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Catalytic, Enantioselective Synthesis of Allenyl Boronates

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Abstract

A method to achieve enantioselective 1,4-hydroboration of terminal enynes to access allenyl boronates under CuH catalysis is described. The reaction typically proceeds in a highly stereoselective manner and tolerates an array of synthetically useful functional groups. The utility of the enantioenriched allenyl boronate products is demonstrated through several representative downstream derivatizations.

Graphical Abstract

Keywords

allenes; asymmetric catalysis; enynes; homogeneous catalysis; hydroboration

INTRODUCTION

Allenyl boron reagents are a valuable class of carbon nucleophiles that are widely used in the propargylation/allenylation of carbonyl compounds.^{1,2} Stereocontrol in such addition reaction has previously been achieved through use of chiral auxiliaries,³ chiral catalytic Lewis/Brønsted acids/bases,⁴ or chiral metal complexes,^{5,6} including enantioselective variants. Enantioenriched, axially chiral allenyl boronates are an attractive class of coupling partners for carbonyl addition reactions, as they are capable of serving as the sole source of stereoinduction in carbonyl addition reactions^{7,8} or can be employed with a chiral promoter to achieve control of absolute and relative stereoinduction towards densely functionalized targets.⁹ Moreover, outside of the realm of carbonyl reactivity, enantioenriched allenyl boronates are versatile building blocks for the synthesis of densely functionalized chiral allenes via transformations such as cross-coupling.^{7,10} Given that existing routes to access

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Notes

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such compounds have drawbacks, the goal of the present study was to simplify access to allenyl boronates through the development of a catalytic, enantioselective synthesis that would employ readily accessible starting materials.

Various methods have been reported for accessing allenyl boronates.^{7,8,11} To prepare enantioenriched allenyl boronates, enantiopure propargyl alcohol derivatives are typically used, which must in turn be synthesized enantioselectively.^{8,11a} We were attracted to an alternative possibility whereby stereoselective 1,4-hydroboration of an enyne could be carried out using a chiral transition metal catalyst. This approach was inspired by early work from Hayashi who demonstrated up to 61% ee in the 1,4-hydroboration of but-1-en-3-yne using a Pd(0)/(*S*)-MeO-MOP catalyst.⁷ Of more direct relevance to the approach described herein, several groups have described pioneering work on stereoselective addition of Cu–H and Cu–Bpin species to 1,3-enynes (Scheme 1).^{12–16} In particular, Hoveyda has previously demonstrated that enynes can react in a stereoselective fashion using chiral bisphosphine-ligated Cu–Bpin and that the resulting propargyl copper species can rapidly tautomerize to an allenyl copper intermediate, which can then be trapped with a carbonyl compound.^{12,13} Buchwald has reported that chiral Cu–H species can mediate addition of 1,3-enynes to carbonyl compounds via the intermediacy of an allenyl copper species.¹⁴ Based on these precedents, we questioned whether this key allenyl copper species could be intercepted with a reactive boron source as a general catalytic strategy for preparing enantioenriched allenyl boron compounds.¹⁷

To reduce this idea to practice, we selected aliphatic enyne **1a** as our pilot substrate and HBPin as the reaction partner. Our investigation commenced with an examination of various commercially available chiral bisphosphine ligands and copper precatalysts (for additional details regarding reaction optimization, see Supporting Information). We were encouraged to find that hydroboration proceeded to afford the desired product **3a** in 19% yield with moderate chiral induction by employing (*R*_a)-Tol-BINAP as the ligand (entry 1). Both yield and ee was improved by switching to (*R*_a)-Segphos (entry 2). With the more bulky (*R*_a)-DTBM-Segphos, the reaction delivered higher yield, albeit with lower ee (entry 3). Subsequent investigations showed that (*S,S*)-Ph-BPE provided satisfactory yield and 98% ee (entries 4–6).¹⁸ Notably only trace quantities of the desired allenyl boronate were observed using a representative chiral monodentate N-heterocyclic carbene ligand (NHC **L9**), indicating that bisphosphine ligands were generally a more effective ancillary ligand class in this transformation. We were able to obtain allenyl boronate **3a** in 81% yield and 99% ee with careful tuning of the amount of HBPin and the reaction temperature (entry 10). We further found that the flanking phenyl substituents on BPE are highly important for high reactivity and enantioselectivity as Me- and Et-substituted analogs were inferior (entry 10 versus entries 11 and 12). Across these experiments, the putative propargyl boronate isomer was generally not detectable.

Having identified optimal reaction conditions, we next investigated the scope by examining a variety of aliphatic enynes. Different alkyl spacer lengths between the phenyl ring and the enyne were well tolerated under the reaction conditions (**3a–c**). Substrates containing different primary alkyl groups including ⁿbutyl, ⁿhexyl, ⁿoctyl, ^tPrCH₂CH₂, and cyclohexylCH₂ were efficiently converted to the corresponding allenyl boronates in good

economical manner. This strategy is compatible with a wide range of aliphatic and aromatic terminal enynes, providing good yields and high ee values. Additionally, this method could be performed on gram-scale with 1 mol % catalyst loading, and the allenyl boronate products were demonstrated to engage in useful downstream reactions. Notably, we demonstrated a unique two-carbon double homologation of an axially chiral allenyl boronate, which is complementary to existing one-carbon homologation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Key Precedents for Cu-Bpin/Cu-H Reactions with 1,3-Enynes to Generate Allenyl Copper Species and Synopsis of This Work.

Scheme 1. Hydroboration of Enynes Containing Two Potential Reaction Sites

^a Reaction conditions: **1** (0.2 mmol), **2** (0.28 mmol), CuCl₂ (5 mol %), (*S,S*)-Ph-BPE (6 mol %), KO^tBu (20 mol %) in THF (1 mL) at −10 °C unless noted otherwise. ^b With 2.8 equiv HBPIn at 0 °C. ^c Run at 0 °C.

Scheme 2. Synthetic Applications of the Chiral Allenyl Boronate **3a**

Table 1

Screening of Reaction Conditions

entry	ligand	T (°C)	yield (%) ^a	ee (%) ^b
1	L1	rt	19	55
2	L2	rt	45	73
3	L3	rt	59	65
4	L4	rt	35	71
5	L5	rt	62	98
6	L8	rt	55	83
7	L9	rt	<10	nd
8 ^c	L5	rt	65	98
9	L5	0	62	99
10 ^{c,d}	L5	0	81	99
11 ^{c,d}	L6	0	<10	nd
12 ^{c,d}	L7	0	19	-72

^a Isolated yield unless noted otherwise.^b The enantioselectivity was determined by SFC analysis.^c With CuCl₂ as the catalyst.^d Using 1.4 equivalents of HBPIn.

rt = room temperature. nd = not determined.

Table 2

Cu-catalyzed enantioselective 1,4-hydroboration of aliphatic enynes.^{a,b,c}

^aReaction conditions: **1** (0.2 mmol), **2** (0.28 mmol), CuCl₂ (5 mol %), (S,S)-Ph-BPE (6 mol %), KO^tBu (20 mol %) in THF (1 mL) at room temperature unless noted otherwise.

^bIsolated yield.

^cThe enantioselectivity was determined by SFC analysis.

^dWith 1 mol % CuCl₂ and 1.2 mol % (S,S)-Ph-BPE.

^eWith 1.6 equiv HBPIn.

^fRun at 0 °C.

Table 3

Cu-catalyzed Enantioselective 1,4-Hydroboration of Aromatic Enynes.^{a,b,c}

^a Reaction conditions: **1** (0.2 mmol), **2** (0.28 mmol), CuCl₂ (5 mol %), (S,S)-Ph-BPE (6 mol %), KO^tBu (20 mol %) in THF (1 mL) at -10 °C unless noted otherwise.

^b Isolated yield.

^c The enantioselectivity was determined by SFC analysis.

^d Run at -20 °C.