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Catalytic enantioselective allylboration of propargylic aldehydes

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ABSTRACT

Homoallylic propargylic alcohols are important building blocks in natural product synthesis. This moiety can be transformed into various other structures by performing other known transformations, which can in turn lead to the synthesis of biologically useful compounds. Herein, a methodology based on Lewis acid assisted Brønsted acid catalysed allylboration of propargylic aldehydes is described. A detailed optimization study followed by a thorough examination of substrate scope have been explored.

1. Introduction

Homoallylic propargylic alcohols are very important end-products and intermediates in natural product synthesis.[1,2] Several characteristic transformations of the alkyne unit, such as hydrometallation/alkylation, catalytic hydrogenation, isomerization and many others can lead to very important synthetic building blocks (Fig. 1).

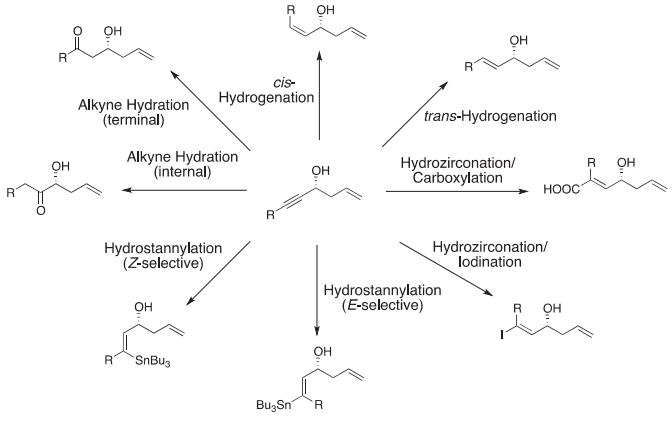

Fig. 1. Possibilities of synthetic manipulations of homoallylic propargylic alcohols.

There are several enantioselective methods available for the addition of allylic boron reagents[3] and other allylmetal reagents[4] onto aldehydes as a means to produce homoallylic alcohols.[5] However, there have been only a few reported examples of additions onto propargylic aldehydes to provide the desired homoallylic propargylic alcohols, and these methods often employ reagents based on a stoichiometric chiral auxiliary.[6] Some of these methods, such as the one developed by Brown and co-workers, involve air-sensitive allylic dialkyl boranes. Although it is a useful method, use of unstable chiral reagents that need to be prepared and reacted in situ without isolation, poses a limitation. On the other hand, catalytic enantioselective variants with stable allylboronic esters have recently been reported in the literature.[7,8] In particular, Hu and co-workers described a catalytic enantioselective allylboration methodology for the synthesis of homoallylic propargylic alcohols involving a chiral phosphoric acid as catalyst, but a detailed substrate scope has not been presented.[8b]

Our group has developed a catalytic enantioselective allylboration methodology[7] exploiting the concept of Lewis acid assisted Brønsted acid catalysis.[9] The development of a synthetic chiral diol (vivol) provided a diol·$SnCl_4$ catalyst that can be used in additions of a wide range of allylic boronates to aliphatic aldehydes, yielding homoallylic alcohols in >90% ee. This method is versatile and has been employed in the synthesis of complex natural products.[7e] Here, we report an asymmetric synthesis of homoallylic propargylic alcohols by the addition of allylic boronates to propargylic aldehydes under this condition (Scheme 1).

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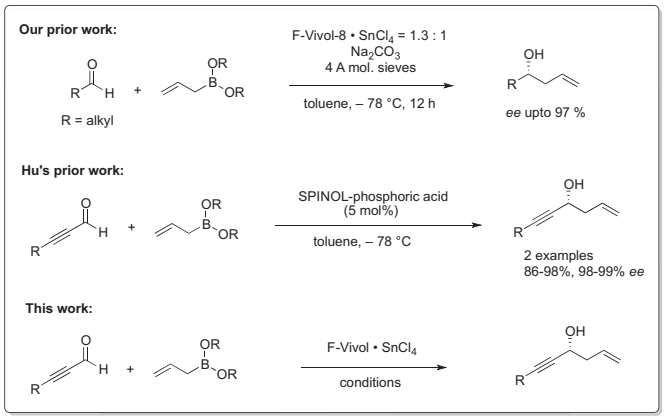


Scheme 1. Catalytic asymmetric allylboration of propargylic aldehydes.

2. Results and discussion

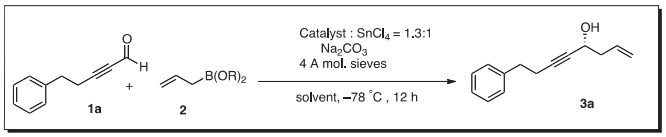
Using aldehyde **1a**, a detailed optimization study was planned with a focus on the varying nature of the chiral diol unit in the catalyst, the catalyst loading, solvent, and different boronates (Table 1). As observed in previous work from our group,[7b] we noted a significant effect of the ring size of the chiral diol catalyst (F-vivol) on the yield and enantioselectivity. A cyclooctyl ring unit on the vivol catalyst provided optimal enantioselectivity when using allylboronate **2a** (entries 1–4). Increasing the catalyst loading to a certain extent improved both the yield and enantioselectivity (entries 5–6). The boronate unit of reagent **2** was found to have a profound effect on the outcome of the reactions. Thus a boronate made from a 1,3-diol, **2b**, was found to be superior compared to **2a** (entry 8 vs entry 6). Placement of substituents on the six-membered boronate was found to be important. Although many boronates with a spiro ring on C_2 were evaluated (entries 12, 13, 16) none of them performed better than boronate **2b** with *gem*-dimethyl unit. Reagent **2f** with one methyl group on C_2 exhibited a poor selectivity (entry 14). Surprisingly, the reaction of allylboronate **2h** with a cyclopropyl ring on C_2 (entry 16) did not proceed at all despite its similarity to **2b**. Solvent is known to have a strong influence in allylboration reactions. Since carbonyl allylboration involves charge separation at the transition state, polarity of the solvent can exert a notable effect.[10] In polar solvents, such as CH_2Cl_2 and mixtures of CH_2Cl_2 and toluene, the background racemic reaction between the allylboronate and aldehyde is faster compared to less polar arene solvents, which led to lower enantioselectivities (entries 17, 18, 19). Lower selectivities were also observed with solvents, such as fluorobenzene, xylene and trifluorotoluene (entries 20–24). Looking at these results, toluene stood out as the best solvent. Different Lewis acids (such as $Yb(OTf)_3$, $La(OTf)_3$, SnF_4, $TiCl_4$, $ZrCl_4$) were tried as alternatives to $SnCl_4$ but none of them were found to be more efficient. Finally we achieved our best reaction conditions when using allylboronate **2b** with 10% F-vivol-8·$SnCl_4$ as catalyst and toluene as the solvent.

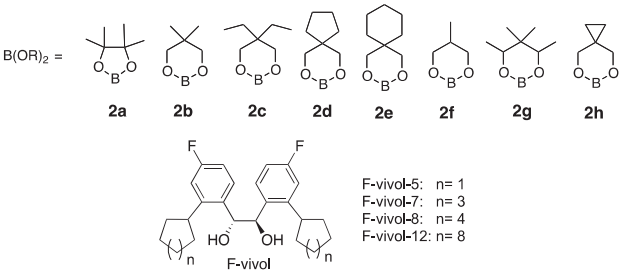
With the optimized conditions in hand, the versatility of this method was explored with different aldehydes and allylic boronates.

During our substrate scope study, we screened 11 propargylic aldehydes with different steric and electronic characteristics (Table 2). The enantioselectivity and the yields ranged from excellent to moderate depending on the substrate used. An interesting trend was observed where the substrates with an aromatic group directly attached to the alkyne provided lower enantioselectivities (entries 8–11) compared to the propargylic aldehydes substituted with an aliphatic chain (entries 1–7). Because the aldehyde carbonyl is relatively far from the alkyne substituent, the exact reason behind this observation is, at this stage, unclear. Excellent selectivity and yield were observed with 3-trimethylsilylpropynal (entry 5). This substrate is important because easy removal of the TMS group can afford a terminal alkyne that can be further transformed into many other synthetic building blocks. The absolute stereochemistry of products **3c**, **3f** and **3i** was determined by comparing specific rotation values with that of previously reported compounds (see Supplementary data).

Because of the easy accessibility of *E*-crotyl boronates via the method reported by Szabo[11] from the corresponding crotyl alcohols, *trans*-crotylborations were also explored and were found to be effective in affording very good yields and enantioselectivities along with the usual, high levels of diastereoselectivity (Table 3). Thus, crotylboration of aldehyde **1a** afforded an excellent yield of *anti*-propionate product **4a** in high enantioselectivity (Table 3, entry 1). Other propargylic aldehydes **1b**, **1c**, **1g** and **1h** also provided very good stereoselectivities (entries 2–5), demonstrating a broad

Table 1
Optimization of the asymmetric allylboration of propargylic aldehyde using aldehyde **1a** as model substrate

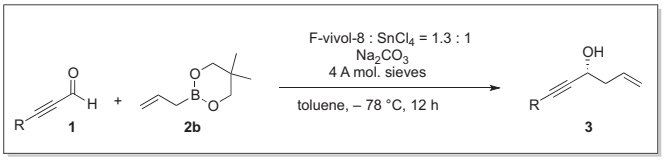


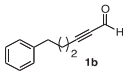
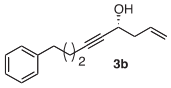
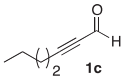
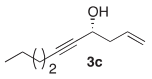
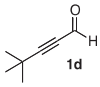
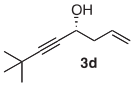
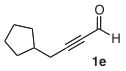
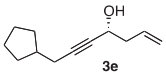
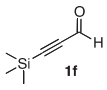
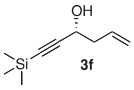
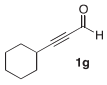
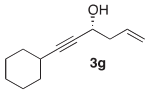
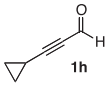
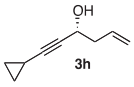
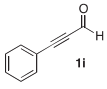
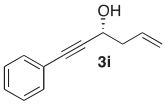
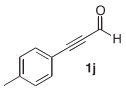
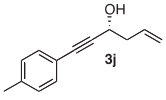
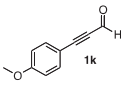
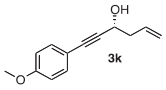
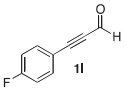
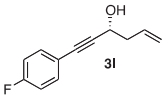


Entries	Catalyst	Solvent	Loading (%)	Allylboronate	Yield (%)[d]	ee (%)[c]
1	F-vivol-5	Toluene	5	**2a**	60	27
2	F-vivol-7	Toluene	5	**2a**	93	60
3	F-vivol-8	Toluene	5	**2a**	87	63
4	F-vivol-12	Toluene	5	**2a**	74	23
5	F-vivol-7	Toluene	10	**2a**	83	76
6	F-vivol-8	Toluene	10	**2a**	85	73
7	F-vivol-7	Toluene	10	**2b**	78	87
8	F-vivol-8	Toluene	10	**2b**	85	87
9	F-vivol-7	Toluene	20	**2b**	84	87
10	F-vivol-8	Toluene	20	**2b**	87	87
11	F-vivol-8	Toluene	10	**2c**	72	75
12	F-vivol-8	Toluene	10	**2d**	85	81
13	F-vivol-8	Toluene	10	**2e**	80	77
14	F-vivol-8	Toluene	10	**2f**	67	35
15	F-vivol-8	Toluene	10	**2g**	14	12
16	F-vivol-8	Toluene	10	**2h**	—	—
17	F-vivol-8	Tol/CH_2Cl_2 (1:1)	10	**2b**	78	81
18	F-vivol-8[a]	Tol/CH_2Cl_2 (1:1)	10	**2b**	82	81
19	F-vivol-8	CH_2Cl_2	10	**2b**	74	75
20	F-vivol-8[b]	Fluorobenzene	10	**2b**	68	72
21	F-vivol-8[b]	*o*-Xylene	10	**2b**	65	64
22	F-vivol-8	Trifluorotoluene	10	**2b**	58	53
23	F-vivol-8	Methyl cyclopentane	10	**2b**	85	83
24	F-vivol-8	Methyl cyclohexane	10	**2b**	85	82

All reactions were performed in 0.56 mmol scale with respect to the aldehydes and 0.7 mmol of allylboronates.
[a] Reaction was performed at −100 °C.
[b] Reaction was performed at −25 °C.
[c] Enantiomeric excesses were measured by chiral HPLC analysis.
[d] Isolated yield.

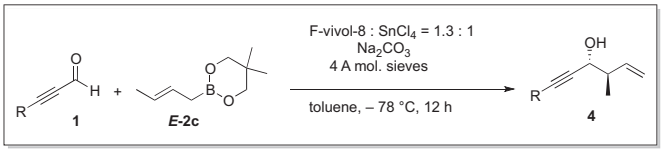
Table 2
Substrate scope study: enantioselective allylation of propargylic aldehydes

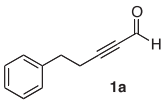
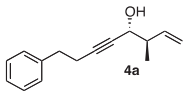
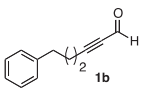
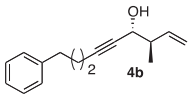
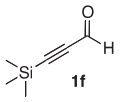
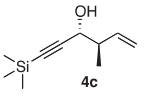
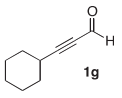
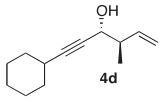
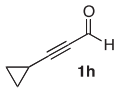
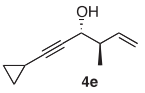


Entry[a]	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1	 1b	 3b	88	78
2	 1c	 3c	84	71
3	 1d	 3d	72	66
4	 1e	 3e	75	64
5	 1f	 3f	84	81
6	 1g	 3g	90	81
7	 1h	 3h	74	81
8	 1i	 3i	80	69
9	 1j	 3j	77	58
10	 1k	 3k	79	50
11	 1l	 3l	80	55

[a] All reactions were performed in 0.56 mmol scale with respect to the aldehyde, 0.7 mmol of allylboronate with 10 mol % catalyst.
[b] Isolated yields.
[c] Enantiomeric excesses were measured by chiral HPLC.

Table 3
Substrate scope study: enantioselective *E*-crotylation of propargyl aldehydes

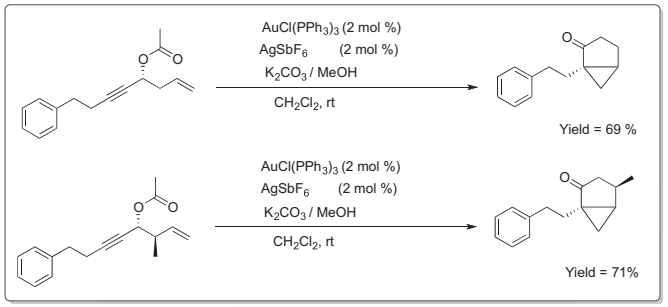


Entry[a]	Aldehyde	Product	Yield (%)[b]	ee (%)[c,d]
1	 1a	 4a	88	91
2	 1b	 4b	82	80
3	 1f	 4c	83	82
4	 1g	 4d	90	84
5	 1h	 4e	87	84

[a] All reactions were performed in 0.56 mmol scale with respect to the aldehyde, 0.7 mmol of *E*-crotyl boronate with 10 mol % catalyst.
[b] Isolated yields.
[c] Enantiomeric excesses were measured by chiral HPLC.
[d] >20:1 dr were observed with all of them.

substrate scope for this method. These results may be attributed to the importance of the closed six-membered transition state[12] through which allylboration reactions are proposed to proceed. Molecular interactions between the catalyst and the larger crotyl boronate may be amplified compared to the parent, unsubstituted allylboronate.

Next we sought to examplify possible applications of the homoallylic propargylic alcohols made using this catalytic enantioselective allylboration methodology. Thus, two of the alcohol products (**3a** and **4a**) were transformed into the corresponding acetate esters and then were subjected to gold/silver catalysed cycloisomerization as first reported by Fürstner and co-workers (Scheme 2)[13a] to generate fused bicyclic rings, which are well-known building blocks present in many natural products, such as sesquisabinene.[1g]



Scheme 2. Cycloisomerization reaction catalysed by gold and silver.

3. Conclusion

In summary, we have presented a novel and useful catalytic enantioselective method for the asymmetric synthesis of homoallylic propargylic alcohols, which are very important intermediates in organic synthesis. A detailed and thorough optimization of reaction conditions were followed by an elaborate evaluation of substrate scope, which demonstrated the broad range of applicability of this method. Moreover, for both simple allylation and *E*-

crotylboration of propargylic aldehydes, interesting outcomes were revealed during optimization studies. The subtle role of solvent and the structure of the boronic ester of the allylboronate will certainly be an important guideline for future work directed at other classes of aldehyde substrates.

4. Experimental section

4.1. General information and materials

All reactions were performed in standard, flame-dried glassware under an inert atmosphere of nitrogen. Unless otherwise specified, reagents were bought from commercial suppliers and used without further purification. Solvents were dried either by distillation or by using a solvent system purchased from MBRAUN. Anhydrous Na_2SO_4 or $MgSO_4$ were used as the drying agent after aqueous workup. All substrates were purified by silica gel chromatography before use. Evaporation and concentration in vacuo were accomplished at water aspirator pressure. Reaction products were purified by column chromatography using silica gel-60 (230–400 mesh). Reactions were monitored by thin layer chromatography with precoated glass plates covered with 0.2 mm silica gel. The spots were visualized by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra were obtained with a Nicolet Magna-IR-750 spectrometer (cm^{-1}, cast film or neat). ^1H, ^{11}B, ^{13}C NMR spectra were obtained on a Varian Inova-300, 400 or Varian Unity-500 instruments, at 27 °C in $CDCl_3$. Residual solvent peaks (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) were employed as reference. Accuracy for coupling constants (J-values) is estimated to be ±0.2 Hz. EIMS (m/z) was measured in a Kratos MS50 instrument. Optical rotation was recorded using a Perkin Elmer 241 polarimeter using the Sodium D line (589 nm) with a cell length of 10.002 cm. Optical purities of the products were measured by chiral HPLC using Chiralcel OD or Chiralpak AS column.

4.2. General procedure

In a flame-dried 10 mL round bottom flask equipped with a stirbar, the corresponding F-Vivol catalyst (0.056 mmol, 0.10 equiv), anhydrous Na_2CO_3 (0.2 equiv) and 4 Å molecular sieves (90 mg, pre dried under vacuum overnight and then stored in an oven) were added. The flask was equipped with a rubber septum and charged with nitrogen, then dry toluene (1.2 mL) was added. The mixture was stirred for 2 min and $SnCl_4$ (1.0 M in CH_2Cl_2, 38.5 μL, 0.0385 mmol, 0.078 equiv) was added. After stirring for 5 min at rt the reaction was cooled to −78 °C where it was maintained for 15 min. Allylboronic acid ester (0.8 mmol, 1.4 equiv) was added dropwise, followed 30 min later by the addition of the aldehyde (0.56 mmol, 1.0 equiv). The reaction was stirred at −78 °C until TLC analysis no longer showed presence of the aldehyde starting material. DIBAL-H (1.5 M in toluene, 2.0 equiv) was cooled to −78 °C and cannulated into the reaction flask, maintain the reaction at −78 °C. After all the remaining aldehyde was reduced (ca. 30–50 min), the excess DIBAL-H was quenched by the addition of 10% HCl (4.0 mL). The reaction was slowly warmed to rt over 1 h and stirred for an additional 30 min. The reaction mixture was then extracted with Et_2O (5×10 mL) and the combined organic extracts were extracted with saturated aq NaCl, dried over Na_2SO_4, filtered and concentrated in vacuo. Column chromatography (silica gel, 5–30% EtOAc in hexanes) gave the corresponding product.

Crotylboration was also carried out in the same way and in the same scale.

*4.2.1. 8-Phenyloct-1-en-5-yn-4-ol (**3a**).* A 87% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=7.8 min, T_{minor}=11.3 min; $[\alpha]_D^{22}$ 22.8 (*c* 1.30, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3375 (broad, m), 3076 (m), 3063 (m), 3027 (m), 2978 (w), 2924 (s), 2859 (m), 2226 (w), 1641 (m), 1496 (m), 1453 (w), 1032 (s), 698 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.24–7.21 (m, 3H), 5.90–5.80 (m, 1H), 5.20–5.15 (m, 2H), 4.39 (tt, J=6.0, 2.0 Hz, 1H), 2.84 (t, J=7.6 Hz, 2H), 2.52 (td, J=7.6, 2.0 Hz, 2H), 2.45–2.41 (m, 2H), 1.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 133.2, 128.4, 128.3, 126.3, 118.7, 85.1, 81.4, 61.7, 42.4, 35.0, 20.8; EIMS m/z 200.1 (M+, 0.2), 199.1 ([M−H]+, 1), 182.1 ($C_{14}H_{14}$, 6), 159.1 ($C_{11}H_{11}O$, 73). EI HRMS calcd for $C_{14}H_{14}$+ ([M−H_2O]+) 182.1096, found 182.1093.

*4.2.2. 8-Phenylnon-1-en-5-yn-4-ol (**3b**).* A 78% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=11.9 min, T_{minor}=14.6 min; $[\alpha]_D^{22}$ 19.9 (*c* 1.30, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3359 (broad, m), 3078 (m), 3063 (m), 3026 (m), 2979 (w), 2939 (s), 2860 (m), 2229 (w), 1642 (m), 1603(m), 1496 (m), 1454 (m), 1431 (m), 1032 (s), 699 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.22–7.18 (m, 3H), 5.91 (ddt, J=17.0, 10.0, 7.5 Hz, 1H), 5.23–5.17 (m, 2H), 4.43–4.44 (m, 1H), 2.72 (t, J=7.5 Hz, 2H), 2.45–2.49 (m, 2H), 2.24 (td, J=7.0, 2.0 Hz, 2H), 2.0 (d, J=5.5 Hz, 1H), 1.84 (app. quintet, J=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 133.3, 128.5, 128.3, 125.9, 118.7, 85.4, 81.2, 61.8, 42.5, 34.8, 30.2, 18.1; EI HRMS calcd for $C_{15}H_{18}ONa$ 237.1250, found 237.1247.

*4.2.3. (4R)-Dec-1-en-5-yn-4-ol (**3c**).* A 71% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=9.0 min, T_{minor}=16.9 min; $[\alpha]_D^{22}$ 27.6 (*c* 1.1, $CHCl_3$). Spectral and analytical properties of the product were in accordance with the literature.[14a]

*4.2.4. 7,7-Dimethyloct-1-en-5-yn-4-ol (**3d**).* A 66% ee was determined by HPLC analysis (Chiralcel OD column, 15% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=13.10 min, T_{minor}=8.0 min; $[\alpha]_D^{22}$ 32.8 (*c* 1.1, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3347 (broad, m), 3078 (m), 2969 (w), 2928 (s), 2867 (m), 2239 (w), 1642 (m), 1476 (m), 1457 (m), 1434 (m), 1362 (m), 1264 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddt, J=17.1, 10.2, 7.1 Hz, 1H), 5.21–5.14 (m, 2H), 4.40 (t, J=6.1 Hz, 1H), 2.44 (m, 2H), 1.99 (br s, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 118.5, 94.2, 79.0, 61.7, 42.6, 30.9, 27.3; EI HRMS calcd for $C_{10}H_{15}ONa$, 174.2200 found 174.2202.

*4.2.5. 7-Cyclopentylhept-1-en-5-yn-4-ol (**3e**).* A 64% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=17.2 min, T_{minor}=9.0 min; $[\alpha]_D^{22}$ 34.3 (*c* 2.2, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3351 (broad, m), 3078 (m), 3011 (m), 2980 (w), 2914 (m), 2866 (w), 2240 (m), 1641 (m), 1429 (m), 1358 (m), 1052 (s), 1030 (s), 813 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddt, J=17.0, 10.4, 7.2 Hz, 1H), 5.19–5.13 (m, 2H), 4.40–4.38 (m, 1H), 2.46–2.41 (m, 2H), 2.20 (dd, J=7.0, 2.0 Hz, 2H) 2.06–1.96 (m, 2H), 1.80–1.72 (m, 2H), 1.66–1.48 (m, 4H), 1.30–1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 118.1, 84.9, 80.2, 61.4, 42.2, 38.5, 31.5, 24.8, 24.0; EI HRMS calcd for $C_{12}H_{17}ONa$ 200.2520 found 200.2551.

*4.2.6. (4R)-1-Trimethylsilylhex-1-en-5-yn-4-ol (**3f**).* A 81% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=16.85 min, T_{minor}=8.97 min; $[\alpha]_D^{22}$ 56.9 (*c* 6.4, $CHCl_3$);

Spectral and analytical properties of the product were in accordance with the literature.[14b]

*4.2.7. 1-Cyclohexylhex-5-en-1-yn-3-ol (**3g**).* A 81% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in

hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=19.9 min, T_{minor}=10.4 min; $[\alpha]_D^{22}$ 58.7 (*c* 1.15, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1), IR (film cast, $CHCl_3$): 3338 (broad, m), 3077 (w), 3006 (w), 2979 (w), 2930 (s), 2854 (s), 2229 (w), 1642 (m), 1448 (m), 1338 (w), 1035 (s), 861 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, *J*=17.0, 10, 7.5 Hz, 1H), 5.18–5.13 (m, 2H), 4.40 (ddd, *J*=11.5, 6, 2 Hz, 1H), 2.46–2.41 (m, 2H), 2.40–2.34 (m, 1H), 1.97–1.94 (m, 1H), 1.80–1.73 (m, 2H), 1.71–1.64 (m, 2H), 1.51–1.47 (m, 1H), 1.44–1.37 (m, 2H), 1.31–1.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 118.5, 90, 80.5, 61.8, 42.6, 32.6, 28.9, 25.8, 24.8; EI HRMS calcd for $C_{15}H_{18}ONa$ 201.1257, found 201.1244.

*4.2.8. 1-Cyclopropylhex-5-en-1-yn-3-ol (**3h**).* A 81% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=24.4 min, T_{minor}=13.4 min; $[\alpha]_D^{22}$ 71.1 (*c* 1.05, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3351 (broad, m), 3078 (m), 3011 (m), 2980 (w), 2914 (m), 2866 (w), 2240 (m), 1641 (m), 1429 (m), 1358 (m), 1052 (s), 1030 (s), 813 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88–5.8 (m, 1H), 5.16–5.11 (m, 2H), 4.36–4.32 (m, 1H), 2.41–2.38 (m, 2H), 2.04–2.02 (m, 1H), 1.25–1.2 (m, 1H), 0.72–0.76 (m, 2H), 0.66–0.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 118.5, 88.9, 75.7, 61.7, 42.5, 8.2, −0.6; EI HRMS calcd for $C_9H_{12}ONa$ 159.0785, found 159.0777.

*4.2.9. (3S)-1-Phenylhex-5-en-1-yn-3-ol (**3i**).* A 69% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ=210 nm, column temperature=25 °C), T_{major}=7.3 min, T_{minor}=9.3 min; $[\alpha]_D^{22}$ 26.0 (*c* 0.36, $CHCl_3$). Spectral and analytical properties of the product were in accordance with the literature.[6h]

*4.2.10. 1-(4-Methylphenyl)hex-5-en-1-yn-3-ol (**3j**).* A 58% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=6.9 min, T_{minor}=8.3 min; $[\alpha]_D^{22}$ 22.6 (*c* 1.2, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3375 (broad, m), 3078 (s), 3029 (s), 2980 (s), 2921 (m), 2860 (s), 2202 (m), 1666 (m), 1643 (m), 1606 (m), 1510 (s), 1440 (m), 1038 (s), 817 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.11 (m, 2H), 5.96 (ddt, *J*=17.0, 10.5, 7.0 Hz, 1H), 5.25–5.19 (m, 2H), 4.64 (t, *J*=6.0 Hz, 1H), 2.58–2.55 (m, 2H), 2.3 (s, 3H), 2.0 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 133.1, 131.6, 129.0, 119.4, 118.9, 88.7, 85.3, 62.1, 42.3, 21.4; EI HRMS calcd for $C_{13}H_{14}ONa$ 209.0937, found 209.0939.

*4.2.11. 1-(4-Methoxyphenyl)hex-5-en-1-yn-3-ol (**3k**).* A 50% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=10.9 min, T_{minor}=7.4 min; $[\alpha]_D^{22}$ 16.1 (*c* 1.4, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3384 (broad, m), 3075 (m), 3006 (m), 2935 (m), 2913 (m), 2837 (m), 2228 (m), 1642 (m), 1606 (s), 1463 (m), 1441 (m), 1031 (s), 1030 (s), 831 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H), 6.83 (d, 2H), 5.96 (ddt, *J*=17.2, 10.0, 7.2 Hz, 1H), 5.26–5.20 (m, 2H), 4.65–4.62 (m, 1H), 3.80 (s, 3H), 2.58–2.55 (m, 2H), 2.13 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 132.8, 118.5, 114.2, 113.6, 113.5, 87.6, 84.7, 61.7, 54.9, 41.9; EI HRMS calcd for $C_{13}H_{14}O_2Na$ 225.0886, found 225.0885.

*4.2.12. 1-(4-Fluorophenyl)hex-5-en-1-yn-3-ol (**3l**).* A 55% ee was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=9.3 min, T_{minor}=10.9 min; $[\alpha]_D^{22}$ 15.6 (*c* 1.4, $CHCl_3$), R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3363 (broad, m), 3078 (s), 2980 (s), 2921 (m), 2860 (s), 2232 (m), 1642 (s), 1602 (s), 1507 (s), 1232 (s), 1440 (m), 1031 (m), 835 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.05–7.0 (m, 2H), 5.98 (ddt, *J*=17.0, 10.5, 7.0 Hz, 1H), 5.29–5.24 (m, 2H), 4.65–4.61 (m, 1H), 2.57–2.54 (m, 2H), 2.2 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, *J*=250 Hz, 1C), 133.6 (d, *J*=8.5 Hz, 2C), 132.9, 119.1, 118.6 (d, *J*=3.4 Hz, 2C), 115.5 (d, *J*=22 Hz, 2C), 89.1, 84.1, 62.0, 42.2; EI HRMS calcd for $C_{12}H_{11}FONa$ 213.0686, found 213.0690.

4.3. Characterization of enantioselective crotylboration products

*4.3.1. Methyl-7-phenyloct-5-en-1-yn-3-ol (**4a**).* A 91% ee was determined by HPLC analysis (Chiralcel OD column, 40% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=7.63 min, T_{minor}=11.26 min; $[\alpha]_D^{22}$ 24.2 (*c* 1.3, $CHCl_3$); IR (film cast, $CHCl_3$): 3400 (broad, m), 3064 (s), 2965 (s), 2928 (m), 2861 (s), 2229 (m), 1640 (s), 1603 (s), 1496 (s), 1454 (s), 1440 (m), 1429 (m), 1419 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.34 (m, 2H), 7.24–7.2 (m, 3H), 5.84–5.74 (m, 1H), 5.18–5.12 (m, 2H), 4.22–4.17 (m, 1H), 2.85 (t, 7.6 Hz, 2H), 2.55 (dt, *J*=7.2, 1.6 Hz, 2H), 2.45–2.37 (m, 1H), 1.92 (d, *J*=5.2 Hz, 1H), 1.1 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 139.5, 128.4, 128.3, 126.3, 116.5, 85.7, 80.3, 66.3, 44.5, 35.0, 20.9, 15.2; EI HRMS calcd for $C_{15}H_{18}ONa$ 237.1250, found 237.1245.

*4.3.2. Methyl-8-phenylnon-1-en-5-yn-4-ol (**4b**).* A 80% ee was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=11.3 min, T_{minor}=12.7 min; $[\alpha]_D^{22}$ 15.3 (*c* 1.8, $CHCl_3$); IR (film cast, $CHCl_3$): 3371 (broad, m), 3064 (s), 2964 (s), 2932 (m), 2862 (s), 2238 (m), 1640 (s), 1602 (s), 1496 (s), 1454 (s), 1430 (m), 1419 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 5.91 (ddd, *J*=17.9, 10.4, 7.5 Hz, 1H), 5.24–5.15 (m, 2H), 4.26 (m, 1H), 2.76 (t, *J*=7.5 Hz, 2H), 2.52–2.44 (m, 1H), 2.28 (td, *J*=7.0, 2.0 Hz, 2H), 1.91 (br s, 1H), 1.87 (m, 2H), 1.18 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 139.6, 128.5, 128.3, 125.9, 116.5, 86.0, 80.1, 66.4, 44.7, 34.8, 30.3, 18.2, 15.3; EI HRMS calcd for $C_{16}H_{20}ONa$ 251.1406, found 251.1402.

*4.3.3. Methyl-1-trimethylsilylhex-1-en-5-yn-4-ol (**4c**).* A 81% ee was determined by Mosher ester analysis; $[\alpha]_D^{22}$ −0.38 (*c* 4.1, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3367 (broad, m), 3080 (w), 2963 (w), 2933 (s), 2173 (w), 1641 (m), 1456 (m), 1251 (s), 1030 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=5.83 (ddd, *J*=17.1, 10.5, 7.7 Hz, 1H), 5.21–5.15 (m, 2H), 4.20 (t, *J*=5.5 Hz, 1H), 2.49–2.44 (m, 1H), 1.90 (d, *J*=6 Hz, 1H), 1.15 (d, *J*=6.8 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 116.7, 105.0, 90.5, 66.6, 44.4,15.3, −0.1; EI HRMS calcd for $C_{10}H_{17}ONa$ 204.3227, found 204.3218.

*4.3.4. Methyl-1-cyclohexylhex-5-en-1-yn-3-ol (**4d**).* A 84% ee was determined by HPLC analysis (Chiralcel OD column, 1.5% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=29.9 min, T_{minor}=26.2 min; $[\alpha]_D^{22}$ 49.3 (*c* 1.2, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3366 (broad, m), 3078 (w), 2932 (w), 2854 (s), 2232 (w), 1640 (m), 1449 (m), 1348 (w), 1024 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J*=17.4, 10.2, 7.5 Hz, 1H), 5.19–5.11 (m, 2H), 4.22 (t, *J*=4.4 Hz, 1H), 2.48–2.38 (m, 2H), 1.90 (d, *J*=4.8 Hz, 1H), 1.83–1.75 (m, 2H), 1.74–1.66 (m, 2H), 1.55–1.40 (m, 3H), 1.36–1.27 (m, 3H), 1.13 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 116.3, 90.6, 79.4, 66.4, 44.7, 32.6, 28.9, 25.8, 24.7, 15.2; EI HRMS calcd for $C_{13}H_{20}ONa$ 215.1406, found 215.1400.

*4.3.5. Methyl-1-cyclopropylhex-5-en-1-yn-3-ol (**4e**).* A 84% ee was determined by HPLC analysis (Chiralcel OD column, 1.5% *i*-PrOH in hexanes, 0.5 mL/min, λ=254 nm, column temperature=25 °C), T_{major}=16.5 min, T_{minor}=18.4 min; $[\alpha]_D^{22}$ 56.3 (*c* 1.0, $CHCl_3$); R_f=0.1 (hexanes/EtOAc 10:1); IR (film cast, $CHCl_3$): 3318 (broad, m), 3081 (m), 3011 (m), 2970 (w), 2931 (m), 2248 (m), 1601 (m), 1540 (s),

1444 (m), 1313 (m), 1221 (s), 1051 (s), 1027 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, J=16.9, 10.6, 7.6 Hz, 1H), 5.17–5.12 (m, 2H), 4.17 (dd, J=6.2, 1.5 Hz, 1H), 2.45–2.37 (m, 1H), 1.87 (br s, 1H), 1.27 (dddd, J=12.5, 9.0, 5.0, 2.0 Hz, 1H), 1.11 (d, J=6.8 Hz, 3H), 0.78 (s, 2H), 0.70–0.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 116.4, 89.6, 74.7, 66.3, 44.7, 15.2, 8.2, −0.6; EI HRMS calcd for $C_{10}H_{14}ONa$ 173.0937, found 173.0931.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.095.

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