Communication

Diastereo- and Enantioselective Synthesis of Homoallylic Amines Bearing Quaternary Carbon Centers

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Diastereo- and Enantioselective Synthesis of Homoallylic Amines Bearing Quaternary Carbon Centers.

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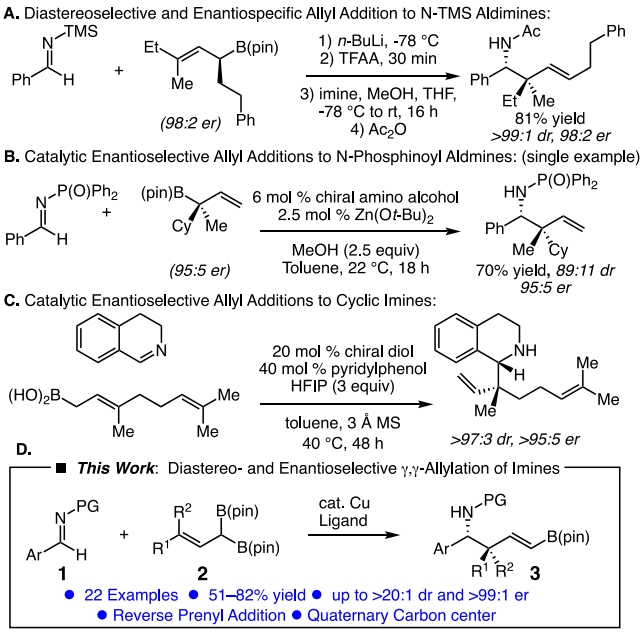
Supporting Information Placeholder

ABSTRACT: A Cu-catalyzed method for the efficient enantio- and diastereoselective synthesis of chiral homoallylic amines bearing a quaternary carbon and an alkenylboron is disclosed. Transformations are promoted by a readily prepared (phosphoramidite)–Cu complex, and involve bench-stable γ,γ-disubstituted allyldiborons and benzyl imines; products are obtained in up to 82% yield, >20:1 dr, and >99:1 er. Reactions proceed via stereodefined boron-stabilized allylic Cu species formed by an enantioselective transmetalation. Utility of the 1-amino-3-alkenylboronate products is highlighted by a variety of synthetic transformations.

Development of catalytic enantioselective methods for the synthesis of chiral amines and all-carbon quaternary stereocenters are both critical objectives in organic synthesis.[1,2] In this regard, the enantioselective allyl addition to imines with appropriately substituted C-based nucleophiles represents a direct route for the concomitant generation of both of these important chemical motifs.[3] While a number of catalytic methods have been reported for the enantio- and diastereoselective additions of γ-substituted allyl reagents (e.g., crotyl) to imines that afford secondary homoallylic amines bearing a vicinal tertiary stereocenter,[4,5] the corresponding quaternary stereocenter variants remain lacking. [6] One example involves the diastereoselective and enantiospecific addition of chiral allylborons to TMS-aldimines via the borinic ester recently reported by Aggarwal (Scheme 1A).[7] In contrast, only two catalytic protocols have been introduced for the enantio- and diastereoselective synthesis of homoallylamines bearing quaternary carbon stereocenters. First, chiral amino alcohols have been shown to catalyze an efficient enantio- and diastereoselective addition of a chiral allyl-B(pin) to aldimines that proceeds by stereospecific allyl transfer to the catalyst (Scheme 1B).[8] Secondly, chiral binaphthyl diols have been shown to catalyze the enantio- and diastereoselective additions of γ,γ-disubstituted allyl boronic acids to cyclic imines in high stereoselectivity (Scheme 1C).[9] Nevertheless, both catalytic protocols present limitations related to the requirement of either pre-formed

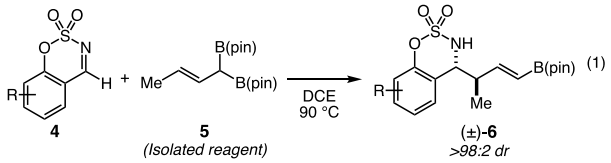
Scheme 1. Enantio- and Diastereoselective Additions to Imines with γ,γ-Disubstituted Allyl Reagents



enantioenriched γ,γ-disubstituted allylboron reagents or unstable achiral allyl boronic acids. To-date, metal-free catalytic methods have proven to be most effective for the enantioselective synthesis of quaternary carbon stereogenic centers in allylic nucleophile additions to imines. Such catalytic protocols possess mechanistic characteristics that maintain the *E* or *Z* alkene isomer of the allyl reagent.[8,9] In contrast, due to their configurational instability, reactions of most π-allylmetal complexes lead to poor diastereoselectivity or are limited to the synthesis of one stereoisomer.[10,11,12]

An emerging strategy for the construction of contiguous stereogenic centers via allylic nucleophile additions to C=O and C=N electrophiles involves the use of allylic

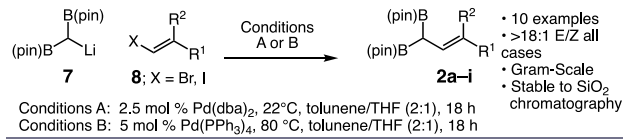
gem-diboronate esters. Murakami reported the in situ generation of these reagents via Pd- or Ru-catalyzed olefin isomerization, followed by enantio- and diastereoselective addition to aldehydes promoted by a chiral phosphoric acid.[13] Subsequently, Cho reported the diastereoselective addition of isolated allyldiboron ester **5** to a variety of cyclic sulfonyl imines, although, the report is limited to the *E*-crotyl reagent (Eq 1).[14]



4 **5** (*Isolated reagent*) (±)-**6** (*>98:2 dr*)

At this juncture, based on our previous work with 1,1-diborylalkanes,[15,16] we postulated that stereodefined γ,γ-disubstituted allyldiboron (e.g., **2**) would result in increased reagent stability, and their participation in enantioselective Cu-catalyzed additions to imines would result in the enantioselective synthesis of secondary homoallylic amines bearing a quaternary carbon stereogenic center (e.g., **3**) (Scheme 1D). A key aspect of this strategy requires reactions to proceed by enantioselective transmetalation through a chiral α-boryl–Cu–allyl nucleophile.

Scheme 2. Synthesis of γ,γ,-Disubstituted Allyldiboronate Esters [a]



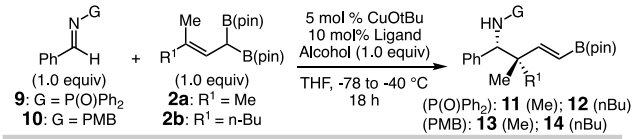
2a: (A) R^1= R^2 = Me (52% yield)
2b: (A) R^1= n-Bu, R^2 = Me (75% yield, gram scale)
2c: (B) R^1= $(CH_2)_2$OTBS, R^2 = Me (50% yield)
2d: (B) R^1= $(CH_2)_2$OTBS, R^2 = Et (32% yield)
2e: (A) R^1= $(CH_2)_2$Ph, R^2 = Me (63% yield)
2f: (B) R^1= $(CH_2)_2$Ph, R^2= Et (41% yield)
2g: (A) R^1= Cy, R^2= Me (72% yield)
2h: (A) R^1= C_3H_5, R^2= Me (58% yield)
E-**2i**: (A) R^1= Et, R^2= Me (51% yield)
Z-**2i**: (A) R^1= Me, R^2= Et (40% yield)

[a]See SI for details.

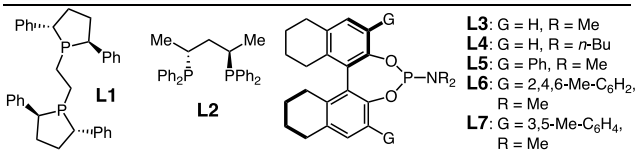
Successful implementation of our plan required the development of a general method for the synthesis of allylic *gem*-diboronate esters (e.g., **2**). To accomplish this goal, we hypothesized that the direct Pd-catalyzed cross coupling of lithiated organodiboron **7**, which can be prepared by deprotonation of diborylmethane with bulky lithium amide bases (LDA or LTMP) on gram-scale with readily available stereodefined vinyl halides would provide the most direct strategy for the synthesis of a variety of stereodefined bis-allylic 1,1-diborons. Building on work by Feringa, [17] we found a wide variety of stereodefined alkenyl halides undergo Pd-catalyzed cross coupling with organolithium **7**, to afford chromatographically stable stereodefined allyldiborons **2a–i** isolated in 32–75% yield (Scheme 2); for example, n-butyl **2b** is often isolated in up to 75% yield on a multigram-scale. As the synthesis of **2c** and **2e** illustrate, the presence of silyl ethers and aryl groups result in equally efficient coupling. The method can also be extended to alkenyl iodides containing α-branched alkyl groups (**2g–h**). Moreover, ethyl-substituted variants **2d**, **2f**, and *E*/*Z*-**2i** can be prepared efficiently.

Next, we began by identifying catalytic conditions for the enantioselective reaction of phosphinoylimine **9** with **2a** (Table 1). Investigation of a variety of bidentate and monodentate phosphine ligands (**L1–L5**, entries 1–5) revealed monodentate phosphoramidite **L4** to be the most effective, delivering **11** in 77% conv. and 85:15 er (entry 4). Similar low enantio- and diastereoselectivity was observed in reactions with Me/n-Bu reagent **2b** (entries 6–8), with **L5** affording **12** in 94% ^{1}H NMR yield, 1.1:1.0 dr, and 90:10 and 91:9 er (entry 8). In addition, phosphoramidite ligands **L6** and **L7** bearing 3,3' mesityl and 3,5-xylyl groups, delivered **12** in low dr but with an increase in enantioselectivity. At this point we hypothesized that the high enantioselectivity of each diastereoisomer of **12** afforded with **L7** is a result of a chiral (**L7**)-Cu-allyl formed in high er by an enantioselective transmetalation, but reacts with both prochiral faces of **9** with limited bias. Such an outcome would be consistent with the poor enantioselectivity observed in reverse prenyl additions (entries 1–5), and likely the result of non-selective binding of imine **9** to the Cu-allyl species. Changing the imine activating group to *p*-MeO-benzyl (PMB) **10**, which results in a less electrophilic imine but more Lewis basic nitrogen, resulted in marked improvement in dr. Treatment of **10** and **2b** with 5 mol % Cu-OtBu, 10 mol % **L7**, and 1 equivalent of MeOH at -40 °C for 18 h delivered **14** in

Table 1. Reaction Optimization of Enantio- and Diastereoselective Cu-Catalyzed Additions to Imines[a]



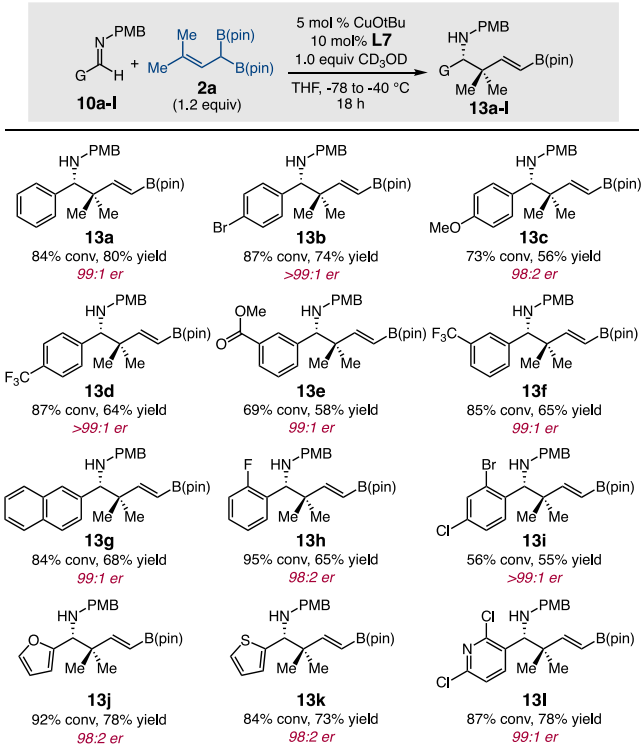
entry	R^1	Ligand	ROH	G	Yield(%); (dr)[b]	er[c]
1	Me	**L1**	MeOH	$P(O)Ph_2$	49	64:36
2	Me	**L2**	MeOH	$P(O)Ph_2$	45	53:47
3	Me	**L3**	MeOH	$P(O)Ph_2$	>98	83:17
4	Me	**L4**	MeOH	$P(O)Ph_2$	77	85:15
5	Me	**L5**	MeOH	$P(O)Ph_2$	54	54:46
6	n-Bu	**L3**	MeOH	$P(O)Ph_2$	66 (3.3:1)	78:22 (maj), 70:30 (min)
7	n-Bu	**L4**	MeOH	$P(O)Ph_2$	74 (2.4:1)	82:18 (maj), 80:20 (min)
8	n-Bu	**L5**	MeOH	$P(O)Ph_2$	94 (1.1:1)	90:10 (maj), 91:9 (min)
9	n-Bu	**L6**	MeOH	$P(O)Ph_2$	74 (2.4:1)	93:7 (maj), 85:15 (min)
10	n-Bu	**L7**	MeOH	$P(O)Ph_2$	74 (1:1.2)	97:3 (maj), 96:4 (min)
11	n-Bu	**L7**	MeOH	PMB	77 (>20:1)[d]	99:1
12	Me	**L7**	MeOH	PMB	36[e]	99:1
13	n-Bu	**L7**	CD_3OD	PMB	***84 (>20:1)***[f]	***99:1***
14	Me	**L7**	CD_3OD	PMB	***65***[f]	***99:1***



[a]Reactions performed under N_2 atmosphere. [b]Yield and diastereomeric ratios (dr) determined by analysis of 400, 500, or 600 MHz ^{1}H NMR spectra of crude reactions with hexamethyldisiloxane as internal standard. [c]Enantiomeric ratios (er) determined by HPLC or SFC analysis; see the SI for details. [d]15% proto-deboration of **2b**. [e]55% proto-deboration of **2a**. [f]<2% proto-deboration of **2a** or **2b**.

77% yield, >20:1 dr, and 99:1 er (entry 11). Furthermore, reaction of **2a** with PMB imine **10** under identical conditions resulted in **13** in 36% yield and 99:1 er (entry 12). In reactions of PMB imine **10** with both **2a** and **2b** it was noted that significant quantities (15–55%) of protodeborated allyldiboron is formed through competitive reaction of the allylic Cu with methanol. To suppress protonation

Scheme 3. Enantioselective Cu-Catalyzed Reverse Prenyl Addition to Aldimines[a–d]



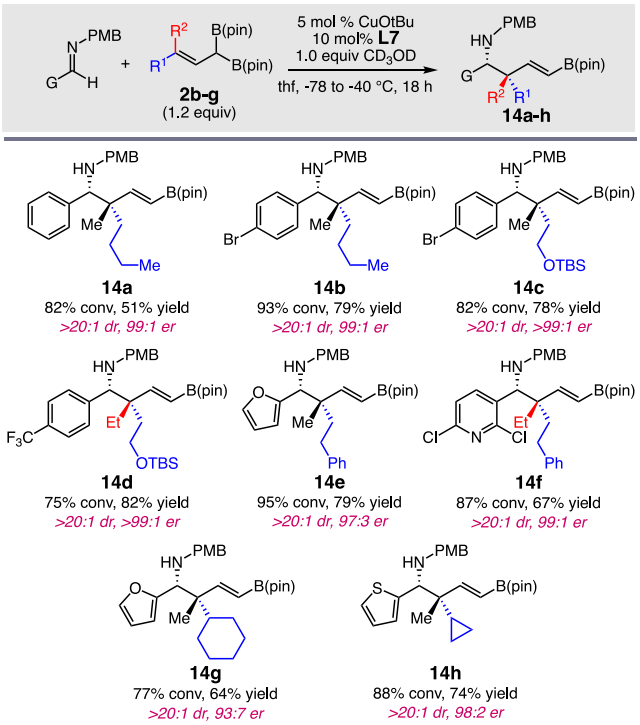
[a]Reactions performed under N_2 atmosphere. [b]Conversion determined by analysis of 400, 500, or 600 MHz ^{1}H NMR spectra of crude reactions with hexamethyldisiloxane as internal standard. [c]Enantiomeric ratios (er) determined by HPLC or SFC analysis; see the SI for details. [d]Yields of isolated product after SiO_2 chromatography and represent an average of at least two runs.

of the Cu-allyl species, we employed CD_3OD to utilize a deuterium isotope effect.[18] As illustrated in entries 13 and 14, reaction in the presence of CD_3OD results in an increase in yield, furnishing **14** in 84% yield (>20:1 dr, and 99:1 er), and **13** in 65% yield (99:1 er).

To investigate substrate scope of the allylic nucleophile addition reaction, we first focused on enantioselective reverse prenyl addition to aryl imines with allyldiboron **2a** (Scheme 4). The catalytic method can be used to prepare a wide array of secondary amines bearing an alkenylboron in good yield (>55%) and high selectivity (>98:2 er). Parent phenyl imine (**13a**), as well as aryl imines bearing electron-donating (**13c**), electron-withdrawing substituents (**13b**, **d–f**), and halogens (**13b**, **h–i**) in various positions are suitable substrates. Naphthyl-derived imines also undergo efficient and selective reverse prenyl addition (**13g**). As the synthesis of **13j–l** illustrates, use of heteroaryl imines, including pyridyl groups, results in equally efficient and enantioselective reactions.[19]

The catalytic method is equally effective for reactions of non-symmetric allyldiboron reagents **2b–j** with aryl imines (Scheme 4), providing stereoselective access to a range of complex homoallylic amines bearing a vicinal quaternary carbon stereogenic center, and a pendant alkenylboron group. Reaction of *E*-allyldiboron reagents that contain n-alkyl groups (**14a-b**), a pendant silyl ether (**14c-d**) or a homobenzyl unit (**14e-f**) react smoothly to furnish secondary amines bearing quaternary carbon stereogenic centers in good yield, dr, and er. Notably,

Scheme 4. Enantio- and Diastereoselective Cu-Catalyzed Synthesis of Quaternary Carbon Stereogenic Centers[a–d]



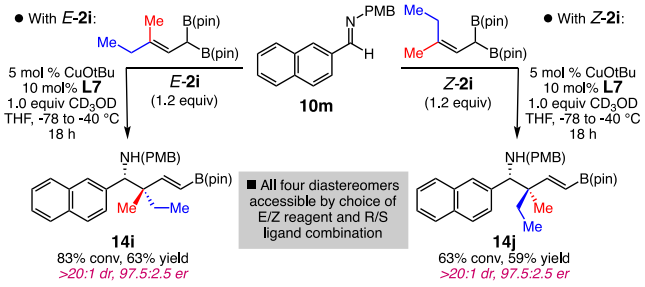
[a]Reactions performed under N_2 atmosphere. [b]Conversion and diastereomeric ratios (dr) determined by analysis of 400, 500, or 600 MHz ^{1}H NMR spectra of crude reactions with hexamethyldisiloxane as internal standard. [c]Enantiomeric ratios (er) determined by HPLC or SFC analysis; see the SI for details. [d]Yields of isolated product after SiO_2 chromatography and represent an average of at least two runs.

reaction of smaller 2-furyl derived-imine with **2e**, affords **14e** with excellent stereocontrol (>20:1 dr, and 97:3 er). Stereoselective synthesis of ethyl-substituted quaternary stereocenters can be achieved with high selectivity through the application of ethyl-derived *E*-allyldiborons **2d-f**; for example, secondary amines **14d** and **14f** are both isolated as single enantio- and diastereomers. Allyldiboron reagents containing more sterically congested α-branched alkyl groups participate under the reaction conditions, although, with mixed results. Cyclohexyl-substituted organodiboron reagent **2g** affords **14g** in 64% yield and >20:1 dr but 93:7 er. In comparison, a smaller cyclopropyl group (e.g., **2h**) results in a

restoration in selectivity (**14h**: 74% yield, >20:1 dr, and 98:2 er).

The efficient transfer of *E* and *Z* alkene stereochemistry from the allyldiboron to the product, indicated that the catalytic method could provide an effective strategy for the stereoselective synthesis of Me/Et quaternary carbon stereogenic centers. Potential diminution in selectivity could arise from poor enantioselective transmetalation and/or stereochemical isomerization of the transient allylic Cu species prior to C–C bond formation. As shown in Scheme 5, reactions of both *E*- and *Z*-**2i** were found to proceed stereospecifically with naphthyl imine **10m** to access both diastereoisomers in high dr and er. For example, Cu-catalyzed reaction of *E*-**2i** delivers *R,S*-**14i** in 63% yield, >20:1 dr, and 97.5:2.5 er, whereas, transformation of *Z*-**2i** results in *R,R*-**14j** in 59% yield, >20:1 dr, and 97.5:2.5 er. These results indicate that the reaction proceeds by an enantioselective transmetalation, followed by Cu-allyl addition to the imine, which is either faster than isomerization or nucleophilic addition via a diastereomeric Cu-allyl isomer. The same mechanism must also be operative for the reverse prenyl addition (Scheme 3).

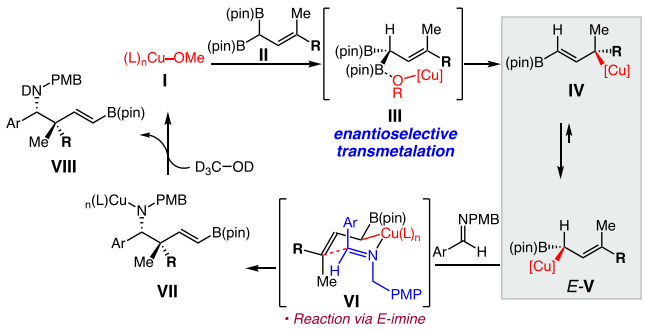
Scheme 5. Cu-Catalyzed Stereospecific Additions with *E*- and *Z*-Methyl/Ethyl AllylDiborons[a]



[a]See SI for details.

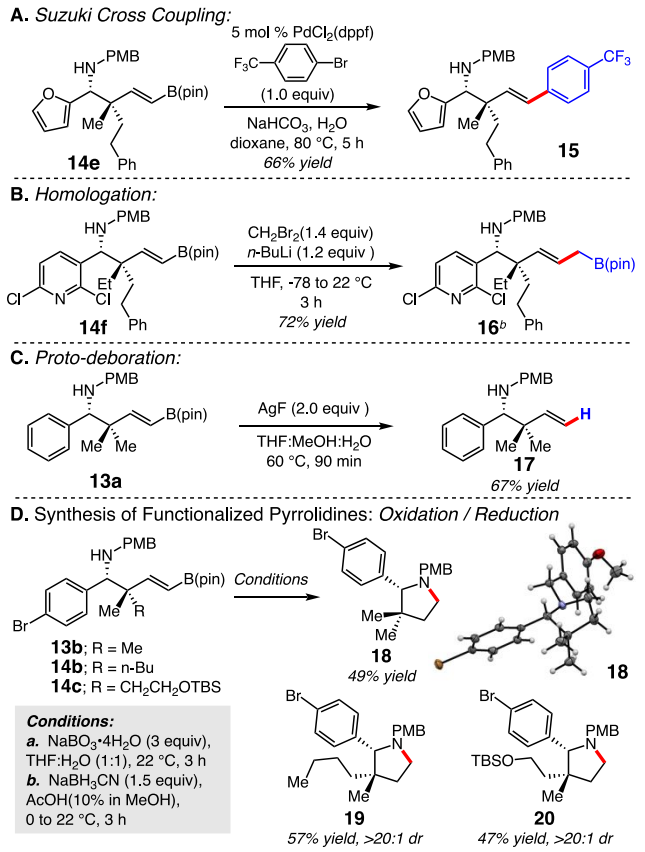
A proposed catalytic cycle and stereochemical model for the enantio- and diastereoselective synthesis of complex homoallylic amines is depicted in Scheme 6. In situ generated (L)-Cu–OMe (**I**) undergoes enantioselective transmetalation with allyldiboron **II** via **III** to generate enantioenriched allylic Cu species **IV**. The orientation of the B(pin) units will be positioned to minimize A(1,3)-strain. Isomerization to less congested and boron-stabilized allylic Cu *E*-**V** is followed by reaction with the *E*-PMB imine via 6-membered cyclic transition state **VI**. Coordination of the *E*-imine to (L)-Cu places both the aryl substituent and the PMB groups axial.[20] Furthermore, to minimize additional 1,3-diaxial interactions, the B(pin) unit is placed in the equatorial position. Following allyl transfer in a highly diastereoselective manner, CD_3OD (or MeOH) then releases the homoallylic amine **VIII** and regenerates (L)-Cu-OCD_3.

Scheme 6. Proposed Catalytic Cycle and Stereochemical Model



The secondary amines prepared through the Cu-catalyzed protocol are amenable to a range of subsequent chemical transformations (Scheme 7). For example, homoallylic amine **14e** undergoes efficient Suzuki-Miyaura cross coupling with *p*-CF_3-C_6H_4Br to afford alkenylarene **15** in 66% isolated yield. Allylboronic ester **16** can be efficiently prepared in 72% yield via the one carbon homologation of **14f**. Additionally, protodeboration of alkenylboronate **13a** proceeds smoothly in the

Scheme 7. Synthetic Utility of Products



[a]See SI for details. [b]Contains ~10% by-product that cannot be removed.

presence of AgF to furnish terminal olefin **17** in 67% yield.[21] Of note, this two-step process represents an example of a formal enantioselective reverse prenylation of an acyclic imine.[22] Finally, the secondary amines can be transformed into pyrrolidines by a two-step sequence. Treatment of alkenylboronates **13b**, **14b-c** with $NaBO_3$•$4H_2O$, results in conversion to the corresponding cyclic hemiaminal, which can be reduced with $NaBH_3CN$

to afford functionalized pyrrolidines **18**, **19** and **20** in 49%, 57%, and 47% yield, respectively over two steps (Scheme 7D). Absolute stereochemistry of the products was determined through X-Ray crystallographic analysis of dimethyl-substituted pyrrolidine **18**, which revealed the stereochemical orientation of the secondary amine to be *R* (Scheme 7D). Furthermore, examination of pyrrolidine **19** by 1D-NOESY confirmed a cis-relationship between the benzylic methine and adjacent methyl group.

In conclusion, we have developed the first catalytic enantio- and diastereoselective process for the synthesis of complex homoallylic amines via the reaction of allyldiboronates with aldimines. A (phosphoramidite)-Cu catalyst promotes enantioselective transmetalation, generating a highly reactive α-boryl-Cu-allyl species. This nucleophile reacts efficiently with a variety of aryl aldimines to generate enantioenriched homoallylic amines in excellent dr and er, bearing either *gem*-dimethyl substitution or a quaternary carbon stereogenic center. Significantly, both product diastereoisomers are rendered accessible by choice of *E*- and *Z*-allyldiboron stereochemistry. Furthermore, utility of the products is highlighted through representative transformations that included cross coupling, homologation, and conversion to functionalized pyrrolidines. Further catalytic stereoselective reactions of allyldiborons are ongoing.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

Authors declare no competing financial interests.

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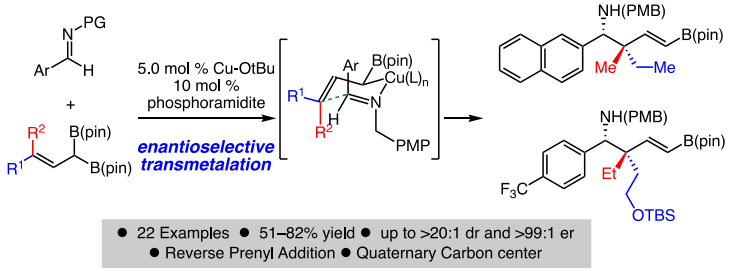

● 22 Examples ● 51–82% yield ● up to >20:1 dr and >99:1 er
● Reverse Prenyl Addition ● Quaternary Carbon center