VIP **Asymmetric Catalysis** *Very Important Paper*

A General Strategy for the Asymmetric Preparation of α-Stereogenic Allyl Silanes, Germanes, and Boronate Esters via Dual Copper Hydride- and Palladium-Catalysis
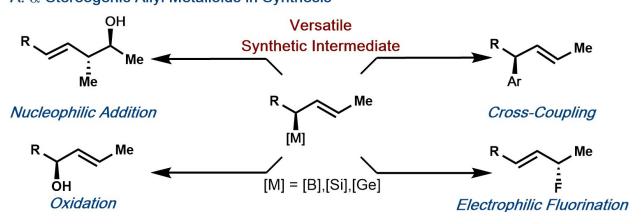
James Levi Knippel, Anton Z. Ni, Alexander W. Schuppe, and Stephen L. Buchwald*

Abstract: α-Stereogenic allyl metalloids are versatile synthetic intermediates which can undergo various stereocontrolled transformations. Most existing methods to prepare α-stereogenic allyl metalloids involve multi-step sequences that curtail the number of compatible substrates and are limited to the synthesis of boronates. Here, we report a general method for the enantioselective preparation of α-stereogenic allyl metalloids utilizing dual CuH- and Pd-catalysis. This approach leverages a stereoretentive Cu-to-Pd transmetalation of an in situ generated alkyl copper species to allow access to enantioenriched allyl silanes, germanes, and boronate esters with broad functional group compatibility.
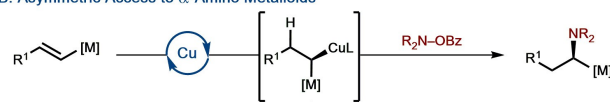
Stereodefined metalloids (–SiR$_3$, –BR$_2$, –GeR$_3$,) are useful synthetic intermediates due to their ability to engage with electrophiles in carbon-carbon and carbon-heteroatom bond forming reactions.[1] Enantioenriched allyl metalloids are particularly important for their diverse applications, including addition into carbonyls,[2] stereospecific cross-couplings,[3] and functional group interconversions (Figure 1A).[4] In many cases, complexes with chiral auxiliaries on the metalloid atom, such as α-pinene[5] or 1,2-diamines,[6] afford enantioenriched allylation products. Employing α-stereogenic allyl metalloids offers a more general approach, as these reagents can transfer chirality in a variety of stereospecific transformations involving the carbon-metalloid bond.[7] However, the use of α-stereogenic allyl metalloids is often limited by the multi-step syntheses for their preparation, which involve unstable intermediates that are not compatible with highly functionalized molecules.[8]

Pioneering approaches to access enantioenriched α-stereogenic allyl metalloids rely on stereospecific substitution reactions of allyl carbonates and pivalates.[7,9] Alter-
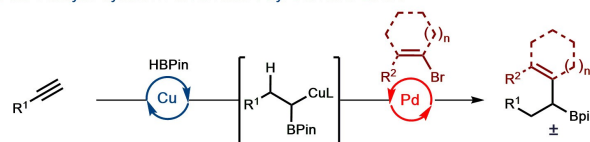
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Figure 1. A) Synthetic utility of allyl metalloids. B) Asymmetric syntheses of α-amino metalloids C) Dual-catalytic preparation of racemic allyl boronate esters from alkynes D) Enantioselective difunctionalization of olefins to generate allyl boronate esters. E) A general approach to generate allyl metalloids via an enantioenriched heterobimetallic intermediate

natively, preformed stereodefined lithiated carbamates can be utilized in homologation reactions to generate both allyl boronate esters and silanes.[10] Catalytic asymmetric strategies have also been described, including Si–H insertions into α- or β-diazoesters,[11] terminal hydrometallations of 1,3-dienes,[12] and enantioselective cross-couplings of racemic and achiral alkyl metalloids.[13] While together these methods provide access to a large number of α-stereogenic allyl metalloids, many require the use of starting materials that

are difficult to prepare, are unstable, or are incompatible with protic and/or reactive functional groups. Given these synthetic challenges, a general protocol that uses readily available precursors for the direct synthesis of various enantioenriched α-stereogenic allyl metalloids (e.g., $-SiR_3$, $-BR_2$, $-GeR_3$) would be highly desirable.

Our group and others have demonstrated that ligated CuH species can catalyze the enantioselective hydrofunctionalization of various olefinic substrates, including vinyl metalloids (Figure 1B).[14] This process proceeds through the intermediacy of a stereodefined alkylcopper species (**I**) which subsequently engages electrophiles such as hydroxylamine esters, carbonyl derivatives, or heterocycles.[15] Additionally, **I** can transmetalate to Pd-oxidative-addition complexes in a stereoretentive manner to enable asymmetric C–C bond forming reactions, including olefin hydroarylation and hydroalkenylation.[16] In 2019, Lalic leveraged this reactivity to prepare benzylic boronate esters, relying on a dual CuH- and Pd-catalyzed hydroarylation of an in situ generated vinyl boronate ester.[17a] During the preparation of this manuscript, Lalic expanded this strategy to enable the Cu-catalyzed preparation of racemic allyl boronates from alkynes.[17b] Concomitantly, Yin disclosed a Ni-catalyzed difunctionalization of terminal olefins to afford enantioenriched α-stereogenic allyl boronate esters.[18] Yet, a general approach for the synthesis of enantioenriched α-stereogenic allyl metalloids beyond boronate esters remains elusive. We herein report that a dual CuH- and Pd-catalyzed strategy offers a general approach for the synthesis of diverse α-stereogenic allyl metalloids (M=B, Si, Ge) (**3**) through the hydroalkenylation of vinyl metalloids (**1**) using ketone derived enol sulfonates (**2**, Figure 1E).[19]

We envisioned that this dual CuH- and Pd-catalyzed synthesis of enantioenriched α-stereogenic allyl metalloids would proceed through a catalytic cycle as depicted in Figure 2. An initial enantiodetermining hydrocupration of vinyl metalloid (**1**) would generate the corresponding geminal heterobimetallic intermediate (**I**). A Cu-to-Pd transmetalation with a Pd^{II} alkenyl oxidative-addition complex followed by reductive elimination would furnish the desired allyl metalloid **3**. The CuH catalyst is regenerated following a σ-bond metathesis with a silane. At the outset, we anticipated several side-reactions which would need to be controlled to promote the efficient formation of **3**. First, both **1** and **3** are competent substrates for Pd-catalyzed cross-coupling reactions, which would lead to byproducts **II** and **IV**, respectively (Figure 2B). In a similar way, hydrocupration of **3** could result in several over-functionalized byproducts (**V**, Figure 2B). Additionally, if the oxidative addition of **2** was substantially faster than the hydrocupration of **1**, the net reduction of **2** to form the undesired olefin could occur (**III**, Figure 2B). We reasoned that by tuning the rate of the Pd-catalyzed portion to approximately match the relative rate of hydrocupration, we would be able to minimize off-cycle reactivity and form the desired α-stereogenic allyl metalloid products in high yield and enantioselectivity.

Initial efforts were focused on the enantioselective synthesis of allyl silanes, as relative to the corresponding allyl
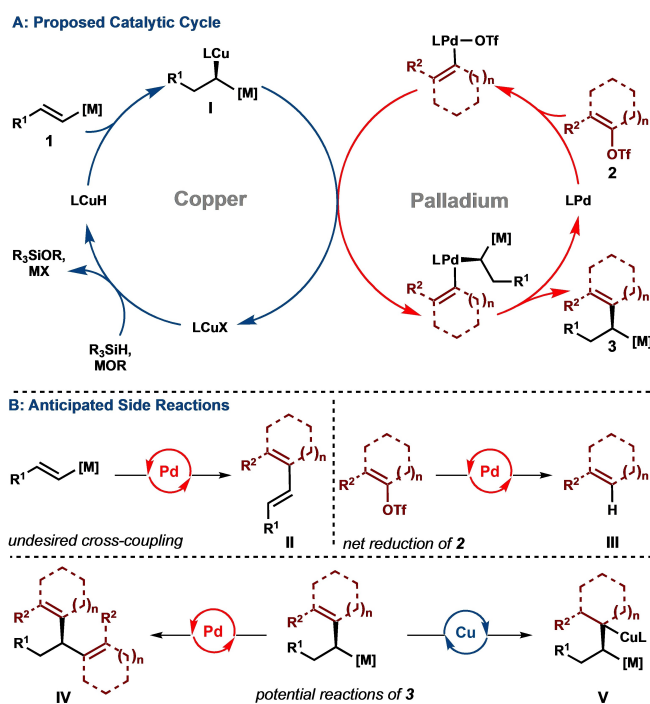

Figure 2. A) Proposed catalytic cycle for dual CuH- and Pd-catalyzed hydroalkenylation of vinyl metalloids. B) Anticipated side-reactions include undesired cross-coupling, net-reduction of the enol triflate, or hydrofunctionalization of product.

boronate esters these compounds feature improved stability. Vinyl silane **1a** along with enol sulfonate **2a** were selected as model substrates for reaction optimization. We found that **3a** could be obtained in excellent yield (98%) and enantioselectivity (99:1 er) using a combination of CuI ligated by (*S*)-DTBM-SEGPHOS (**L1**) and air-stable Pd-(cinammyl)(dppbz)Cl (Table 1, entry 1). The use of dppbz-ligated Pd-precatalyst was key to the success of the transformation, as the use of catalysts derived from ligands that are known to undergo oxidative addition more readily, such as BrettPhos, primarily resulted in net reduction of the enol triflate to the corresponding olefin (entry 6). These observations are consistent with our previous work on olefin and alkyne hydroalkenylation.[16b–c] The use of other copper(I) salts (entries 2–4), or chiral Cu ancillary ligands (entry 5) resulted in diminished yields of **3a**. Ethereal solvents (THF, MTBE, and 1,4-dioxane) provided the desired product in similar yield and selectivity (entries 1, 7, 8); in contrast, the use of toluene was found to be significantly less effective (entry 9). While the formation of **3a** was largely unimpacted by the reaction concentration (entry 10), other substrates coupled more efficiently at a higher concentration (1.1 M, Table S2). Unless otherwise noted, all subsequent reactions were performed at 1.1 M, with respect to **1**.
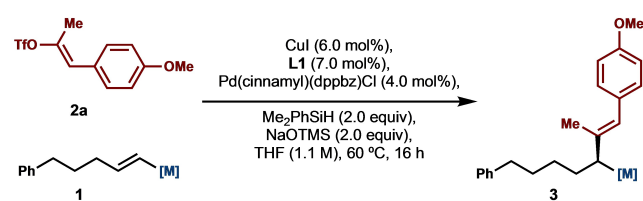
We then investigated the impact of the metalloid identity and its substituents on the formation of the corresponding enantioenriched α-stereogenic allyl metalloid (Scheme 1). Under the optimized reaction conditions, substituted α-stereogenic allyl silanes and germanes were readily prepared. Allyl silanes with both $-SiMe_2Ph$ (**3a**) and $-SiMe_3$

Table 1: Optimization of the enantioselective synthesis of allyl metalloids.[a]

Entry	Variation from Listed Conditions	¹H NMR Yield (%)	er
1	None	98	99:1
2	CuOAc	65	99:1
3	CuCl	56	99:1
4	CuBr	91	97:3
5	L2	61	99:1
6	Pd(cinnamyl)(Cl) and BrettPhos	6	n.d.
7	MTBE	95	98:2
8	1,4-dioxane	86	99:1
9	PhMe	54	97:3
10	1.1 M	95	99:1

L1
(S)-DTBM-SEGPHOS
Ar = 3,5-(t-Bu)₂-4-MeOC₆H₂

R¹=H, **L2**
(S)-DTBM-MeO-BIPHEP

dppbz

BrettPhos
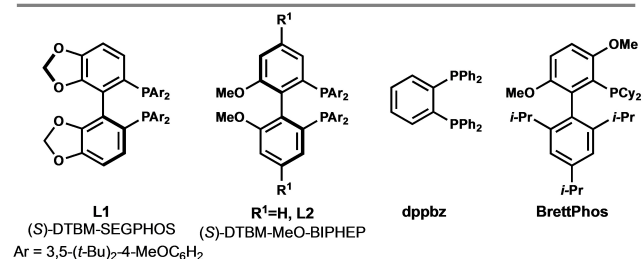
[a] Reaction conditions: 0.2 mmol of vinyl silane (**1 a**), alkenyl coupling partner (**2 a**) (0.3 mmol, 1.5 equiv). Yields were determined by ¹H NMR spectroscopy of crude reaction mixtures relative to a 1,1,2,2-tetrachloroethane internal standard. n.d.: not determined.

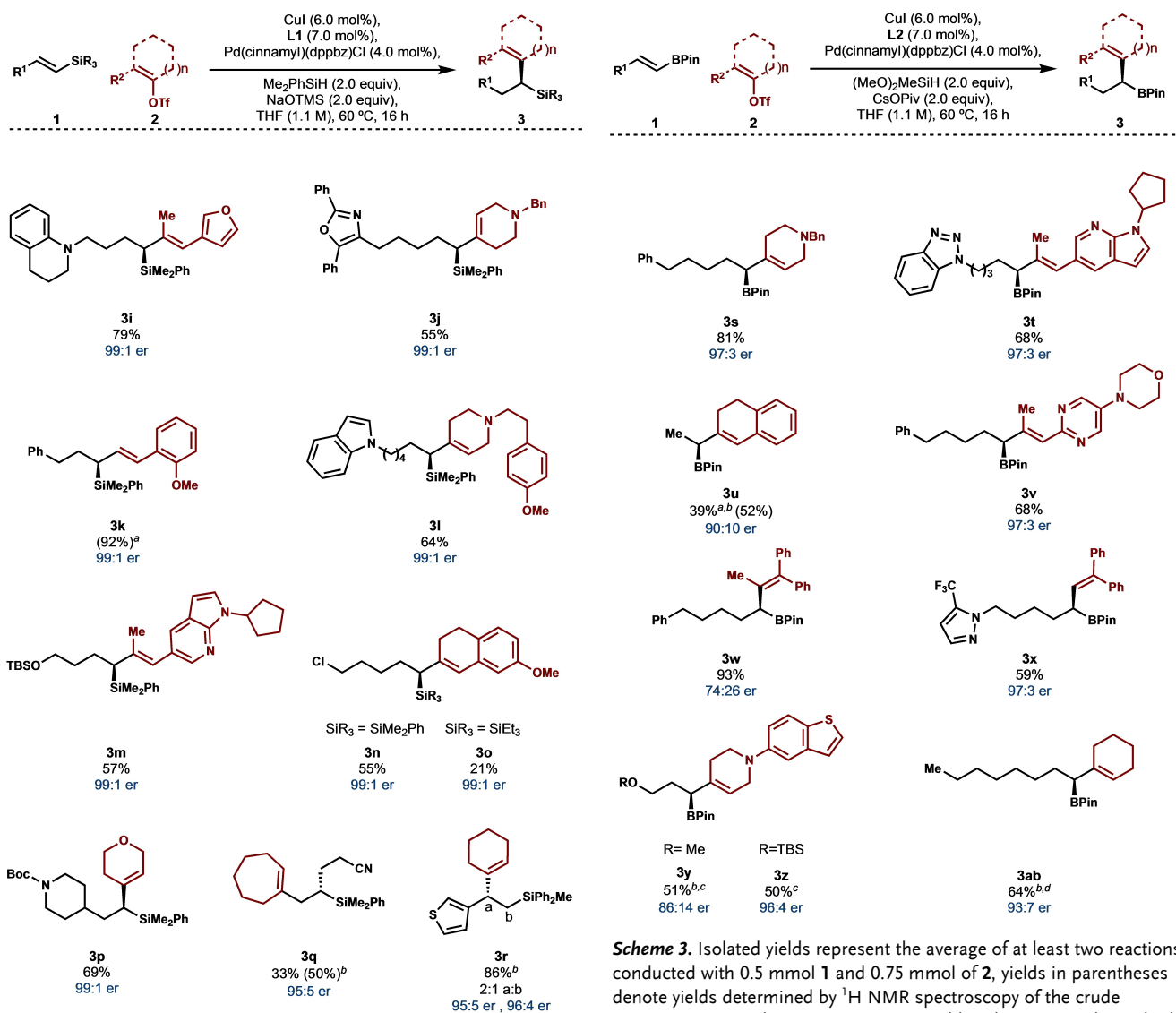|			
─SiMe₂Ph	─SiMe₃	─SiEt₃	─SiMe₂t-Bu
3a	**3b**	**3c**	**3d**
83% 10%ᵃ	63%	44%	19%
99:1 er 87:13 er	99:1 er	99:1 er	99:1 er
─SiPh₂Me	─GeMe₃	─GeEt₃	─BPin
3e	**3f**	**3g**	**3h**
53%	69%	10%	58%ᵇ
99:1 er	99:1 er	99:1 er	96:4 er

Scheme 1. Isolated yields represent the average of at least two reactions conducted with 0.5 mmol of **1** and 0.75 mmol of **2 a**. ᵃ Z-vinyl silane was utilized ᵇ Reaction performed with **L2** in place of **L1**, CsOPiv in place of NaOTMS, and (MeO)₂MeSiH in place of Me₂PhSiH.

(**3b**) substituents, the most commonly used groups in allyl silane transformations,[1b,2,4b–e] could be obtained with excellent enantioselectivity. As in previous CuH-catalyzed transformations,[14,20] the use of the *Z* olefin was less effective (10% yield, 87:13 er) due to a slower rate of hydrocupration. A decrease in the yield of **3** was observed

as the metalloid substituents increased in size, such as from –SiMe₃ (**3b**) to –SiMe₂t-Bu (**3d**), or –GeMe₃ (**3f**) to –GeEt₃ (**3g**). We attribute this to slower hydrocupration or transmetalation steps that arise from steric interactions with the olefin substrate. Subjecting a vinyl boronate ester to the conditions optimized for vinyl silanes resulted in a minimal amount of the α-stereogenic allyl boronate ester, replacing NaOTMS with the weaker base CsOPiv, in conjunction with (MeO)₂MeSiH and **L2**, provided **3h** with good yield and enantioselectivity (see below).

We next explored the variety of α-stereogenic allyl silanes that could be accessed utilizing our optimized reaction conditions (Scheme 2). Allyl silanes bearing acyclic (**3i**, **3k**, **3m**) and cyclic (**3j**, **3l**, **3n**, **3o**, **3p**, **3r**) olefins could be prepared from the corresponding vinyl silanes (**1**) and enol triflates (**2**), in good yields and enantiopurities. Furthermore, a vinyl bromide could be utilized as an alkenyl coupling partner to generate the corresponding 1,2-disubstituted olefin product (**3k**). Heterocyclic substructures, including an oxazole (**3j**), furan (**3i**), thiophene (**3r**), (aza)indole (**3l**, **3m**), piperidine (**3l**), and tetrahydroquinoline (**3i**), were well tolerated under the reaction conditions and resulted in good to excellent yields of the enantioenriched α-stereogenic allyl silane. Products containing sensitive functional groups that are often not compatible with previous methods for the synthesis of allyl silanes, such as a nitrile (**3q**), a protected alcohol (**3m**), an alkyl chloride (**3n**, **3o**), and a carbamate (**3p**) were readily prepared utilizing this protocol. We again observed that modifying the steric environment around the silicon atom had a significant impact on the yield (**3n**, **3o**, cf. Scheme 1). Employing a 1,1-disubstituted vinyl silane provided the anti-Markovnikov product (**3q**) with excellent enantioselectivity, albeit with a diminished yield (33%), which we attributed to the slower hydrocupration of 1,1-disubstituted olefins.[21] To investigate the influence of the β-silicon effect on the regioselectivity of the hydroalkenylation, a competition experiment was conducted utilizing a 1-silyl-2-aryl- disubstituted olefin. The reaction showed a slight selectivity for functionalization of the benzylic position, providing a 2:1 mixture of the homoallyl and allyl silane regioisomers (**3r**), with both isomers obtained with excellent stereospecificity (95:5 and 96:4 er).

We then examined the scope of α-stereogenic allyl boronate esters that could be prepared utilizing the modified reaction conditions (Scheme 3). Under slightly modified reaction conditions, a variety of pharmaceutically-relevant structural elements were incorporated into the enantioenriched allyl boronate ester products, including morpholine (**3v**), pyrazole (**3x**), benzothiophene (**3y**, **3z**), benzotriazole (**3t**), and piperidine (**3s**). Allyl boronates containing cyclic (**3s**, **3y**, **3z**, **3ab**), benzofused (**3u**), and trisubstituted olefins (**3t**, **3v**, **3x**) could be accessed with high enantioselectivity. A tetrasubstituted allyl boronate was formed with diminished enantioselectivity (**3w**). We suspect this is due to a slower transmetalation of the highly encumbered oxidative addition complex, which allows for the epimerization of the intermediate organocopper species, leading to poor enantiopurity of **3w**. Hydroalkenylation of a vinyl boronate bearing

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Scheme 2. Isolated yields represent the average of at least two reactions conducted with 0.5 mmol of **1** and 0.75 mmol of **2**, yields in parentheses denote yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture relative to a 1,1,2,2-tetrachloroethane internal standard. [a] The corresponding vinyl bromide was utilized in place of the enol triflate. Due to product instability, the yield was determined by ^{1}H NMR spectroscopy of the crude reaction mixture relative to a 1,1,2,2-tetrachloroethane internal standard. [b] The reaction was conducted at 45 °C instead of 60 °C

Scheme 3. Isolated yields represent the average of at least two reactions conducted with 0.5 mmol **1** and 0.75 mmol of **2**, yields in parentheses denote yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture relative to a 1,1,2,2-tetrachlorethane internal standard. [a] This product quickly decomposed to form the aromatized material. [b] The reaction was conducted at 45 °C instead of 60 °C. [c] The product allyl boronate was oxidized to the allyl alcohol utilizing H$_2$O$_2$ and NaOH prior to isolation [d] The reaction was performed with NaOTMS in place of CsOPiv, and Me$_2$PhSiH in place of (MeO)$_2$MeSiH and the er was determined following oxidation to the allyl alcohol utilizing H$_2$O$_2$ and NaOH.

a pendant methyl ether furnished **3y** with attenuated enantioselectivity (86:14 er). Replacing the methyl ether with the non-coordinating *tert*-butyl dimethylsilyl (TBS) ether provided the analogous hydroalkenylation product **3z** with 96:4 er, which suggests that coordination of the pendant alkyl ether may be interfering with the reaction, in line with previous observations in the hydroalkenylation of olefins.[16b] Utilizing the reaction conditions optimized for allyl boronates, **3ab** was isolated in high yield, but with poor selectivity (81%, 60:40 er). The enantioselectivity of this transformation could be increased by utilizing NaOTMS and

Me$_2$PhSiH in place of CsOPiv and (MeO)$_2$MeSiH, with a diminished yield (64%, 93:7 er).

To further demonstrate the utility of this method, larger-scale hydroalkenylations of both a vinyl boronate ester and vinyl silane were executed. Utilizing Schlenk techniques with lowered catalyst loadings, we obtained the allyl metal-loid products **3ab** and **3ac** in good yield with excellent enantioselectivity (Scheme 4). The enantioenriched allyl boronate **3ab** was subsequently derivatized through stereo-specific C–C bond forming reactions (Scheme 5). A Suzuki–Miyaura coupling with 3,4,5-trimethoxybromobenzene provided arylated product **4** with olefin transposition, and
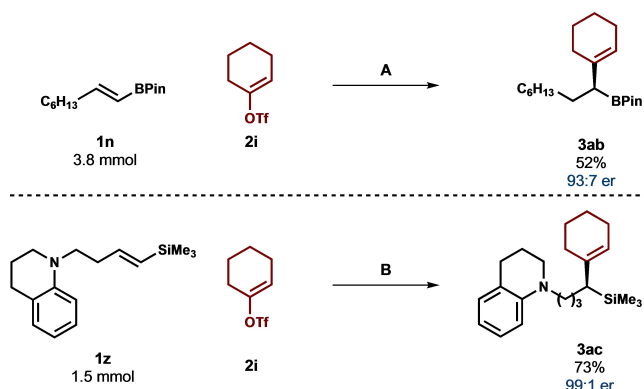
Scheme 4. Reagents and conditions: (A) **1n** (1.0 equiv), **2i** (1.5 equiv), CuI (3.0 mol%), **L1** (4 mol%), Pd(cinnamyl)(dppbz)Cl (2.0 mol%), Me₂PhSiH (2.0 equiv), NaOTMS (2.0 equiv), THF (1.1 M), 45 °C, 18 h. The er was determined following oxidation to the allyl alcohol utilizing H₂O₂ and NaOH. (B) **1z** (1.0 equiv), **2i** (1.5 equiv), CuI (3.0 mol%), **L1** (4 mol%), Pd(cinammyl)(dppbz)Cl (1.0 mol%), Me₂PhSiH (2.0 equiv), NaOTMS (2.0 equiv), THF (1.1 M), 60 °C, 18 h.
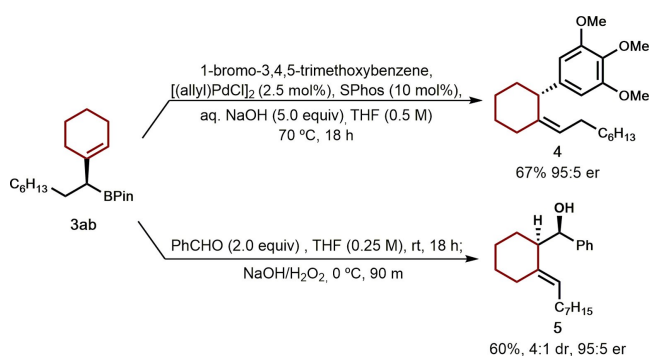
Scheme 5. Derivatizations were performed using 0.1 mmol of **3ab**. Yields of **4** and **5** represent isolated yields of the purified products.

allylation of benzaldehyde yielded homoallyl alcohol **5**, with both products being obtained in 95:5 er.

We have described a general method for the preparation of α-stereogenic allyl metalloids (M = Si, B, Ge). This dual CuH- and Pd-catalyzed protocol allows for the enantiose-lective preparation of diverse allyl silanes, germanes, and boronate esters in good to excellent yield. This operationally simple method can be performed at the gram scale. A number of synthetically relevant substructures could be tolerated, including protected amines, alkyl chlorides and heterocycles. These enantioenriched α-stereogenic allyl met-alloids have the potential to be further elaborated through a variety of well understood stereospecific reactions to allow access to increasingly complex targets.

Conflict of Interest

The authors declare the following competing financial interest(s): MIT has patents on some ligands and precata-lysts that are described in this manuscript, from which S.L.B. and former co-workers receive royalty payments.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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