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Copper−Hydride-Catalyzed Enantioselective Processes with Allenyl Boronates. Mechanistic Nuances, Scope, and Utility in Target-Oriented Synthesis

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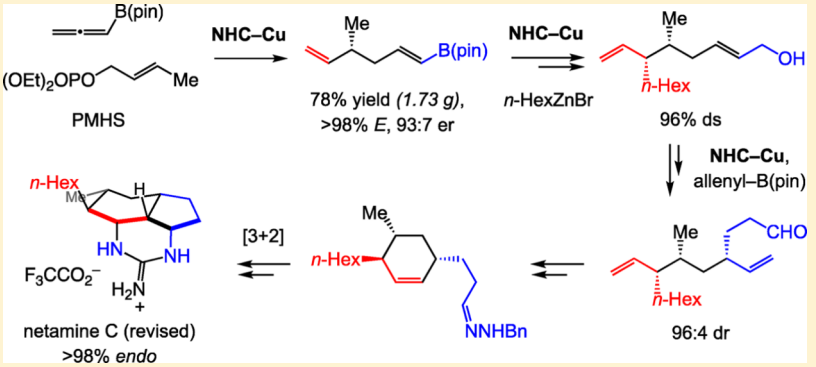
Supporting Information



ABSTRACT: Synthesis of complex bioactive molecules is substantially facilitated by transformations that efficiently and stereoselectively generate polyfunctional compounds. Designing such processes is hardly straightforward, however, especially when the desired route runs counter to the inherently favored reactivity profiles. Furthermore, in addition to being efficient and stereoselective, it is crucial that the products generated can be easily and stereodivergently modified. Here, we introduce a catalytic process that delivers versatile and otherwise difficult-to-access organoboron entities by combining an allenylboronate, a hydride, and an allylic phosphate. Two unique selectivity problems had to be solved: avoiding rapid side reaction of a Cu−H complex with an allylic phosphate, while promoting its addition to an allenylboronate as opposed to the commonly utilized boron−copper exchange. The utility of the approach is demonstrated by applications to concise preparation of the linear fragment of pumiliotoxin B (myotonic, cardiotonic) and enantioselective synthesis and structure confirmation of netamine C, a member of a family of anti-tumor and anti-malarial natural products. Completion of the latter routes required the following noteworthy developments: (1) a two-step all-catalytic sequence for conversion of a terminal alkene to a monosubstituted alkyne; (2) a catalytic S_N2'- and enantioselective allylic substitution method involving a mild alkylzinc halide reagent; and (3) a diastereoselective [3+2]-cycloaddition to assemble the polycyclic structure of a guanidyl polycyclic natural product.

1. INTRODUCTION

Catalytic processes that can deliver organic molecules in an efficient, diastereo- and enantioselective manner are central to advances in biology and medicine. It is also crucial that the products contain functional groups that are ubiquitous in bioactive targets and can be easily converted to a wide range of derivatives. Myriad substructures and stereoisomers related to medicinally relevant entities then become accessible without the need for costly revision of synthesis routes.

At the heart of the present studies are catalytic reactions that begin with the addition of a copper−boryl complex to an unsaturated hydrocarbon, generating an intermediate that then reacts in situ with an electrophile.[1] Transformations involving allenes[2] are particularly noteworthy (Scheme 1a).[3] A related set of reactions are promoted by a Cu−H complex.[4] A distinction between Cu−B(pin)- (pin = pinacolato) and Cu−H-catalyzed reactions is that the products afforded by the former strategy bear a versatile C−B bond (vs a hydrocarbon). The stereochemically defined alkenyl−B(pin) moiety in **ii** (Scheme 1a) has indeed been found to be pivotal to synthesis of complex bioactive molecules.[3c]

A less developed strategy entails the reaction of a chiral Cu−H catalyst and an unsaturated organoboron substrate. There are only two known examples of this type, both involving an alkenylboronate (see **iv** via **iii**, Scheme 1a). In one, vinyl−B(pin) is merged with a monosubstituted allylic electrophile (R = H; enantioselective),[5] and in the other it is combined with a disubstituted allylic electrophile (R = aryl, alkyl; diastereo- and enantioselective).[6] Apart from the need for high

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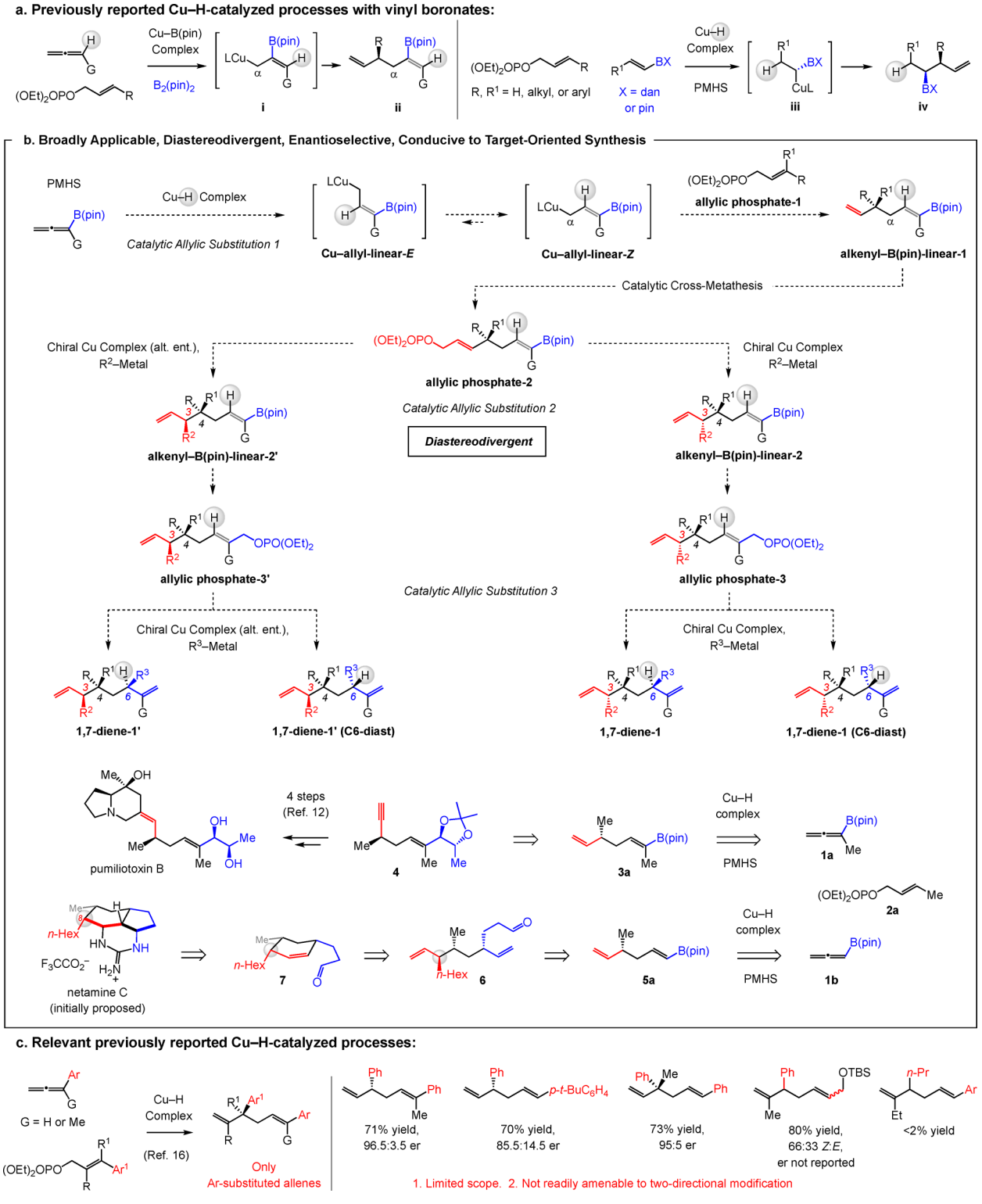
Scheme 1. Background and Goals of the Study



S_N2' selectivity and enantioselectivity, successful implementation hinges on two chemoselectivity requirements being satisfied: (1) The Cu–alkoxide complex must react preferentially with the silyl hydride to produce a Cu–H species (vs an alkenyl–B(pin)[7] moiety to give a Cu–alkenyl species. (2) The Cu–H complex must add to the alkenylboronate substrate and not the allylic phosphate as, otherwise, unsaturated hydrocarbon byproducts would be formed.

The proposed Cu–H-catalyzed allylic substitutions[8] would proceed via **Cu–allyl-linear-*E*** (Scheme 1b), which, after isomerizing to the lower energy **Cu–allyl-linear-*Z***,[9] undergoes an S_N2'-selective allylic substitution to deliver **alkenyl–B(pin)-linear-1**. There is a key difference between this sequence and the formerly reported multicomponent reactions that involve non-boryl-substituted allenes (Scheme 1a). Conversion of the C–B bond in **alkenyl–B(pin)-linear-1** to

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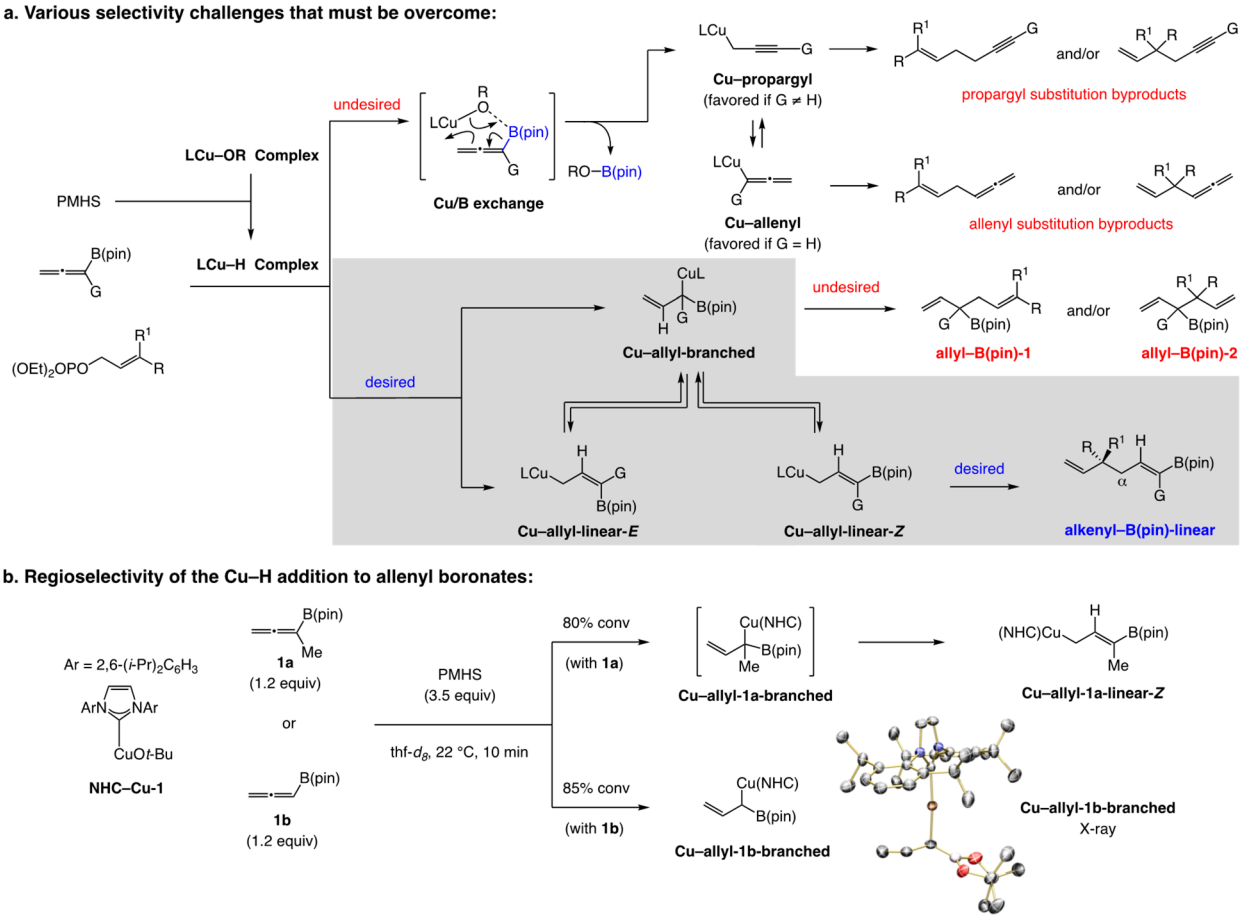
Scheme 2. Various Selectivity Challenges and Relevant Investigations[a]



[a]See the Supporting Information for details.

a C−C bond constituted a linear chain growth. In contrast, the same sequence via **ii** (Scheme 1a) allows for, predominantly if not exclusively, the formation of a methyl-bearing trisubstituted alkene, which, while valuable, is limited in applicability. Chemo- and stereoselective functionalization at the termini can lead to complex stereochemical arrays, not only diastereo- and enantioselectively, but also diastereodivergently. For instance, after **alkenyl−B(pin)-linear-1** is transformed to **allylic phosphate-2** by chemoselective cross-metathesis (Scheme 1b), a second catalyst-controlled allylic substitution might deliver **alkenyl−B(pin)-linear-2** and **alkenyl−B(pin)-linear-2′** in *either* diastereomeric form, depending on the Cu complex enantiomer utilized. It is worth noting that catalytic approaches for diastereo- and enantioselective synthesis of vicinal carbon-substituted stereogenic centers, especially in a stereodivergent manner, are scarce.[10]

A Lewis acidic boryl unit within the product, while synthetically desirable, poses a new challenge: C−C bond forming transformations must involve organometallic reagents that, although sufficiently reactive, are not excessively nucleophilic. Conversion of the alkenyl−B(pin) moiety to yet another allylic phosphate would be followed by a third catalyst-controlled allylic substitution, this time yielding **1,7-diene-1** or **1,7-diene-1 (C6-diast)** or **1,7-diene-1′** or **1,7-diene-1′ (C6-diast)**. By performing the initial process with the alternative catalyst enantiomer (i.e., formation of *ent*-**1,7-diene-1** or *ent*-**1,7-diene-1 (C6-diast)**), the remaining four possible stereoisomers may be selectively synthesized by the same sequence. Each allylic substitution would have to proceed with high efficiency and exceptional regio- and stereochemical control.

The proposed strategy has the necessary attributes for multistep synthesis applications and preparation of several isomers. Diastereoselective catalytic cross-coupling of the alkenyl boronate moiety in **3a** (Scheme 1b) with an appropriate partner, followed by conversion of the alkene terminus to an alkyne moiety, would generate enyne **4**, a compound previously converted to pumiliotoxin B, a naturally occurring anti-malarial, cardiotonic agent,[11] after just four additional steps.[12] Transformation with the same allylic phosphate (**2a**) but involving monosubstituted allenyl−B(pin) **1b** could deliver **5a**, two-directional modification of which by additional allylic substitutions might furnish **6** and **7**. The resulting cyclohexenyl compound may be used for the first enantioselective total synthesis of natural product netamine C,[13] a member of a family of potent anti-tumor and anti-malarial compounds[14] (Scheme 1b). Because the stereochemistry at C8 has been the subject of some debate,[15] and since the approach could allow access to either isomeric form (i.e., it is diastereodivergent), it would be possible to establish the stereochemical identity of the natural product rigorously.

Several points regarding a related study[16] (Scheme 1c), published during the final stages of this work, merit note. (1) Although the reported yields and enantioselectivities are often

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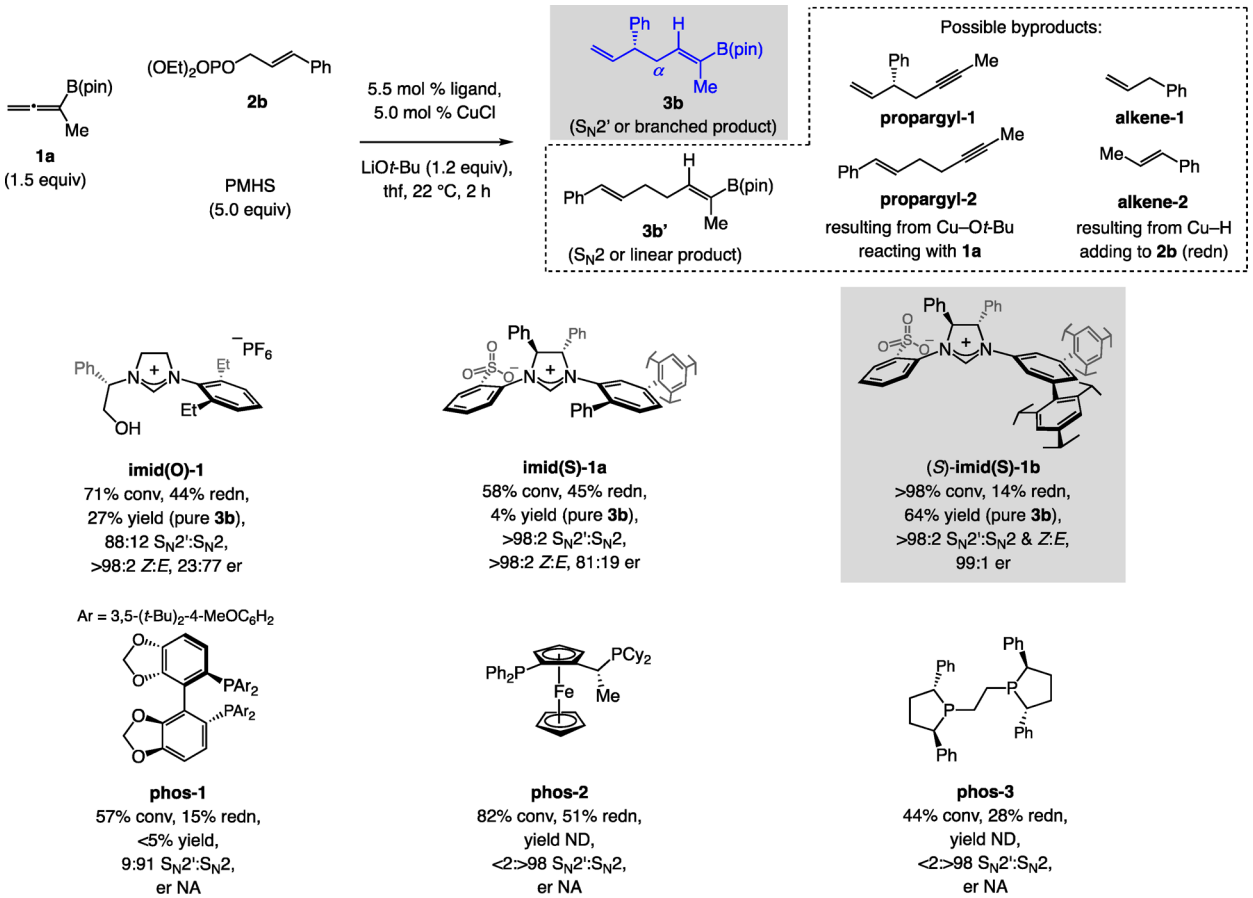
Scheme 3. Ligand Screening for Reactions with 1,1-Disubstituted Allenyl Boronate 1a[a]



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Supporting Information for details. Abbreviations: redn, reduction; NA, not applicable.

high, the approach has shortcomings that make it unsuitable to target-oriented synthesis. A key limitation is that the allenyl substrates as well as the allylic phosphate must each contain an aryl substituent; otherwise, reactions are inefficient and/or non-stereoselective (low *E*:*Z* ratios and/or enantioselectivity). (2) Products are much less amenable to two-directional modification, because they either contain two disubstituted alkenes (one of which must be an aryl olefin), or one di-, or one trisubstituted aryl alkene. (3) While a terminal alkene in a 1,5-diene product was converted (by cross-metathesis) to the corresponding alkenyl–B(pin) derivative, such products are distinct from **alkenyl–B(pin)-linear-1** in three aspects, all central to the utility of the strategy (see Scheme 1b): a remaining disubstituted aryl olefin (vs a terminal alkene), a stereogenic center that is allylic (vs homoallylic) to the alkenyl–boronate unit, and the lack of a pathway to generate a stereodefined trisubstituted alkene (e.g., G = Me in **alkenyl–B(pin)-linear-1**).

2. RESULTS AND DISCUSSION

2.1. Mechanistic Challenge. The proposed approach poses several unique reactivity/selectivity issues. One relates to the possibility of B/Cu exchange (Scheme 2a). As far as we know, allenyl–B(pin) compounds have been utilized only as precursors to Cu–allenyl or Cu–propargyl intermediates[17] but not as substrates for Cu–X addition [e.g., X = H or B(pin)]. This is less of an issue with alkenyl–B(pin) compounds (Scheme 1a) because with an allenyl boronate the intermediacy of a six-membered ring transition state (Scheme 2a) is not only feasible, it is probably favored (vs direct exchange at the more congested C–B bond), rendering B/Cu exchange more facile. Control experiments support this contention. We find that **1a** and **1b** as well as vinyl–B(pin) are fully converted to their organocopper derivative in the presence of an NHC–Cu–alkoxide (NHC = N-heterocyclic carbene) complex in just 10 min (at 22 °C). However, when an equal mixture of **1a** or **1b** and vinyl–B(pin) are subjected to the same conditions, only the allenyl boronates react and there is no Cu–vinyl species formed.[18] These findings indicated that conditions that ensure efficient Cu–H addition to an allene as opposed to B/Cu exchange would be needed (e.g., larger amounts of copper hydride and/or sizable metal alkoxide; see below).

Another complication is the regioselectivity of Cu–H addition to an allenyl boronate. As with the reactions involving an alkenyl boronate (see Scheme 1a), a boryl substituent's ability to stabilize electron density at the carbon of an incipient Cu–C bond favors the more hindered branched Cu–allyl derivative (**Cu–allyl-branched**), Scheme 2a); DFT studies support this possibility.[18] Nevertheless, unlike the previous

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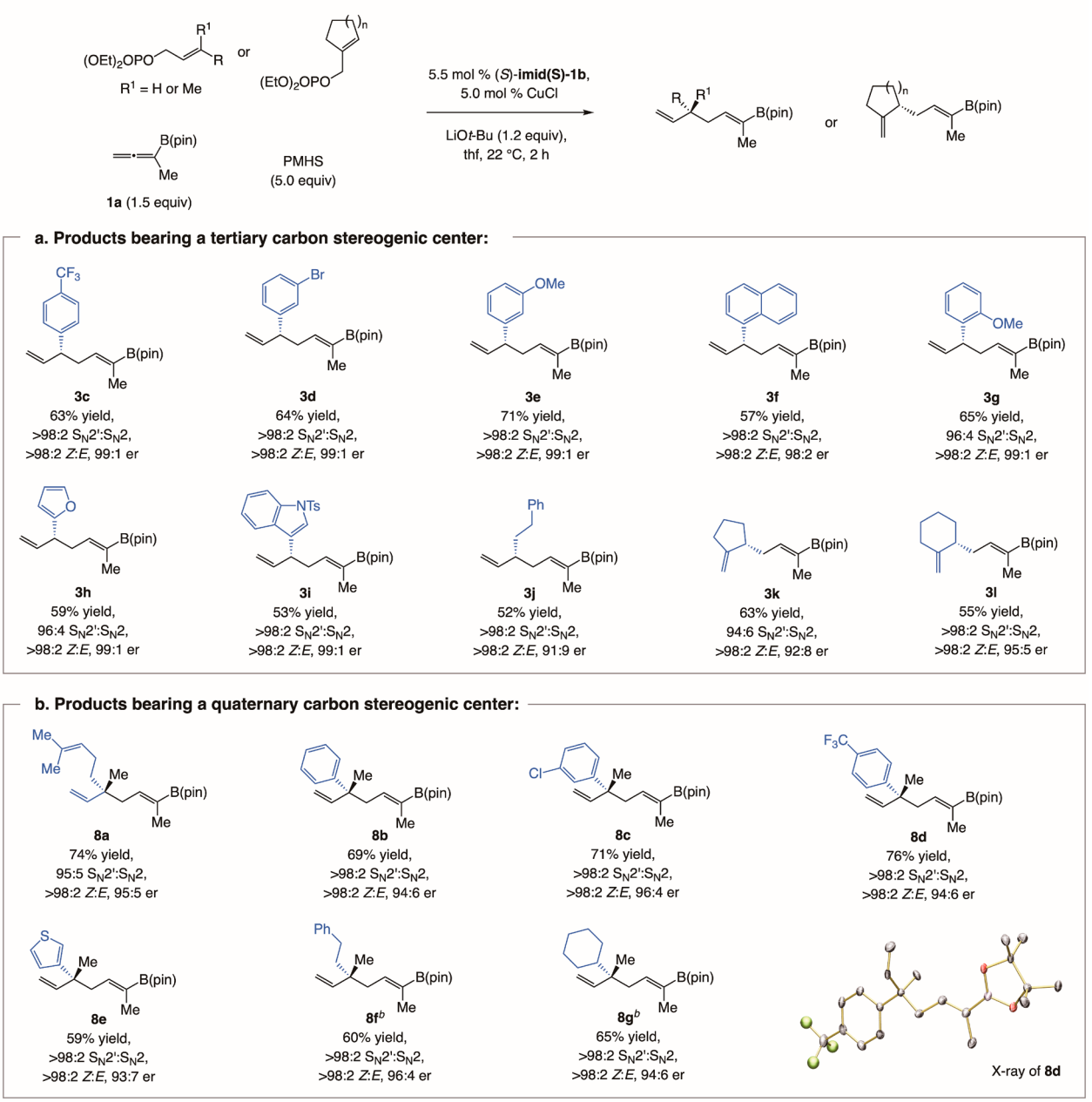
Scheme 4. Scope of Catalytic Processes with 1,1-Disubstituted Allenyl Boronate 1a[a]



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). Reaction mixtures typically contain 10−20% of side products from allylic phosphate reduction. [b]With 2.0 equiv **1a**. See the Supporting Information for details.

cases, **Cu−allyl-branched** might either react directly with an allylic phosphate to afford allylic boronate byproducts, depending on whether the S_N2 or S_N2' mode of addition dominates, or might partially be converted to **Cu−allyl-linear-*Z*** and/or **Cu−allyl-linear-*E***, which would result in product mixtures. For the desired **alkenyl−B(pin)-linear** to be formed, isomerization of **Cu−allyl-branched** to **Cu−allyl-linear-*Z*** must be faster than its reaction with an allylic phosphate. The kinetic preference for the more congested **Cu−allyl-branched** can also render Cu−H addition to an allylic phosphate more competitive.

In search of further insight, we probed the reaction of **NHC−Cu-1** with equivalent amounts of **1a** or **1b** in the presence of polymethylhydrosiloxane (PMHS; at 22 °C; Scheme 2b). In the case of disubstituted allenyl boronate **1a**, for which the branched Cu−allyl isomer was not detected, there was 80% conversion to **Cu−allyl-1a-linear-*Z*** after just 10 min. When monosubstituted **1b** was used, on the other hand, not only was **Cu−allyl-1b-branched** generated as the sole product (85% conversion, 10 min), it was sufficiently stable for us to obtain an X-ray structure (Scheme 2b). The transformation involving **1a** probably proceeds via **Cu−allyl-1a-branched**, and the increased steric pressure in the latter causes it to collapse readily to **Cu−allyl-1a-linear-*Z***. Whether the higher stability of **Cu−allyl-1b-branched** would lead to

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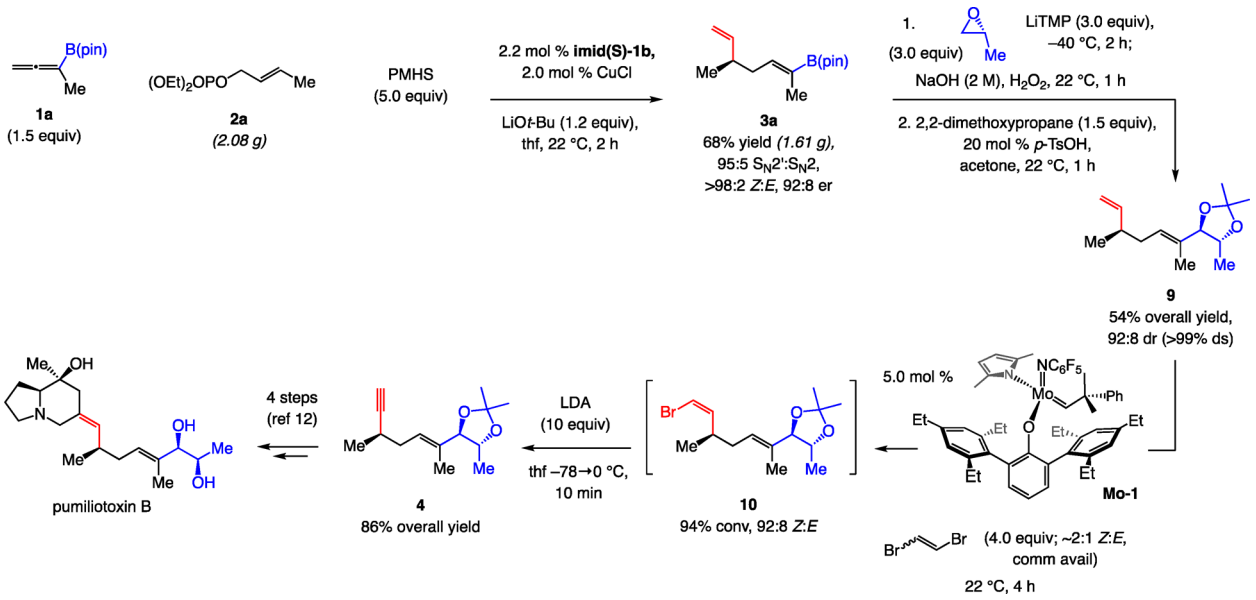
Scheme 5. Application to Diastereo- and Enantioselective Synthesis of the Linear Fragment of Pumiliotoxin B[a]



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', and *Z*:*E* selectivity were determined by analysis of ^1H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Supporting Information for details.

inefficient transformations with disubstituted allenyl–B(pin) **1b** remained to be determined.

2.2. Feasibility and Identifying an Effective Catalyst. As the model reaction, we selected 1,1-disubstituted allenylboronate **1a** (prepared in two steps[19]) and allylic phosphate **2b** (Scheme 3); PMHS was the hydride source. We began with disubstituted allene **1a**, as we surmised that transformations might be less complicated due to relatively rapid formation of **Cu–allyl-1a-linear-*Z*** (vs the more persisting **Cu–allyl-1b-branched**). Based on the initial mechanistic studies (Scheme 2b), we reasoned that excess PMHS and the sizable LiO*t*-Bu would favor conversion of the in situ generated Cu–O*t*-Bu complex to the corresponding Cu–H species (vs B/Cu exchange, yielding **Cu–propargyl**), minimizing B/Cu exchange and thus reduction byproduct formation (dotted box, Scheme 3). Still, in view of the steric requirement for the addition of the same complex to the disubstituted allene, we remained concerned that Cu–H addition to **2b** would be competitive.

With the **imid(O)-1**-derived complex, optimal for Cu–B(pin)-catalyzed allylic substitutions with allenes[3c] (see Scheme 1a), there was significant reduction (44%; see dotted box, Scheme 3) and enantioselectivity was low (23:77 enantiomeric ratio (er)). But at least the process was S_N2'-selective (88:12 **3b**:**3b′**) and **3b** was obtained in 27% yield (>98:2 *Z*:*E*). We then examined several catalysts derived from sulfonate-containing NHC ligands, wherein a metal salt bridge involving the pendant Lewis basic group within the chiral ligand and the phosphate moiety can engender high S_N2' selectivity.[20] The process with **imid(S)-1a** was more regioselective (>98:2 $S_N2':S_N2$), furnishing **3b** in 81:19 er. All the same, as suspected, competitive Cu–H addition to the allylic phosphate persisted (45% reduction). Then, to our surprise, the reaction involving **imid(S)-1b**, a member of a class of chiral NHC ligands originally designed and developed in these laboratories,[21] afforded no more than 14% byproduct formation (removable by silica gel chromatography) along with **3b** in 64% yield, >98:2 $S_N2':S_N2$ ratio, and 99:1 er. These findings show that the substitution pattern within the NHC's aryl moiety is critical to whether Cu–H addition to **1a** can effectively compete with its undesired reaction with the allylic phosphate (see Scheme 7 and related discussion below for further analysis). The amount of LiO*t*-Bu was central to minimizing competitive B/Cu exchange. For example, with 2.5 equiv metal alkoxide (vs 1.2 equiv), **propargyl-1** was formed predominantly (14:86 **3b**:**propargyl-1**); this is likely due to faster B/Cu exchange when a *tert*-butoxyl borate derivative of allenyl boronate **1a** is involved.[17b,18]

Catalysts derived from **phos-1**–**phos-3**, previously used in other Cu–H-catalyzed processes,[4,22] were ineffective. There was rampant byproduct formation due to breakdown in chemoselectivity with up to ~60% Cu–H addition to the allylic phosphate, and the undesired linear product was the predominant isomer (i.e., 91% to >98% S_N2).

2.3. Scope with Disubstituted Allenyl Boronate 1a. Transformations between 1,2-disubstituted allylic phosphates and 1,1-disubstituted allenyl–B(pin) **1a** (Scheme 4a) afforded 1,5-dienes with an electron-rich or an electron-poor aryl group (**3c**–**e**), a congested *o*-substituted aryl moiety (**3f**,**g**), or a heteroaryl fragment (**3h**,**i**). These products were isolated in 53–71% yield, >98% S_N2' and *Z* selectivity, and 98:2–99:1 er. Alkyl-substituted (**3j**; see Scheme 5 for another example) as well as cyclic allylic phosphates were effective substrates (**3k**,**l**).

Reactions with geraniol-derived allylic phosphate (Scheme 4b) proceeded to >98% conversion within two h at room temperature, affording **8a** in 74% yield, 95:5 $S_N2':S_N2$ selectivity, >98:2 *Z*:*E* selectivity, and 95:5 er. As represented by **8b**–**g**, products bearing an aryl-, heteroaryl-, or alkyl-substituted stereogenic center and a *Z*-trisubstituted alkenyl–B(pin) moiety were obtained with similar efficiency and stereoselectivity. The latter data have an additional notable dimension because the corresponding Cu–B(pin)-catalyzed multicomponent processes (Scheme 1a), while efficient, afford only the linear product (S_N2 addition). This difference in

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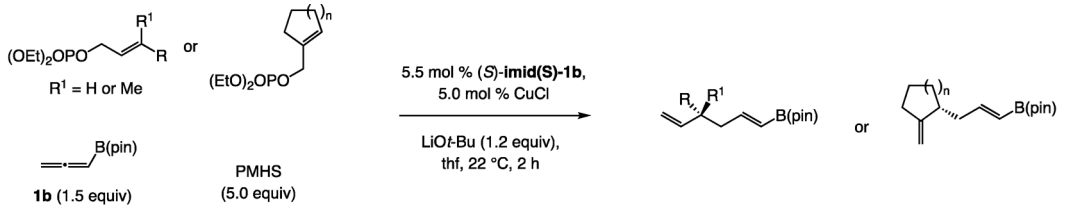
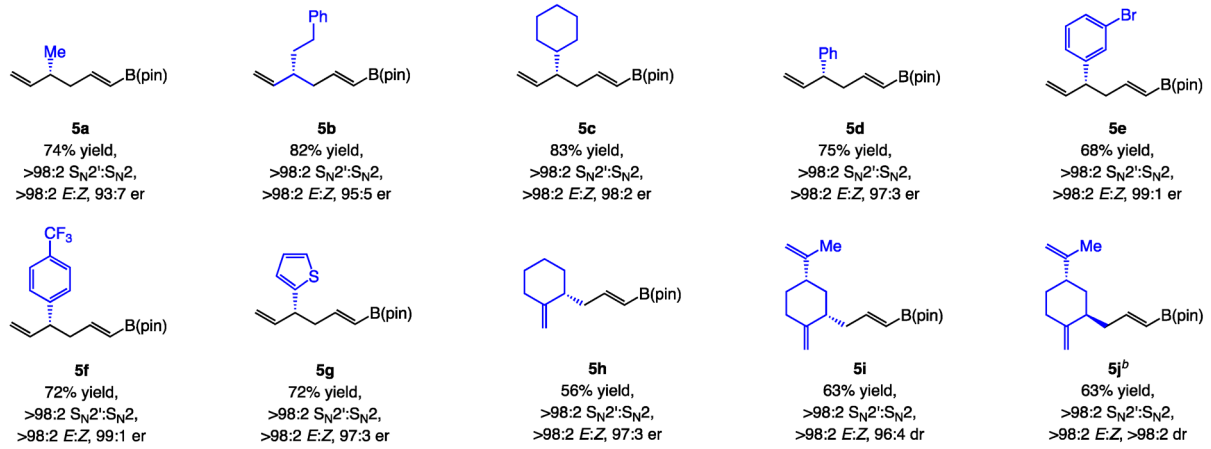
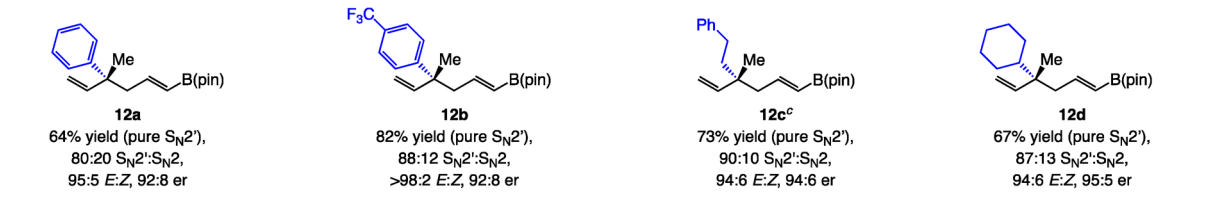
Scheme 6. Scope of Catalytic Processes with 1,1-Disubstituted Allenyl Boronate[a]



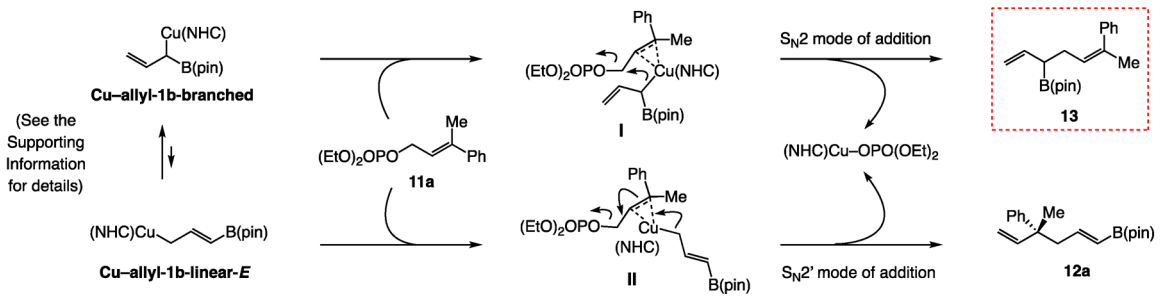
a. Products bearing a tertiary carbon stereogenic center:



b. Products bearing a quaternary carbon stereogenic center:



c. A rationale for the lower S_N2' selectivity for 12a-d:



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', and *Z*:*E* selectivity were determined by analysis of ^{1}H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). Reaction mixtures typically contain 5% of side products from allylic phosphate reduction. [b](*R*)-**imid(S)-1b** was used. [c]For 6 h at 4 °C. See the Supporting Information for details.

regioselectivity, compared to the highly S_N2'-selective reactions with 1,2-disubstituted allylic phosphates, may be attributed to the steric pressure inflicted by the sizable B(pin) moiety and a substituent at the incipient quaternary carbon center. Cu–H-catalyzed transformations with an allenyl–B(pin) substrate are faster probably because the bulky boronate is more distal from the site of C–C bond formation.

2.4. Formal Synthesis of Pumiliotoxin B. The utility of the approach hinges on whether the *Z*-trisubstituted alkenyl–B(pin) and the monosubstituted alkene moiety within the products can be functionalized chemo- and stereoselectively. To probe this matter, we chose to synthesize the linear fragment of pumiliotoxin B (Scheme 5). We prepared 1.61 g of 1,5-diene **3a** by using 2.2 mol% of the chiral ligand (*S*)-**imid(S)-1b** (68% yield, 95:5 S_N2':S_N2 selectivity, >98:2 *Z*:*E* selectivity and 92:8 er). We then took advantage of a method outlined by Aggarwal[23] to effect a stereospecific cross-coupling of the trisubstituted alkenyl–B(pin) moiety with enantiomerically pure propylene oxide. Acetonide formation led to **9** in 54% overall yield and 92:8 dr (i.e., C–C bond-forming step proceeded with >99% diastereospecificity (ds)). The latter sequence is not feasible with the products generated by the

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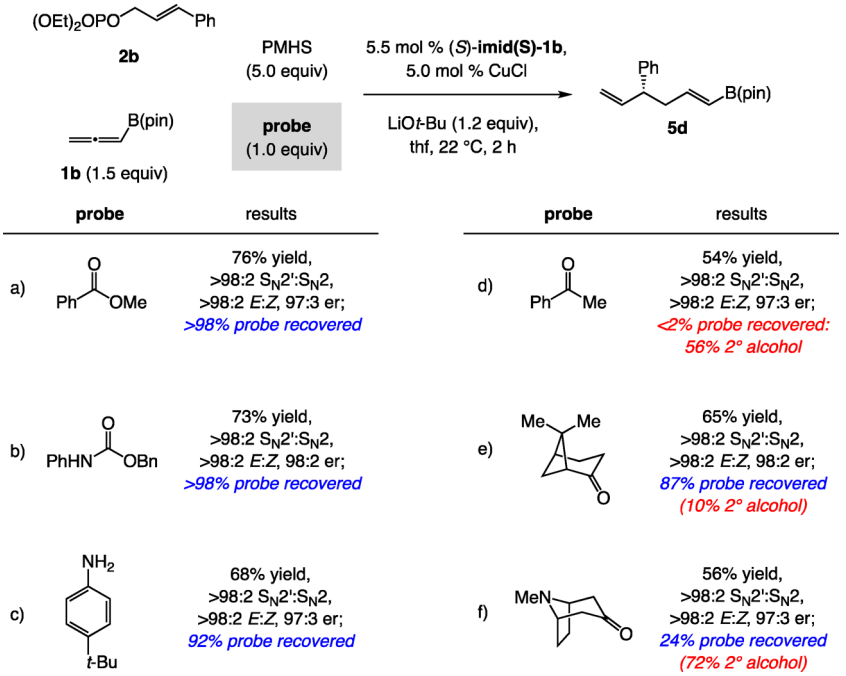
Scheme 7. Probing Polar Functional Group Compatibility[a]



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', *Z*:*E* selectivity, and the products derived from the probe were determined by analysis of ^1H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Supporting Information for details.

recent Cu–H-catalyzed approach,[16] further underlining the importance of the alkenyl–B(pin) moiety in the products generated by the present strategy.

Conversion of the terminal alkene in **9** to alkyne **4** was more complicated than expected. A two-step bromide formation/elimination sequence[24] led to modification at both olefinic sites Oxidative cleavage of the less substituted alkene and subjection of the resulting aldehyde to the Ohira–Bestmann conditions,[25] afforded the desired alkyne as equal mixture of diastereomers, presumably due to epimerization.[26] We therefore devised the following two-step/one-pot protocol. *Z*-Selective cross-metathesis[27] with 5.0 mol% **Mo-1** and commercially available 1,2-dibromoethene (~2:1 *Z*:*E* mixture), followed by the addition of LDA for 10 min (−78 → 0 °C) delivered **4** in 86% overall yield (Scheme 5). Spectroscopic analysis indicated 94% conversion to **10**, formed as a 92:8 *Z*:*E* mixture. It is worth noting that Ru-based complexes cannot be used to access halogen-substituted alkenes,[27] and that selective synthesis of *Z*-alkenyl halide is key because elimination of the *E* isomer to the corresponding alkyne is less facile.[28]

The seven-step sequence to **4** (32% overall yield, including the two-step preparation of **1a**) compares favorably with the elegant pathway reported by Overman and co-workers in their seminal studies (11 steps).[12] The previously reported overall yield is somewhat higher (39%). However, aside from the significantly lower amounts of waste generated by the present route the total reaction time is only 10 h, as opposed to 108 h needed for the former sequence.

2.5. Reactions with Monosubstituted Allenyl Boronate 1b. In the case of **1b**, the less sterically hindered C–B bond can lead to faster Cu–allene formation, and the greater stability of **Cu–allyl-branched-1b** could mean lower regioselectivity and more byproduct formation and/or a sluggish process (see Scheme 2b). Ligand screening indicated that Cu–H addition to the allylic phosphate was again problematic.[18] While adventitious B/Cu exchange with the less sterically hindered monosubstituted **1b** (vs **1a**) could be addressed with excess PMHS, the presence of a less hindered allene did less than we hoped to counter competitive Cu–H addition to an allylic phosphate. This was the case until we used the catalyst derived from **imid(S)-1b**, the reaction with which generated only 4% byproduct from Cu–H addition to the allylic phosphate, far less than when **imid(O)-1** or **imid(S)-1a** was used (49% and 19%, respectively). The main side reaction was B/Cu exchange, which led to 12% allenyl substitution.

Similar to the processes with **1a**, excess LiO*t*-Bu gave more allenyl side products (see Scheme 2a; e.g., >98% with 3.0 equiv LiO*t*-Bu). As before, the reactions with phosphine ligands were largely S_N2-selective and generated up to 22% of the reduction byproducts.

Alkyl- (**5a–c**), aryl- (**5d–f**), heteroaryl- (**5g**), and carbocyclic-substituted (**5h–j**) 1,5-dienes were obtained in 56–83% yield and with exceptional regio-, diastereo-, and enantioselectivity (Scheme 6a). The high diastereocontrol for **5i** and **5j** shows that either product isomer can be generated when a chiral allylic phosphates with complete catalyst control.

Multicomponent reactions with a trisubstituted allylic phosphate and monosubstituted allenyl–B(pin) were efficient and stereoselective (**12a–d**, Scheme 6b). Still, additions to alkenyl sites with a sterically demanding *o*-substituted aryl group were efficient (e.g., *o*-bromo derivative of **12a**: 10% yield after oxidation to alcohol, >98:2 S_N2:S_N2', 65:35 er). A characteristic of the reactions in Scheme 6b is their lower regioselectivity compared to when 1,1-disubstituted allene **1a** is involved (95:5 to >98:2 for **8a–g** vs 80:20–90:10 S_N2':S_N2 for

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12a–d). Another distinguishing attribute is that S_N2 addition leads to chiral allylboronate side products (see **13**, Scheme 6c vs **3b'**, Scheme 3). These findings suggest that the preference for S_N2' selectivity arises from higher reactivity—and not greater stability—of **Cu–allyl-1b-linear** (i.e., Curtin–Hammett kinetics is operative). Reaction via **I** (Scheme 6c), involving the more sterically demanding branched Cu–allyl complex to form a tertiary C–C bond, thus becomes competitive with reaction via **II**, leading to a more congested quaternary carbon center site.

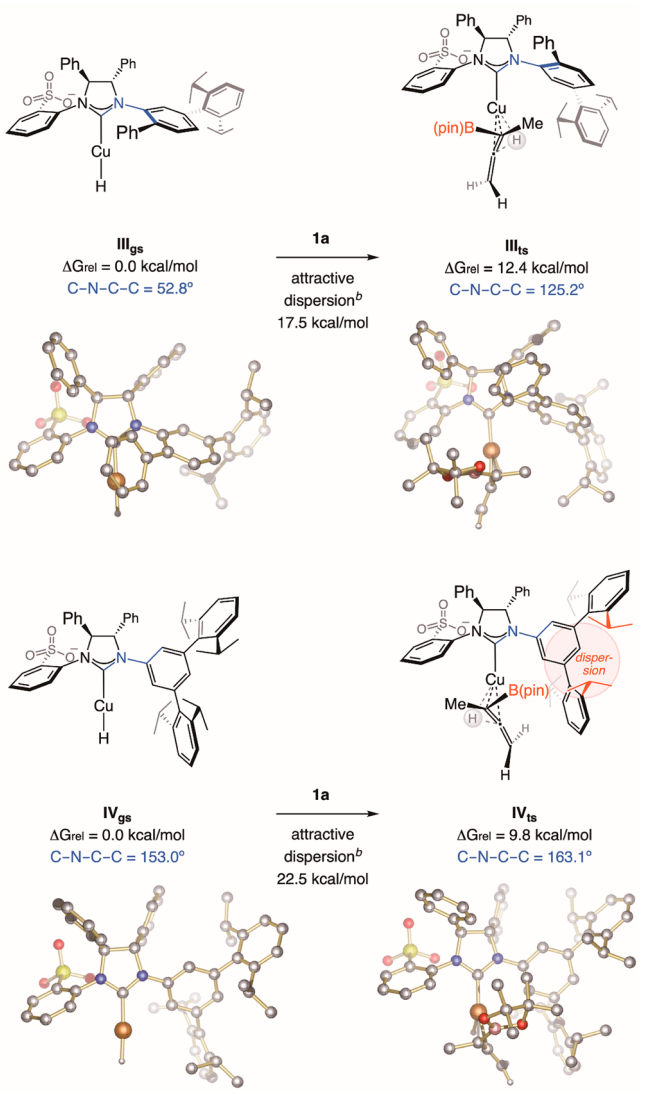
2.6. Functional Group Compatibility. To probe the compatibility of the above methods to some of the more commonly occurring functional units, the experiments summarized in Scheme 7 were carried out. The catalytic reaction proceeds without any complication in the presence of a carboxylic ester or a carbamate (Scheme 7a,b). The presence of an unprotected aniline did not have any inhibitory effect (entry c). The same is not true with ketones, however; with acetophenone present, while **5d** was generated with slightly lower efficiency but without any diminution in selectivity, the ketone reacted completely to generate the derived secondary alcohol (hydride addition; 75:25 er) and a mixture of unidentifiable side products. Further studies showed competitive reactivity with a ketone site is less problematic if the carbonyl group is relatively hindered (entries e and f). The last case (entry f) further underlines the fact that basic amines do not adversely impact the rate of the multicomponent process.

2.7. Rationale for Unique Selectivity with imid(S)-1b. The key mechanistic question at this point was: Why is the copper complex derived from **imid(S)-1b**[17b] uncommonly effective in promoting a multicomponent process? Control experiments indicated that the Cu–H complexes derived from **imid(S)-1a** and **imid(S)-1b** are similarly efficient in their reaction with an allylic phosphate.[18] This implies that what makes the Cu–H complex derived from **imid(S)-1b** uniquely effective is its ability to react more efficiently with an allenyl boronate.

For better understanding, we carried out DFT calculations (at the MN15/Def2-TZVPP//M06L/Def2-SVP level), which indicated that the energy barrier for $\mathbf{III}_{gs} \rightarrow \mathbf{III}_{ts}$ (Scheme 8) is higher compared to $\mathbf{IV}_{gs} \rightarrow \mathbf{IV}_{ts}$ (12.4 and 9.8 kcal/mol, respectively). This may be due to several factors. (1) The absence of an *o*-aryl substituent in the **imid(S)-1b**-derived Cu–H complex allows the NAr ring to adopt a nearly coplanar orientation with respect to the ligand heterocycle on the NHC (C–N–C–C dihedral angle of 125.2° and 163.1° for $\mathbf{III}_{ts}$ and $\mathbf{IV}_{ts}$, respectively). Steric repulsion between the allene and the N-aryl moiety is therefore minimized. (2) In the complex derived from **imid(S)-1b**, the B(pin) and the protruding isopropyl substituents seem to prefer being in a sterically repulsive orientation ($\mathbf{IV}_{ts}$). This may be attributed to molecular recognition due to attractive dispersion forces between the bulky isopropyl groups and the B(pin) moiety.[29] The magnitude of Grimme's D2 dispersion on the reaction barriers (ωB97XD single-point calculations) indicate that the corresponding attractive forces are approximately 5.0 kcal/mol larger for conversion of $\mathbf{IV}_{gs}$ to $\mathbf{IV}_{ts}$ (22.5 kcal/mol as opposed to 17.5 kcal/mol for $\mathbf{III}_{gs} \rightarrow \mathbf{III}_{ts}$). Nevertheless, we are aware that, recent support for such interactions[28] aside, the precise contribution by dispersion interactions in solution is subject to debate.[30]

2.8. Total synthesis of Netamine C. *2.8.1. Gram-Scale Preparation of a Boryl-Substituted 1,5-Diene.* Heterocyclic

Scheme 8. Regarding Higher Efficiency with imid(S)-1b (vs imid(S)-1a)[a]



[a]DFT calculations were carried out at the MN15/Def2-TZVPP//M06-L/Def2-SVP level. [b]Corresponds to Grimme D2 dispersion obtained at the ωB97XD/Def2-TZVPP//M06-L/Def2-SVP level. See the Supporting Information for details. Abbreviations: gs, ground state; ts, transition state.

natural products, such as netamine C, are typically assembled through modification of an amine, or by condensing a guanidinyl substrate with an enone or an α-halocarbonyl compound.[31] Our plan was based on a completely different strategy where an aliphatic aldehyde would be utilized, an approach which, to the best of our knowledge, has not been previously explored.

We prepared 1.73 g of 1,5-diene **5a** by a multicomponent process performed with 2.0 mol% catalyst loading (Scheme 9a). We formerly reported an alternative route for preparation of **5a**, entailing catalytic enantioselective allylic substitution with a propargyl(pinacolato)boron reagent.[20] The route, which involves commercially **1b**, furnished **5a** directly in 73% yield, and 93:7 er within 2 h. In the previously reported approach, 36 h was needed for a three-step sequence that gave the same product in 41% overall yield and 91:9 er. Cross-metathesis of **5a** and bis-phosphate **14a**, derived from commercially available

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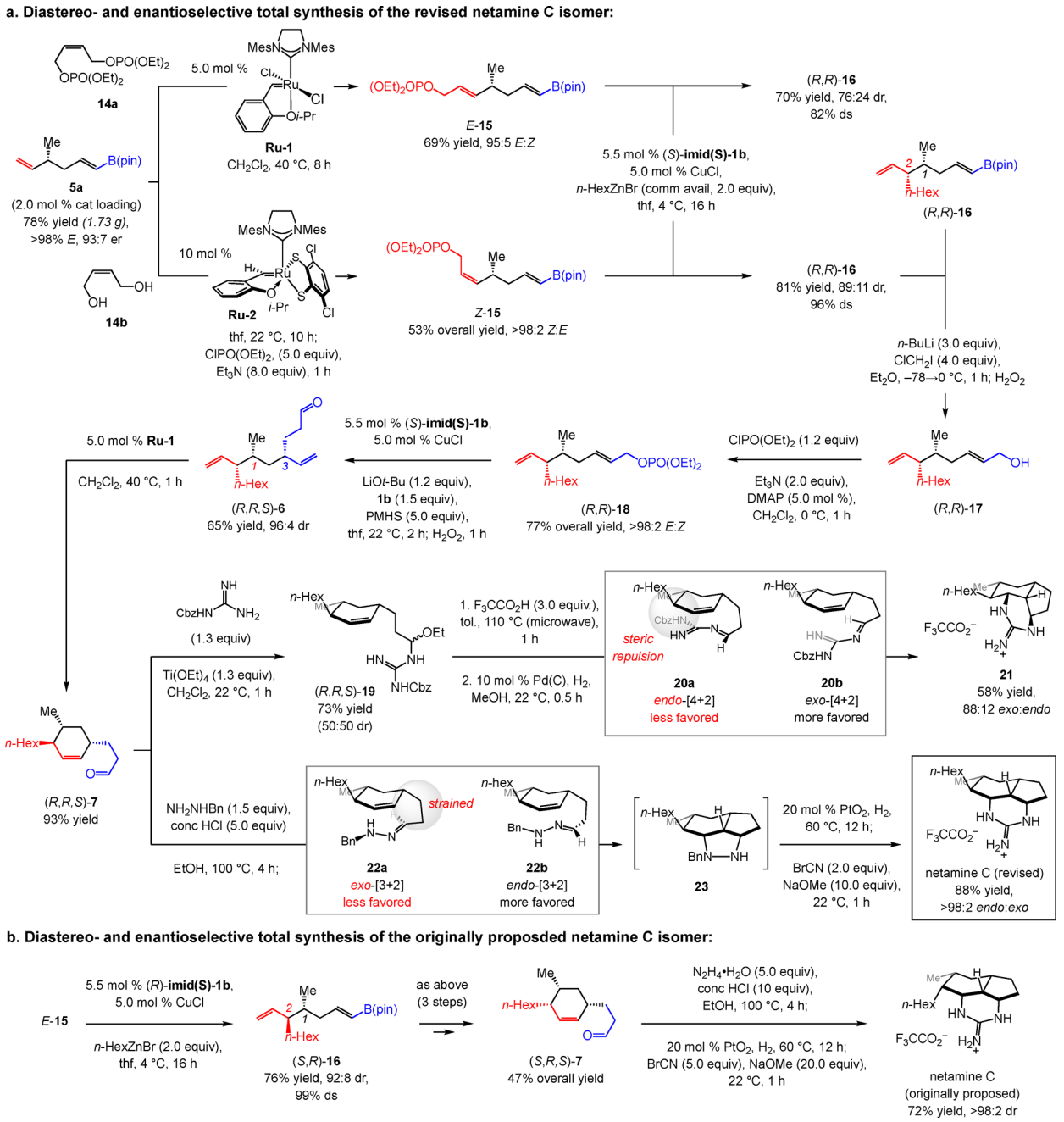
Scheme 9. Total Synthesis and Stereochemical Identity of Netamine C[a]



[a]All reactions were performed under N_2 atmosphere. Conversion (>98% in all cases), S_N2', and Z:E selectivity were determined by analysis of ^1H NMR spectra of the unpurified mixtures (±2%). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Enantioselectivities were determined by HPLC analysis (±1%). See the Supporting Information for details.

diol **14b**, delivered allylic phosphate *E*-**15** in 69% yield and 95:5 *E*:*Z* ratio; this chemoselective reaction allowed us to use the alkenyl–B(pin) moiety as masked allylic phosphate, to be utilized later for a pair of allylic substitutions.

2.8.2. A Mild Catalytic Allylic Substitution Compatible with a B(pin) Moiety. Achieving an efficient S_N2'- and diastereoselective allylic substitution to introduce an *n*-hexyl moiety was next. The main issue here was that the Lewis acidic boronate does not tolerate an alkyllithium, an alkylmagnesium halide, a dialkylzinc compound, or a trialkylaluminum reagent—organometallic species commonly used for such transformations.[32] We had to identify a process that would involve a milder, but sufficiently nucleophilic, alkylmetal reagent.

A search of the relevant literature led us to two approaches, one entailing an in situ-generated alkylborane and a *Z*-allylic chloride,[33] and the other an alkylzinc halide and an aryl-substituted secondary allylic carbonate.[34] In the earlier study, the only example of a reaction with a substrate containing an allylic substituent proceeded with relatively low efficiency and stereoselectivity. Adopting the latter approach would mean generating a secondary allylic alcohol from the monosubstituted alkene, demanding manipulations that could probably cause loss of enantioselectivity (i.e., via the aldehyde). We

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therefore set out to identify conditions for an efficient, regio-, and stereoselective catalytic allylic substitution, involving a primary *E*-allylic phosphate that contains an α-branched allylic unit and a mild alkylmetal reagent.

Exploratory studies revealed that an alkylzinc halide would be suitable, and ligand screening showed that only the catalyst derived from **imid(S)-1b** is effective, (primary allylic bromide formed otherwise). Subjection of *E*-**15** to *n*-hexylzinc bromide (commercially available) and 5.0 mol% of the in situ-generated NHC−Cu complex derived from (*S*)-**imid(S)-1b** afforded (*R*,*R*)-**17** in 70% yield and 76:24 dr (82% diastereospecificity, ds). To improve efficiency and stereoselectivity, we examined the same reaction except with *Z*-**15** (Scheme 9a), prepared by cross-metathesis between **5a** and **14b** with catechothiolate **Ru-2**,[35] followed by phosphate formation (53% overall yield, >98:2 *Z*:*E*). We accordingly isolated (*R*,*R*)-**16** in higher yield (81%) and with improved stereoselectivity (89:11 dr, 96% ds). Notably, the same isomer was generated predominantly, regardless of *E*- or the *Z*-allylic phosphate being used.[36] To the best of our knowledge, the above processes are the first cases of catalytic S_N2'- and enantioselective allylic substitutions with an alkylzinc halide reagent.[32]

The alkenyl−B(pin) terminus was converted to allylic alcohol (*R*,*R*)-**17** and then its corresponding phosphate (*R*,*R*)-**18** (77% overall yield, >98:2 *E*:*Z*). Another multicomponent allylic substitution with allenyl−B(pin) **1b** and catalyzed by the Cu−H complex derived from (*S*)-**imid(S)-1b**, followed by oxidative workup, afforded γ-alkyl-substituted aldehyde (*R*,*R*,*S*)-**6** (65% yield, 96:4 dr). Ring-closing metathesis gave cyclohexenyl intermediate (*R*,*R*,*S*)-**7** in 93% yield (Scheme 9a). We were thus able to address every issue relating to absolute or relative stereochemical control by a blend of three different allylic substitutions, all facilitated by the Cu complex derived from **imid(S)-1b**.

2.8.3. A Cycloaddition That Generates the Desired Polycyclic Stereoisomer. To assemble the polycyclic core, we first opted for an intramolecular [4+2] cycloaddition[37] involving a 1,3-diazo-1,3-butadiene precursor (**20**, Scheme 9a). *N*-Guanidinyl acetal (*R*,*R*,*S*)-**19** was accessed by the use of a procedure[38] originally introduced for generating *N*-acyl-*N*,*O*-acetals (73% yield). Treatment of (*R*,*R*,*S*)-**19** with trifluoroacetic acid (110 °C, microwave, 1 h) and catalytic hydrogenation, however, furnished the undesired diastereomer **21** in 88:12 *exo*:*endo* selectivity (58% yield). Examination of molecular models pointed to considerable steric pressure in the *endo* transition state **20a**, favoring the *exo* alignment (i.e., favoring **20b** → **21**).

To achieve *endo* selectivity, we turned to a [3+2] cycloaddition strategy.[39] We reasoned that, to attain the proper orientation, the unfavorable *exo* pathway (**22a**) would have to bear substantial strain. We prepared the necessary *N*-benzyl hydrazone and heated it to 100 °C for 4 h, leading to **23**, which was directly subjected to catalytic hydrogenolysis, sodium methoxide, and cyanogen bromide,[40] respectively. The three-step/one-vessel protocol furnished the polycyclic product corresponding to the revised netamine C structure in 88% yield and >98:2 dr (Scheme 9a). The 10-step (eight-vessel) synthesis route (14% overall yield) was thus completed.

2.8.4. Synthesis of the Originally Proposed Netamine C. Comparison of the ^{1}H and ^{13}C NMR spectra of the above product showed it to be identical to the natural product, supporting Snider's proposed structural revision.[15] We sought to confirm this assignment further, highlighting the diastereodivergency of the approach, by synthesis and spectroscopic analysis of the originally proposed isomer (Scheme 9b).[14] Subjection of *E*-**15** to the aforementioned conditions, except with (*R*)-**imid(S)-1b**, afforded the alternative diastereomer (*S*,*R*)-**16** in 76% yield and 92:8 dr (99% ds); comparison of these data with those obtained when (*S*)-**imid(S)-1b** was used (76:24 dr) indicated that the reaction involving *E*-**15** and (*R*)-**imid(S)-1b** represents the matched combination. The derived alkenyl boronate was converted to (*S*,*R*,*S*)-**7** as described earlier (47% overall yield, 3 steps). The originally proposed netamine C stereoisomer[14] was obtained in 72% overall yield (for 3 steps) and as a single diastereomer by treatment of the latter aldehyde with hydrazine hydrate and concentrated HCl, followed by catalytic hydrogenolysis and cyanogen bromide (one-vessel protocol). When we instead used benzyl hydrazine in the reaction with (*S*,*R*,*S*)-**7**, there was no detectable conversion to the desired product, probably due to steric repulsion caused by the *n*-hexyl substituent (oriented toward the side chain). Spectroscopic analysis reconfirmed the stereochemical assignment.

3. CONCLUSIONS

The strategies introduced here represent an efficient, regio- and enantioselective way of preparing versatile, multifunctional organoboron compounds that can be used to prepare organic molecules that possess important biological activities. High efficiency was made possible by achieving high chemoselectivities, at times innately countering the desired sequence of events. Multi-gram quantities of the requisite sulfonate-containing imidazolinium salt **imid(S)-1b** can be accessed in four steps and 54% overall yield by a revised procedure developed as part of this study.[18] Furthermore, 2.0 mol% ligand loading suffices for reactions that are performed on gram scale.

We can only go as far as our catalyst takes us, and for this set of transformations several aspects of the NHC−Cu complex derived from **imid(S)-1b** carried us a significant distance. While other sulfonate bearing Cu complexes also afford unusually high S_N2' selectivity (compared to other NHC− or bisphosphine−Cu catalysts), a key distinction here is the subtle but crucial influence of the substitution pattern at one of the N-aryl moieties of the chiral ligand, allowing the rate of Cu−H addition to an allene to be faster than its reaction with an allylic phosphate.

The applications in multistep synthesis, aside from confirming that the approach is indeed readily applicable to preparation of relatively complex organic molecules, are noteworthy for several reasons. In the case of the linear fragment of pumiliotoxin B, the alkenyl−B(pin) group was first used to effect a diastereoselective coupling with an enantiomerically pure epoxide, and then the alkene terminus was transformed to a monosubstituted alkyne by a catalytic *Z*-selective cross-metathesis/elimination protocol. Sequences like this have not been widely used and underscore the considerable applicability of the poly-unsaturated organoboron products obtained. Netamine C and its diastereomer were synthesized by first converting the terminal alkene and then the alkenyl−B(pin) unit, both to an appropriate allylic phosphate in preparation for regio- and stereoselective allylic substitution.

The netamine C synthesis features three allylic substitutions, all uniquely facilitated by the *same* NHC−Cu complex. One allylic substitution provided access to 1,5-diene **5a** by a highly S_N2'-selective and enantioselective Cu−H-catalyzed process,

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another afforded (*R*,*R*)-**16** after a mild, yet sufficiently nucleophilic, alkylzinc bromide (formerly unknown), and a third delivered (*R*,*R*,*S*)-**6** through a Cu−H-catalyzed multicomponent transformation. The outcome of each C−C bond-forming process is catalyst-controlled, constituting a flexible and stereodivergent strategy for accessing every possible stereoisomeric combination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05465.

Experimental details for all reactions and analytic details for all products (PDF)

X-ray crystallographic data for **Cu−allyl-1b** (CIF)

X-ray crystallographic data for **8d** (CIF)

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Notes

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