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Indium-Mediated Asymmetric Barbier-Type Allylations: Additions to Aldehydes and Ketones and Mechanistic Investigation of the Organoindium Reagents

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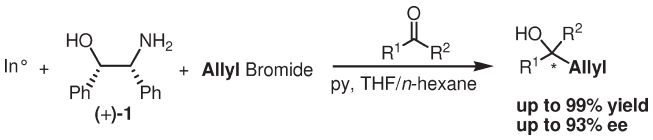

We report a simple, efficient, and general method for the indium-mediated enantioselective allylation of aromatic and aliphatic aldehydes and ketones under Barbier-type conditions in a one-pot synthesis affording the corresponding chiral alcohol products in very good yield (up to 99%) and enantiomeric excess (up to 93%). Our method is able to tolerate various functional groups, such as esters, nitriles, and phenols. Additionally, more substituted allyl bromides, such as crotyl and cinnamyl bromide, can be used providing moderate enantioselectivity (72% and 56%, respectively) and excellent diastereoselectivity when employing cinnamyl bromide (>95/5 *anti*/*syn*). However, the distereoselectivity when using crotyl bromide was poor and other functionalized allyl bromides under our method afforded low enantioselectivities for the alcohol products. In these types of indium-mediated additions, solvent plays a major role in determining the nature of the organoindium intermediate and we observed the susceptibility of some allylindium intermediates to hydrolysis in protic solvents. Under our reaction conditions using a polar aprotic solvent, we suggest that an allylindium(III) species is the active allylating intermediate. In addition, we have observed the presence of a shiny, indium(0) nugget throughout the reaction, irrespective of the stoichiometry, indicating disproportionation of indium halide byproduct formed during the reaction.

Introduction

The generation of stereogenic centers is a vital part of the synthesis of natural products and potential drug candidates, and the methodology developed for the asymmetric synthesis is a cornerstone in organic synthesis.[1] The metal-mediated asymmetric allylation of various carbonyls continues to be a valuable tool in the formation of the chiral alcohol functionality.[2] In particular, indium has been shown to be an effective metal in both allylations and propargylations.[3b,d,e,j,k] In the past few decades, indium has become a popular metal due to the ability of organoindium intermediates to tolerate functionality and ambient conditions along with indium being nontoxic.[3]

The first indium-mediated allylation reaction was performed by Butsugan and co-workers,[4] in which they used In° (1.5 equiv), allyl iodide (1.5 equiv), and benzaldehyde (1 equiv) in *N*,*N*-dimethylformamide (DMF) providing the racemic homoallylic alcohol in 87% yield. Later Loh and coworkers executed the first asymmetric indium-mediated allylation of benzaldehyde using cinchonidine as the chiral director.[5] They were able to afford the (*R*)-enantiomer in modest enantiomeric excess of 75% using an excess of allyl

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bromide (6 equiv). Not only has indium been used to mediate the allylation of aldehydes but it also has been shown to be effective in the allylation of ketones.[6] The latter additions are desirable due to the ability to synthesize chiral tertiary homoallylic alcohols, yet they are less extensively explored compared to the corresponding asymmetric addition to aldehydes.[7] Loh et al. reported that the asymmetric allylation of acetophenone using indium, cinchonidine, and 6 equiv of allyl bromide gave nearly racemic alcohol product whereas the allylation of trifluoroacetophenone afforded the homoallylic alcohol in 70% ee.[6b] Additionally, indium has been used in the addition of substituted allyl bromides to aldehydes,[8] specifically Bustugan and co-workers achieved a 34:66 *syn*/*anti* ratio using indium, crotyl bromide, and benzaldehyde.[4]

Our own efforts in organometallic addition reactions began with screening various limonene-based amino alcohols as effective chiral directors in the diethylzinc addition to aldehydes.[9] This led us to study the effectiveness of other terpene-derived amino alcohols as chiral directors in the indium-mediated Barbier-type asymmetric allylation of aldehydes. Accordingly, we examined various limonene and pinene-based amino alcohols synthesized in our laboratory,[10] along with commercially available ones in the indium-mediated Barbier-type allylation of aldehydes and ketones.[11,12] These studies revealed an efficient and simple one-pot procedure using a commercially available amino alcohol for the formation of chiral homoallylic alcohols in moderate to excellent enantioselectivity. Herein, we describe the full report on this work in our study of the asymmetric indium-mediated allylation of aldehydes and ketones using simple and substituted allyl and crotyl bromides. We will also give an account of our investigation of the allylindium intermediates formed using indium metal (In°) and allyl bromides under different solvent conditions.

Results and Discussion

Indium-Mediated Asymmetric Barbier-Type Allylations of Aldehydes. Following the stoichiometry that was reported in the literature for these types of indium-mediation allyations, we began our investigation by mixing benzaldehyde (1 equiv), a chiral ligand (2 equiv), In° (2 equiv), and allyl bromide (6 equiv) at −78 °C for 1.5 h. Under these conditions, we obtained the corresponding homoallylic alcohol in high yield but low enantioselectivity of 40% using limonene-derived (1*S*,2*S*,5*R*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol[13] as the chiral director. Next, we screened various commercially available chiral amino alcohols in this reaction. We were pleased to find that (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (+)-**1** proved to be an effective chiral director under our indium-mediated Barbier-type reaction conditions and gave the product alcohol in 60% ee.

We speculated that the enantioselectivity could be further improved by adjusting the stoichiometry of allyl bromide. We reasoned that the excess of allyl bromide could either be interacting with the chiral auxiliary or affecting the nature of the allylindium intermediates formed during the reaction. Hence, we rationalized that reducing the equivalents of allyl bromide would minimize the interference with the ligand and/or control the allylindium species formed, thereby increasing both conversion and enantioselectivity of the reaction. In addition, a stoichiometric amount of a Lewis base, such as pyridine, was added with the aim of scavenging the intermediate indium salts and thereby minimizing their influence on enantioselectivity. We decided to use heteroaromatic Lewis bases that contained a structural motif similar to cinchonidine, an effective chiral auxiliary for allyl indium reactions.[5,6b] Using quinine (2 equiv) as the Lewis base, In° (2 equiv), (+)-**1** (2 equiv), and allyl bromide (6 equiv), we were able to afford the homoallylic alcohol **2a** in good conversion of 84% but low enantioselectivity of 30% ee (Table 1, entry 1). Changing the Lewis base to 2,2-bipyridine showed only a slight improvement in the enantiomeric excess (Table 1, entry 2). Employing pyridine and increasing the equivalents of allyl bromide afforded **2a** in good enantiomeric excess of 76% (Table 1, entry 3). By simply decreasing the equivalents of allyl bromide from six to two, we significantly improved the enantioselectivity to 93% for **2a** (Table 1, entry 4). We were pleased to find that the addition of pyridine did indeed improve enantioselectivity and conversion. Enantiomeric excess dropped to 60% and the conversion to 65% in the absence of pyridine (Table 1, entry 5). We found that reducing the amount of either In°, allyl bromide, or the chiral ligand resulted in lower yield and enantioselectivity **2a** (Table 1, entries 6−8). It should be pointed out that we observed the presence of shiny indium

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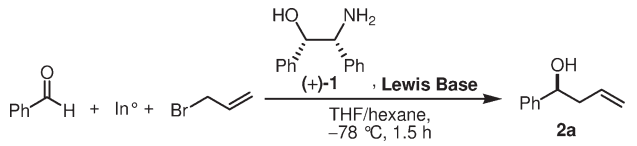
(13) (1*S*,2*S*,5*R*)-2-Amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol was synthesized from the *cis*-limonene epoxide and ammonia (unpublished results).

TABLE 1. Optimization of Enantioselective Allylation of Benzaldehyde[a]



entry	In°	(+)-**1**	Lewis base (equiv)	allyl bromide	% conv[b]	% ee[b] (*S*)[c]
1	2	2	quinine (2)	6	84	30
2	2	2	2,2-bipyridine (2)	2	85	36
3	2	2	py (2)	6	99	76
4	2	2	py (2)	2	99	93
5	2	2	py (0)	2	65	60
6	1	2	py (2)	2	50	66
7	2	2	py (2)	1	55	70
8	1	1	py (1)	1	50	79

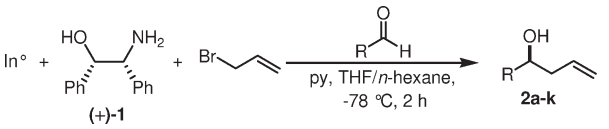
[a]Table values refer to number of equivalents. Reactions run with benzaldehyde (0.5 mmol). [b]Determined by chiral GC analysis. [c]Absolute configuration determined by comparison of the optical rotation with literature value.[6b,15]

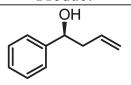
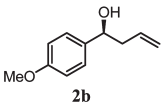
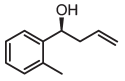
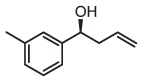
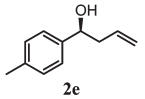
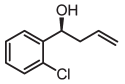
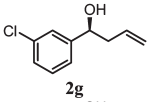
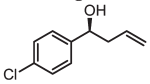
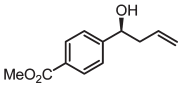
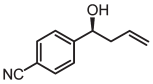
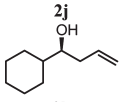
nuggets throughout the duration of this reaction, indicating the disproportionation of indium bromide salts.[14]

For the rest of our investigations we used the optimized stoichiometry of 2 equiv each of In°, allyl bromide, (+)-**1**, and pyridine with respect to aldehyde in THF:*n*-hexane (7:1) (Table 2).[11] We found that our method provided the homoallylic alcohol in excellent yields (90−99%) and enantioselectivities (76−93% ee) (Table 2, entries 1 to 7). This method demonstrates the chemoselectivity of the allylindium intermediates in the presence of other functional groups such as an ester providing only allylation of the aldehyde yielding **2e** (Table 2, entry 5). Under our reaction conditions, aldehyde allylation occurs in the presence of a nitrile affording **2f** in high enantiomeric excess of 80% (Table 2, entry 6). Additionally, these results show that the para-substituted aldehydes which are electron-donating through resonance (Table 2, entries 2 and 8), give a higher enantiomeric excess than those with an electron-withdrawing group in the para position (Table 2, entries 9 and 10). Possibly the electron-withdrawing groups increase the reactivity of the aldehydes, therefore decreasing the enantioselectivity for those substrates under these reaction conditions. We also demonstrated the allylation of an aliphatic aldehyde, specifically cyclohexanecarbaldehyde, yielding **2g** in high yield and enantiomeric excess (Table 2, entry 7).

Indium-Mediated Asymmetric Barbier-Type Allylations of Aldehydes with Substituted Allyl Bromides. We next turned our attention to see whether this indium-mediated allylation could be extended to substituted allyl bromides. Using our optimized reaction conditions, we began our study by simply replacing allyl bromide with crotyl bromide (Scheme 1). Although the enantioselectivity for the reaction was good (72% ee for both *syn*- and *anti*-product alcohols **3**), the diastereoselectivity was poor (43:57 *syn*/*anti*). To improve the diastereoselectivity, we examined the effects of reaction

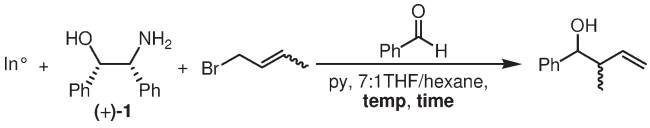
TABLE 2. The Asymmetric Indium-Mediated Barbier-Type Allylation of Aldehydes[a]



Entry	Carbonyl	Product	% yield[b]	% ee[c] (*S*)[d]
1	benzaldehyde	 **2a**	90	93
2	4-methoxybenzaldehyde	 **2b**	92	89
3	2-methylbenzaldehyde	 **2c**	94	88
4	3-methylbenzaldehyde	 **2d**	97	79
5	4-methylbenzaldehyde	 **2e**	92	87
6	2-chlorobenzaldehyde	 **2f**	97	78
7	3-chlorobenzaldehyde	 **2g**	90	80
8	4-chlorobenzaldehyde	 **2h**	92	93
9	methyl 4-formylbenzoate	 **2i**	94	76
10	4-formylbenzonitrile	 **2j**	99	80
11	cyclohexanecarbaldehyde	 **2k**	93	93

[a]Reactions run with In° (2.0 mmol), **1a** (2.0 mmol), pyridine (2.0 mmol), allyl bromide (2.0 mmol), and aldehyde (1.0 mmol) in THF/*n*-hexane at −78 °C for 1.5 h. [b]Isolated yield of analytically pure product. [c]Determined by chiral GC analysis. [d]Absolute configuration determined by comparison of the optical rotation with literature value,[6b,15] all others were assigned by analogy.

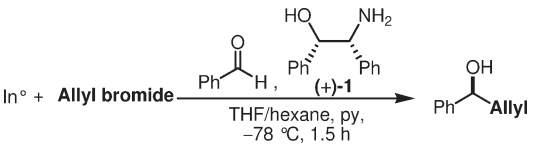
SCHEME 1. Allylation of Benzaldehyde with Crotyl Bromide and (+)-1

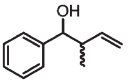
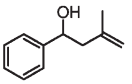
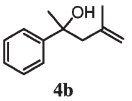
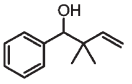
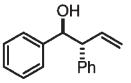


(14) (a) Kloo, L.; Rosdahl, J.; Taylor, M. J. *Polyhedron* **2002**, *21*, 519–524. (b) Tuck, D. G. *Chem. Soc. Rev.* **1993**, *22*, 269–276.

(15) For an asymmetric Reformatsky reaction with indium and cinchonidine see: Johar, P. S.; Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 711–713.

TABLE 3. The Asymmetric Indium-Mediated Barbier-Type Allylation of Benzaldehyde with Functionalized Allyl Bromides



Entry	Allyl Bromide	Product	% Yield	% ee (dr *anti/syn*)[a]
1	Crotyl bromide	 **3**	99	72[b] (57:43)
2	Methallyl bromide	 **4a**	70	45[b]
3[c]	Methallyl bromide	 **4b**	55	16[b]
4	Prenyl bromide	 **5**	54	56[b]
5	Cinnamyl bromide	 **6**	50	56[d] (>95:5)

[a] *Syn*/*anti* ratio determined by ^{1}H NMR. [b] Determined by chiral GC analysis. [c] The reaction was conducted with acetophenone and the optimized ketone conditions, in THF at 25 °C for 24 h. [d] Determined by chiral HPLC analysis.

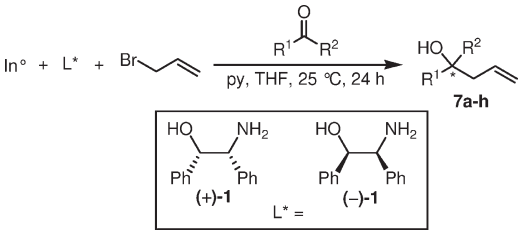
temperature. However, increasing the reaction temperature from −78 to 25 °C resulted in a similar ratio (45:55 *syn*/*anti*). Increasing the temperature further to 65 °C yielded a mixture of **3** with a slight bias favoring the *syn* diasteromer (58:42 *syn*/*anti*). Additionally, heating crotyl bromide and In° under reflux for 30 min prior to the addition of ligand and pyridine did not enhance the diastereoselectivity any further. During the course of these reactions, the presence of shiny indium nuggets was observed as previously seen in our other indium-mediated allylation reactions.

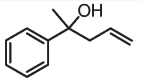
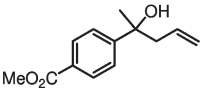
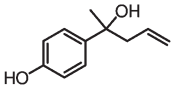
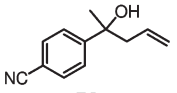
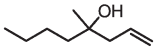
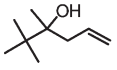
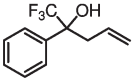
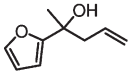
We also examined this reaction using other substituted allylic bromides (Table 3). Using the optimized reaction conditions, methallyl bromide reacted with benzaldehyde to give **4a** in 70% yield and 45% ee (Table 3, entry 2). The methallylation of acetophenone took 24 h at 25 °C and afforded **4b** in a moderate yield of 55% and very low enantiomeric excess of 16% (Table 3, entry 3). The allylation of benzaldehyde with prenyl bromide gave **5** in 54% yield and 56% ee (Table 3, entry 4), which was lower than the published results.[5] Under Barbier-type conditions, cinnamyl bromide reacted with benzaldehyde and furnished **6** in a very high diastereomeric ratio (>95:5 *anti*) and moderate enantiomeric excess of 56% (Table 3, entry 5). The high diastereoselectivity realized in this reaction can be attributed to the reversibility of this reaction in THF. The low conversion is more than likely due to the increased steric bulk of the phenyl substituent. These results demonstrate that sterically demanding substituted allyl bromides decrease the enantioselectivity with use of our method and negatively influence the efficiency of our chiral director.

Indium-Mediated Asymmetric Barbier-Type Allylations of Ketones. Our successful asymmetric allylation of aldehydes under Barbier-type reaction conditions warranted the study of allylation of ketones under the optimized allylation conditions used for aldehydes. Unfortunately, the reaction of allyl bromide with acetophenone under the Barbier conditions gave abysmal conversion of less than 5% to the corresponding homoallylic alcohol. We suspected that since ketones are generally less reactive, higher temperatures would be needed. We were pleased to find that running the reaction for 24 h at 25 °C provided the corresponding homoallylic alcohol in moderate yield and enantiomeric excess (Table 4, entry 1).[11] Using an excess of allyl bromide (3- to 6-fold) decreased the yield of the product while maintaining the same level of asymmetric induction. This result confirmed that 2 equiv of allyl bromide is optimal and supported our hypothesis that an excess of allyl bromide affects the efficiency of the reaction. Even in the allylation of ketones, we observed the transformation of gray indium powder into shiny indium flakes during the reaction.

This method is fairly general and provided the corresponding tertiary homoallylic alcohols for both aliphatic and aromatic ketones in moderate to high yield and enantioselectivity (Table 4).[11] In addition, either enantiomer of the commercially available amino alcohol, (+)-**1** or (−)-**1**, afforded the antipodal homoallylic alcohol products (Table 4, entries 7 and 8). The ligand can also be recycled and reused as demonstrated in the allylation of triflouroacetophenone affording (*R*)-**7g** in excellent yield and enantioselectivity (Table 4, entry 8). This method can be applied to heteroaromatic compounds as shown by the allylation of 2-acetylfuran, which provided an excellent yield of >99% but only moderate enantiomeric excess (Table 4, entry 9). Also documented by others, the allylindium reagent was able to

TABLE 4. The Asymmetric Indium-Mediated Barbier-Type Allylation of Ketones[a]



Entry	Ketone	Product	L*	% yield[b,c]	% ee[d,e]
1	acetophenone	 **7a**	(–)-**1**	72	57 (*R*)
2	methyl 4-acetylbenzoate	 **7b**	(+)-**1**	74	48[f] (*S*)
3	4'-hydroxyacetophenone	 **7c**	(+)-**1**	77	41[f] (*S*)
4	4-acetylbenzonitrile	 **7d**	(+)-**1**	92	48 (*S*)
5	2-hexanone	 **7e**	(–)-**1**	77	45 (*S*)
6	pinacolone	 **7f**	(–)-**1**	81	64 (*S*)
7	α,α,α-trifluoroacetophenone	 (*S*)-**7g** (*R*)-**7g**	(+)-**1**	94	80 (*S*)
8			(–)-**1**[g]	>99	78 (*R*)
9	2-acetyl furan	 **7h**	(+)-**1**[g]	>99	44 (*S*)

[a]Reactions run with In° (1.0 mmol), 2-amino-1,2-diphenylethanol (1.0 mmol), pyridine (1.0 mmol), allyl bromide (1.0 mmol), and ketone (0.5 mmol) in THF at room temperature for 24 h. [b]Isolated yield of analytically pure product; all products greater than 90% by ^{1}H NMR. [c]Based on unreacted starting material. [d]Determined by chiral GC analysis. [e]Absolute configuration determined by comparison of the optical rotation with literature value,[17] all others were assigned by analogy. [f]Determined by chiral RP-HPLC analysis. [g]Reaction run with recovered and purified ligand.

tolerate functionality, such as phenol, ester, and nitrile, showing the versatility of the indium-mediated allylations compared to allylations mediated by Gringard reagents (Table 4, entries 2 to 4). Under our reaction conditions, aliphatic ketones showed only moderate enantiomeric induction (Table 4, entries 5 and 6). On the other hand, trifluoroacetophenone afforded (*S*)-**7g** in 80% ee (Table 4, entry 7). In the indium-mediated allylation of ketones (+)-**1** is a better chiral director than cinchonidine.[6b] This methodology not only expands the scope of indium-mediated additions but also provides a simple synthesis of tertiary, chiral alcohol centers, a desirable functionality.[16]

Mechanistic Studies. Although indium has gained appeal in Barbier-type asymmetric allylation reactions, little is known about the mechanism. Perusal of the literature showed that despite intensive research efforts in this area, the nature of the active species remains elusive due the fleeting nature of the indium intermediates.[3n,18,4] Reactions of allylhalides with indium metal can produce several organoindium species such as allylindium(I), allylindium(III) dihalide, diallylindium(III) halide, triallylindium(III), and allylindium sesquihalide depending on solvent and reaction conditions.

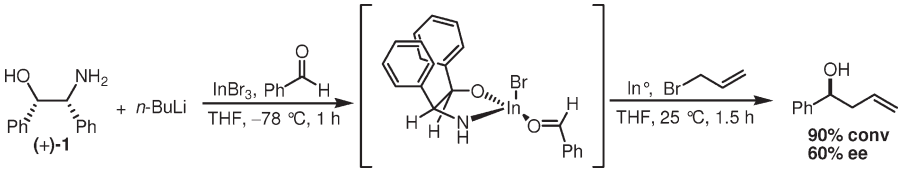
In 1974, Gynane and Worral suggested alkylindium sesquihalides, $R_3In_2X_3$, as intermediates in the reaction of

(16) (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704.

(17) (a) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573. (b) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704.

(18) (a) Babu, S. A.; Yasuda, M.; Shibata, I.; Akio Baba, A. *J. Org. Chem.* **2005**, *70*, 10408–10419. (b) Capps, S. M.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Tetrahedron Lett.* **1998**, *39*, 2853–2856. (c) Tussa, L.; Lebreton, C.; Mosset, P. *Chem.—Eur. J.* **1997**, *3*, 1064–1070.

SCHEME 2. Formation of a Possible Indium(III) Center Intermediate



In° with various alkyl iodides based on mass and vibrational spectral analyses.[19] In analogy, Araki et al. proposed an allylindium sesquihalide as the reactive intermediate in anhydrous DMF as evidenced by the observation of ^{1}H NMR signals at 1.7 and 2.1 ppm with relative integration of 2:1.[4] Later, Chan et al. prepared an allylindium reagent from the reaction of In° and In^I with diallylmercury in a mixture of DMF and D_2O and attributed the observed ^{1}H NMR signal at 1.7 ppm to allylindium(I).[20] Araki et al. reported that in the reaction of indium(I) iodide with allyliodide in THF-d_8, an allylindium(III) diiodide species is formed and it gives a signal at 2.0 ppm in the ^{1}H NMR spectrum.[21] More recently, Pretie and co-workers reported similar results in DMF-d_7 where two allylic signals, 1.75 and 2.02 ppm, were observed upon reacting In° with allyl bromide and the ratio of these signals varied with time.[22] We felt that observing the organoindium intermediates that are formed during the reaction of allyl bromides and substituted allyl bromides with indium metal in various aprotic, protic, and aqueous solvents by ^{1}H NMR spectroscopy would provide insight into the mechanism of these reactions.

Mechanistic Studies of Indium with Allyl Bromides. We began our investigation by mixing allyl bromide and indium in various ratios in DMF-d_7 and followed the reactions by ^{1}H NMR spectroscopy. Regardless of the stoichiometry, we observed the aforementioned peaks at 1.7 and 2.1 ppm. However, we found them to be present in roughly a 1:1 ratio. This led us to concur that two distinct allyl indium species are formed when indium is reacted with allyl bromide in anhydrous solvents. We also observed a single ^{1}H NMR signal at 1.7 ppm in the reaction of allyl bromide with indium in D_2O. Moreover, addition of D_2O to the allylindium solution in DMF-d_7 selectively hydrolyzed the allylindium resonating at 2.1 ppm leaving the ^{1}H NMR signal at 1.7 ppm. Additionally, when air was bubbled through a separate allylindium solution in DMF-d_7, the peak at 2.1 ppm remained unchanged, but the peak at 1.7 ppm disappeared. It is reasonable to infer that the allylindium responsible for the signal at 1.7 ppm is oxidatively unstable whereas the allylindium responsible for the signal at 2.1 ppm is hydrolytically unstable.

As previously stated, the maximum enantioselectivity and quantitative conversion to the homoallylic alcohol product was achieved with use of a 2:2:1 ratio of In° allyl bromide, and carbonyl, respectively. We also found that the addition of pyridine had a beneficial effect on the yield and enantiomeric purity of the alcohol product. To investigate the role of pyridine, we mixed allyl bromide, indium, and pyridine in

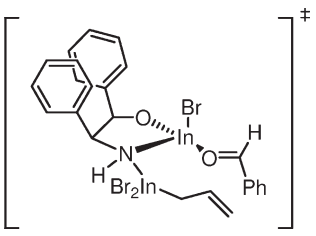


FIGURE 1. Proposed transition state complex containing an allylindium(III) intermediate.

DMF-d_7 and analyzed the reaction mixture by ^{1}H NMR spectroscopy. In this instance, we observed only one allyl indium signal at 2.1 ppm. This result suggested that, under our reaction conditions, the allyl indium responsible for the signal at 2.1 ppm could be the active allylating species and is formed exclusively in the presence of pyridine. Additionally, when benzaldehyde was added to a mixture of allylindiums in DMF-d_7, the signal at 2.1 ppm disappeared while the signal at 1.7 ppm persisted, indicating again that the allyl indium species responsible for the signal at 2.1 ppm is likely the active allylating intermediate. It should be pointed out that shiny indium flakes were observed throughout these NMR tube reactions indicating possible disproportionation of allylindium intermediates.

We have observed repeatedly and reproducibly the presence of metallic indium throughout the duration of these reactions. Conventionally it is accepted that the reduction of In(III) to In(0) proceeds through several one-electron reductions where In(II) and In(I) are fleeting intermediates due to the reactivity of the $5s^2$ configuration (eq 1).[23] Hence, it is plausible that these indium species are in equilibrium and the disproportion of various allylindium intermediates results in the regeneration of In° (eq 2). In fact, a recent paper reported such an equilibrating allylindium species when allyl bromide and indium(0) were reacted in an ionic liquid (IL) and observed the interconversion of an In(I) species into In(III) species.[24] Apparently, organoindium intermediates are not formed in discrete amounts, but rather are in equilibrium with each other and their concentration depends on reaction conditions and solvents.

$$\mathrm{In(III)} \rightarrow \mathrm{In(II)} \rightarrow \mathrm{In(I)} \rightarrow \mathrm{In(0)} \quad (1)$$

$$3\mathrm{In^+(soln)} \rightarrow 2\mathrm{In^\circ(s)} + \mathrm{In^{3+}(soln)} \quad (2)$$

Consequently, the formation of a single allylindium intermediate in D_2O was puzzling. To address this question, we studied the reaction of allyl bromide with In° in D_2O in an NMR tube. We noticed gas evolution along with the

(19) Gynane, M. J. S.; Worrall, I. J. *J. Organomet. Chem.* **1974**, *81*, 329–334.
(20) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228–3229.
(21) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291–296.
(22) Pretie, M; Pèrez-Carvajal, A. *Synlett* **2006**, *19*, 3337–3339.
(23) Pardoe, J. A. J.; Downs, A. J. *Chem. Rev.* **2007**, *107*, 2–45.
(24) Law, M. C.; Cheung, T. W.; Wong, K. Y.; Chan, T. H. *J. Org. Chem.* **2007**, *72*, 923–929.

TABLE 5. ^{1}H NMR Spectroscopy Study of Allyl Bromides with Indium(0)

entry	allyl bromide	solvent	allylindium	allylic protons (δ, ppm)[a]	product alcohol
1	crotyl bromide	MeOH-d_4	crotylindium[b]	1.83−1.91, m	**3**
2	crotyl bromide	D_2O	crotylindium[b]	1.63−1.70, m	**3**
3	cinnamyl bromide	MeOH-d_4	cinnamylindium	2.11, d J = 8.75 Hz	**6**
4	cinnamyl bromide	D_2O	cinnamylindium	1.93, d J = 8.75 Hz	**6**
5	prenyl bromide	MeOH-d_4	prenylindium	1.83, d J = 9 Hz	**5**
6	methallyl bromide	MeOH-d_4			3-deuterio-2-methylprop-1-ene

[a]m = multiplet, d = doublet. [b]*E*- and *Z*-crotyl indium.

formation of a white precipitate. In an attempt to dissolve the white solid in a deuterated solvent, we added $CDCl_3$ to the NMR tube and monitored the chloroform layer by ^{1}H NMR spectroscopy. We could clearly see the absence of any allylindium intermediates in the $CDCl_3$ layer and identified the presence of deuterated propene. The subsequent addition of benzaldehyde to the NMR tube, however, showed the formation of homoallylic alcohol indicating incomplete hydrolysis of the allylindium intermediates and their insolubility in chloroform. We therefore suggest that a mixture of allylindium intermediates are formed even in aqueous solutions and the hydrolytically unstable allylindum intermediate is converted to deuterated propene in D_2O. The white precipitate was isolated by centrifugation, dissolved in DCl and analyzed by ^{1}H NMR spectroscopy. Since no organic component could be detected in this solution the white precipitate presumably is indium deuteroxide.

We were still intrigued by the nature of the active allylating species under our reaction conditions and decided to further examine the asymmetric indium-mediated allylation of benzaldehyde using (+)-**1**. We synthesized the lithium salt of chiral ligand (+)-**1** then added indium tribromide as a complexing Lewis acid followed by benzaldehyde. After stirring for 1 h at −78 °C, we then transferred this solution to a mixture of In° and allyl bromide in THF at 25 °C. This reaction afforded **2a** in essentially quantitative yield and 60% ee, a value identical with that obtained with 1:1:1 stoichiometry of In°:benzaldehyde:allyl bromide (vide supra) (Scheme 2). We tentatively suggest that the identity of the In(III) complex may be similar to that shown in Scheme 2. The simplest transition state that incorporates all the experimental data is provisionally proposed borrowing the analogy from Et_2Zn addition to carbonyl compounds and oxazaborolindine (Figure 1).[25] This would result in a *si*-face attack of the aldehyde, which is in agreement with the fact the *S*-homoallylic alcohol is obtained when using (+)-**1** as the chiral director. The phenyl rings should aid in blocking the top face of the chiral In(III) complex therefore forcing coordination from the bottom face, which is similar to the rationale that was proposed to explain the enantioselectivity exhibited by the chiral reagent oxazaborolidine in asymmetric additions to aldehydes. Additionally in D_2O, racemic homoallylic alcohol product is obtained due to the fact that our chiral director is insoluble in this solvent and therefore cannot form the chiral In(III) complex.

We next focused on the nature of the organoindium intermediates that are formed from the substituted allyl bromides under aqueous or protic conditions. Crotyl bromide and indium react in both D_2O and methanol-d_4 to give a mixture of crotylindium intermediates, presumably *cis*- and *trans*-crotylindium, which then reacts with benzaldehyde to form **3** (Table 5, entries 1 and 2). However, cinnamyl bromide gives essentially a single organoindium species in both D_2O and methanol-d_4 and the addition of benzaldehyde yielded the *anti*-homoallylic alcohol **6** (Table 5, entries 3 and 4). Prenyl bromide reacts with In° in methanol-d_4 to from an allylindium intermediate that produces **5** in the presence of benzaldehyde (Table 5, entry 5). In contrast, methallylindium intermediate, formed by the reaction of methallyl bromide and In°, is hydrolyzed rapidly to deuterated isobutene in methanol-d_4 and no homoallylic alcohol product is observed upon the addition of benzaldehyde. Since we conducted these reactions in aqueous or protic solvents we did not observe any downfield allylindium signal by ^{1}H NMR spectroscopy.[26]

Conclusions

We have developed methodology for the asymmetric indium-mediated allylation of aldehydes and ketones achieving excellent yield and enantioselectivity to the corresponding chiral alcohol products using a recyclable and reusable commercially available amino alcohol. This methodology was extended to the addition of substituted allyl bromides including crotyl, cinnamyl, prenyl, and methallyl bromide to benzaldehyde. Unfortunately, these substituted allyl bromides did not afford high enantioselectivity and/or distereoselectivity, aside from cinnamyl bromide, which produced a very high diastereomeric ratio (>95:5 *anti*) but a moderate enantiomeric excess of 56% ee. We were also able to demonstrate the chemoselectivity of allylindium reagents using our methodology. In addition, this provides a simple way to synthesize secondary or tertiary chiral alcohols under Barbier-type conditions.

We have shown that solvent plays a major role in the formation of organoindium intermediates. It is plausible that aqueous solvents such as D_2O induce the formation of a more hydrolytically stable organoindium species while polar aprotic solvents such as DMF-d_7 produce organoindium species of two different oxidation states as evidenced by ^{1}H NMR spectroscopy. Our mechanistic studies show that

(25) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151–3152.

(26) Yasuda, M.; Haga, M.; Baba, A. *Organometallics* **2009**, *28*, 1998–2000.

contrary to what is conventionally thought, allylindium compounds are not entirely hydrolytically stable. The allylindium intermediate formed with 3-bromo-2-methylbutene was rather unstable in methanol and water and was hydrolyzed almost immediately. On the other hand, some allylindium intermediates are more stable and react with benzaldehyde in both water and methanol to provide the corresponding alcohol product. However, in our studies, the addition of pyridine allows the sole formation of the allyl indium(+3) species by possible coordination. We have also proposed a transition state model containing an In(III) center where the allylindium species is coordinated from the bottom, which is in agreement with the fact that we obtain the (*S*)-homoallylic alcohol product. Therefore, we believe that an In(III) intermediate forms under our reaction conditions and then reacts with the electrophile, either an aldehyde or ketone, to provide the corresponding homoallylic alcohol product.

Experimental Section

General Procedure for the Allylation of Aldehydes 2a−k. An oven-dried 50 mL round-bottomed flask was cooled under argon and charged with (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (2 mmol), indium powder (2 mmol), anhydrous THF (14 mL), anhydrous pyridine (2 mmol), and allyl bromide (2 mmol). The mixture was stirred vigorously at 25 °C for 30 min, at which time *n*-hexane (2 mL) was added, the solution was cooled to −78 °C (dry ice/acetone bath), and freshly distilled aldehyde (1 mmol) was added dropwise. After 2 h the reaction was quenched with saturated ammonium chloride (2 mL) and allowed to warm to 25 °C. Deionized water was added and the mixture was extracted with *n*-hexane (2 × 5 mL), then the combined organic layers were dried with anhydrous magnesium sulfate, filtered through a small plug of silica gel, and evaporated to give the alcohol product as an oil.

4-Chloro-α-(2-propenyl)benzenemethanol, 2h (Table 2, entry 8). Following the general procedure above, **2h** was obtained as a clear, colorless oil (0.168 g, 92% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.44−2.50 (m, 2H), 2.77 (s, 1H, OH), 4.66−4.71 (t, J = 6.3 Hz, 1H), 5.12−5.18 (m, 2H), 5.69−5.86 (m, 1H), 7.18−7.33 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 43.8, 72.5, 118.8, 127.2, 128.5, 132.9, 133.9, 142.2. Enantiomeric excess was determined to be 93% by chiral GC analysis. GC conditions: 151 °C isothermal; t_R for the (*R*)-alcohol = 37.45 min, t_R for the (*S*)-alcohol = 38.32 min.

General Procedure for the Allylation of Benzaldehyde with Substituted Allyl Bromides to Provide Products 3, 4a, 5, and 6. An oven-dried 25 mL round-bottomed flask equipped with a stirbar was cooled under argon and charged with indium powder (1 mmol), (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1 mmol), anhydrous THF (7 mL), anhydrous pyridine (1 mmol), and allyl bromide (1 mmol). The flask was purged with argon (4 vacuum-backfill cycles) and the mixture was stirred vigorously at 25 °C for 30 min, at which time dry *n*-hexane (1 mL) was added, the solution was cooled to −78 °C (dry ice/acetone bath), and freshly distilled benzaldehyde (0.5 mmol) was added dropwise. After 1.5 h the reaction was quenched with saturated ammonium chloride (1 mL) and allowed to warm to 25 °C. The organic layer was diluted with *n*-hexane (5 mL), decanted, dried with anhydrous magnesium sulfate, filtered through a small plug of silica gel ,and evaporated under reduced pressure.

2-Methyl-1-phenylbut-3-en-1-ol, 3 (Table 3, entry 1). Following the general procedure above, **3** was obtained as a clear, yellow oil (0.080 g, 99% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (d, J = 6.75 Hz, 3H, *anti*), 1.02 (d, J = 6.75 Hz, 3H, *syn*), 2.51 (sextet, J = 7.75 Hz, 2H, *anti*), 2.61 (sextet, J = 7.75 Hz, 2H, *syn*), 4.36 (d, J = 8 Hz, 1H, *anti*), 4.61 (d, J = 5.5 Hz, 1H, *syn*), 5.02−5.09 (m, 2H, *syn*), 5.17−5.25 (m, 2H, *anti*), 5.69−5.89 (m, 2H, both *diast*.), 7.24−7.37 (m, 10H, both *diast*.). ^{13}C NMR (62.9 MHz, $CDCl_3$): *syn* δ 14.2, 44.8, 77.5, 115.7, 126.7, 127.5, 128.2, 140.5, 142.8; *anti* δ 16.7, 46.5, 78.1, 117.0, 127.0, 127.8, 128.4, 140.8, 141.5, 142.6. Enantiomeric excess was determined to be 72% by chiral HPLC analysis. HPLC conditions: 99:1 hexanes/^{i}PrOH, 1.0 mL/min, t_R for all diastereomers = 17.67, 19.22, 21.23, 22.27.

General Procedure for the Allylation of Ketones 4b and 7a−h. To a 25 mL round-bottomed flask charged with stir bar were added cooled under Argon, indium (1 mmol), 2-amino-1,2-diphenylethanol (1 mmol), and THF (7 mL). Pyridine (1 mmol) and allyl bromide (1 mmol) were added and the entire mixture was allowed to mix for 30 min at which point the ketone (0.5 mmol) was added dropwise. After 24 h, the reaction was quenched with saturated ammonium chloride (NH_4Cl, 6 mL) and transferred to a separatory funnel with either hexanes (5 mL) or ethyl acetate (EtOAc, 5 mL). The aqueous phase was removed and the organic phase was washed with dilute hydrochloric acid (HCl, 2 × 8 mL) and brine (1 × 8 mL), dried with magnesium sulfate ($MgSO_4$), filtered through a silica plug, and evaporated in vacuo to yield the alcohol product.

2-Phenyl-2-triflouromethyl-3-buten-2-ol, (*S*)-7g (Table 4, Entry 8). Following the general procedure above, (*S*)-**7g** was obtained as a yellow oil (0.102 g, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (s, OH), 2.86 (dd, J = 15, 10 MHz, 1H), 2.99 (dd, J = 15, 10 MHz, 1H), 5.24−5.29 (m, 2H), 5.54−5.62 (m, 1H), 7.36−7.43 (m, 3H), 7.59 (d, J = 7.5 MHz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.2, 94.8, 122.0, 126.5, 128.4, 130.4, 136.9, 145.5, 151.4. Enantiomeric excess was determined to be 80% by chiral GC analysis. GC conditions: 121 °C isothermal, t_R for the (*R*)-alcohol = 20.93 min, and t_R for the (*S*)-alcohol = 21.32 min.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.