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

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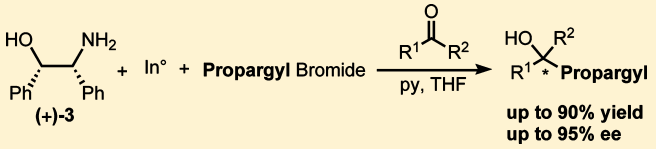
Supporting Information

ABSTRACT: We report a simple, efficient, and general method for the indium-mediated enantioselective propargylation of aromatic and aliphatic aldehydes under Barbier-type conditions in a one-pot synthesis affording the corresponding chiral alcohol products in very good yield (up to 90%) and enantiomeric excess (up to 95%). The extension of this methodology to ketones demonstrated the need for electrophilic ketones more reactive than acetophenone as the reaction would not proceed with just acetophenone. Using the Lewis acid indium triflate [$In(OTf)_3$] induced regioselective formation of the corresponding homoallenic alcohol product from acetophenone. However, this methodology demonstrated excellent chemoselectivity in formation of only the corresponding secondary homopropargylic alcohol product in the presence of a ketone functionality. Investigation of the organoindium intermediates under our reaction conditions shows the formation of allenylindium species, and we suggest that these species contain an indium(III) center. 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

In recent years, homopropargylic alcohols have received much attention as intermediates in the preparation of more complex molecules and as structural moieties in many biologically active compounds.[1] The triple bond moiety provides a functional handle for further manipulations and organic transformations in organic synthesis. Hence, these homopropargylic alcohols are employed as key building blocks in the construction of more complex molecules. Various asymmetric methodologies have been developed for the synthesis of homopropargylic alcohols from aldehydes and allenylmetal reagents.[2] Currently, there are far fewer examples employing metal-mediated propargylations of ketones in the total synthesis of more complex molecules,[3] as this methodology has not been as greatly developed.[4] One of the first asymmetric boron-mediated additionS of the allenyl group to aldehydes was accomplished by Yamamoto and co-workers,[5] and in one of a few examples, it has recently been shown that an air-stable chiral allenylborane made from propargyl Grignard can produce both secondary and tertiary homopropargylic alcohols with excellent enantioselectivity.[6]

Many researchers have explored the use of indium in organic reactions.[7] For instance, several examples of asymmetric indium-mediated allylations have been reported.[8] However, only a few examples have been reported for the asymmetric indium-mediated propargylation of aldehydes.[9] Additionally, there are only two reported examples employing indium metal in the propargylation of a specific class of ketones, azetidine-2,3-diones, where the observed stereoselectivity arose from the configuration of the chiral center on the ring.[10] Currently, there are no reports of indium being used to promote the enantioselective addition of the propargyl group to ketones using a chiral director.

It is known that many allenylmetals can undergo a metallotropic rearrangement resulting in either the homopropargylic alcohol (**1**) or allenic alcohol (**2**) upon reaction with a carbonyl substrate (Scheme 1).[11] As with other metals, it has been found that when indium metal is employed, the ratio of **1**:**2** can be varied by changing the solvent or substitution of the propargyl halide.[12] Chan and co-workers have studied the identity of the organoindium species under various conditions finding that more substituted propargyl bromides lead to the allenic alcohol product.[12b] Under their reaction conditions (R = H), the homopropargylic alcohol (**1**) was observed to be the sole product when various aldehydes were reacted with the

Scheme 1. Metallotropic Rearrangement Providing Either Homopropargylic (1) or Allenic Alcohol (2) Products

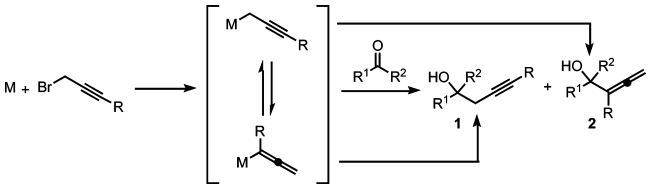


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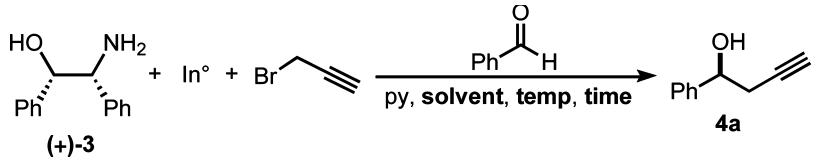
Table 1. Optimization of the Asymmetric Indium-Mediated Propargylation of Benzaldehyde[a]



entry	time (h)	temp (°C)	solvent	% convn[c] (isolated yield)	% ee[d] (*S*)[e]
1	2	−78	THF	58	76
2	3	0	THF	87	84
3	3	−20	THF	89	83
4	3	−40	THF	88	84
5	3	−60	THF	48	89
6	15	−78 to 25 (slow)	THF	91 (90)	88
7	15	−78 to 25 (slow)	THF/*n*-hexanes (7:1)	>97	89
8	15	25	THF	>97	77
9	15	25	THF/EtOAc (1:7)	85	61
10[b]	15	25	THF	>97	76
11	15	25	THF (open to air)	58	57

[a]Reactions run with In^0 (1.0 mmol), (+)-**3** (1.0 mmol), pyridine (1.0 mmol), propargyl bromide (1.0 mmol), and aldehyde (0.5 mmol) in THF. [b]The reaction was run with InI (1.0 mmol). [c]Percent conversion determined by ^{1}H NMR. [d]Determined by chiral GC analysis. [e]Absolute configuration determined by comparison of the optical rotation with literature value.[6a]

organoindium intermediates. However, the propargylation with ketones proved to be far less straightforward.

Previously, we reported the highly enantioselective allylation of aldehydes and ketones using allyl bromide, indium, pyridine, and commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol ((+)-**3**) as the chiral auxiliary.[13] Herein, we describe a full report of the use of indium and (+)-**3** to mediate the asymmetric addition of propargyl bromide to aldehydes[9b] and ketones under Barbier-like conditions.

RESULTS AND DISCUSSION

Indium-Mediated Asymmetric Barbier-Type Propargylations of Aldehydes. We began our study by using indium to promote the propargylation of benzaldehyde with our previously successful chiral director, (+)-**3**. Using the optimal stoichiometry employed in the enantioselective allylation reactions,[13a] indium(0) (2 equiv), (+)-**3** (2 equiv), propargyl bromide (2 equiv), and pyridine (2 equiv) were reacted with benzlaldehyde (1 equiv) in tetrahydrofuran (THF) under various parameters (Table 1). The enantioselectivity of the reaction run at −78 °C for 2 h was 76% (Table 1, entry 1); however, the conversion to the homopropargylic alcohol was moderate (58%). Next, the reaction was investigated at elevated temperatures, which showed an increase in conversion and enantioselectivity for the following temperatures: 0, −20, and −40 °C (Table 1, entries 2 to 4). When the reaction was performed at −60 °C high enantioselectivity (89% ee) was observed with lowered production of alcohol product (48% conversion) (Table 1, entry 5). This result indicated that the enantioselectivity was increasing when the reaction was performed at slightly higher temperatures than −78 °C. Therefore, the reaction was conducted at −78 °C, and the reaction was allowed to warm slowly over a period of 16 h without removing the ice bath, providing a higher conversion of 91% and improved enantioselectivity of 88% ee (Table 1, entry 7).

The solvent system was examined beginning with a mixture of THF and *n*-hexanes (7:1) that had been used in the allylation of aldehydes,[13c] and it was found to yield results similar to those using only THF (Table 1, entry 8). Using only THF, the reaction was also allowed to proceed for 15 h at room temperature, which provided a decrease in enantioselectivity (77% ee) (Table 1, entry 9). Using a mixture of THF and ethyl acetate (EtOAc) produced both lower conversion and enantiomeric excess (Table 1, entry 10). Finally, the reaction was conducted using indium(I) iodide (InI) instead of indium(0), and the yield and enantiomeric purity of the corresponding homopropargylic alcohol were essentially identical to those obtained using indium metal at room temperature for 15 h (Table 1, entry 11). It should be pointed out that 58% conversion and 57% enantiomeric excess were obtained under non-inert conditions (Table 1, entry 11). On the basis of these results, we observed the highest enantioselectivity (88% ee) and conversion (91%) when the flask was cooled to −78 °C, followed by addition of benzaldehyde, and allowed to slowly warm overnight (Table 1, entry 7).

With the optimal reaction condition in hand, the generality of this reaction was explored *via* screening of a variety of structurally diverse aldehydes (Table 2).[9b] Both aromatic and aliphatic aldehydes were converted to the corresponding homopropargylic alcohols in very good yield and high enantioselectivities. Benzaldehyde was converted to 4-phenyl-1-butyn-4-ol (**4a**) in 90% yield and 88% ee (Table 2, entry 1). Gratifyingly, functionalized benzaldehyde derivatives provided the corresponding homopropargylic alcohol in high yields as well. 4-Methoxybenzaldehdye, 4-chlorobenzaldehyde, and 4-cyanobenzaldehdye gave the corresponding homopropargylic alcohols **4b**, **4c**, and **4d** in 84%, 88%, and 83% ee, respectively (Table 2, entries 2, 3, and 4, respectively). Most notably, 3-hydroxybenzaldehdye produced 85% ee for the corresponding homopropargylic alcohol (**4e**), showing that this reaction tolerates an unprotected phenol (Table 2, entry 5). We were pleased to find that the propargylation of aliphatic aldehydes under our reaction conditions resulted in very high enantioselectivities for the corresponding secondary alcohol products. The unsubstituted aliphatic aldehyde, *n*-butyraldehdye, gave **4f** in 74% ee (Table 2, entry 6). As expected, the

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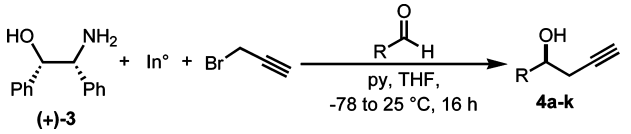
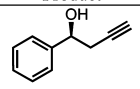
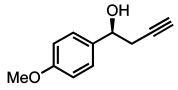
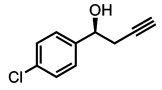
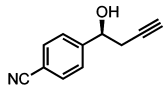
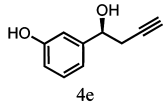
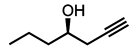
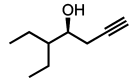
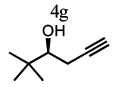
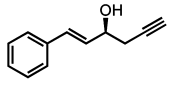
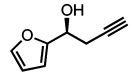
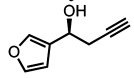
Table 2. Enantioselective Indium-Mediated Propargylation of Aromatic Aldehydes[a]



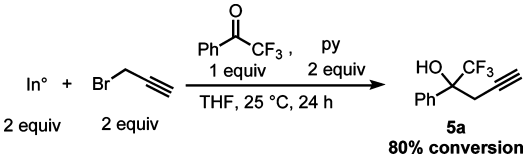
Entry	Carbonyl	Product	% yield[b]	% ee[c]
1	benzaldehyde	 4a	90	88 (S)[d]
2	4-methoxybenzaldehyde	 4b	82	88 (S)
3	4-chlorobenzaldehyde	 4c	89	84 (S)
4	4-formylbenzonitrile	 4d	75	83 (S)
5	3-hydroxybenzaldehyde	 4e	90	85[e] (S)
6	butyraldehyde	 2f	63	74[e] (R)
7	2-ethylbutanal	 4g	60	83 (S)
8	pivalaldehyde	 4h	53	95 (S)
9	cinnamaldehyde	 4i	71	75 (S)
10	furan-2-carbaldehyde	 4j	78	78 (S)
11	furan-3-carbaldehyde	 4k	69	78 (S)

[a]Reactions run with In^0 (1.0 mmol), (+)-**3** (1.0 mmol), pyridine (1.0 mmol), propargyl bromide (1.0 mmol), and aldehyde (0.5 mmol) in THF (see Table 1, entry 3). [b]Isolated yield. [c]Determined by chiral GC analysis. [d]Absolute configuration determined by comparison of the optical rotation with literature value.[6a] All others were assigned by analogy. [e]Enantiomeric excess determined by chiral GC analysis of the acetylated homopropargylic alcohol.

enantioselectivity of the reaction increased with increasing substitution at the α-carbon of the aldehyde inducing 83% enantiomeric excess for 2-ethylbutanal and 95% enantiomeric excess for the more substituted pivalaldehyde (Table 2, entries 7 and 8). The α,β-unsaturated aldehyde, cinnamaldehyde, produced the corresponding homopropargylic alcohol product (**4i**) in good yield (71%) and enantioselectivity (75% ee) (Table 2, entry 9). Finally, the heteroaromatic aldehydes 2- and 3-furaldehdye both furnished the homopropargylic alcohol, **4j** and **4k**, respectively, in good enantiomeric excess (78%) (Table 2, entries 10 and 11, respectively). We were very pleased to observe excellent enantioselectivities under our indium-mediated propargylation conditions for the addition to a variety of aldehydes. Additionally, we observed the presence of a shiny metal nugget throughout these propargylation reactions, as we had previously seen in the indium-mediated allylation reactions, indicative of disproportionation of initially formed indium intermediate.[13a] The synthesis of secondary homopropargylic alcohols using this methodology provided the products in high enantiomeric purity.

Indium-Mediated Asymmetric Barbier-Type Propargylations of Ketones. We began this study by investigating the optimal reaction conditions for the synthesis of tertiary homopropargylic alcohol from acetophenone, a representative ketone. Each reaction was conducted using the optimal stoichiometry mentioned above for the propargylation of aldehydes. The reaction was examined under a variety of conditions including, a range of temperatures (−78 to 65 °C) and time durations (2 h to 4 days), omission of pyridine and chiral ligand, and an excess of propargyl bromide (6 equiv); it was found that the addition of allenylindium to acetophenone did not occur under any of these conditions and starting material was recovered. Apparently, acetophenone is not reactive enough for this propargylation reaction. Additionally, the following ketone substrates were subjected to this indium-mediated propargylation reaction: 4-acetylbenzonitrile, methyl 4-acetylbenzoate, *p*-hydroxyacetophenone, 2-acetylfuran, and 2-bromo-1-(2-nitrophenyl)ethanone. However, these ketones were unreactive toward propargylation under our reaction conditions and were recovered fully from the reaction mixture. We then investigated this reaction using a more electrophilic ketone, such as trifluoroacetophenone (Scheme 2). The

Scheme 2. Indium-Mediated Propargylation of a More Reactive Ketone, Trifluoroacetophenone



reaction was conducted at 25 °C and monitored for a 24-h time period. Under these reaction conditions, the addition of allenylindium afforded the desired tertiary alcohol product, 1,1,1-trifluoro-2-phenylpent-4-yn-2-ol (**5a**), in very good yield (80%). This result indicated that the allenylindium intermediate requires more electrophilic ketone substrates for the propargylation reaction to occur.

Further probing of this methodology was conducted with the goal of activating acetophenone *via* additives and/or Lewis acids, which would hopefully induce the addition of allenylindium to the ketone. All reactions were conducted by mixing indium metal (2 equiv), (+)-**3** (2 equiv), pyridine (2 equiv), and propargyl bromide (2 equiv) in THF under argon (Ar) for 30 min. The additives and acetophenone (1 equiv) were then added, and the reaction was mixed for 24 h followed by acidic quenching (Table 3). The following additives and Lewis acids were investigated using catalytic and stoichiometric amounts: indium(III) bromide ($InBr_3$), aluminum(III) chloride ($AlCl_3$), lithium chloride (LiCl), lithium iodide (LiI),[14] iodine (I_2), and saturated ammonium chloride (NH_4Cl), with and

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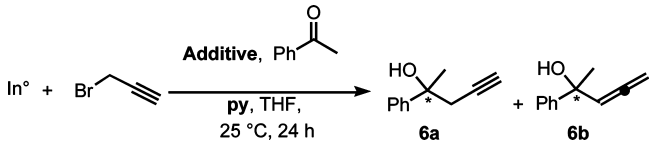
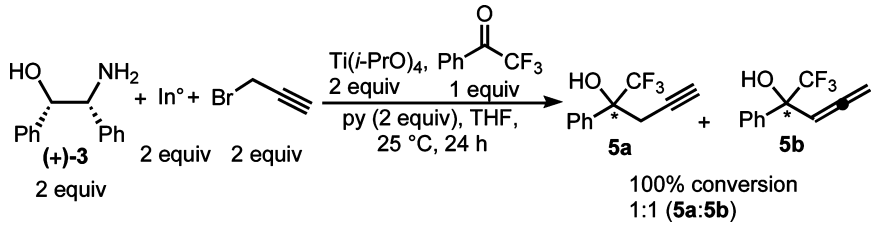
Table 3. Screening of Additives in the Enantioselective Addition of Propargyl Bromide to Acetophenone[a]



entry	additive	additive (equiv)	Py	conversion (%)[b] (**6a**:**6b**)[c]
1[d]	$BF_3{\cdot}OEt_2$	1	no	17 (3:2)
2[d]	$BF_3{\cdot}OEt_2$	0.1	yes	<3 (100:0)
3[d,e]	Ti(*i*-PrO)$_4$	2	yes	89 (1:1)
4	In(OTf)$_3$	1	yes	90 (1:3)
5[f]			no	62 (1:1)
6[f]			yes	<2 (100:0)
7[f]	In(OTf)$_3$	0.5	yes	48 (1:1)
8[f]	In(OTf)$_3$	0.5	no	85 (1:14)

[a]Reactions run with In^0 (1 mmol), pyridine (1 mmol), propargyl bromide (1 mmol), additive (1 mmol, 0.5 mmol, 0.25 mmol, or 0.1 mmol), and acetophenone (0.5 mmol) in THF. [b]Percent conversion determined by ^{1}H NMR. [c]Regioisomer ratio (**6a**:**6b**) was determined by ^{1}H NMR. [d]Reactions run with (+)-**3** (1 mmol). [e]Ti(*i*-PrO)$_4$ was mixed with indium, the ligand, pyridine, and propargyl bromide for 30 min prior to addition of acetophenone. [f]Proparyl bromide was added last, 30 min after the other reagents were allowed to mix.

Scheme 3. Indium-Mediated Propargylation of Trifluoroacetophenone in the Presence of the Additive Ti(*i*-PrO)$_4$



without pyridine. Despite these reagents, the reaction was not successful and starting material was recovered.

Using 1 equiv of boron trifluoride ($BF_3{\cdot}OEt_2$) and omitting pyridine induced 17% conversion of acetophenone to two alcohol products, as a mixture of regioisomers with a slight preference toward formation of the homopropargylic alcohol (3:2, **6a**:**6b**) (Table 3, entry 1). Next, the effect of using the additive titanium(IV) isopropoxide (Ti(*i*-PrO)$_4$) was examined, as it has shown to be effective in zinc-mediated addition reactions.[15] Two equivalents of Ti(*i*-PrO)$_4$ were mixed with the other reagents for 30 min prior to acetophenone addition, hoping that addition order might aid in forcing the propargylation to occur. We were very pleased to observe an 89% conversion of acetophenone to products; however, the regioselectivity of the addition was not controlled and a mixture of regioisomers (1:1) was obtained (Table 3, entry 3). Lastly, the additive indium(III) triflate (In(OTf)$_3$) was examined. The reaction was conducted using In(OTf)$_3$ (1 equiv) and pyridine without the addition of (+)-**3**, which provided the highest conversion of acetophenone (90%) (Table 3, entry 4). Interestingly, this Lewis acid reversed the regioselectivity to formation of the allenic alcohol product, **6b** (1:3, **6a**:**6b**). Since we were interested in synthesizing the tertiary homopropargylic alcohol product, we did not pursue this reaction further.

It was found that 1 equiv of In(OTf)$_3$ effectively caused the addition to acetophenone, forming the homoallenic alcohol product in fair regioselectivity (Table 3, entry 4). Since Baba and co-workers reported that pyridine stabilized the allylindium(III) species, we employed both In(OTf)$_3$ and pyridine to activate this propargylation.[16] Unfortunately, only a moderate conversion of 48% occurred and a 1:1 mixture of **6a** and **6b** was produced (Table 3, entry 7). Possibly the pyridine complexes with the indium triflate species causing deactivation and subsequent retardation of the reaction. Very good conversion of acetophenone (85%) was observed when In(OTf)$_3$ was used alone as a promoter (Table 3, entry 8). In addition, higher regioselectivity was observed, forming the allenic alcohol product in greater than 90%. It is possible that the indium triflate isomerizes the initially formed allenylindium to propargylindium and allenylindium reacts relatively more readily with ketones than propargylindium. We are actively investigating the selective synthesis of allenylindium under the Barbier condition. Apparently, the presence of In(0) and In(III) triflate are necessary for the addition to the essentially inert acetophenone to occur under these Barbier-type reaction conditions.

The successful indium-mediated addition to ketones occurred using a more electrophilic ketone, trifluoroacetophenone, and also in the presence of Ti(i-PrO)$_4$ when acetophenone was used. The latter reaction showed no regiochemical preference for either alcohol product, which demonstrated equilibrium and/or isomerization between organoindium intermediates. Therefore, the reaction was performed using trifluoroacetophenone (1 equiv) and Ti(*i*-PrO)$_4$ (2 equiv), hoping to observe preferentially reaction with one of the intermediates (Scheme 3). Complete conversion of the ketone substrate was seen; however, selectivity was not observed as the products were an equal mixture of alcohols (1:1, **5a**:**5b**). Hence, while this additive induces the addition, it does not provide regiochemical control.

Finally, these studies implicate that pyridine was preventing the propargylation of acetophenone rather than promoting it. In order to confirm whether pyridine was causing a detrimental effect, the reaction was conducted without pyridine under the

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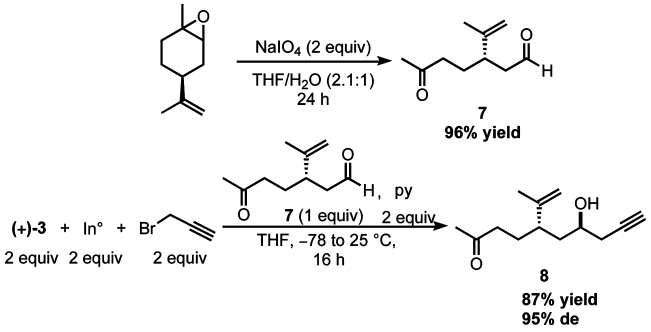
typical conditions using indium metal (2 equiv), (+)-**3** (2 equiv), and propargyl bromide at room temperature in THF. Acetophenone (1 equiv) was added, and after 24 h the reaction was quenched. Again, acetophenone was completely unreactive, and hence, it was concluded that pyridine was not an inhibitor of this reaction. By examining these results and the products obtained from conducting the reaction without the chiral ligand (Table 4 entry 1), it appears that the ligand **3** might be detrimental to this reaction. It is worth noting that under all of these reactions shiny indium metal was observed throughout the reaction, indicative of disproportionation of indium intermediates.[13a,17]

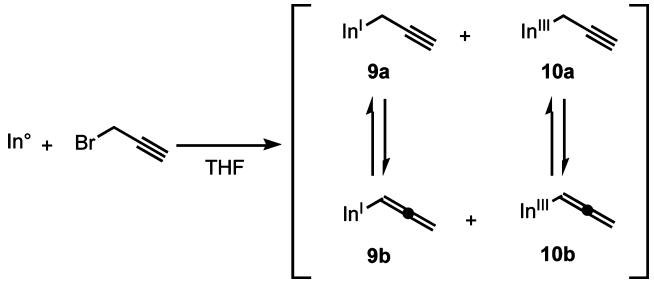
Chemoselective Indium-Mediated Asymmetric Barbier-Type Propargylations. Since the addition of propargyl bromide to acetophenone was very difficult under our indium-mediated reaction conditions, we speculated that the chemoselective propargylation of an aldehyde in the presence of a ketone should be possible. The synthesis of the appropriate substrate, (*S*)-6-oxo-3-(prop-1-en-2-yl)heptanal (**7**) was accomplished using an epoxide cleavage reaction.[18] Compound **7** was subjected to the propargylation reaction, and the corresponding secondary homopropargylic alcohol product (**8**) was produced in high yield (87%) and high diastereoselectivity (95% de) without observing any appreciable addition to the ketone group (Scheme 4).

Scheme 4. Chemoselective Asymmetric Indium-Mediated Propargylation of an Aldehyde in the Presence of a Ketone



Mechanistic Studies. This study began with the desire to extend the asymmetric indium-mediated allylation reaction to the synthesis of secondary and tertiary homopropargylic alcohols using indium. However, the addition to the less reactive electrophile, acetophenone, proved to be difficult. Until recently, little was known about the nature of the allylindium intermediates and even less was known about the intermediates that are formed from the reaction of indium and propargyl bromide. On the basis of knowledge of the allenylmetal system,[11] up to four intermediates are plausible when indium metal is reacted with propargyl bromide (Scheme 5). When we started our research in this area, it was not unambiguously determined whether the propargyl and allenylindium intermediates are distinct indium(I) and indium(III) species or coordinated indium(III) and noncoordinated indium(III) species. However, recent reports by Baba,[16] Hammond,[17] and Koszinoveski[19] state that various organoindium(III) species are produced under Barbier-type conditions. Therefore, the most likely intermediates under our reaction conditions are either propargylindium(III) species (**10a**) or allenylindium(III) species (**10b**) or a mixture of both.

Scheme 5. Plausible Organoindium Intermediates from the Reaction of Indium(0) with Propargyl Bromide[12b,16,17,19]



Chan and co-workers have performed experimental and theoretical studies on the propargyl-allenylindium system in THF and water.[12b] These studies reported that the allenylindium intermediates (**9b** and **10b**), rather than propargylindium intermediates (**9a** and **10a**), were present in the reaction of indium(0) and propargyl bromide regardless of solvent conditions. In THF, the reaction appeared to be sluggish, requiring sonication. In D_2O, the presence of one intermediate was observed, which was labeled allenylindium(I). However, Baba and co-workers observed that indium formed organoindium(III) compounds under aqueous Barbier condition.[16] Chan and co-workers also reported that two species were observed in the reaction of indium(0) and propargyl bromide in deuterated THF (THF-d_8), one that corresponded to Chan's allenylindium(I) species and the other was labeled allenylindium(III). However, the oxidation level of these intermediates were not confirmed, beyond that two allenylindium intermediates appear under THF medium and one in aqueous medium, where both could be different allenylindium(III) intermediates.

Hammond et al. recently investigated the nature of the organoindium intermediates that were formed using indium metal and difluoropropargyl bromide in a THF/H_2O (1:1) solvent mixture and reported two organoindium(III) species based on ^{1}H NMR analysis.[17] The species observed were identified as propargylindium(III) intermediates. It was proposed that these propargylindium(III) intermediates were in equilibrium with the allenylindium(III) forms where the propargylindium(III) species were favored due to sterics and the substitution pattern of the starting propargyl bromide. When these intermediates were reacted with electrophiles, such as aldehydes, the propargyl isomer, rather than the allenyl isomer, was produced. This result was explained using the Curtin–Hammett principle.[20] Hammond also proposed that the propargylindium(III) complexes were formed through the intermediacy of indium(I) species. Under our Barbier-type conditions using simple propargyl bromide, we suggest that allenylindium(III) intermediates predominate.

Koszinoveski investigated the oxidation states of allylindium species, and their data support the theory that the intermediates generated under these reaction conditions are organoindium(III) species.[19] Solutions of allylindium species generated from the reaction of indium and allyl bromide or allyl iodide in various solvents including DMF, THF, and water were examined using ESI mass spectrometry. It was found that allylindium(III) cations and anions, such as $InR_2(solv)^+$ and $InRX_3^-$, were detected. Apparently, organoindium chemistry in these solvents is dominated by indium(III) species through the transient formation of organoindium(I) species.

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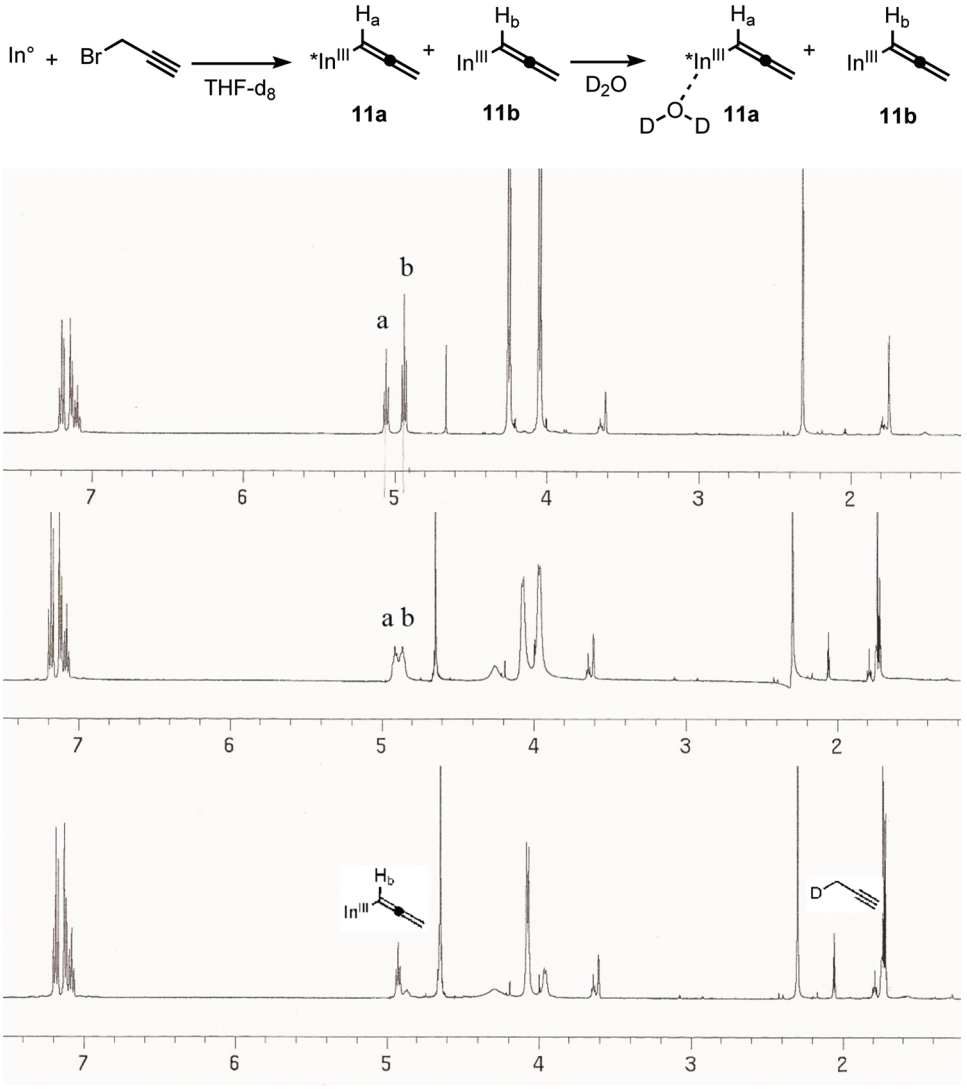

Figure 1. Investigation of allenylindium intermediates under polar aprotic solvent and aqueous conditions.

Our studies on the indium-mediated propargylation of aldehydes produced the secondary homopropargylic alcohol products. In order to identify the intermediates formed in this reaction, indium(0) and propargyl bromide were reacted in a ratio of 1:1 in THF-d_8, and after 30 min at room temperature the reaction was analyzed by ^{1}H NMR spectra. Two sets of allenic peaks were observed (Figure 1, top spectra), where one signal was farther downfield and was identified as **11a** and the upfield signal was identified as **11b**. These species were identified as two allenylindium(III) intermediates, based on the work of Baba,[16] Hammond,[17] and Koszinoveski.[19] Upon addition of D_2O, the signals coalesced and diminished in size, and the signal assigned to species **11a** appeared to shift upfield as the electron density of the indium increased (Figure 1, center spectra). The resulting spectra showed that **11a** had been hydrolyzed to deuterated propyne and **11b** remained unchanged (Figure 1, bottom spectra). The **11a** and **11b** species could be represented by any one of the following: allenyl$_3$In(III), allenyl$_2$In(III)Br, allenylIn(III)Br$_2$, or allenylIn-(III) coordinated to THF. Since the signal for **11a** (represented with an asterisk on the indium atom) appeared further downfield and appeared to be Lewis acidic, the possibility exists that this species could have more bromide ions coordinated to the indium(III) center. Our data indicated that two allenyl intermediates were formed in THF solvent and one is relatively more hydrolytically unstable. This hydrolytic instability explains the single allenyl intermediate signal observed under aqueous conditions by earlier workers in his area.[12b]

It should also be noted that for all reactions that we conducted, the metallic indium was never fully consumed and unreacted indium flakes were always seen at the end of the reaction. A disproportionation must occur to generate indium(0) throughout the reaction. The stable forms of indium are In(0), In(I), and In(III) as dictated by its electronic configuration of $5s^25p^1$. However, it is thought that the reduction of In(III) to In(0) proceeds through a one-electron reduction series where In(II) is a fleeting intermediate due to the reactivity of the $5s^1$ configuration (eq 1).[21] Because the presence of metallic indium is observed repeatedly and reproducibly throughout the duration of the reaction, it is plausible that three indium species are in equilibrium. The formation of the allenylindium(I) and allenylindium(III) result in the constant production of indium(0) (eq 2). This indicates that the organoindium intermediates are in equilibrium with each other throughout the reaction.

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

$$3In^{+}(soln) \rightarrow 2In^{0}(s) + In^{3+}(soln) \quad (2)$$

When this reaction was conducted in deuterated chloroform ($CDCl_3$) using indium(0), propargyl bromide, and acetophenone, a signal appeared that would correspond to a single allenylindium species (**12**). After 24 h, acetophenone and the allenylindium intermediate remained unreacted. Additionally, full conversion of propargyl bromide did not occur, and both propargyl bromide and allenylindium were still present. In polar noncoordinating solvents, we suggest that one allenylindium(III) species is formed.

We also investigated the asymmetric propargylation reaction with benzaldehyde using indium(I) iodide (InI) and propargyl bromide. We observed excellent conversion (97%) of benzaldehyde to the corresponding homopropargylic alcohol (76% ee) (Table 1, entry 10). Since the reaction of InI with propargyl bromide is anticipated to generate allenylindium(III) species and comparable results were obtained for the reaction with indium(0), it is safe to conclude that allenylindium(III) species are likely the active propargylating species under our reaction conditions.

CONCLUSIONS

In summary, we have demonstrated a general method for the indium-promoted enantioselective proparglylation of both aromatic and aliphatic aldehydes using commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as a chiral auxiliary and using only 2 equiv of propargyl bromide. The homopropargylic alcohol products are obtained in high yield and with enantiomeric excesses up to 95%. To our knowledge, the enantioselectivities reported herein are the highest obtained for indium-promoted propargylations. Furthermore, the amino alcohol ligand, which is commercially available in either enantiomer, can be recovered via a simple acid−base extraction.[22]This methodology was investigated in the propargylation of ketones; however, it was observed that acetophenone was not a good substrate for this reaction. However, more electrophilic triflouroacetophenone underwent propargylation readily. The Lewis acid $In(OTf)_3$ promoted indium-mediated propargylation of acetophenone to preferentially afford the corresponding allenic alcohol product.[23] While formation of the tertiary homopropargyl alcohol product using this indium-mediated reaction did not occur with ketones, we demonstrated that aldehydes can be propargylated chemoselectivity in the presence of ketone functionality.

Investigation of the intermediates generated when indium metal and propargyl bromide were reacted showed the formation of the allenylindium species over the propargylindium species. Two species were observed under polar aprotic solvent conditions that were tentatively assigned as allenylindium(III) intermediates. It was observed that these intermediates were susceptible to hydrolysis. In all of the reactions discussed herein, shiny indium flakes were observed throughout the course of the experiments, implicating the disproportionation of initially formed organoindium species.

EXPERIMENTAL SECTION

General Procedure for the Propargylation of Aldehydes 4a–k. An oven-dried 25 mL round-bottom flask with egg-shaped stirbar was cooled under argon and charged with (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (1 mmol), indium powder (1 mmol) and anhydrous THF (7 mL). The flask was vacuum purged with argon (5×), at which time anhydrous pyridine (1 mmol) and propargyl bromide (1 mmol) were added and the mixture was stirred vigorously at 25 °C. After 30 min at room temperature, the solution was cooled to −78 °C (dry ice/acetone bath), and freshly distilled aldehyde (0.5 mmol) was added dropwise. After 16 h the reaction was quenched with 1 M HCl (3 mL), the layers were separated and the aqueous layer was extracted with diethyl ether/*n*-hexanes 1:1 (2 × 3 mL). The combined organic layers were washed with 1 M HCl (3 mL), DI H_2O (3 mL), and brine (3 mL), dried with anhydrous magnesium sulfate, filtered through a silica plug, and evaporated to give the alcohol product as an oil.

Acetylation of Homopropargylic Alcohols. A 10 mL flask with a stirbar was charged with alcohol, pyridine (3−5 equiv), and hexanes. The flask was cooled to 0 °C in an ice bath, and acetyl chloride (3−5 equiv) was added dropwise; a white precipitate formed immediately. After 16 h at 25 °C, the reaction was transferred to a separatory funnel with DI water and washed with saturated sodium bicarbonate (3×), DI water, and brine. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to provide the acetylated product as an oil, which was used for GC analysis.

1-Phenyl-3-butyn-1-ol, 4a (Table 2, entry 1).[6a] Following the general procedure above, **4a** was obtained as a clear, colorless oil (0.058 g, 90% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01 (t, J = 2.8 Hz, 1H), 2.33 (d, J = 3.3 Hz, 1H, OH), 2.58 (dd, J = 2.8, 6.5 Hz, 2H), 4.81 (dt, J = 3.3, 6.5 Hz, 1H), 7.29−7.35 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.5, 71.0, 72.4, 80.7, 125.8, 128.0, 128.5, 142.4. Enantiomeric excess was determined to be 88% by chiral GC analysis. GC conditions: 141 °C isothermal, t_R for the (*R*)-alcohol, 24.87 min; t_R for the (*S*)-alcohol, 25.94 min. The absolute stereochemistry was determined by comparison of the sign of optical rotation with reported literature values, $[\alpha]^{28}_D$ = +11.18 (1.7, MeOH).[6a]

1-(4-Methoxyphenyl)but-3-yn-1-ol, 4b (Table 2, entry 2).[24] Following the general procedure above, **4b** was obtained as a clear, yellow oil (0.072 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (t, J = 2.0 Hz, 1H), 2.62−2.64 (m, 2H), 3.81 (s, 3H), 4.83 (t, J = 6.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.5, 55.44, 71.0, 72.1, 81.0, 113.9, 127.2, 134.8, 159.4. Enantiomeric excess was determined to be 88% by chiral GC analysis. GC conditions: 161 °C isothermal, t_R for the (*R*)-alcohol, 36.57 min; t_R for the (*S*)-alcohol, 37.87 min.

1-(4-Chlorophenyl)but-3-yn-1-ol, 4c (Table 2, entry 3).[24] Following the general procedure above, **4c** was obtained as a clear, colorless oil (0.080 g, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10 (t, J = 2.5 Hz, 1H), 2.63−2.65 (m, 2H), 4.87 (dd, J = 6.0, 7.0 Hz, 1H), 7.35 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.6, 71.5, 71.8, 80.3, 127.3, 128.8, 133.8, 141.0. Enantiomeric excess was determined to be 84% by chiral GC analysis. GC conditions: 161 °C isothermal, t_R for the (*R*)-alcohol, 30.22 min; t_R for the (*S*)-alcohol, 31.89 min.

4-(1-Hydroxybut-3-ynyl)benzonitrile, 4d (Table 2, entry 4).[25] Following the general procedure above, **4d** was obtained as a clear, orange oil (0.064 g, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (t, J = 2.0 Hz, 1H), 2.61 (ddd, J = 2.5, 6.5, 16.5 Hz, 1H), 2.65 (ddd, J = 3.0, 6.0, 16.5 Hz, 1H), 4.92 (t, J = 6.5 Hz, 1H) 7.51 (d, J = 8.0 Hz, 2H), 7.62−7.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.4, 71.5, 71.8, 79.8, 111.5, 118.9, 126.8, 132.4, 147.9. Enantiomeric excess was determined to be 83% by chiral GC analysis. GC conditions: 180 °C isothermal, t_R for the (*R*)-alcohol, 39.21 min; t_R for the (*S*)-alcohol, 41.54 min.

3-(1-Hydroxybut-3-ynyl)phenol, 4e (Table 2, entry 5).[26] Following the general procedure above, **4e** was obtained as a clear, orange oil (0.073 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.05 (t, J = 2.5 Hz, 1H), 2.59 (dd, J = 2.5, 6.5 Hz, 2H), 4.77 (t, J = 6.5 Hz, 1H), 6.74 (dd, J = 2.0, 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.2, 70.8, 72.3, 81.0, 112.7, 115.1, 117.5, 129.7, 144.3, 156.7. Enantiomeric excess was determined to be 85% by chiral GC analysis of the diacetylated alcohol. GC conditions: 150 °C isothermal, t_R for the (*S*)-alcohol, 102.67 min; t_R for the (*R*)-alcohol, 103.85 min.

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Hept-1-yn-4-ol, 4f (Table 2, entry 6).[6a] Following the general procedure above, **4f** was obtained as a clear, colorless oil (0.035 g, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J = 7.5 Hz, 3H), 1.35−1.57 (m, 4H), 2.07 (t, J = 3 Hz, 1H), 2.33 (ddd, J = 2.5, 7.0, 16.5 Hz, 1H), 2.44 (ddd, J = 3.0, 7.5, 17 Hz, 1H), 3.75−3.81 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 18.9, 27.5, 38.5, 69.7, 70.9, 81.1. Enantiomeric excess was determined to be 74% by chiral GC analysis. GC conditions: 91 °C isothermal, t_R for the (*S*)-alcohol, 13.41 min; t_R for the (*R*)-alcohol, 13.87 min.

5-Ethylhept-1-yn-4-ol, 4g (Table 2, entry 7)..[27] Following the general procedure above, **4g** was obtained as a clear, colorless oil (0.042 g, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, J = 5.0 Hz, 3H), 0.92 (t, J = 5.0 Hz, 3H), 1.27−1.51 (m, 5H), 2.06 (t, J = 3.0, 1H), 2.37 (ddd, J = 3.0, 7.5, 17 Hz, 1H), 2.44 (ddd, J = 4.5, 7.5, 16.5 Hz, 1H), 3.77 (dt, J = 5.0, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.4, 11.5, 21.0, 21.8, 24.8, 45.5, 70.7, 71.4, 81.6. Enantiomeric excess was determined to be 83% by chiral GC analysis of the acetylated alcohol. GC conditions: 91 °C isothermal, t_R for the (*S*)-alcohol, 35.71 min; t_R for the (*R*)-alcohol, 36.38 min.

2,2-Dimethylhex-5-yn-3-ol, 4h (Table 2, entry 8).[6a] Following the general procedure above, **4h** was obtained as a clear, colorless oil (0.033 g, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (s, 9H), 2.07 (t, J = 5.5 Hz, 1H), 2.26 (ddd, J = 3.0, 10.5, 16.5 Hz, 1H), 2.44 (dt, J = 2.5, 17.0 Hz, 1H), 3.46 (dd, J = 3.0, 10.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 25.7, 34.7, 70.6, 77.6, 82.5. Enantiomeric excess was determined to be 95% by chiral GC analysis of the acetylated alcohol. GC conditions: 80 °C isothermal, t_R for the (*S*)-alcohol, 37.98 min; t_R for the (*R*)-alcohol, 42.15 min.

1-Phenylhex-1-en-5-yn-3-ol, 4i (Table 2, entry 9).[24] Following the general procedure above, **4i** was obtained as a clear, yellow-orange oil (0.068 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.11 (t, J = 3.5 Hz, 1H), 2.55 (ddd, J = 2.5, 6.5, 16.5 Hz, 1H), 2.61 (ddd, J = 2.5, 5.5, 16.5 Hz, 1H), 4.50 (q, J = 6.0 Hz, 1H), 6.31 (dd, J = 6.0, 16.0 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 7.26−7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.9, 70.8, 71.3, 80.4, 126.7, 128.0, 128.7, 130.1, 131.5, 136.5. Enantiomeric excess was determined to be 75% by chiral GC analysis. GC conditions: 151 °C isothermal, t_R for the (*R*)-alcohol, 57.18 min; t_R for the (*S*)-alcohol, 58.94 min.

1-(Furan-2-yl)but-3-yn-1-ol, 4j (Table 2, entry 10).[6a] Following the general procedure above, **4j** was obtained as a clear, orange-yellow oil (0.053 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (t, J = 2.5 Hz, 1H), 2.78 (dd, J = 2.5, 6.0 Hz, 2H), 4.89 (t, J = 6.5 Hz, 1H), 6.35 (s, 2H), 7.40 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.2, 66.2, 71.2, 80.0, 106.7, 110.3, 142.4, 154.8. $[\alpha]^{25}_D$ = +10.0° c = 6.4 in MeOH. Enantiomeric excess was determined to be 78% by chiral GC analysis. GC conditions: 111 °C isothermal, t_R for the (*R*)-alcohol, 33.41 min; t_R for the (*S*)-alcohol, 34.53 min.

1-(Furan-3-yl)but-3-yn-1-ol, 4k (Table 2, entry 11).[28] Following the general procedure above, **4k** was obtained as a clear, yellow oil (0.047 g, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.09 (t, J = 3.0 Hz, 1H), 2.61−2.70 (m, 2H), 4.85 (t, J = 6.0 Hz, 1H), 6.46 (s, 2H), 7.40 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4, 65.5, 71.3, 80.5, 108.6, 127.5, 139.4, 143.5. Enantiomeric excess was determined to be 78% by chiral GC analysis. GC conditions: 115 °C isothermal, t_R for the (*R*)-alcohol, 37.76 min; t_R for the (*S*)-alcohol, 40.62 min.

Indium-Mediated Propargylation of a Trifluoroacetophenone, 1,1,1-Trifluoro-2-phenylpent-4-yn-2-ol, 5a (Scheme 2). To a 25 mL round-bottom flask charged with stir bar, cooled under Ar, were added indium (0.115 g, 1 mmol), and anhydrous THF (7 mL). The flask was backfilled with Ar (3×). Pyridine (0.081 mL, 1 mmol) and propargyl bromide (0.11 mL, 1 mmol) were added, and the entire mixture was allowed to mix for 30 min followed by dropwise addition of 2,2,2-trifluoroacetophenone (0.068 mL, 0.5 mmol). After 24 h, the reaction was quenched with dilute HCl (6 mL) and transferred to a separatory funnel with hexanes/Et_2O (1:1) solution (6 mL). The organic phase was washed with hexanes/Et_2O (2 × 3 mL). The combined organic layers were washed with dilute HCl (2 × 6 mL), DI water (1 × 6 mL), brine (1 × 6 mL), dried with $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to provide **5a** as a yellow oil (80% conversion of 2,2,2-trifluoroacetophenone). ^{1}H NMR (500 MHz, $CDCl_3$): 2.09 (t, J = J = 2.5 Hz, 1H), 3.11 (d, J = 2.5 Hz, 1H), 3.12 (d, J = 2.5 Hz, 1H), 7.25−7.43 (m, 3H), 7.57−7.63 (m, 2H).

General Procedure for the Investigation of Additives in the Propargylation of Acetophenone, 2-Phenylpent-4-yn-2-ol, 6a and 2-Phenylpenta-3,4-dien-2-ol, 6b (Table 3).[6b,29] To a 25 mL round-bottom flask charged with stir bar, cooled under Ar, were added indium (1 mmol), (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (1 mmol), and anhydrous THF (7 mL). The flask was backfilled with Ar (3×). Pyridine (1 mmol, where applicable) and propargyl bromide (1 mmol) were added, and the entire mixture was allowed to mix for 30 min. Dropwise addition of acetophenone (0.5 mmol) and the appropriate additive (0.1, 0.5, 1, or 2 mmol) occurred, and after 24 h the reaction was quenched with dilute HCl (6 mL) and transferred to a separatory funnel with hexanes/Et_2O (1:1) solution (6 mL). The organic phase was washed with hexanes/Et_2O (2 × 3 mL). The combined organic layers were washed with dilute HCl (2 × 6 mL), DI water (1 × 6 mL), and brine (1 × 6 mL), dried with $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to provide the alcohol products, **6a** and **6b**. Percent conversion was determined by ^{1}H NMR spectroscopy. **6a** (propargyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (s, 3H), 2.06 (t, J = 2.5 Hz, 1H), 2.71 (dd, J = 2.0, 13.5 Hz, 1H), 2.78 (dd, J = 2.5, 14.5 Hz, 1H), 7.27−7.31 (m, 1H), 7.35−7.40 (m, 2H), 7.48−7.54 (m, 2H); **6b** (allenyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68 (s, 3H), 4.98 (dd, J = 2.0, 4.5 Hz, 2H), 5.58 (t, J = 6.5 Hz, 1H), 7.27−7.31 (m, 1H), 7.35−7.40 (m, 2H), 7.48−7.54 (m, 2H).

Indium Mediated Propargylation of Trifluoroacetophenone in the Presence of the Additive Ti(*i*-PrO)$_4$, 1,1,1-Trifluoro-2-phenylpent-4-yn-2-ol, 5a and 1,1,1-Trifluoro-2-phenylpenta-3,4-dien-2-ol, 5b (Scheme 3). To a 25 mL round-bottom flask charged with stir bar, cooled under Ar, were added indium (0.115 g, 1 mmol), (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (0.213 g, 1 mmol), and anhydrous THF (7 mL). The flask was backfilled with Ar (3×). Pyridine (0.081 mL, 1 mmol) and propargyl bromide (0.11 mL, 1 mmol) were added, and the entire mixture was allowed to mix for 30 min followed by dropwise addition of 2,2,2-trifluoroacetophenone (0.068 mL, 0.5 mmol). After 24 h, the reaction was quenched with dilute HCl (6 mL) and transferred to a separatory funnel with hexanes/Et_2O (1:1) solution (6 mL). The organic phase was washed with hexanes/Et_2O (2 × 3 mL). The combined organic layers were washed with dilute HCl (2 × 6 mL), DI water (1 × 6 mL), and brine (1 × 6 mL), dried with $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to provide **5a** and **5b** as a yellow oil (100% conversion, 1:1, **5a**:**5b**). **5a** (propargyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07 (t, J = 2.5 Hz, 1H), 3.11 (d, J = 2.5 Hz, 1H), 3.12 (d, J = 2.5 Hz, 1H), 7.23−7.45 (m, 3H), 7.59−7.65 (m, 2H); **5b** (allenyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (dd, J = 1.5, 6.5 Hz, 1H), 5.20 (dd, J = 1.5, 6.5 Hz, 1H), 5.86 (t, J = 6.5 Hz, 1H), 7.23−7.45 (m, 3H), 7.59−7.65 (m, 2H).

General Procedure for the Investigation on the Effect of Reagent Addition and Indium(III) Triflate in the Indium-Mediated Propargylation of Acetophenone, 2-phenylpent-4-yn-2-ol, 6a and 2-phenylpenta-3,4-dien-2-ol, 6b (Table 4)..[6b,29] To a 25 mL round-bottom flask charged with stir bar, cooled under Ar, were added indium (1 mmol), In(OTf)$_3$ (0.5 mmol), pyridine (1 mmol), acetophenone (0.5 mmol), and anhydrous THF (7 mL). The flask was backfilled with Ar (3×). Propargyl bromide (1 mmol) was added, and the entire mixture was allowed to mix for 24 h. The reaction was quenched with dilute HCl (6 mL) and transferred to a separatory funnel with hexanes/Et_2O (1:1) solution (6 mL). The organic phase was washed with hexanes/Et_2O (2 × 3 mL). The combined organic layers were washed with dilute HCl (2 × 6 mL), DI water (1 × 6 mL), and brine (1 × 6 mL), dried with $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to provide **6a** and **6b** as a clear oil. Table 4, entry 4: (85% conversion, 1:14, **6a**:**6b**). **6a** (propargyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (s, 3H), 2.06 (t, J = 2.5 Hz, 1H), 2.71 (dd, J = 2.0, 13.5 Hz, 1H), 2.78 (dd, J = 2.5, 14.5 Hz, 1H), 7.27−7.31 (m, 1H), 7.35−7.40 (m, 2H), 7.48−7.54 (m, 2H); **6b** (allenyl isomer) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68 (s, 3H), 4.98 (dd, J = 2.0, 4.5 Hz, 2H), 5.58 (t, J = 6.5 Hz, 1H), 7.27−7.31 (m, 1H), 7.35−7.40 (m, 2H), 7.48−7.54 (m, 2H).

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Chemoselective Asymmetric Indium-Mediated Propargylation of an Aldehyde in the Presence of a Ketone, 7 and 8 (Scheme 4). *(S)-6-Oxo-3-(prop-1-en-2-yl)-heptanal, 7 (Scheme 4).* To a 100 mL round-bottom flask were added sodium metaperiodate ($NaIO_4$, 4.278 g, 20 mmol) and DI water (13 mL) followed by vigorous mixing for 10 min. After the brief period of stirring, THF (27 mL) was added, subsequent dropwise addition of (−)-limoneneoxide (1.64 mL, 10 mmol) occurred, and the reaction was allowed to stir for 24 h, at which point the iodine salts were filtered off. Ether (Et_2O, 15 mL) was added to the filtrate, which was transferred to a separatory funnel, and the aqueous phase was washed with Et_2O (3 × 15 mL). The organic layers were combined and washed with DI water (1 × 10 mL) and brine (1 × 10 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield 7 (1.612 g, 96% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (s, 3H), 1.65−1.70 (m, 1H), 1.81−1.83 (m, 1H), 2.09 (s, 3H), 2.36 (t, J = 8.0, 15.0 Hz, 2H), 2.40−2.42 (m, 2H), 2.63−2.64 (m, 1H), 4.74 (d, J = 1.5 Hz, 1H), 4.80 (d, J = 1.5 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.4, 26.4, 30.0, 40.8, 40.9, 47.5, 115.4, 145.2, 201.9, 208.4.

(5S)-7-Hydroxy-5-(prop-1-en-2-yl)dec-9-yn-2-one, 8 (Scheme 4). To a 50 mL round-bottom flask charged with stir bar, cooled under Ar, were added indium (0.230 g, 2 mmol), (+)-(1*S*,2*R*)-2-amino-1,2-diphenylethanol (0.426 g, 2 mmol), and anhydrous THF (14 mL). The flask was backfilled with Ar (3×). Pyridine (0.162 mL, 2 mmol) and propargyl bromide (0.22 mL, 2 mmol) were added, and the entire mixture was allowed to mix for 30 min. The flask was then cooled to −78 °C (dry ice/acetone bath), followed by dropwise addition of 7 (0.210 g, 1 mmol). After 2 h, the reaction was quenched with dilute HCl (6 mL) and transferred to a separatory funnel with hexanes/Et_2O (1:1) solution (6 mL). The organic phase was washed with hexanes/Et_2O (2 × 3 mL). The combined organic layers were washed with dilute HCl (2 × 6 mL), DI water (1 × 6 mL), and brine (1 × 6 mL), dried with $MgSO_4$, filtered through a silica plug, and evaporated *in vacuo* to provide a clear oil **8** (0.181 g, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) major diastereomer: δ 1.44−1.49 (m, 1H), 1.57 (s, 3H), 2.02 (t, J = 3.0 Hz, 1H), 2.09 (s, 3H), 1.59−1.62 (m, 4H), 2.31−2.32 (m, 2H), 2.33−2.37 (m, 2H), 3.65−3.71* (m, 1H), 4.76 (d, J = 8.0 Hz, 1H), 4.81 (d, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 27.1, 27.9, 30.1, 39.7, 41.5, 43.2, 67.8, 70.7, 81.1, 113.6, 146.1, 209.3. dr 39:1 *(via integration of signals at 3.65−3.71 and 3.74−3.79); 95% de.

NMR Studies. *NMR Study in THF-d_8 and D_2O, 11a and 11b (Figure 1).* A dry 2 dram vial with a stirbar was charged with indium (0.015 mmol, 17 mg) and deuterated solvent (0.75 mL). The flask was sealed and purged with argon, followed by the addition of propargyl bromide (0.015 mmol, 0.013 mL). After 1 h at room temperature, the solution was transferred via syringe to a dry NMR tube under argon, the solution was analyzed by ^{1}H NMR, and D_2O was added. Allenylindium*(III) ^{1}H NMR (250 MHz, THF-d_8): δ 4.21 (d, J = 6.5 Hz, 2H), 5.11 (t, J = 6.5 Hz, 1H). Allenylindium(III): δ 3.98 ppm (d, J = 6.5 Hz, 2H), 4.99 (t, J = 6.5 Hz, 1H). After addition of D_2O: Allenylindium(III): δ 4.11 ppm (d, J = 6.5 Hz, 2H), 4.98 (t, J = 6.5 Hz, 1H). Deuterated propyne: δ 2.11 ppm (s, 1H).

NMR Study in $CDCl_3$, 12. A dry NMR tube cooled under Ar was charged with indium (0.017 g, 0.15 mmol) and $CDCl_3$ (0.75 mL). Propargyl bromide (0.016 mL, 0.15 mmol) and acetophenone (0.01 mL, 0.075 mmol) were added, and the mixture was sonicated for 1 h. At 1 and 24 h the spectrum was observed using ^{1}H NMR, and the same spectrum was obtained. ^{1}H NMR (500 MHz, $CDCl_3$): allenylindium δ 4.96 (d, J = 6.5 MHz, 2H), 5.98 (t, J = 6.5 MHz, 1H); propargyl bromide 2.37 (s, 1H), 2.54 (t, J = 3.5 MHz, 2H).

■ ASSOCIATED CONTENT

Supporting Information

^{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.

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Dr. Genevieve M. Halpenny synthesized all of the indium(III) triflate used in this study.

■ DEDICATION

Dedicated to Professor Joseph Bunnett on the occasion of his 90th birthday and his valuable contributions to organic chemistry.

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