction of In and 1,4-dibromobutyne with 1 equiv of electrophile, butadienyl compounds are produced (Scheme 3a).[33,34] However, the reaction mixture is more complex in the presence of 2 equiv of electrophile, producing a mixture of diols including the 1,6-diol, compound **3**, with remarkable diastereoselectivity (Scheme 3b). Persuasive mechanisms accounting for the product mixtures were proposed based on the structure of the intermediate, allowing the authors to develop a modified strategy for an efficient synthesis of asymmetric diols (Scheme 4).[32]

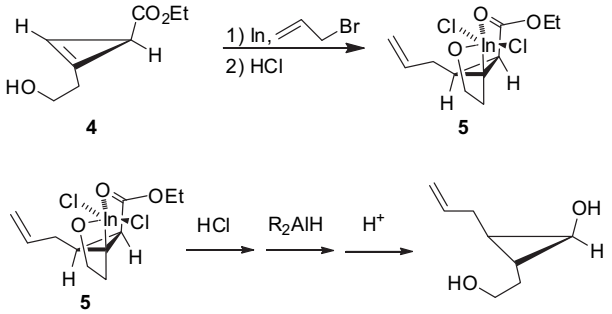


Scheme 3.



Scheme 4.

Another exemplary study illustrating the power of identifying the structure of organoindium intermediates is that of Araki et al.[35] They were able to crystallize a product from indium mediated allylation of substituted cyclopropenes. The reaction of substituted cyclopropene, **4**, with indium powder and allyl iodide in THF followed by workup in HCl adds the allyl group cis to the ester substituent, **5**, Scheme 5. Although strictly speaking **5** is not the intermediate, it is highly analogous to the intermediate. Protonation and reduction of **5** results in the allylated cyclopropane.



Scheme 5.

The crystal structure of **5** unambiguously establishes the importance of chelation of the indium by the hydroxyl and carbonyl oxygens in the regio- and stereoselectivity of the allylation. When the reaction is performed in water rather than THF, the regio- and stereoselectivity are reversed. Based again on the crystal structure of **5**, this is easily rationalized by hydration of the indium interfering with the intramolecular oxygen coordination.

Unfortunately, the structure of the intermediates for most indium mediated allylations are not nearly as well understood. The oxidation state of the metal in the organoindium intermediates has proven to be an intriguing question. Chan and Yang have interpreted ^{1}H NMR

studies of transient organoindium intermediates to suggest that the indium may prefer the In(I) oxidation state in aqueous solvents.[36,37] However, most characterized indium compounds occur as In(III), and very recent crystal structures of allylindium compounds have been obtained, all demonstrating In(III) complexes.[38–43] The structure remains ambiguous because many organoindium intermediates are not sufficiently stable to be isolated.

3. Organoindium compounds analogous to proposed allylindium intermediates

The purpose of this section is not to exhaustively review the literature, but rather to illustrate the range of known indium compounds that may offer precedence for organoindium intermediates proposed in the literature. There are many isolated and characterized organoindium compounds that may be analogous to the allylindium intermediates, including $R_3In_2X_3$, RIn, $RInX_2$, R_2InX, and R_3In, (R=a wide variety of alkyl, aryl, alkenyl, and alkynyl groups, but rarely allyl or benzyl), Fig. 1, compounds **6**–**10**.

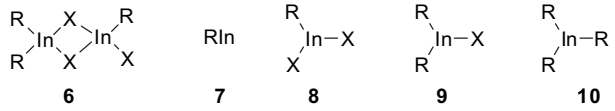


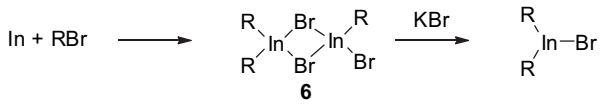
Fig. 1. Known organoindium compounds that offer precedence for intermediates.

The earliest work in this area was done by Dennis et al.[44] in 1934 who prepared trimethylindium by transmetallation of dimethyl mercury with indium metal. Schumb and Crane[4] reacted triphenylindium with stoichiometric amounts of Br_2 or I_2 in benzene to prepare R_2InX and $RInX_2$ (R=phenyl, X=Br or I). In these very early works, compounds were characterized only by elemental analysis.

In 1967, Clark and Picard[5] prepared trimethylindium by transmetallation with methyl lithium. By reacting trimethylindium with $InCl_3$ they prepared R_2InX (R=methyl, X=Cl), which occurred as a dimer in benzene. Similar compounds were prepared with X=I, F, and −OMe. The pyridine adducts of R_2InX (R=methyl, X=Cl, I) were prepared, isolated, and characterized by elemental analysis, IR, and ^1H NMR.

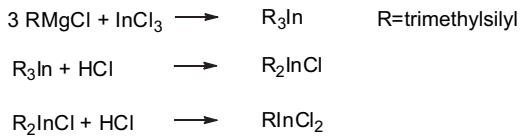
In 1972, Gynane et al.[6] and Poland and Tuck[9] concurrently synthesized a series of $RInX_2$ (R=methyl, ethyl, propyl, butyl; X=Br or I) by oxidative addition of the organohalide to InX. The compounds were characterized by Raman, IR, ^1H NMR, MS, molecular weight (in solution), and elemental analysis, and they were shown to exist as dimers or higher associations.

Gynane et al.[7,8] reacted In(0) with alkyl halides. MS, IR, and Raman spectra indicated that many of the compounds existed as the sesquihalides, **6**, $R_3In_2X_3$ (e.g., R=Et, X=Br or I, Scheme 6). Interestingly, reaction of the sesquihalide with KBr or KI produced a complex mixture from which the volatile R_2InX could be separated (Scheme 6).



Scheme 6.

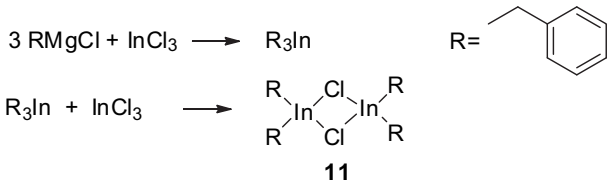
Beachley and Rusinko[45] prepared the series $RInX_2$, R_2InX, and R_3In where R=(trimethylsilyl)methyl and X=Cl. The compound $In(CH_2SiMe_3)_3$ was synthesized by transmetallation with the corresponding Grignard reagent and $InCl_3$. R_2InX and $RInX_2$ could be prepared and isolated quantitatively by reacting R_3In with either $InCl_3$ or HCl in the proper ratio, suggesting that the reactions go to completion (Scheme 7). The compounds were characterized by molecular weight, ^1H NMR, and IR. Across the series, the ^1H NMR resonance of the In−CH_2− protons occurred within 0.3 ppm of each other ($RInCl_2$ at 0.23, R_2InCl at 0.33, and R_3In at 0.02 ppm), illustrating the challenges of distinguishing the structure of organoindium compounds by relying on NMR alone.



Scheme 7.

Nomura et al.[46,47] prepared and studied a series of trialkylindium compounds, and Robinson et al.[48] synthesized R_2InX (R=$Ph_2C_6H_3$− and X=Cl) with a transmetallation between RLi with $InCl_3$. These compounds were characterized by elemental analysis and ^1H and ^{13}C NMR.

1989 Barron[49] applied Beachley's strategy[45] to synthesize the series R_2InX, $RInX_2$, and R_3In with R=benzyl and X=Cl. R_2InX and $RInX_2$ were found to be dimers, e.g., **11**, while the R_3In was a monomer (Scheme 8). Knochel et al.[50] recently synthesized (benzyl)(propyl)indium halide.

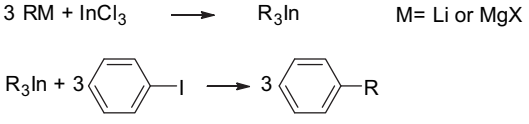


Scheme 8.

Koszinowski et al.[51] reacted charge-tagged alkyl iodides (e.g., R=trimethyl-(4-iodobutyl)-ammonium iodide) with indium powder and detected the $[R_2InI_2]^-$ indate by electrospray-ionization mass spectrometry.

A wide range of R_3In compounds have been reported, and Sarandeses et al.[52–55] pioneered their applications in coupling reactions with electrophiles. The structure of these organoindium intermediates have been determined largely by analogy to earlier reports,[5,45–47] stoichiometry of the preparation, and yield of products after reacting the organoindium with electrophiles.

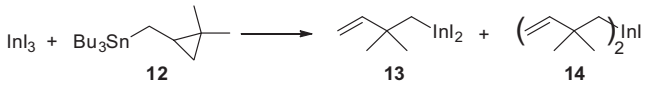
For example, in 2001 Sarandeses et al.[53] reported the formation of triorganoindiums (R_3In) by transmetallation in THF of Li or Mg precursors (R=a wide range of alkyl, vinyl, aryl, and alkynyl groups but not allyl, Scheme 9). The organoindium compounds were not isolated but used directly for coupling to aryl halides, during, which all three of the organic groups were transferred (Scheme 9).[53,55,56] They also reported the formation of R_2InX and $RInX_2$ (controlled by the ratio of $InCl_3$ to RLi), which transferred two and one R groups, respectively, in the subsequent coupling reaction. All three of the compounds of the series R_3In, R_2InX, and $RInX_2$ series have comparable reactivity.[53]



Scheme 9.

Similarly, Oshima et al. prepared R_3In (R=phenyl, aryl, vinyl, and alkyl).[57] Others, for example, Lee et al.[58,59] and Minehan et al.,[60,61] have extended the reaction chemistry of R_3In compounds. Lee[62] also prepared tetraorganoindates, R_4InLi.

Very recently, Baba et al.[63–65] reported an interesting transmetallation between substituted cyclopropylmethylstannanes, **12**, and InI_3 to produce butenylindium species. As illustrated in Scheme 10, both monobutenyl (**13**, $RInI_2$) and dibutenyl (**14**, R_2InI) complexes could be prepared.



Scheme 10.

Organoindium compounds with the indium in the +1 oxidation state are relatively rare.[36,66–68] As has been well demonstrated, In(I), as the free ion and in most compounds, typically disproportionates to In(III) and In(0).[3,26,67–70] Furthermore, water oxidizes In(I) to In(III), generating hydrogen gas.[71–74]

CyclopentadienylIn(I) has been prepared in ether by reacting $InCl_3$ with excess sodium cyclopentadienide, and it is very air sensitive.[66] CpIn(I) is a Lewis base, forming boron trihalide adducts, such as $CpInBX_3$.[75]

Beachley et al.[74] synthesized and characterized a series of CpIn(I) compounds, which are extremely water sensitive, being hydrolyzed to hydrogen gas and In(0) metal.[74] In spite of its hydrolytic sensitivity, CpIn(I) reacts with aldehydes in 4:1 THF/water, adding the cyclopentadienyl ring to the carbonyl carbon, similar to the reactivity of allylindium reagents.[37]

4. Reported allylindium compounds and their reactivities

While a number of allylindium compounds have been reported (Fig. 2), until recently, none had been fully characterized. An early effort to produce allyl or benzylindium compounds by oxidative addition of allyl halide to InX resulted in decomposition to an orange solid and HBr gas.[9] In a very brief communication, Gynane et al. reported the preparation of the highly reactive allyl and benzyl compounds ($RInX_2$, R=allyl or benzyl, X=Br or I) if stabilized as dioxane adducts,[76] but, to our knowledge, the full paper was never published.

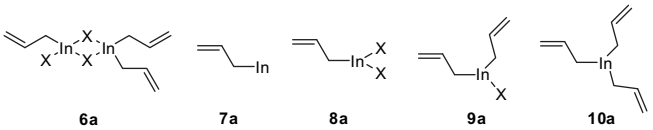
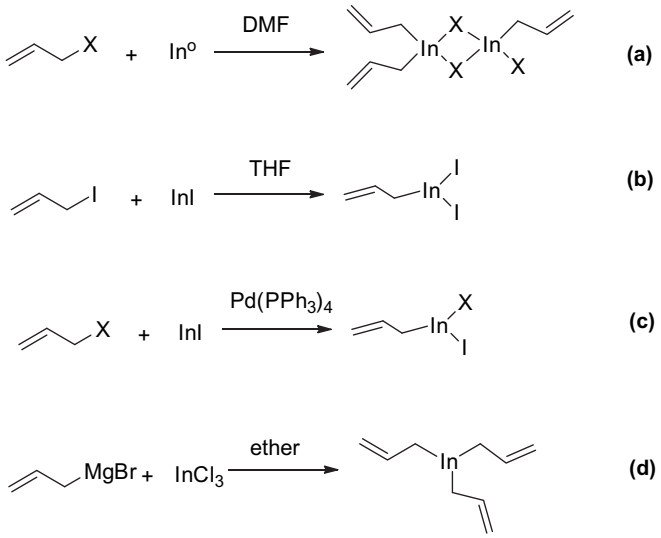


Fig. 2. Allylindium compounds proposed as intermediates.

In a series of papers, Araki et al.[10,77–84] have described preparation of allylindium intermediates using four different strategies, and these compounds offer a rich and varied chemistry. Based on partial characterization and the chemistry of analogs, they have suggested structures for the intermediates (Scheme 11a–d), and they have compared the reactivity of the allylindium species generated by each of the strategies.

As will be described in detail in the following section, in 1988 Araki et al. reacted allyl iodide with indium powder in DMF to form an allylindium intermediate that has proven exceedingly useful to synthetic chemists.[10,11] They assigned this intermediate a sesquihalide structure (Scheme 11a).

In 1989, Araki et al.[77] reacted allyl iodide with InI and reported the IR and ^1H NMR spectra in THF-d_8, which were consistent with allylindium(III) diiodide, $RInX_2$ (with ^1H NMR signals at 5.96 (1H), 4.92 (2H), and 2.14 ppm (2H)) (Scheme 11b). Furthermore, this structure is consistent with the products of analogous reactions with alkyl halides.[6,9]

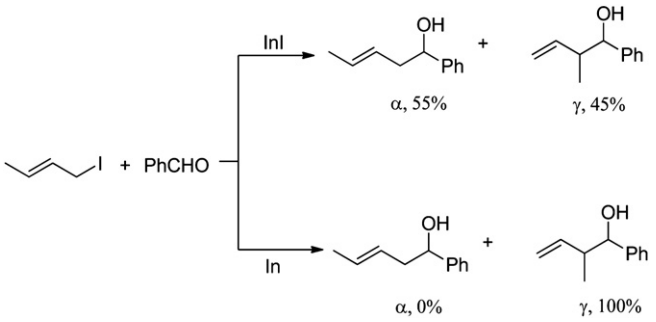


Scheme 11.

Later Araki et al.[78] invoked a similar structure as an intermediate in reactions catalyzed by $Pd(PPh_3)_4$ (Scheme 11c). They found that they could do indium mediated allylations with a wide variety of leaving groups by reacting allylX (for example, X=Cl, OAc, OPh, OH, SMe) with InI in the presence of 5 mol % $Pd(PPh_3)_4$. To get evidence for the structure of the intermediate, they reacted InI with allyl chloride in the presence of the catalyst in DMF-d_7, yielding peaks at 5.96 (1H), 4.67 (2H), and 2.08 ppm (2H), within approximately 0.2 ppm of the peaks of the formal allylindium diiodide described earlier.[77] In a later paper, the same indium intermediate was invoked using $Ni(acac)_2$ as the catalyst.[79]

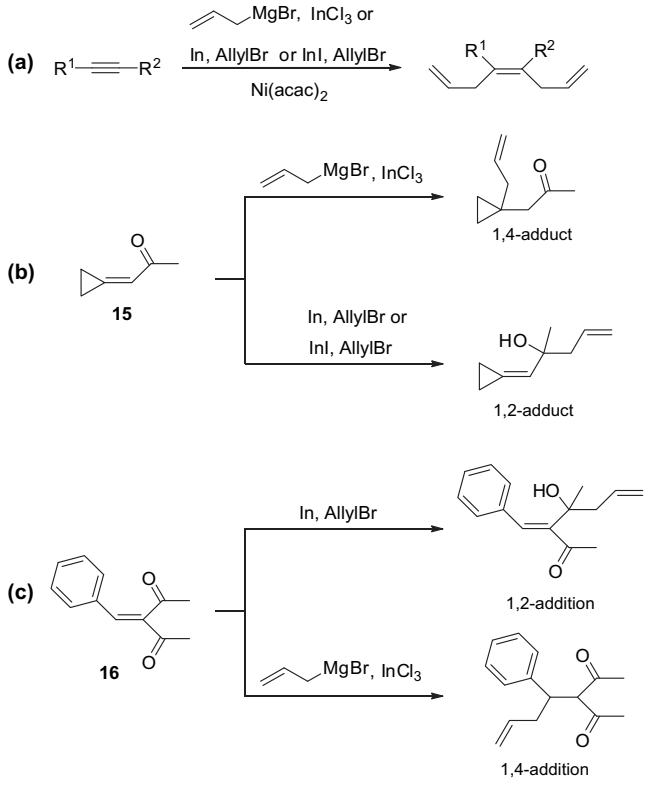
Araki et al.[80–83] reacted $InCl_3$ in THF with allylmagnesium bromide in ether at −78 °C, warmed to room temperature, and then used the presumed triallylindium in further reactions (Scheme 11d). (A recent paper by Okuda et al.[43] describes synthesis and full characterization of triallylindium, and this paper is discussed below).

Araki et al.[77] compared the regioselectivity of the allylindium compound prepared by indium metal and allyl halide, the presumed indium sesquihalide, with that prepared from InI and allyl iodide. When they mediated the addition of crotyl iodide to benzaldehyde with InI, the regioselectivity α/γ ratio was 55:45. In contrast, the mediation with indium metal gave only γ coupling (Scheme 12).



Scheme 12.

In a demonstration of the importance of the structure of the intermediate, they compared the reactivity of the formal indium sesquihalide (Scheme 11a), allylindium diiodide (Scheme 11b), and triallylindium (Scheme 11d). For nickel catalyzed bis-allylation of internal alkynes (Scheme 13a),[81] the reactivity of the three compounds is similar, although yields are higher for the formal triallylindium. For the allylation of methylenecyclopropanes, **15**, (Scheme 13b),[82] triallylindium gives the 1,4-adduct while the other two compounds give the 1,2-adduct. Similarly, in reaction with α,β-unsaturated carbonyls, e.g., **16** (Scheme 13c),[80] indium sesquihalides gave 1,2-addition while triallylindium gave 1,4-addition.



Scheme 13.

In similar studies, Araki et al.[35,84] demonstrated that the inorganic ligand (e.g., I vs OAc) on the indium center can affect reactivity. For example, in some cases the crotylation and cinnamylation of aldehydes proceeded with very different *syn*/*anti* ratios depending on the nature of the intermediate. Again, although the precise structures of the intermediates were not determined, putative structures were given based on the method of preparation. The data in Table 1 show that the *syn*/*anti* ratios for γ crotylation of benzaldehyde (Scheme 14a) vary drastically with the intermediate. In contrast, Table 2 shows that while the yield varies slightly, the stereochemical outcome of cinnamylation of *o*-salicylaldehyde (Scheme 14b) is largely independent of intermediate structure. (In the papers, the authors did not note the stereochemical purity of the crotyl or cinnamyl halide starting materials).

Finally, the yield and cis/trans ratio for the allylation of substituted cylcopropenes, e.g., **17**, (Scheme 14c) depends on the structure of the organoindium intermediate, as indicated in Table 3.[35]

Table 1
Dependence of yield and stereochemical outcome on putative intermediate structure for the crotylation of benzaldehyde in THF at room temperature[84]

Reactants	Putative intermediate	Yield	*syn*/*anti*
In, crotyl bromide	$Crotyl_3In_2Br_3$	78%	56:55
Crotyl chloride, InI, $Pd(PPh_3)_4$	CrotylInICl	98%	37:63
Crotyl acetate, InI, $Pd(PPh_3)_4$	CrotylInI(OAc)	72%	71:29

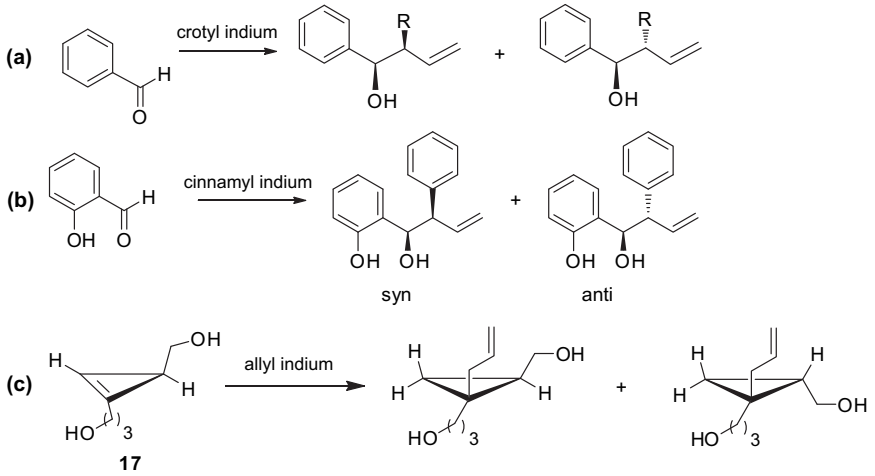
Table 2
Dependence of yield and stereochemical outcome on putative intermediate structure for the cinnamylation of *o*-salicylaldehyde in THF at room temperature[84]

Reactants	Putative intermediate	Yield	*syn*/*anti*
Cinnamyl chloride, InI, $Pd(PPh_3)_4$	CinnamylInICl	86	24:76
Cinnamyl acetate, InI, $Pd(PPh_3)_4$	CinnamylInI(OAc)	86	21:79
CinnamylLi, $InCl_3$	$Cinnamyl_3In$	50	27:73

Table 3
Dependence of yield and stereochemistry on putative intermediate structure for the allylation of substituted cyclopropene, 1-(3-hydroxypropyl)-3-(hydroxymethyl) cyclopropene[35]

Reactants	Putative intermediate	Yield	cis/trans
In, allyl iodide	$R_3In_2I_3$	72%	72:28
In, allyl bromide	$R_3In_2Br_3$	58%	56:44
Allylmagnesium bromide, $InCl_3$	R_3In	36%	53:47
Allyl bromide, InBr	$RInBr_2$	48%	31:69
Allyl iodide, InI	$RInI_2$	54%	23:77

These studies demonstrate very clearly that various preparations of allylindium compounds often lead to intermediates of similar, but not identical, reactivity.



Scheme 14.

5. In situ studies of allylindium intermediates during reaction of allyl halides with indium metal

Because it is readily available and makes rapid measurements in solution, most efforts at in situ characterization of indium intermediates during IMA have been done by ^{1}H NMR. The peaks of the protons α to indium (see **18** in Fig. 3) are most informative because they do not overlap with the multiplets of the hydrogens bonded to sp^2 carbons, they are well shifted from their signal in the starting material due to difference in electronegativities of Br and In, and they are the protons closest to the metal and thus most sensitive to information about the metal center.

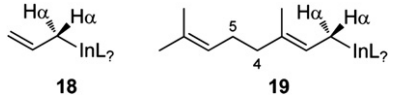


Fig. 3. Protons whose signals in the NMR spectra are most helpful.

On the other hand, these signals are often broad and almost always fall into a relatively narrow range of the spectrum, between 1.6 and 2.1 ppm (see Table 4). Furthermore, coupling constants, resulting from splitting by the hydrogens on the olefin carbons, are not very sensitive to the nature of the metal center.

Table 4
^{1}H NMR signals observed for protons alpha to indium during reaction of allyl halide with indium powder in NMR tube

d-Solvent	Peak A/ppm	Peak B/ppm	Refs.
DMF	2.0	1.7	10,36,70,91,94,95
D_2O	[a]	1.7	36,42,70
THF	2.03	1.74	89,95
MeOH	1.92	1.68	90
Ionic liquid	2.02	1.75	92
$CDCl_3$	2.1	1.7	93
DMSO	1.75	1.62	94
DMSO/D_2O	[a]	1.60	94
THF/D_2O	[a]	1.90	94

[a] Not observed.

In the first communication characterizing an intermediate of IMA, Araki et al.,[10] reacted indium with allyl iodide in deuterated DMF in an NMR tube and observed signals for the allylic protons at 1.75 and 2.02 ppm with relative integrations of approximately 2:1. They interpreted these signals as consistent with the sesquihalide structure, **6a**. In the following full paper, Araki et al.[11] reported the ^{1}H NMR of the intermediate, **19**, where the allyl=geranyl (3,7-dimethyl-2,6-octadienyl, Fig. 3). The selection of this compound is curious because the signals for the protons on C-4 and C-5 overlap with the protons alpha to the indium from 1.88 to 2.12 ppm, making interpretation (including relative integrations) impossible. Thus, it could neither support nor contradict the assignment of the structure.

In 1999, Chan and Yang[36] repeated the experiment, reacting allyl bromide with indium in DMF-d_7. They found the same two signals at 1.75 and 2.02 ppm for the alpha protons, but the relative integrations varied with time, indicating the two signals represented different compounds, inconsistent with the sesquihalide, **6a**. When they performed the reaction in D_2O, they found one broad doublet at 1.7 ppm, which they attributed to allylindium(I). Chan and Yang[36] offer three lines of evidence to support an In(I) intermediate in aqueous solutions: ionization potentials, preparation of the intermediate beginning with InI, and failure to prepare the intermediate beginning with $InBr_3$. Since then, various authors have suggested alternative interpretations for each of these observations.

First, the ionization potential (IP) is the energy required to remove an electron from a gaseous atom to produce a gaseous ion.[85] Thus, IPs ignore the substantial energy of the In–In bonds in the metallic reactant and, more importantly, the solvation and ion-pairing energies in the products. In spite of their irrelevance to IMA, discussion of the IPs of indium has proliferated in the literature.[3,12,15,37,86,87] Much more relevant than IPs, reduction potentials, E^o, accurately represent the relative energies of the free indium ions, and they indicate that In^{3+} is more stable in water than In^{1+} (E^o=−0.126 V for +/0; E^o=−0.338 V for+3/0).[3,68,71–73] Thus, in water In^{3+} is more stable than In^+ by a substantial 80 kcal/mol. However, even reduction potentials are an incomplete indicator in predicting the formal oxidation state of the indium intermediates because they ignore the contributions of the C–In bonds.

Second, the claim that the ^{1}H NMR doublet of the intermediate at 1.7 ppm was produced by transmetallation of In^+ and diallylmercury in water is also arguable because In^+ rapidly disproportionates to In^0 and In^{3+} in water (Scheme 15).[3,67–72] Thus, it is more likely that the diallylmercury was actually reacting with In^{3+} than In^{1+}.Two authors[69,70] have reported the presence of a shiny indium metal nugget throughout the IMA reaction, possibly resulting from disproportionation of indium intermediates during the reaction.

$$3\ In^{+1}{}_{(aq)} \rightarrow 2\ In^{0}{}_{(s)} + In^{+3}{}_{(aq)} \qquad K=1 \times 10^{11}$$

Scheme 15.

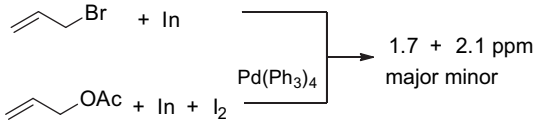
Third, it has been shown that $InBr_3$ rapidly undergoes hydrolysis in water to produce insoluble indium(III) hydroxides.[88] Consequently, it is not surprising that the reaction of $InBr_3$ and diallylmercury was unsuccessful.

These NMR tube experiments[36] prompted subsequent studies by others, but none of these studies was able to assign the oxidation state(s) of the indium intermediates. For example, in 2002, Takai and Ikawa[89] reported that reaction of In(0) with allyl bromide in THF-d_8 produced a peak for allylindium dibromide (**8a**) at 2.03 ppm and diallylindium bromide (**9a**) at 1.74 ppm, but the assignments were not justified.

Vilaivan et al.[90] reacted allyl bromide with indium in methanol-d_4 and observed signals at 1.92 and 1.68 ppm. Addition of *N*-benzylidenebenzylamine consumed the intermediate corresponding to the peak at 1.92 ppm. Preite and Pérez-Carvajal (2006)[91] reacted allyl bromide with indium in DMF-d_7 and observed signals at 2.02 and 1.75 ppm. They noted that the peaks must belong to two different intermediates because of their changing relative integrations over time. The peak at 2.02 ppm disappeared rapidly in the presence of water.

In 2007, Chan et al. studied indium mediated allylations in ionic liquids, [*N*-butylpyridine][BF_4] and [*N*-butylpyridine][Br].[92] Again, reaction of indium powder with allyl bromide in an NMR tube yielded two compounds, one with a peak at 1.75 and another at 2.02 ppm. With time, the peak at 1.75 decreased while the peak at 2.02 ppm increased. Adding an imine, *N*-benzylideneaniline, to a mix of the two intermediates and monitoring by ^{1}H NMR demonstrated that the intermediate at 1.75 ppm was more reactive than that at 2.02 ppm. By analogy to their earlier results,[36] they assigned the peak at 1.75 ppm to allylindium(I). They then reacted allyl bromide with InBr to generate the presumed allylindium dibromide ($RInX_2$), which had peaks at 2.04, 4.71, and 4.88 ppm, consistent with the peaks generated with indium powder and allyl bromide. Therefore, they assigned the second intermediate the structure allylindium dibromide.

In contrast with Araki[78] (vide supra, Scheme 11a and c), Yanada et al.[93] detected the same allylindium intermediates whether starting with indium metal and allyl bromide or with indium metal, iodine, allyl acetate, and 5 mol % $Pd(PPh_3)_4$. By ^1H NMR in $CDCl_3$ they found two intermediates as evidenced by the protons alpha to the indium giving signals at 1.7 ppm (major) and 2.1 (minor) (Scheme 16).



Scheme 16.

The data for reaction of allyl bromide with In powder are summarized in Table 4. In non-aqueous solvents, two peaks were consistently observed. As a general rule, the intermediate responsible for Peak A (the downfield peak) was unstable in water, but stable to oxygen. The intermediate responsible for Peak B (upfield) was stable in water and unstable to air, presumably reacting with oxygen. Surprisingly then, the latter intermediate did not react with *N*-methylmorpholine-*N*-oxide, an oxidizing agent.[70]

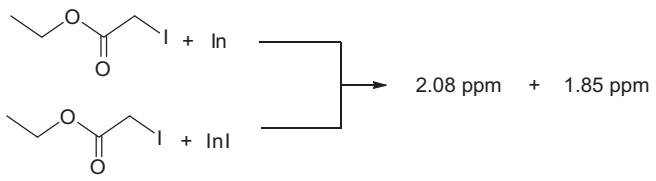
Similar NMR tube studies have explored the reaction of substituted allyl halides with indium (see Table 5). Lombardo et al.[96] reacted 3-bromopropenyl acetate with indium in THF-d_8 and interpreted the complex spectra as evidence for three intermediates (Scheme 17). They noted that they did not have evidence for the oxidation states of indium in these intermediates, but suggested that they may all be In(III). In contrast, in D_2O, they found evidence only for the (*Z*) γ, **20**, (Scheme 17) intermediate with the protons alpha to the In at 1.57 ppm.

Table 5
^1H NMR signals observed for protons alpha to indium during reaction of substituted allyl halides with indium powder in NMR tube

Allyl halide	Solvent	Peaks/ppm	Refs.
3-Bromopropenyl acetate	D_2O	1.57	96
Cinnamyl bromide	MeOH	2.11	70
Cinnamyl bromide	D_2O	1.93	70
Crotyl bromide	MeOH	1.83–1.91	70
Crotyl bromide	D_2O	1.63–1.70	70
Prenyl bromide	MeOH	1.83	70
ICH_2CO_2Et	THF	2.08, 1.85	97
$BrCH_2CO_2Et$	THF	1.96, 1.81	97

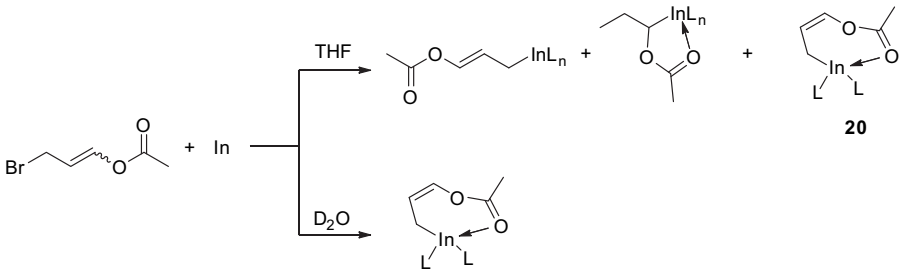
presumably including *trans* and *cis* isomers (1.83–1.91 ppm in methanol-d_4 and 1.63–1.70 ppm in D_2O). Indium and prenyl bromide generated a single intermediate in methanol-d_4 with a doublet at 1.83 ppm. Reaction of indium with (bromomethyl)acrylate in organic solvents generated two intermediates (singlets at 1.83 and 2.06 ppm in methanol-d_4 and 1.89 and 2.20 ppm in THF-d_8) while reaction in water generates a single intermediate, represented by a singlet at 1.83 ppm. In all these cases, reaction with benzaldehyde yielded the expected alcohol.

While the Reformatsky reaction is not an IMA, the intermediate is analogous to those discussed in this article. In 2004, Baba et al.[97] carefully recorded and interpreted spectra while reacting ICH_2CO_2Et with indium in THF-d_8. They observed peaks attributable to two different intermediates at 2.08 and 1.85 ppm (Scheme 18). While both reacted with benzaldehyde, the compound corresponding to the peak at 1.85 ppm reacted more rapidly. They also observed a singlet at 1.84 ppm, which they showed to be the methyl protons of CH_3CO_2Et. Interestingly, when they reacted ICH_2CO_2Et with InI, they found very similar results: intermediate peaks at 2.08 and 1.86 ppm with the same relative reactivities toward benzaldehyde. Again, production of CH_3CO_2Et was observed. The authors were cautious in their interpretation, simply commenting that 'it is informative that the same kinds of transient active species are involved in both the indium metal and In(I)X systems'.



Scheme 18.

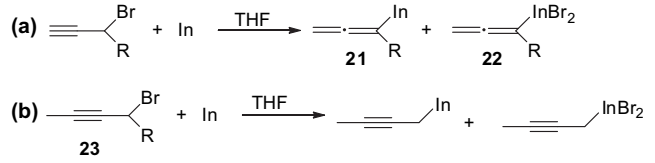
Reaction of unsubstituted propargyl bromide with indium was similar to that of allyl bromide.[98] In THF, two discrete intermediates were detected by ^1H NMR (doublets at 4.22 and 4.02 ppm). In this case, the intermediate giving the more upfield signal proved to be more reactive toward water and less reactive toward electrophiles than the intermediate showing peaks more downfield. In D_2O, only the upfield doublet (4.04 ppm) appeared. Reaction of propargyl bromide with InBr produced a compound with a spectrum matching the more upfield intermediate. By ^{13}C NMR, both



Scheme 17.

Singaram and his students[70] reacted cinnamyl bromide with indium, generating a single intermediate, which displayed a doublet (at 2.11 ppm in methanol-d_4 and 1.93 ppm in D_2O). Reaction of indium with crotyl bromide yielded overlapping signals, intermediates showed peaks very far downfield (211.5 and 211.2 ppm) suggesting an allenyl structure, which was confirmed by DEPT measurements. In analogy with their earlier work,[36] they assigned the structures as allenylindium(I), **21**, and

allenylindium(III) dibromide, **22** (Scheme 19a). Reaction of 3-bromo-1-butyne with indium gave entirely analogous results. Reaction of 1-bromo-2-butyne, **23**, gave similar results except that the intermediates preferred the propargyl configuration (Scheme 19b).



Scheme 19.

Reactions of 1-halo-2-alkynes with indium have been studied by ^{19}F NMR. Wang and Hammond[69] studied the reaction of *gem*-difluoropropargyl bromides, **24**, (Fig. 4) with indium powder in aqueous THF. They observed the appearance of a single peak at −88 ppm, which disappeared when benzaldehyde was added. Further studies by Hammond[38,39] are discussed below.

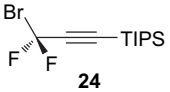


Fig. 4. Example of difluoropropargyl compound.

ESI-MS, which offers the opportunity to detect ions in solution without fragmenting them, suggests a more complex picture. In a powerful combination of MS with variable temperature ^1H NMR and conductivity, Koszinowski[95] recently demonstrated that multiple allylindium complexes are in solution, many of them in equilibrium with each other. All species were identified by their initial *m*/*z* ratio and isotopic patterns, as well as by fragmentation patterns of the individual ions. Furthermore, careful selection of the voltages on the heated capillary and the tube lens supported the interpretation that the signals represent what is in solution rather than ions formed or altered in the electrospray process.

After reacting indium powder with allyl halide, Koszinowski found three species that occur in either DMF and THF for X=Br or I and R=allyl: InR_2^+, $InRX^+$, $InRX_3^-$, all with varying degrees of solvation. In DMF but not THF, InR^{2+} was also detected. In THF but not DMF, di- and trinuclear species were found: $In_2R_4X^+$, $In_2R_3X_2^+$, $In_2R_3X_4^-$, $In_2R_2X_5^-$, and $In_3R_4X_6^-$. The differences in the two solvents were attributed to DMF being a very strong donor solvent while THF is relatively weak.

In 1:1 aqueous DMF, the reaction of indium powder with allyl iodide yielded solvated InR^{2+}, InI^{2+}, $InRI^+$, and $InRX_3^-$. The low solubility of allyl halides and the high surface tension in 100% water make measurements more challenging, but for X=I, Koszinowski demonstrated the existence of $In_2R_3I_2^+$ and $In_2R_2I_3^+$ in water.[95]

While recognizing that ESI-MS detects only charged species, so is blind to RIn, Koszinowski notes that he finds only evidence for In(III) species in solution and does not find even indirect evidence for allylindium(I) (such as In_2R^+ or $InRX^-$).

Koszinowski complemented these studies with variable temperature ^1H NMR spectroscopy.[95] At room temperature, his results correspond to those described above in Table 4, showing two doublets at 1.75 and 1.95 ppm. In DMF, increasing the temperature leads to broadening, and then merging at 333 K, of the two doublets. Decreasing the temperature to 213 K sharpens the upfield doublet and broadens the downfield doublet. In THF, both doublets broaden and merge at high temperatures, but neither broadens at low temperature. Perhaps most interesting, in water the single doublet at 1.7 ppm is unaffected by temperature from 278 to 313 K.

Taken together, Koszinowski[95] proposed two equilibria (Scheme 20) consistent with his data while recognizing that other equilibria seem likely.

$$R_3In_2X_3 \leftrightarrow InR_2^+ + InRX_3^-$$

$$InRX_3^- + RInX_2 \leftrightarrow In_2R_2X_5^-$$

Scheme 20.

The first equilibrium has a larger K in relatively polar solvents, like DMF and water. The K of the second equilibrium is larger in solvents like THF because of its low donor strength, which favors aggregation.

The value of indium mediated allylations and propargylations is enormously increased by their enantioselectivity.[16,21–25,99–104] Several authors have used the enantioselectivity to propose hypothetical transition states during the attack on electrophiles by the organoindium intermediates, but there has been no direct evidence of the structure of the enantiomeric complex between allylindium and various chiral ligands. Cook et al.[103] offered preliminary ^1H NMR evidence that BINOL complexes with allylindium intermediates, but the structure of those complexes remains an intriguing question that richly merits further study.

6. Stoichiometry of reaction of allyl halides with indium metal

The stoichiometry of the formation of organoindium intermediates can offer important evidence for the oxidation state of the indium.[31,69,94,95]

If allylIn(I) is formed, several reasonable balanced equations, Eqs. 1–3, can be hypothesized.[69] The simplest is Eq. 1, with an In/allyl bromide stoichiometry of 1:1. However, the bromine radical produced in Eq. 1 would rapidly form Br_2, which would then oxidize In(0), so a more reasonable hypothesis for forming allylindium(I) is Eq. 2, with an In/allyl bromide ratio of 2:1.

$$In^0 + \text{allyl bromide} \rightarrow \text{allylIn(I)} + Br \quad (1)$$

$$2In^0 + \text{allyl bromide} \rightarrow \text{allylIn(I)} + InBr \quad (2)$$

In aqueous solution, InBr is known to undergo disproportionation followed by hydrolysis to form $In(OH)_3$.[67,68,71–73,88] If this pathway is operable, then an In/allyl bromide ratio of 4:3 would result, Eq. 3.

$$4In^0 + 3\text{allyl bromide} + 3H_2O \rightarrow 3\text{allylIn(I)} + In(OH)_3 + 3HBr \quad (3)$$

Many equations can be written for the formation of In(III) intermediates, and they all have a 2:3 stoichiometry. For example, if indium sesquihalide, $R_3In_2Br_3$, is formed, the balanced chemical equation is Eq. 4.[10,11]

$$2In^0 + 3\text{allyl bromide} \rightarrow \text{allyl}_3In_2Br_3 \quad (4)$$

If a mixture of R_2InBr and $RInBr_2$ are formed, then the reaction could be represented by Eq. 5.

$$2In^0 + 3\text{allyl bromide} \rightarrow \text{allyl}_2InBr + \text{allylInBr}_2 \quad (5)$$

If $allyl_3In(III)$ is formed in aqueous solution, the most likely balanced reaction is Eqs. 3 and 6, with a 2:3 ratio. The production of $In(OH)_3$ and HBr in Eqs. 8 and 11 is consistent with the observed white precipitate and the decrease in pH over the course of the reaction in aqueous solutions.[12,31,105]

$$2In^0 + 3\text{allylbromide} + 3H_2O \rightarrow \text{allyl}_3In(III) + In(OH)_3 + 3HBr \quad (6)$$

Formation of other In(III) complexes likely would have the same stoichiometry.[31,94,95]

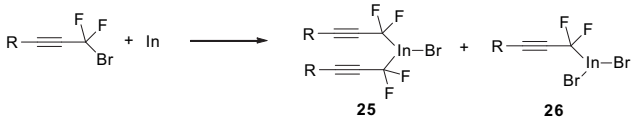
At least two authors have experimentally determined the stoichiometry of the formation of the organoindium intermediate (not including the reaction with the electrophile, which could change the In/allyl bromide ratio). Wang and Hammond[69] determined the stoichiometry by reacting varying quantities of metallic In with 1-TIPS-3,3,3-difluorobromopropyne, **24**, in THF/water. When 0.6 equiv of In was added, less than 1% of the metallic indium remained after consumption of all of the bromide, consistent (within the reported precision) with either a 2:3 or 1:2 ratio.

Bowyer et al.[31,94] reacted In metal with excess allyl bromide in deuterated 60% ethanol/40% D_2O in an NMR tube and monitored the consumption of the allyl bromide by integration and comparison with an internal standard. They found a ratio of 2:3 (2:2.99 with a relative standard deviation of 5%), consistent with formation of In(III) complexes.[94,95]

Thus, reports of the stoichiometry of the reaction of allyl bromide with indium metal are consistent with the formation of In(III) intermediates.

7. Crystal structures of organoindium intermediates

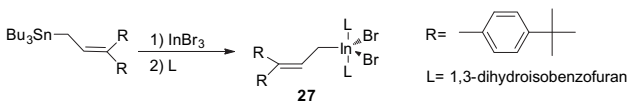
In the first determination of a crystal structure for an organoindium intermediate, Hammond et al.[38,39] reacted 3-substituted-1,1,1-difluorobromo-2-alkynes with indium powder in 1:4 THF-d_8/D_2O and observed two ^{19}F NMR peaks (−88.8 and −89.1 ppm) attributable to two intermediates. They were able to separate the two by flash chromatography and stabilize them by addition of DMSO, which presumably serves as a stabilizing ligand. ^{13}C NMR indicated that the intermediates were predominantly in the propargyl form, based on the absence of a downfield peak for the allenyl isomer. When the reaction is performed with 3-triphenylsilyl-1,1,1-difluorobromo-2-alkyne, both species could be crystallized and their X-ray crystal structure determined. The crystal structures unambiguously established the compounds as dipropargylIn(III) bromide (**25**, R_2InBr) and propargylIn(III) dibromide (**26**, $RInBr_2$) (Scheme 21). Both compounds are trigonal bipyramidal with the propargyl and bromide ligands equatorial. Two DMSO ligands occupy the axial positions. Elemental analysis for C, H, In, F, and Br confirmed the structures. The monopropargyl compound proved to be more reactive toward electrophiles and less reactive toward water than the dipropargyl compound.[38,39]



Scheme 21.

By ^{19}F NMR after short reaction times (e.g., 5 min), Xu and Hammond[39] detected fleeting intermediates at −88 and −112 ppm that precede the formation of the compounds described above. No paramagnetic species were detected by EPR, leading them to propose the intermediacy of low valent indium compounds. These species reacted rapidly with chlorobenzaldehyde to generate propargyl alcohols. Xu and Hammond make the important point that if fleeting intermediates are highly reactive, they can be more important under Barbier conditions (in which the electrophile is present during the formation of the organometallic species) than are preformed or isolable intermediates.[39]

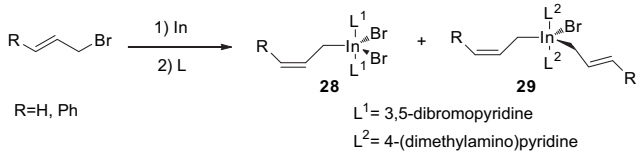
In a dramatic series of three papers in which they synthesized and fully characterized a series of allylindium intermediates, Baba et al.[40,41,42] have added greatly to our understanding of the organoindium intermediates during IMA. In the first paper,[40] they reacted $InBr_3$ with $Bu_3SnAllyl$, stabilizing the product with bulky substituents (R=*tert*-butylphenyl) and a strong Lewis base, 1,3-dihydroisobenzofuran (Scheme 22).



Scheme 22.

They were able to obtain a crystal structure for allyl$InBr_2 \cdot L_2$, **27**, which had a trigonal bipyramidal structure with the substituted allyl and two bromides equatorial and the two ligands axial. By ^1H NMR, the protons on the carbon alpha to the In were at 2.20 ppm (ACN-d_3) either with or without the ligands. The isolated compound was a good nucleophile, reacting with benzaldehyde to produce the corresponding homoallylic alcohol, albeit in a yield of 15% (the low yield was attributed to the bulky substituents on the allyl group). Direct reaction of the product of the allylstannane and $InBr_3$ with benzaldehyde (i.e., without isolating the intermediate as a solid) produced the same homoallylic alcohol in comparable (12%) yield.

In an even more significant contribution, Baba et al.[41] generated the cinnamylindium intermediate reductively, reacting cinnamyl bromide (Scheme 23, R=phenyl) with indium powder in THF to generate and isolate two intermediates, cinnamyl$InBr_2$ ($RInBr_2$) and cinnamyl$_2$InBr (R_2InBr). By adding 3,5-dibromopyridine as a ligand (L^1), they crystallized cinnamyl$InBr_2 \cdot L_2$, **28a**. In solution, the protons on the carbon alpha to the In were at 2.23 ppm. By adding 4-(dimethylamino)pyridine as a ligand (L^2), they crystallized cinnamyl$_2$InBr$\cdot L_2$, **29a**, which showed a signal at 1.97 ppm. The X-ray crystal structures of both were determined and again were shown to be trigonal bipyramidal with the cinnamyl and bromide groups in the equatorial positions. Both compounds, after isolation, reacted quantitatively with benzaldehyde to produce the homoallylic alcohol; the dicinnamyl compound, **29a**, was more reactive.

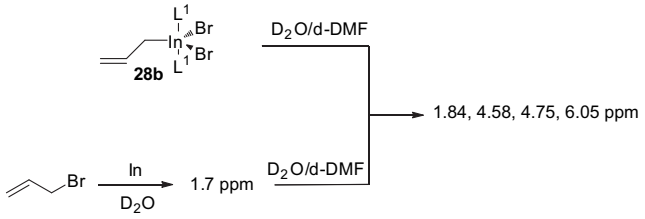


Scheme 23.

Most recently and significantly, Baba et al.[42] reacted unsubstituted allyl bromide (Scheme 23, R=H) with indium powder in THF. Analogous to their previous study, by adding L^1=3,5-dibromopyridine, they crystallized allyl$InBr_2 \cdot L_2$, ($RInBr_2$), **28b**, which showed an ^1H NMR peak at 2.31 ppm. By adding L_2=4-(dimethylamino)pyridine, they crystallized allyl$_2$InBr$\cdot L_2$, **29b**, (R_2InBr), which showed a resonance at 1.94 ppm. Both were characterized by X-ray crystal structure and again were shown to be trigonal bipyramidal with the allyl and bromide groups in the equatorial positions. Both isolated compounds reacted with benzaldehyde to produce the homoallylic alcohol in good yield. Consistent with earlier ^1H NMR tube experiments, the monoallylIn(III) dibromide (**28b**) was relatively stable to water, showing no detectable decomposition after 30 min in 3:1 DMF/water, while the diallyl complex (**29b**) was more water sensitive.

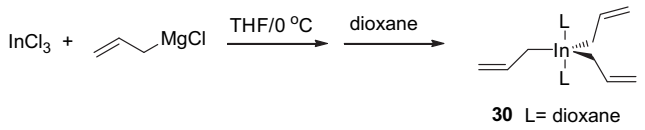
In order to compare their intermediate with that produced in water, they reacted allyl bromide with indium powder in D_2O to generate the ^1H NMR peak at 1.7 ppm attributed earlier to allylindium(I).[36] They then added DMF-d_7 and found that the spectrum of that intermediate matched the spectrum of the isolated allyl$InBr_2 \cdot L_2$, **28b**, when both were dissolved in DMF/D_2O. Because

of the matching spectra and similar reactivity, it is most reasonable to conclude that the intermediate of IMA in water is monoallylIn(III) dibromide (**28b**, Scheme 24).



Scheme 24.

Most recently, Okuda et al.[43] prepared triallylindium using transmetallation with $InCl_3$ and allylmagnesium chloride. Maintaining the solutions at low temperature until final purification of the compounds proved critical to successful synthesis of the compounds. Interestingly, ^1H NMR signals at room temperature are so broad due to fluxionality as to be almost lost in background. However, at −90 °C in THF-d_8, resonances were observed, including the alpha protons at 1.44 ppm. An X-ray crystal structure showed the compound, **30**, to be trigonal bipyramidal with the three allyl groups equatorial and either dioxane or THF in the two axial positions (Scheme 25).



Scheme 25.

By controlling the ratio of equivalents of indium chloride and Grignard reagent, the authors also prepared the R_2InCl and $RInCl_2$ analogs, which showed ^1H NMR doublets for the alpha protons at 1.65 and 2.00 ppm, respectively. The 2-methallyl analogs for all three compounds were also prepared and characterized. Unfortunately, these compounds have not yet been tested for allylation of electrophiles.

8. Conclusion

A better understanding of the mechanism and structure of the intermediates can lead to more rational use of IMA for synthesis. Until recently, two paradigms have dominated the literature, viewing the intermediate as a sesquihalide $R_3In_2X_3$ (in organic solvents) or as allylindium(I) (in water). However, recent contributions employing a variety of new strategies, including NMR, ESI-MS, kinetic studies, conductivity, and X-ray crystal structures, demonstrate that the structures are more accurately described as diallylindium bromide and monoallylindium dibromide.

Numerous questions remain. What is the mechanism for formation of diallylindium bromide and monoallylindium dibromide? Certainly other allylindium intermediates exist—what are their structures and how does structure determine reactivity? What equilibria exist among the various species? Answers to these fundamental questions will further the understanding of the rich and variable chemistry of allylindium intermediates and allow more rational design of syntheses.

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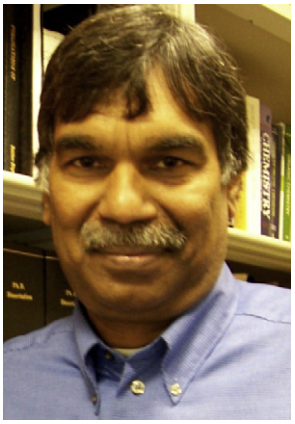

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