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Direct Synthesis of *B*-Allyl and *B*-Allenyldiisopinocampheylborane Reagents Using Allyl or Propargyl Halides and Indium Metal Under Barbier-Type Conditions

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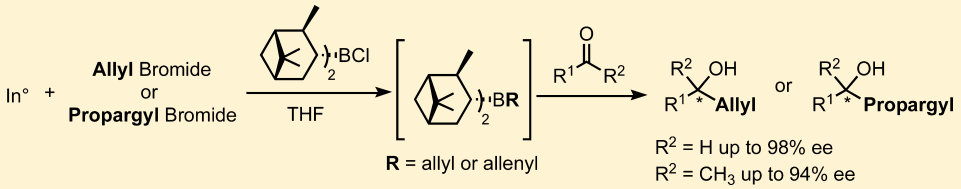
Supporting Information



ABSTRACT: We report the first one-pot process for the asymmetric addition of allyl, methallyl, and propargyl groups to aldehydes and ketones using *B*-chlorodiisopinocampheylborane (^{d}DIP-Cl) and indium metal. Under Barbier-type conditions, indium metal was used to generate allyl- and allenylindium intermediates, and subsequent reaction with ^{d}DIP-Cl successfully promoted the transfer of these groups to boron forming the corresponding chiral borane reagents. The newly formed borane reagents were reacted with aldehydes and ketones to produce the corresponding alcohol products in high yields and up to excellent enantioselectivity (98% ee). This method produced excellent enantioenriched secondary homoallylic alcohols from the allylation and methallylation of benzaldehyde. Using this method, the methallylation and cinnamylation of ketones afforded the highest enantioselectivities, while the propargylation of both aldehydes and ketones provided low enantiomeric excesses. In addition, this procedure provided the first synthesis of *B*-allenyldiisopinocampheylborane, which was characterized by ^{1}H and ^{11}B NMR spectroscopy. This is the first example of the direct synthesis of allylboranes that contained substitutions from the corresponding allyl bromide and indium, thereby expanding the utility of the DIP-Cl reagent. Hence, a general and straightforward route to these chiral organoborane reagents in one-pot has been developed along with the asymmetric Barbier-type allylation and propargylation of aldehyde and ketone substrates using these chiral organoborane reagents in subsequent coupling reactions.

INTRODUCTION

B-Chlorodiisopinocampheylborane (DIP-Cl) has proven to be an excellent reagent in several types of organic transformations providing enantiomerically enriched products. DIP-Cl has been employed extensively in the asymmetric reductions of prochiral ketones affording excellent enantioselectivity for the alcohol products.[1] Both enantiomers of DIP-Cl can be readily prepared in high yield and optical purity along with being commercially available. Hence, ^{d}DIP-Cl and ^{l}DIP-Cl provide either enantiomer of the alcohol product from the corresponding ketone where higher enantioselectivities are observed for aryl ketones when compared to the less sterically demanding aliphatic ones.[2] This methodology is still currently being used in total synthesis of both natural products and drug candidates.[3] This reagent has also demonstrated utility in the enantioselective halogenative cleavage of *meso*-epoxides[4] and asymmetric aldol reactions.[5] Finally, DIP-Cl can be converted to *B*-allyl-, methallyl-, or crotyldiisopinocampheylborane[6] allowing for the asymmetric addition to aldehydes and broadening the scope of this reagent's use. Currently, the addition of these reagents to ketones is limited to the simple allylation reaction.

The use of *B*-allyldiisopinocampheylborane in the synthesis of complex natural products has become one of the most widely used methods for the formation of numerous secondary chiral centers.[7] Since these chiral reagents are so widely used and show great potential in the formation of a variety of tertiary homoallylic alcohols using both substituted and functionalized allyl groups, a direct synthetic route to the various organoboranes would be valuable. Unfortunately, the synthesis of these highly useful reagents has not changed over the last two decades. Commonly, as these reagents cannot be purchased directly aside from *B*-allyldiisopinocampheylborane, the chiral organoboranes are prepared fresh by the reaction of a desired allylmagnesium or allyllithium reagent with either *B*-chloro- or *B*-methoxydiisopinocampheylborane.[8] The construction of the *B*-allyldiisopinocampheylborane reagent is thus limited by the ability to make the corresponding organometallic reagent.[9] As evidenced by several reports, indium has successfully mediated various addition reactions;[10] hence, we looked to examining organoindium reagents as possible intermediates in the

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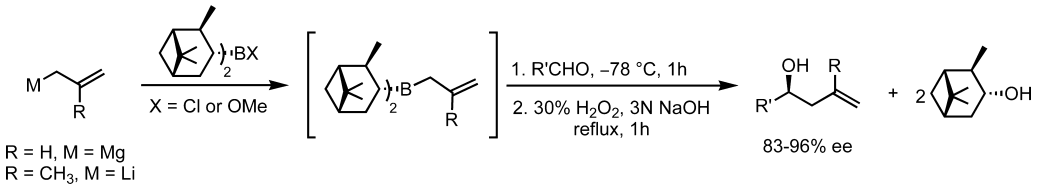
Scheme 1. Synthesis of *B*-Allyldiisopinocampheylborane and *B*-Methallyldiisopinocampheylborane Using Brown's Method



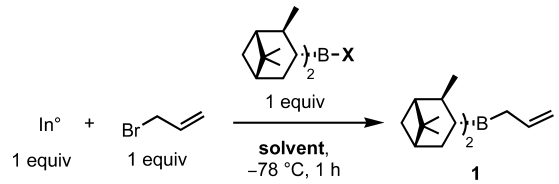
formation of *B*-organodiisopinocampheylborane reagents. A method for the synthesis of *B*-allyl-, *B*-methallyl-, and *B*-allenyldiisopinocampheylboranes using indium metal and the corresponding allyl and propargyl bromide is described herein.

RESULTS AND DISCUSSION

Synthesis of *B*-Allyldiisopinocampheylborane Using Indium Metal. The first synthesis of *B*-allyldiisopinocampheylborane (Ipc_2BALL) reagents was reported by Brown et al. in 1983 using allylmagnesium bromide and either *B*-chlorodiisopinocampheylborane or *B*-methoxydiisopinocampheylborane in diethyl ether at −78 °C for 1 h and then at 0 °C for 1 h.[8a,11] Upon filtration of the magnesium salts, formed as byproduct, the resulting organoborane can be coupled to aldehydes at −78 °C for 1 h. Oxidation with alkaline hydrogen peroxide yields the chiral homoallylic alcohol product in high enantiomeric excess, along with 2 equiv of isopinocampheol as a byproduct. The resulting alcohols are usually separated by distillation, column chromatography, or both. The synthesis of *B*-methallyldiisopinocampheylborane cannot proceed via the corresponding Grignard reagent and must be synthesized using methallyllithium.[12] The organolithium reagent must be prepared from gaseous isobutene and *n*-butyllithium in diethyl ether and then added to either the *B*-chloro- or *B*-methoxydiisopinocampheylborane to yield *B*-methallyldiisopinocampheylborane.[13] The addition of an aldehyde followed by oxidative workup yields the corresponding homoallylic alcohols in moderate yields and excellent enantioselectivities while addition to ketones was not as extensively explored providing good enantioselectivity (Scheme 1).

Our efforts began with the investigation of the ability of organoindium intermediates to facilitate the formation of the simplest organoborane reagent, *B*-allyldiisopinocampheylborane (Table 1). Therefore, we examined the reaction of indium metal (1 equiv), allyl bromide (1 equiv), and either DIP-Cl (1 equiv) or DIP-OMe (1 equiv) under conventional methods (−78 °C, 1 h) using diethyl ether to check by ^{11}B NMR spectroscopy if the allylindium reagent was able to transfer the allyl group to boron. However, starting with *B*-methoxydiisopinocampheylborane (^{d}DIP-OMe), the allyl group did not transfer to the boron as evidence by a single signal at +54 ppm, which corresponded to ^{d}DIP-OMe (Table 1, entry 1). Examination of other solvents including toluene and THF, in order to complete this transformation, did not provide the desired Ipc_2BALL either (Table 1, entries 2 and 3). The ineffective ability to synthesize the borane reagent from ^{d}DIP-OMe indicates that organoindium reagents will not exchange readily with the *B*-methoxy functionality. Since it is known that indium reagents are not particularly oxophilic, we used *B*-chlorodiisopinocampheylborane (^{d}DIP-Cl). The reaction of ^{d}DIP-Cl with indium and allyl bromide in THF yielded the corresponding B-allyldiisopinocampheylborane (**1**) as indicated by the disappearance of the ^{d}DIP-Cl signal at +73 ppm and the appearance of the *B*-allyldiisopinocampheylborane peak at +79 ppm in the ^{11}B NMR spectrum (Table 1, entry 4). Finally, we found that allylindium was indeed able to transfer the allyl group to boron even at room temperature providing the desired *B*-allyldiisopinocampheylborane reagent (Table 1, entry 5).

Table 1. Investigation of the Synthesis of *B*-Allyldiisopinocampheylborane Using Indium Metal, Allyl Bromide, and ^{d}DIP-Cl or ^{d}DIP-OMe[a]



Entry	X	Solvent	Organoborane	^{11}BNMR(δ, ppm)
1	OMe	Diethyl ether	-	+54
2	OMe	Toluene	-	+54
3	OMe	THF	-	+54
4	Cl	THF	$^d Ipc_2B$ **1**	+79
5[a]	Cl	THF	$^d Ipc_2B$ **1**	+79

[a]Reaction run at 25 °C for a period of 30 min.

With the successful formation of the *B*-allyldiisopinocampheylborane reagent (**1**) from allylindium, it was used in the reaction with benzaldehyde under literature reaction conditions with the expectation of the reported excellent enantioselectivities usually observed by these reagents. However, a much lower than expected enantioselectivity of 77% ee was observed for the corresponding homoallylic alcohol (**2**). We speculated that the presence of the indium salts formed during the reaction were interfering with the allylboration step. In the preparation of the allylboranes from allylmagnesium bromide, the residual magnesium salts were precipitated from the reaction media and filtered prior to the addition of the aldehyde. With this in mind, *n*-hexane was added to the newly formed *B*-allyldiisopinocampheylborane, and a bright orange solid precipitated immediately. After filtration of this solid, excellent asymmetric induction was achieved in the synthesis of **2** (92% ee) using the supernatant solution. We also obtained identical results (93% ee) when the reaction mixture was used without the filtration of the orange precipitate (Scheme 2). Thus, we were able to efficiently generate **1** from the in situ formation of the allylindium intermediate followed by the effective coupling with benzaldehyde.

In order to confirm the observed stoichiometry of 1:1:1 indium(0)/allyl bromide/DIP-Cl, we monitored the formation of *B*-allyldiisopinocampheylborane by ^1H and ^{11}B NMR. In^0/allyl bromide/DIP-Cl (1:1:1) and deuterated (THF-d_8) were added to a vial under argon and stirred for 30 min at 25 °C. After being stirred at room temperature under argon for 30 min, the solution was transferred via syringe to a dry NMR tube

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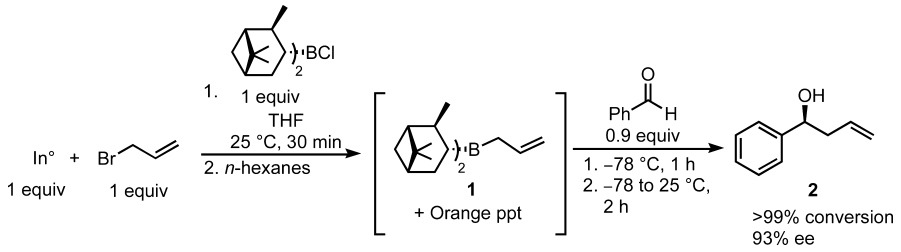
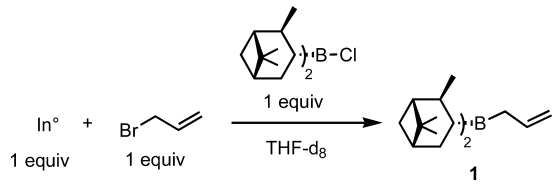
Scheme 2. Indium-Mediated Synthesis of *B*-Allyldiisopinocampheylborane and Subsequent Coupling with Benzaldehyde



and monitored for the formation of **1** (Scheme 3). Formation of the allylborane reagent was observed based on comparison to

Scheme 3. Synthesis of *B*-Allyldiisopinocampheylborane in THF-d_8



the unreacted allyl bromide in the ^{1}H NMR spectrum. In addition, the presence of both allylindium intermediates was not seen.[14] In separate experiments, an excess of In^0 was added to ensure complete consumption of the allyl bromide. With 1.5 and 2 equiv of In^0, the conversion to allylborane did not increase significantly. Therefore, it is safe to conclude that only 1 equiv of indium and allyl bromide is necessary to complete the formation to the corresponding allylindium species and transfer of the allyl group to DIP-Cl.

Given the reaction shown in Scheme 3, the anticipated byproduct from the addition of the two allylindium intermediates to DIP-Cl would be InCl and $InBr_2Cl$, respectively.[15] It has been reported that indium(I) salts are notoriously susceptible to disproportionation, especially in THF, and have limited solubility in hexanes.[16] It is therefore likely that when formed, some disproportionation of the In^I to In^0 and In^{III} would occur. In fact, we observe some indium metal throughout the reaction even though there is nearly quantitative formation of the organoborane. This is likely due heterogeneous disproportionation with the production of In^0 during the reaction (eq 1). In addition, an unstable intermediate in the disproportionation reaction is In^{II}. When two of the In^{II} species are formed, they can dimerize and form an indium−indium bond (eq 2). Also, a second pathway is possible where the disproportionation of the In^I and In^{III} leads to dimerization and the formation of two In^{II} metal centers with an In−In bond (eq 3).[17]

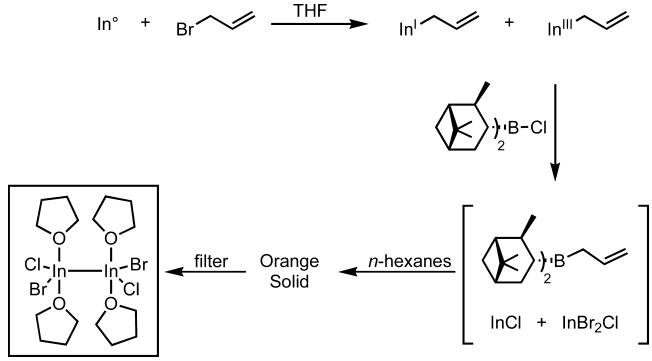
$$3InX \rightarrow 2In^0 + InX_3 \quad (1)$$

$$2In^{2+} \rightarrow [In{-}In]^{4+} \quad (2)$$

$$InX + InX_3 \rightarrow [In_2X_4] \quad (3)$$

As discussed earlier, the orange precipitate formed, during the synthesis of the organoborane reagents, crystallized into clear blocks when stored at 10 °C. X-ray analysis identified the crystal as $[InBrCl(THF)_2]_2$ containing an indium−indium bond (Scheme 4).

Scheme 4. Formation of $[InBrCl(THF)_2]_2$ Crystals



The complex crystallized as colorless blocks and consists of two five-coordinate (trigonal bipyramidal) indium atoms. There are four molecules of the complex in the unit cell of the primitive monoclinic space group $P2_1/c$. Each indium is coordinated by the other indium, two THF molecules, and a mixture of two chlorine or bromine atoms. The molecule is an analogue of $[InCl_2(THF)_2]_2$ (Figure 1). There is complete

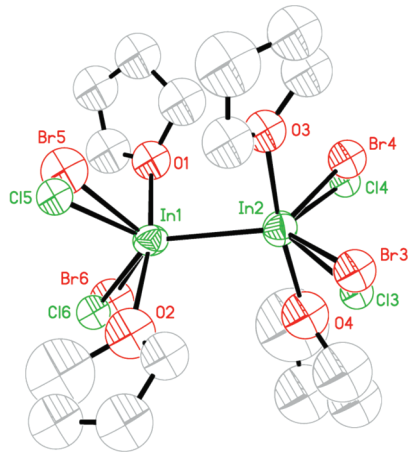


Figure 1. ORTEP diagram of $In_2Br_2Cl_2(THF)_4$ showing disordered chlorines and bromines.

disorder of the bromine and chlorine atoms as well as disorder in three of the four THF molecules. The disorder was modeled by examination of successive Fourier difference maps to determine the atomic positions of the disordered components.[18] All disordered atoms were modeled at 50% occupancy. The chlorine and bromine atoms were refined with anisotropic thermal motion parameters, while the disordered carbons and oxygen were refined isotropically.

Synthesis of B-Substituted Allyl- or Allenyldiisopinocampheylborane Using Indium Metal. With the successful

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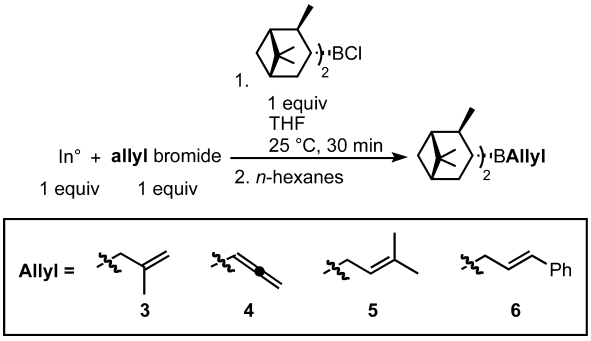
formation of the organoborane reagent from the corresponding organoindium, we looked to extend this reaction to other more structurally diverse allyl bromides and propargyl bromide (Scheme 5). Gratifyingly, when 3-bromo-2-methyl-2-propene

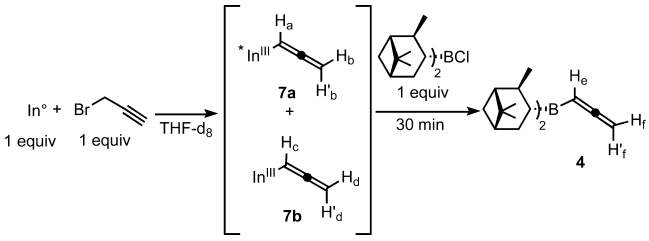
Scheme 5. Synthesis of Organoboranes via Indium



was reacted with indium(0) and ^{d}DIP-Cl in THF at room temperature under Barbier-type reaction conditions, the corresponding organoborane (**3**) was formed. When propargyl bromide was utilized under the aforementioned reaction conditions, the product (**4**) could not be conclusively determined and further investigation was conducted, as discussed below. Similarly, the reaction using prenyl bromide, resulted in the formation of the corresponding to *B*-3,3-dimethylallyldiisopinocampheylborane (**5**). Typically reagent (**5**) is formed via hydroboration of 3-methyl-1,2-butadiene using *B*-diisopinocampheylborane.[19] Finally, cinnamyl bromide was examined and it was believed that *B*-cinnamyldiisopinocampheylborane (**6**) was likely formed. This compound has also not been reported in the literature. In addition, examination of compounds **3** to **6** in the coupling reaction with benzaldehyde and/or acetophenone will be discussed later and help to confirm the generation of these allylborane reagent. These results indicated that indium and the appropriate allyl halide could be used to form the corresponding allylborane reagents under these Barbier-type conditions, and further studies were conducted.

We were eager to apply *B*-allenyldiisopinocampheylborane in the coupling reaction with carbonyls; however, further confirmation of this new reagent was undertaken prior to the coupling reaction. The formation of *B*-allenyldiisopinocampheylborane had been monitored via ^{11}B NMR spectroscopy previously, but the signal corresponding to this reagent appears at +74 ppm, which is extremely close to the +73 ppm signal corresponding to the starting material ^{d}DIP-Cl, making this data inconclusive. In order to verify the formation of product **4**, we added benzaldehyde at room temperature. However, this resulted in immediate reduction giving benzyl alcohol as the primary product. By cooling the reaction to −78 °C, the homopropargylic alcohol was observed as the sole product. The reagent was in fact formed as evidenced by the generation of the homopropargylic alcohol from benzaldehyde. Since a diisopinocampheylborane reagent with an allenyl group was not fully characterized in the literature, we looked to explore this reaction by ^{1}H NMR. When the reaction of indium metal and propargyl bromide was conducted previously in THF-d_8 by our group, two signals appeared that were identified as two separate allenylindium species (**7a** and **7b**), which could be two different complexes, allenylindium(I), allenylindium(III), or some coordinated allenylindium(III) species.[20] Recent reports by Baba,[21] Hammond,[22] and Koszinoveski[23] state that the various organoindium species produced under Barbier-type conditions are a variety of organoindium(III) intermediates. Hence, we labeled both observed species as two different forms of allenylindium(III). One species was further upfield than the other, and the signal at 4.95 ppm for H_a was assigned as allenylindium(III)* **7a**. The signal at 5.15 ppm for H_c was assigned as allenylindium(III) **7b**.[21,24] Since we had previously seen two allenylindium intermediates in studies,[20] we suggested that the indium center in **7a** may be coordinated to solvent causing this signal to be shifted upfield and added an asterisk to this assignment in order to signify the difference between the two allenylindium intermediates. The reaction shown below was conducted in THF-d_8 using indium(0) (1 equiv), propargyl bromide (1 equiv), and ^{d}DIP-Cl (1 equiv). The reaction was allowed to proceed for 30 min followed by observation by ^{1}H NMR spectroscopy. The presence of either allenylindium intermediate was not observed; rather, two new allenyl signals for H_e and H_f/H'_f were observed at 5.73 and 4.64 ppm, respectively. These were assigned to a single allenylborane species (**4**) and demonstrated that both allenylindium intermediates must have promoted the transfer of the allenyl group to boron (Scheme 6).

Scheme 6. Synthesis of *B*-Allenyldiisopinocampheylborane in THF-d_8



In Situ Generation of Allenylborane Reagents Followed by Coupling with Carbonyl Substrates. With the successful formation of the different organoborane species **1** and **3**−**6**, we then turned to investigating their reactions with various carbonyl substrates. Initially, we focused on the coupling of **4** with carbonyls, as the formation of the *B*-allenyldiisopinocampheylborane reagent had not been previously reported. Although the conditions for the addition to aldehydes were optimized, the lowered reactivity of ketones required separate optimization of temperature and time conditions (Scheme 7). Using the reaction conditions for the addition reactions with benzaldehyde, the reaction flask was cooled to −78 °C and acetophenone was added. After the mixture was stirred for 1 h, the ice bath removed and the reaction warmed over a period of 2 h, at which point BF_3·OEt_2 and acetaldehyde were introduced and the reaction proceeded overnight. These aldehyde propargylation conditions resulted in 83% conversion of acetophenone to 2-phenylpent-4-yn-2-ol (**7**) and 36% ee. Allowing the reaction to proceed for a longer time period (2 h) at both lower and higher temperatures along with the addition of acetophenone at slightly higher temperature of 0 °C did not significantly improve the enantioselectivity. Hence, the optimal reaction conditions for the reaction of **4** with acetophenone were the same as the reaction when benzaldehyde was allylated. Further reactions were conducted under the conditions described in Table 2.

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Scheme 7. Temperature and Time Reaction Conditions for the Enantioselective Propargylation of Acetophenone with *B*-Allenyldiisopinocampheylborane

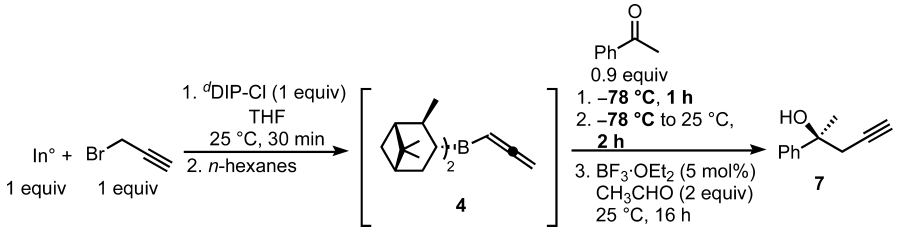
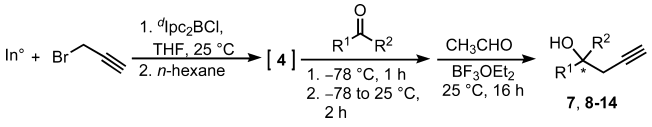
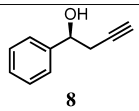
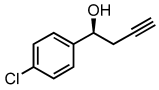
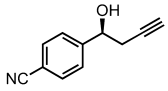
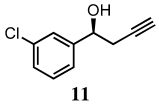
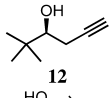
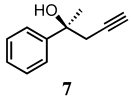
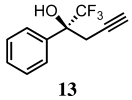
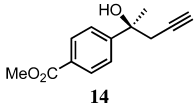


Table 2. Evaluation of the Enantioselective Propargylation of Aldehydes and Ketones with *B*-Allenyldiisopinocampheylborane Generated under Barbier-Type Conditions[a]

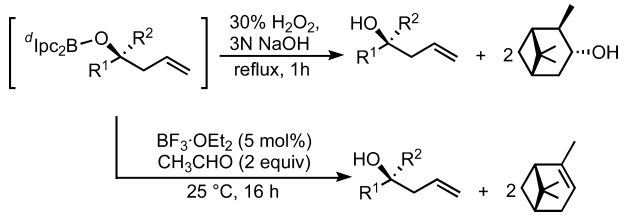


Entry	Carbonyl	Product	Yield[b] (%)	ee (%) (*S*)[c]
1	benzaldehyde	 **8**	82	41[d]
2	4-chlorobenzaldehyde	 **9**	56	35[d]
3	*p*-cyanobenzaldehyde	 **10**	65	35[d]
4	3-chlorobenzaldehyde	 **11**	72	39[d]
5	pivalaldehyde	 **12**	97	29[d]
6	acetophenone	 **7**	77	36[e]
7	trifluoroacetophenone	 **13**	79	12[e]
8	methyl 4-acetylbenzoate	 **14**	51	4[e]

[a]Reactions run with In^0 (5 mmol), propargyl bromide (5 mmol), [d]DIP-Cl (5 mmol), carbonyl (4.5 mmol), $BF_3{\cdot}OEt_2$ (0.25 mmol), and acetaldehyde (10 mmol) in THF and *n*-hexanes. [b]Isolated yield. [c]Assigned by analogy. [d]Determined by chiral GC analysis. [e]Determined by chiral HPLC analysis.

It should be pointed out that in addition to optimizing the reaction conditions for the coupling reaction with ketones, the workup for these reactions had been modified to improve isolation of the desired alcohol. Typically, an oxidative workup is employed to isolate the newly formed homoallylic alcohol in the reaction of **1** with aldehydes and ketones.[8a] However, the oxidative workup also oxidizes both of the boron–carbon bonds of **1** forming 2 equiv of isopinocampheol. The separation of the desired alcohol and the byproduct formed by this oxidation workup can be difficult, either by distillation, flash chromatography, or even sublimation,[25] as the two alcohols often have similar physical properties. In order to circumvent the tedious separation of the two alcohol products, a reductive workup was employed (Scheme 8).[26]The addition of a large excess of acetaldehyde to the reaction mixture produces *α*-pinene and ethanol via *β*-hydride transfer to the acetaldehyde. However, it was realized that only 2 equiv of acetaldehyde along with 0.5 mol % $BF_3{\cdot}Et_2O$ were necessary to catalyze the formation of pinene. It was observed that the use of a large excess of acetaldehyde was detrimental to our system producing the corresponding homoallylic from acetaldehyde. In this system, it is thought that InX_3 can catalyze oxonia-type rearrangement and/or transfer of the allylic group from the product homoallylic alcohol to acetaldehyde.[27] This modified reductive workup allows for easy separation and isolation of the homoallylic or homopropargylic alcohol product using a silica plug. Both the pinene and alcohol products are isolated in high yield and purity.

Scheme 8. Comparison of Oxidative vs Reductive Workup



With the optimal conditions in hand, we investigated the formation of homopropargylic alcohols from the coupling of **4** with various aldehydes and ketones (Table 2). The addition of *B*-allenyldiisopinocampheylborane to benzaldehyde afforded the homopropargylic alcohol (**8**) in 82% yield and a modest enantioselectivity of 41% (Table 2, entry 1). Electron-withdrawing 4-chloro- and *p*-cyanobenzaldehyde were implemented in this reaction and provided the homopropargylic alcohols, **9** and **10**, respectively, in moderate yields and enantioselectivities (Table 2, entries 2 and 3). 3-Chlorobenzaldehyde yielded 72% of **11** in 39% ee (Table 2, entry 4), and even the very sterically demanding trimethylacetaldehyde resulted in only 29% ee of **12** (Table 2, entry 5). The reaction of acetophenone with **4** provided **7** in a good yield of 77% and low enantioselectivity of 36% ee (Table 2, entry 6). Using a more reactive ketone, such as triflouroacetophenone, seemed promising, as this substrate had provided the corresponding homoallylic alcohol in high enantioselectivity.[15] However, the homopropargylic alcohol product (**13**) was obtained in high

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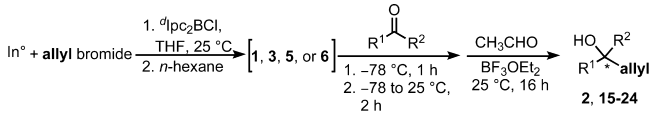
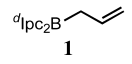
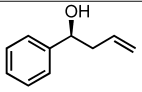
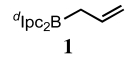
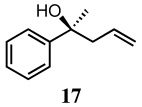
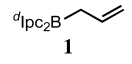
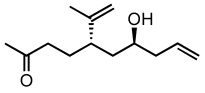
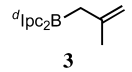
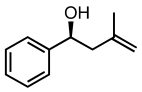
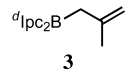
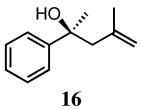
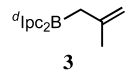
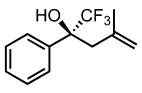
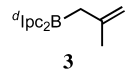
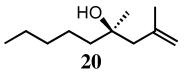
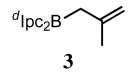
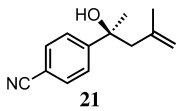
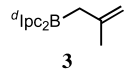
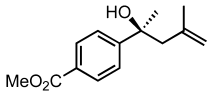
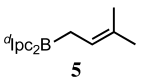
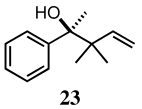
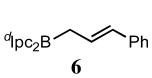
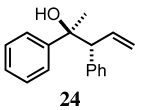
Table 3. Evaluation of the Enantioselective Addition to Aldehydes and Ketones Using *B*-Allyl and Substituted Allyldiisopinocampheylboranes[a]



Entry	Organoborane	Carbonyl	Product	Yield (%)[b,c]	% ee (*S*)[d] (dr *anti*:*syn*)[e]
1	 **1**	benzaldehyde	 **2**	99	93[f]
2	 **1**	acetophenone	 **17**	70	24[f]
3	 **1**	(*S*)-6-oxo-3-(prop-1-en-2-yl)heptanal	 **18**	64	90 de[g]
4	 **3**	benzaldehyde	 **15**	58	98[f]
5	 **3**	acetophenone	 **16**	80	78[f]
6	 **3**	trifluoroacetophenone	 **19**	90	15[f]
7	 **3**	heptan-2-one	 **20**	90	80[f]
8	 **3**	4-acetylbenzonitrile	 **21**	60	4[h]
9	 **3**	methyl 4-acetylbenzoate	 **22**	72	94[h]
10	 **5**	acetophenone	 **23**	65	2[f]
11	 **6**	acetophenone	 **24**	71	86[h] (*anti*) (15:1)

[a]Reactions run with In^0 (5 mmol), methallyl bromide (5 mmol), [d]DIP-Cl (5 mmol), acetophenone (4.5 mmol), $BF_3{\cdot}OEt_2$ (0.25 mmol), and acetaldehyde (10 mmol) in THF and *n*-hexanes. [b]Isolated yield of analytically pure product; all products greater than 90% by ^1H NMR. [c]Based on unreacted starting material. [d]Determined by comparison of elution order from the GC with known standards; all others were assigned by analogy. [e]Diasteomeric ratio was determined by chiral HPLC analysis. [g]Diasteomeric excess was determined by ^1H NMR analysis. [f]Determined by chiral GC analysis. [h]Determined by chiral HPLC analysis.

yield of 79% but a low enantioselectivity of 12% ee (Table 2, entry 7). Methyl 4-acetylbenzoate produced the corresponding homopropargylic alcohol (**14**) in moderate yield of 51%, as an essentially racemic mixture (4% ee) (Table 2, entry 8). These results indicate that the pocket created by this chiral borane reagent does not provide a large enough steric hindrance in the transition state leading to lowered enantioselectivity. Although the enantioselectivities realized by the reaction of **4** with various aldehydes and ketones is modest, this result represents the first reported synthesis of B-allenyldiisopinocampheylborane and its subsequent coupling to aldehydes and ketones to yield enantioenriched products.[28] At this point, the exploration of the other B-reagents was conducted and the subsequent coupling with aldehydes and ketones to obtain a variety of enantioenriched secondary and tertiary homoallylic alcohol products.

In Situ Generation of *B*-Allyl and Substituted Allylborane Reagents Followed by Coupling with

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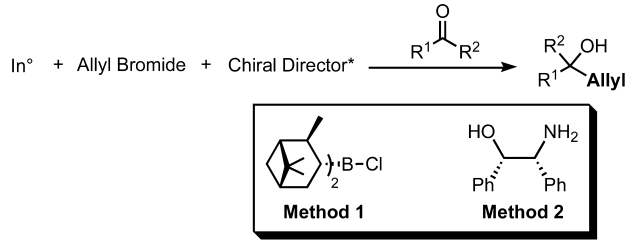
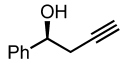
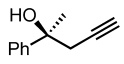
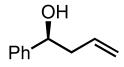
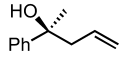
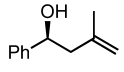
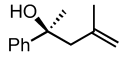
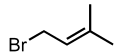
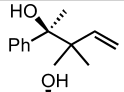
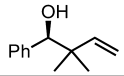
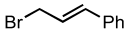
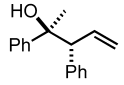
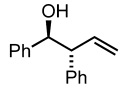
Table 4. Boron vs Indium: Comparison of the Enantioselectivities of the Two Barbier-Type Nucleophilic Asymmetric Additions to Carbonyls



Entry	Allyl Bromide	Carbonyl	Product	Method	Yield (%)	% ee
1				1	82	41
2				2	90	88
3				1	77	36
4				2	0	0
5				1	99	93
6				2	90	93
7				1	70	24
8				2	87	58
9				1	58	98
10				2	70	45
11				1	80	78
12				2	55	16
13				1	65	2
14				2	54	56
15				1	71	88 de; 86 ee
16				2	50	90 de; 56 ee

Carbonyl Substrates. Both chiral borane reagents *B*-allyldiisopinocampheylborane (**1**) and *B*-methallyldiisopinocampheylborane (**3**) were formed efficiently via the reaction of the corresponding allyl halide and indium metal under Barbier-type conditions, and the reaction of **1** with benzaldehyde had been optimized demonstrating excellent enantioselectivity. However, **3** had yet to be applied to the coupling reaction with ketones. The optimal reaction conditions for the methallyl addition to both benzaldehyde and acetophenone were explored using **3**. Using the aforementioned coupling reaction conditions, benzaldehyde was added to the reaction at −78 °C, which led to the formation of the corresponding 1-phenyl-3-butenol (**15**) in 60% conversion and 98% ee (Table 3, entry 4). We were pleased with this enantioselectivity albeit with moderate conversion and proceeded to optimization of the methallylation of acetophenone. Starting with the typical reaction conditions, acetophenone was coupled with **3** providing 4-methyl-2-phenylpent-4-en-2-ol (**16**) in high conversion (83%) and enantioselectivity (78%) (Table 3, entry 5). These results showed promise that this chiral boron reagent could efficiently produce high enantiomeric excess in the formation of tertiary alcohol products. In an attempt to improve enantioselectivity, longer warming time periods and the additions of acetophenone to a 0 °C ice bath were investigated; however, these conditions did not improve the enantioselectivity over 78%. On the basid of these results, it was concluded that the most favorable conditions for the methallylation of acetophenone occurred when the flask was cooled to −78 °C for a period of 1 h, followed by removal of the cooling bath, and after 2 h, $BF_3{\cdot}OEt_2$ (0.25 equiv) and acetaldehyde (2 equiv) were added. In addition, this method was superior to the asymmetric indium-mediated Barbier-type methallylation reaction, since under those conditions the production of **16** from acetophenone occurred in a lower yield of 55% and much lower enantiomeric excess of 16% ee.[15]

With the optimal conditions worked out for the methallylation of both aldehydes and ketones, we investigated the ability of **3** to be coupled with a variety of ketones. We also looked at the coupling of **1** with a few carbonyl substrates. Since the optimal temperature and time conditions for the allylation, methallylation, and propargylation of aldehydes and ketones using these chiral borane reagents was the same, we proceeded with using these conditions for the coupling reaction

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of the other substituted allylborane reagents. Starting with the simple allylation of benzaldehyde using **1**, the corresponding **2** was formed in excellent yield (99%) and enantioselectivity (93%) (Table 3, entry 1). 2-Phenylpent-4-en-2-ol (**17**) was obtained in 70% yield and low enantioselectivity of 24% ee from acetophenone and **1** (Table 3, entry 2); however, this result demonstrates an improved enantiomeric control for the allylation of acetophenone using *B*-allyldiisopinocampheylborane where only 2% ee was obtained previously.[13] Next, the chemoselectivity of this reaction was explored by using (*S*)-6-oxo-3-(prop-1-en-2-yl)heptanal,[29] which contains both aldehyde and ketone functionality. It was found that the corresponding secondary homoallylic alcohol (**18**) was obtained in 64% yield, excellent chemoselectivity, and high diastereoselectivity (90% de) (Table 3, entry 3).

The methallylation of benzaldehyde using **3** provided 3-methyl-1-phenyl-3-butenol (**15**) in an acceptable yield and excellent ee (98%) (Table 3, entry 4). The coupling of **3** with acetophenone produced **16** in good yield of 80% and enantioselectivity of 78% ee (Table 3, entry 5). The more reactive ketone, triflouroacetophenone, was subjecting to the coupling reaction and excellent yield for the corresponding alcohol product, 1,1,1-trifluoro-4-methyl-2-phenylpent-4-en-2-ol (**19**), was observed, but the enantioselectivity was poor (15% ee) (Table 3, entry 6). Next, the methallylation of an aliphatic ketone, specifically heptan-2-one, using **3** was examined. Satisfyingly, 2,4-dimethylnon-1-en-4-ol (**20**) was produced in high yield (90%) and enantioselectivity (80% ee), which demonstrates the efficiency of **3** in the methallylation of not very sterically demanding aliphatic ketones (Table 3, entry 7).

The methallylation of both 4-acetylbenzonitrile and methyl 4-acetylbenzoate gave moderate to good yields of 60% and 72%, respectively (Table 3, entries 8 and 9). Unfortunately, 4-acetylbenzonitrile provided a racemic alcohol product (**21**) when coupled with **3** (Table 3, entry 8), which might be due to the lone pair of the nitrogen interfering with the organoborane reagent. On the other hand, methyl 4-(2-hydroxy-4-methylpent-4-en-2-yl)benzoate (**22**) was produced in excellent enantiomeric excess (94%) (Table 3, entry 9). These results indicate that the presence of the ester functionality imparts this substrate to exhibit higher enantioselectivity under these reaction conditions when compared to acetophenone. Additionally, this entry highlights the chemoselectivity of the organoborane species, selectively reacting with the ketone over the ester.

The prenylation of acetophenone was investigated using **5**, and it was found that the corresponding alcohol product (**23**) was obtained in moderate yield of 65%. Unfortunately, the enantioselectivity for the addition to acetophenone was low (2% ee) (Table 3, entry 10).[30] Gratifyingly, the reaction of **6**, obtained from cinnamyl bromide, with acetophenone produced 2,3-diphenylpent-4-en-2-ol (**24**) in high diastereoselectivity for the *anti*-product (15:1 *anti*/*syn*). This chiral borane reagent **6** also exhibited high enantioselectivity providing the antialcohol in 86% ee and good yield of 71% (Table 3, entry 11). This reaction demonstrated the ability to couple a substituted allyl group with acetophenone in good yield and stereoselecitivity along with expanding the utility of these allylating boron species

Comparison of Enantioselective Methods: Boron vs Indium. The results of the coupling of the organoborane reagents with various aldehydes and ketones allows a comparison to our previous method of asymmetric indium-mediated Barbier-type allylations and propargylations.[15,20,31] Comparison of the use of chiral organoborane reagents (method 1) and organoindium reagents with a commercially available chiral auxiliary, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (method 2), in the asymmetric addition to carbonyls revealed that these methods are mutually complementary (Table 4). It can be seen that the direct organoindium addition (method 2) would be preferred when synthesizing the corresponding homopropargylic alcohol from benzaldehyde yielding 88% ee, as compared to 41% ee (Table 4, entries 1 and 2). On the other hand, when a tertiary homopropargylic alcohol is desired the allenylborane reagent exhibit superior performance while under the indium-mediated method the propargylation does not proceed (Table 4, entries 3 and 4). When comparing the allylation of benzaldehyde either method affords an enantioselectivity of 93% (Table 4, entries 5 and 6). However, the asymmetric indium-mediated allylation of acetophenone induced better enantioselectivity of 58% ee when compared with the allylborane reagent, which led to the formation of the homoallylic alcohol in 24% ee (Table 4, entries 7 and 8).

The methallylation of both benzaldehyde and acetophenone with the organoindium reagent afforded moderate ee's of 45% and 16%, respectively (Table 4, entries 10 and 12). The chiral organoborane reagent method is relatively superior with enantioselectivities of 98% ee for 3-methyl-1-phenylbut-3-enol and 78% ee for 4-methyl-2-phenylpent-4-en-2-ol (Table 4, entries 9 and 11). A direct comparison of the two methods for the addition of either a prenyl or cinnamyl group to benzaldehyde or acetophenone could not be discussed as both methods were not conducted on both substrates. Hence, a general comparison of the methods in the addition to carbonyls to provide the corresponding substituted alcohol products was discussed. For the prenylation of carbonyls, method 2 appears to be more effective, providing 56% ee for the secondary alcohol product, 2,2-dimethyl-1-phenylbut-3-en-1-ol (Table 4, entry 14), while method 1 showed a decreased enantiomeric control of 2% ee for the tertiary alcohol product 3,3-dimethyl-2-phenylpent-4-en-2-ol (Table 4, entry 13). Conversely, in the addition of cinnamyl moiety to carbonyls, the chiral organoborane reagent method provides enhanced enantioselectivity of 86% ee (Table 4, entry 15) when compared to the asymmetric indium-mediated addition method yields moderate enantioselectivity of 56% (Table 4, entry 16).

■ CONCLUSION

In summary, we have described the first method for the synthesis of allyl-, substituted allyl-, and allenyldiisopinocampheylboranes from the corresponding organoindium reagents. These highly useful reagents are formed in a simple one-pot procedure under Barbier-type conditions starting from the corresponding allyl or propargyl bromide with indium powder and *B*-chlorodiisopinocampheylborane. Indium offers a straightforward and general route to various organoboranes, in comparison to other reported and widely used methods for their synthesis, which differ depending on the desired borane reagent. A modified reductive method for product isolation was employed.

Upon coupling with aldehydes, the in situ formed *B*-allyldiisopinocampheylborane yields the homoallylic alcohol products with excellent and expected enantioselectivities. Interestingly, this method provides increased enantioselectivity for the tertiary homoallylic alcohol product compared to

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literature when *B*-allyldiisopinocampheylboranes was reacted with acetophenone. This was the first use of *B*-methallyldiisopinocampheylboranes in the addition to various aldehydes and ketones providing up to excellent enantioselectivity. We also report here the first synthesis of *B*-allenyldiisopinocampheylborane and demonstrated its effectiveness in the synthesis of enantiomerically enriched homopropargylic alcohols from ketones, albeit with low enantiomeric excess. In addition to the coupling reactions with carbonyls, *B*-allenyldiisopinocampheylborane reagent is now readily available to delineate its synthetic potential.[32] More substituted allyl bromides were used in the formation of the substituted allylborane reagents via reaction with indium metal, which were taken on to react with acetophenone leading to more structurally diverse tertiary homoallylic alcohols. This is the first example of using these substituted allylborane reagent in the coupling with ketones. Specifically, the enantioselective addition of cinnamyl produced the corresponding alcohol product in good diastereoselectivity (88%) and enantioselectivity (86%). The ability of indium to transfer the allyl functionality to ^{d}DIP-Cl, forming allylboranes, is a powerful tool for synthetic organic chemistry.

We have demonstrated the ability of organoindium reagents to form a variety of chiral borane reagents by simply using indium metal and the corresponding organo halide. In addition, these reagents have shown utility in the subsequent formation of both enantioenriched secondary and tertiary alcohol products. Using indium to generate these versatile nucleophiles allows for ease of preparation of the desired chiral borane reagent. This facile one-pot method has shown generality in the addition to both aldehydes and ketones.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *B*-Allyl or Allenyldiisopinocampheylboranes 1 and 3−6. An oven-dried 25 mL round-bottom flask equipped with a stirbar was cooled under argon, charged with indium powder (0.574 g, 5 mmol), and sealed with a rubber septum. Anhydrous THF (2.4 mL) was added, and the flask was degassed via vacuum backfill cycles (5×). *B*-Chlorodiisopinocampheylborane (1.60 g, 5 mmol) was weighed under argon in a glovebox, dissolved in THF (1 mL), and added to the indium suspension via syringe. The appropriate allyl or propargyl bromide (5 mmol) was then added via syringe, and the reaction became slightly exothermic. After 30 min, *n*-hexanes (5 mL) was added, and a precipitate formed immediately. ^{11}B NMR verified formation of the chiral borane reagent. The solution was used as a 0.5 M solution for the addition to aldehydes and ketone.

*B-Allyldiisopinocampheylborane, **1** (Table 1, Entries 4 and 5).*[8a] ^{11}B NMR: δ +79 ppm. The solution was used as a 0.5 M solution for the addition to aldehydes and ketones.

*B-Methallyldiisopinocampheylborane, **3** (Scheme 5).*[8a] ^{11}B NMR: δ +79 ppm. The solution was used as a 0.5 M solution for the addition to aldehydes and ketones.

*B-Allenyldiisopinocampheylborane, **4** (Scheme 5).* Following the general procedure above, **4** was synthesized and used in subsequent coupling reactions with aldehydes and ketones in order to confirm the synthesis of this reagent by formation of the corresponding homopropargylic alcohol products. ^{11}B NMR: δ +74 ppm. ^{1}H NMR (500 MHz, THF-d_8) δ (ppm): 4.64 (d, J = 6.5 Hz, 2H), 5.73 (t, J = 6.5 Hz, 1H).

*B-3,3-Dimethylallyldiisopinocampheylborane, **5** (Scheme 5).*[33] ^{11}B NMR: δ +52, +74 ppm. The solution was used as a 0.5 M solution for the addition to acetophenone.

*B-Cinnamyldiisopinocampheylborane, **6** (Scheme 5).*[34] ^{11}B NMR: δ +74 ppm. The solution was used as a 0.5 M solution for the addition to acetophenone.

General Procedure for the Coupling of Chiral Borane Reagents 1 and 3−6 with Aldehydes and Ketones to Provide Alcohol Products 2 and 7−24. To a solution of freshly prepared **1** or **3−6** (0.5 M, 5 mmol) cooled to −78 °C (dry ice/acetone) was added the carbonyl (4.5 mmol) dropwise. After 1 h at −78 °C, the ice bath was removed, and the flask was allowed to warm to room temperature over a period of 2 h, at which time $BF_3{\cdot}EtO_2$ (0.25 mmol, 0.03 mL) and acetaldehyde (10 mmol, 0.56 mL) were added via syringe and the solution was stirred at room temperature overnight. The solution was diluted with Et_2O, washed with 1 M HCl (2 × 10 mL), 1 M NaOH (3 × 10 mL), water (10 mL), and brine (10 mL), dried with anhydrous magnesium sulfate ($MgSO_4$), concentrated under vacuum, and purified by flash chromatography on a short silica column. Pinene was eluted with hexanes followed by elution of homoallylic alcohol with an Et_2O/hexanes mixture. The corresponding alcohol product was isolated as an oil or solid.

Acetylation of 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 and 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 and used for GC analysis.

1-Phenyl-3-butyn-1-ol, 8 (Table 2, Entry 1).[35] Following the general procedure above, **8** was isolated as clear, colorless oil (0.539 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09 (t, J = 2.5 Hz, 1H), 2.65 (dd, J = 1, 2.5 Hz, 1H), 2.66 (d, J = 2.5 Hz, 1H), 4.88−4.90 (m, 1H), 7.31−7.42 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.5, 71.0, 72.3, 80.7, 125.8, 128.0, 128.5, 142.4. Enantiomeric excess was determined to be 41% by chiral GC analysis. GC conditions: 140 °C isothermal, t_R for the (*R*)-alcohol =24.66 min, and t_R for the (*S*)-alcohol =25.75 min. The absolute stereochemistry was determined by comparison of elution order from the GC with known standards, all others were assigned by analogy.

1-(4-Chlorophenyl)-3-butyn-1-ol, 9 (Table 2, Entry 2).[36] Following the general procedure above, **9** was isolated as a clear, colorless oil (0.455 g, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.08 (t, J = 2.5 Hz, 1H), 2.44 (d, J = 3.5 Hz, 1H), 2.58−2.67 (m, 2H), 4.86 (ddd, J = 2.5, 5.5 6.5 Hz, 1H), 7.34 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.4, 71.3, 71.6, 80.2, 127.2, 128.7, 133.7, 140.9. Enantiomeric excess was determined to be 35% by chiral GC analysis. GC conditions: 160 °C isothermal, t_R for the (*R*)-alcohol = 30.87 min, and t_R for the (*S*)-alcohol = 32.55 min.

4-(1-Hydroxybut-3-ynyl)-benzonitrile, 10 (Table 2, Entry 3).[37] Following the general procedure above, **10** was isolated as a white solid (0.450 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10 (t, J = 3 Hz, 1H), 2.52 (d, J = 4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.4, 71.4, 71.8, 79.5, 111.8, 118.7, 126.6, 132.4, 147.6. Enantiomeric excess was determined to be 35% by chiral GC analysis. GC conditions: 180 °C isothermal, t_R for the (*R*)-alcohol = 38.43 min, and t_R for the (*S*)-alcohol = 40.56 min.

1-(3-Chlorophenyl)-3-butyn-1-ol, 11 (Table 2, Entry 4).[38] Following the general procedure above, **11** was isolated as white solid (0.585 g, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.09 (t, J = 2.5 Hz, 1H), 2.61 (ddd, J = 3, 7, 17 Hz, 1H), 2.65 (ddd, J = 2.5, 5.5, 17 Hz, 1H), 4.86 (t, J = 6 Hz, 1H), 7.26−7.32 (m, 3H). 7.41−7.42 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.4, 71.4, 71.6, 80.1, 124.0, 126.1, 128.1, 129.8, 134.5, 144.5. Enantiomeric excess was determined to be 39% by chiral GC analysis. GC conditions: 160 °C isothermal, t_R for the (*R*)-alcohol =29.99 min, and t_R for the (*S*)-alcohol =30.87 min.

2,2-Dimethyl-5-hexyn-3-ol, 12 (Table 2, Entry 5).[38] Following the general procedure above, **12** was isolated as a clear, colorless oil (0.49 g, 97% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.93 (s, 9H), 2.07 (t, J = 2.5 Hz, 1H), 2.26 (ddd, J = 3, 10, 17 Hz, 1H), 2.45 (dt, J = 3, 17 Hz, 1H), 3.46 (dd, J = 2.5, 10 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 29% by chiral GC analysis of the acetylated

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homoallylic alcohol. GC conditions: 80 °C isothermal, t_R for the (*S*)-alcohol = 34.40 min, and t_R for the (*R*)-alcohol = 37.73 min.

2-Phenylpent-4-yn-2-ol, 7 (Table 2, Entry 6).[39] Following the general procedure above, **7** was isolated as a clear, colorless oil (0.555 g, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 2.06 (t, J = 2.5 Hz, 1H), 2.70 (dd, J = 2.5, 14.0 Hz, 1H), 2.77 (dd, J = 2.5, 14.0 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.0 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1, 34.5, 72.4, 73.1, 80.3, 124.6, 127.0, 128.2, 145.4. Enantiomeric excess was determined to be 36% by chiral HPLC analysis. HPLC conditions: 98:2 hexanes/^{i}PrOH, 0.5 mL/min, λ = 251 nm, t_R for the (*S*)-alcohol = 28.96 min, and t_R for the (*R*)-alcohol = 35.66 min.

1,1,1-Trifluoro-2-phenylpent-4-yn-2-ol, 13 (Table 2, Entry 7).[20] Following the general procedure above, **13** was isolated as a yellow oil (0.684 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.07 (t, J = 2.5 Hz, 1H), 3.11 (d, J = 2.5 Hz, 1H), 3.13 (d, J = 3.0 Hz, 1H), 7.41−7.43 (m, 3H), 7.59 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 73.5, 82.2, 85.4, 126.4, 128.4, 129.0, 136.2, 139.4. Enantiomeric excess was determined to be 12% by chiral HPLC analysis of the homoallylic alcohol. HPLC conditions: 95:5 hexanes/^{i}PrOH, 0.5 mL/min, λ = 231 nm, t_R for the (*R*)-alcohol = 54.99 min, and t_R for the (*S*)-alcohol = 57.74 min.

Methyl 4-(2-Hydroxypent-4-yn-2-yl)benzoate, 14 (Table 2, entry 8).[40] Following the general procedure above, **14** was isolated as a yellow oil (0.980 g. 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 2.06 (t, J = 2.5 Hz, 1H), 2.71 (dd, J = 2.5, 14.0 Hz, 1H), 2.77 (dd, J = 2.5, 14.0 Hz, 1H), 3.91 (s, 3H), 7.56 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.3, 29.1, 34.5, 52.0, 72.0, 80.6, 124.7, 128.9, 129.5, 134.4, 151.2, 166.8. Enantiomeric excess was determined to be 4% by chiral HPLC analysis of the homoallylic alcohol. HPLC conditions: 90:10 hexanes/^{i}PrOH, 0.5 mL/min, λ = 239 nm, t_R for the (*S*)-alcohol = 81.49 min, and t_R for the (*R*)-alcohol = 86.45 min.

(*S*)-1-Phenyl-3-buten-1-ol, 2 (Table 3, Entry 1).[41] Following the general procedure above, **2** was isolated a clear, colorless oil (0.660 g, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50−2.57 (m, 2H), 4.76 (dd, J = 5, 7.5 Hz, 1H), 5.15−5.21 (m, 2H), 5.79−5.87 (m, 1H), 7.28−7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.8, 73.3, 118.5, 125.9, 127.6, 128.5, 134.5, 143.9. Enantiomeric excess was determined to be 93% by chiral GC analysis of the acetylated homoallylic alcohol. GC conditions: 115 °C isothermal, t_R for the (*R*)-alcohol = 45.28 min, and t_R for the (*S*)-alcohol = 45.86 min. The absolute stereochemistry was determined by comparison of elution order from the GC with known standards; all others were assigned by analogy.

(*S*)-2-Phenylpent-4-en-2-ol, 17 (Table 3, Entry 2).[41] Following the general procedure above, **17** was isolated as a yellow oil (0.520 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 2.52 (dd, J = 6, 13.5 Hz, 1H), 2.70 (dd, J = 7.5, 14.0 Hz, 1H), 5.13−5.15 (m, 2H), 5.60−5.69 (m, 1H), 7.27 (d, J = 9.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.9, 48.4, 69.2, 119.5, 124.8, 126.7, 128.2, 133.7, 144.9. Enantiomeric excess was determined to be 24% by chiral GC analysis. GC conditions: 120 °C isothermal, t_R for the (*R*)-alcohol = 29.85 min, and t_R for the (*S*)-alcohol = 30.13 min. The absolute stereochemistry was determined by comparison of elution order from the GC with known standards; all others were assigned by analogy.

(*S*)-6-Oxo-3-(prop-1-en-2-yl)heptanal (Table 3, Entry 3).[20] 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 (−)-limonene oxide (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 and 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-.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.

(5*S*)-7-Hydroxy-5-(prop-1-en-2-yl)dec-9-en-2-one, 18 (Table 3, Entry 3). Following the general procedure above, **18** was isolated as a yellow oil (0.360 g, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) major diastereromer: δ = 1.57 (s, 3H), 1.70−1.72 (m, 1H), 2.10 (s, 3H), 2.32−2.36 (m, 3H), 2.14−2.22 (m, 4H), 3.65−3.71* (m, 1H), 4.68 (d, J = 9.5 Hz, 1H), 4.69 (d, J = 13.0 Hz, 1H), 5.03−5.04 (m, 2H), 5.76−5.84 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 22.7, 27.3, 31.6, 40.7, 41.7, 43.4, 68.5, 113.4, 118.0, 134.9, 146.4, 209.2. dr 95:5 *(via integration of signals at 3.54−3.58 and 3.65−3.71); 90% de.

1-Phenyl-2-methyl-3-buten-1-ol, 15 (Table 3, Entry 4).[42] Following the general procedure above, **15** was isolated as a clear, colorless oil (0.423 g, 58% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.15 (d, J = 2.5 Hz, 1H), 2.45 (d, J = 7 Hz, 2H), 4.83 (dt, J = 2, 7 Hz, 1H), 4.88 (s, 1H), 4.94 (s, 1H), 7.28−7.41 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 48.4, 71.5, 114.1, 125.8, 127.5, 128.4, 142.4, 144.1. Enantiomeric excess was determined to be 98% by chiral GC analysis of the acetylated homoallylic alcohol. GC conditions: 115 °C isothermal, t_R for the (*S*)-alcohol = 60.61 min, and t_R for the (*R*)-alcohol = 61.51 min.

4-Methyl-2-phenylpent-4-en-2-ol, 16 (Table 3, Entry 5).[42] Following the general procedure above, **16** was isolated as a yellow oil (0.635 g, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 3H), 1.57 (s, 3H), 2.43 (s, 1H, OH), 2.53 (d, J = 13.0 Hz, 1H), 2.63 (dd, J = 2.5, 9.0 Hz, 1H), 4.76 (s, 1H), 4.90 (s, 1H), 7.24 (t, J = 7.0 Hz, 1H) 7.34 (t, J = 8.0 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 30.6, 52.0, 93.9, 115.7, 124.8, 126.5, 128.1, 142.7, 148.0. Enantiomeric excess was determined to be 78% by chiral GC analysis. GC conditions: 115 °C isothermal, t_R for the (*S*)-alcohol = 47.97 min, and t_R for the (*R*)-alcohol = 48.95 min.

1,1,1-Trifluoro-4-methyl-2-phenylpent-4-en-2-ol, 19 (Table 3, Entry 6).[43] Following the general procedure above, **19** was isolated as a yellow oil (0.932 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.54 (s, 3H), 2.49 (d, J = 13.0 Hz, 1H), 2.59 (d, J = 13.5 Hz, 1H), 4.71 (s, 1H), 4.85 (s, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.5, 52.0, 82.3, 115.6, 124.8, 126.5, 128.0, 142.5, 147.9, 157.9. Enantiomeric excess was determined to be 12% by chiral GC analysis. GC conditions: 120 °C isothermal, t_R for the (*R*)-alcohol = 23.13 min, and t_R for the (*S*)-alcohol = 24.13 min.

2,4-Dimethylnon-1-en-4-ol, 20 (Table 3, Entry 7).[44] Following the general procedure above, **20** was isolated as a clear, colorless oil (0.690 g, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3H), 1.26−1.34 (m, 6H), 1.83 (s, 3H), 2.14 (d, J = 7.5 Hz, 1H), 2.19 (d, J = 14.0 Hz, 2H), 2.23 (d, J = 6.0 Hz, 1H), 4.75 (s, 1H), 4.93 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.7, 25.0, 26.9, 32.4, 42.5, 49.2, 84.2, 114.8, 142.9. Enantiomeric excess was determined to be 80% by chiral GC analysis of the homoallylic alcohol. GC conditions: 115 °C isothermal, t_R for the (*S*)-alcohol = 15.63 min, and t_R for the (*R*)-alcohol = 15.99 min.

4-(2-Hydroxy-4-methylpent-4-en-2-yl)benzonitrile, 21 (Table 3, Entry 8).[45] Following the general procedure above, **21** was isolated as a yellow oil (0.543 g, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 3H), 1.56 (s, 3H), 2.53 (d, J = 13.0 Hz, 1H), 2.63 (d, J = 13.5 Hz, 1H), 4.74 (s, 1H), 4.92 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H) 7.62 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.1, 28.5, 51.6, 73.1, 108.5, 111.5, 118.8, 125.7, 131.9, 141.5, 163.3. Enantiomeric excess was determined to be 4% by chiral HPLC analysis. HPLC conditions: 98:2 hexanes/^{i}PrOH, 0.5 mL/min, λ = 234 nm, t_R for the (*R*)-alcohol = 45.56 min, and t_R for the (*S*)-alcohol = 49.81 min.

Methyl 4-(2-Hydroxy-4-methylpent-4-en-2-yl)benzoate, 22 (Table 3, Entry 9).[43] Following the general procedure above, **22** was isolated as a yellow oil (0.760 g. 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 3H), 1.55 (s, 3H), 2.51 (d, J = 14.0 Hz, 1H), 2.63 (d, J = 13.5 Hz, 1H), 3.89 (s, 3H), 4.72 (s, 1H), 4.87 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz,

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$CDCl_3$): δ = 24.9, 30.7, 51.8, 73.3, 82.7, 116.1, 124.9, 128.4, 129.4, 142.0, 153.2, 167.0. Enantiomeric excess was determined to be 94% by chiral HPLC analysis. HPLC conditions: 90:10 hexanes/^{i}PrOH, 0.5 mL/min, λ = 242 nm, t_R for the (*S*)-alcohol = 18.21 min, and t_R for the (*R*)-alcohol = 50.36 min.

3,3-Dimethyl-2-phenylpent-4-en-2-ol, 23 (Table 3, Entry 10).[46] Following the general procedure above, **23** was isolated as a yellow oil (0.557 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (s, 3H), 2.03 (s, 3H), 5.01 (dd, *J* = 1.5, 16.5 Hz, 1H), 5.05 (dd, *J* = 11, 14.0 Hz, 1H), 5.07 (dd, *J* = 1.5, 9.5 Hz, 1H), 7.41−7.44 (m, 3H), 7.52 (t, *J* = 9.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6, 26.5, 50.1, 79.1, 113.6, 127.1, 128.3, 128.5, 137.1, 145.3. Enantiomeric excess was determined to be 2% by chiral GC analysis. GC conditions: 135 °C isothermal, t_R for the (*R*)-alcohol = 35.79 min, and t_R for the (*S*)-alcohol = 37.72 min.

2,3-Diphenylpent-4-en-2-ol, 24 (Table 3, Entry 11).[47] Following the general procedure above, **24** was isolated as a yellow oil (0.761 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 3H), 4.02−4.04 (m, 1H), 4.93−4.86 (m, 1H), 6.11−6.19* (m, 1H), 7.20−7.30 (m, 6H), 7.41−7.44 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 55.5, 76.3, 117.8, 125.6, 127.7, 128.3, 128.6, 129.7, 133.14, 137.6, 140.3, 146.6. Diastereomeric ratio was determined to be 15:1 by chiral HPLC analysis. Enantiomeric excess was determined to be 86% by chiral HPLC analysis. HPLC conditions: 98:2 hexanes/^{i}PrOH, 0.5 mL/min, λ = 230 nm, t_R for the *syn*-alcohol = 12.85 min, t_R for the *syn*-alcohol = 14.07 min, t_R for the (*R*)-alcohol = 22.35, and t_R for the (*S*)-alcohol = 39.64 min dr 15:1 *(via integration of signals at 6.11−619 and 6.24−6.32).

■ 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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Notes

The authors declare no competing financial interest.

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