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Copper-Catalyzed Diastereo-, Enantio-, and (*Z*)-Selective Aminoallylation of Ketones through Reductive Couplings of Azatrienes for the Synthesis of Allylic 1,2-Amino Tertiary Alcohols

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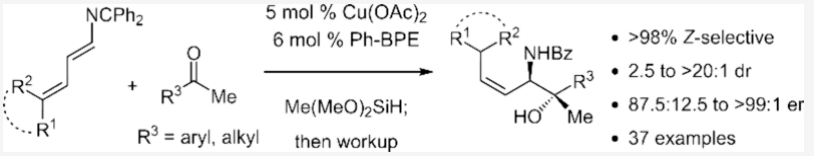

ABSTRACT: We introduce a method for the (*Z*)-selective aminoallylation of a range of ketones to prepare allylic 1,2-amino tertiary alcohols with excellent diastereo- and enantioselectivity. Copper-catalyzed reductive couplings of 2-azatrienes with aryl/alkyl and dialkyl ketones proceed with Ph-BPE as the supporting ligand, generating *anti*-amino alcohols with >98% (*Z*)-selectivity under mild conditions. The utility of the products is highlighted through several transformations, including those that leverage the (*Z*)-allylic amine moiety for diastereoselective reactions of the alkene. Calculations illustrate Curtin−Hammett control in the product formation over other possible isomers and the origin of (*Z*)-selectivity.

1. INTRODUCTION

Carbonyl allylation is a cornerstone of chemical synthesis, facilitating access to homoallylic alcohols, valuable building blocks for the assembly of complex molecules.[1] Several of these transformations afford enantioenriched products with vicinal stereogenic centers, bearing either *anti* or *syn* relative stereochemistry, through the use of substituted allyl nucleophiles. Within this group, however, few reactions also allow for the selective formation of a (*Z*)-alkene. Such an allylation requires the use of a chiral nucleophile bearing a multisubstituted olefin. Most instances wherein a (*Z*)-homoallylic alcohol with two stereogenic centers is formed by this strategy utilize a preformed allyl metalloid[2] (or metal[3]), which is prepared in an enantiospecific manner or less frequently in an enantioselective reaction (Scheme 1).[4,5] Alternatively, enantioenriched allylic electrophiles may be catalytically and enantiospecifically transformed to allyl metal nucleophiles for subsequent carbonyl addition.[6,7]

In comparison, there is a dearth of methods for the catalytic enantioselective generation of an allyl metal that is capable of undergoing direct carbonyl addition. An example from Sato and co-workers in 2007 is the only extensive study in this regard (Scheme 1), where they demonstrated an N-heterocyclic carbene−Ni-catalyzed reductive coupling of dienes with aldehydes.[8,9] Although unsymmetrical dienes react with good regioselectivity, it is only 1,4-diphenylbutadiene that leads to high enantioselectivity. Allylboron reagents that undergo catalytic enantioselective addition to aldehydes and allow for retention of stereochemistry of an attached (*Z*)-alkene have also been recently developed.[10] But notably, all allylations to afford homoallylic alcohols containing (*Z*)-alkenes and vicinal stereogenic centers have been carried out only with aldehydes as the electrophile.

Aminoallylation, an important class of carbonyl allylations, has gained recent attention as a means to prepare 1,2-amino alcohols enantioselectively (Scheme 1). Both the Krische[11] and Sieber[12] groups have utilized *N*-substituted allenes as an umpolung approach toward *β*-amino alcohols, the latter illustrating *syn*- or *anti*-selective processes in couplings with aryl/alkyl ketones through CuH catalysis;[13,14] however, these methods lead to products containing terminal olefins.

The Buchwald group has illustrated the feasibility of (*Z*)-selective allylation with chiral CuH catalysts, showing that terminal aryl dienes undergo addition to benzimidazole electrophiles with Ph-BPE as the supporting ligand for copper (Scheme 1).[15] Inspired by that disclosure, we have developed a (*Z*)-selective aminoallylation of ketones through reductive coupling of 2-azatrienes, a new class of enamine umpols reported by our laboratory.[16] Reactions are highly stereoselective and take place with both aryl/alkyl and dialkyl ketones, significantly expanding the chemical space available within enantioenriched 1,2-amino tertiary alcohols that may be readily accessed through C−C bond formation.[12,17] Function-

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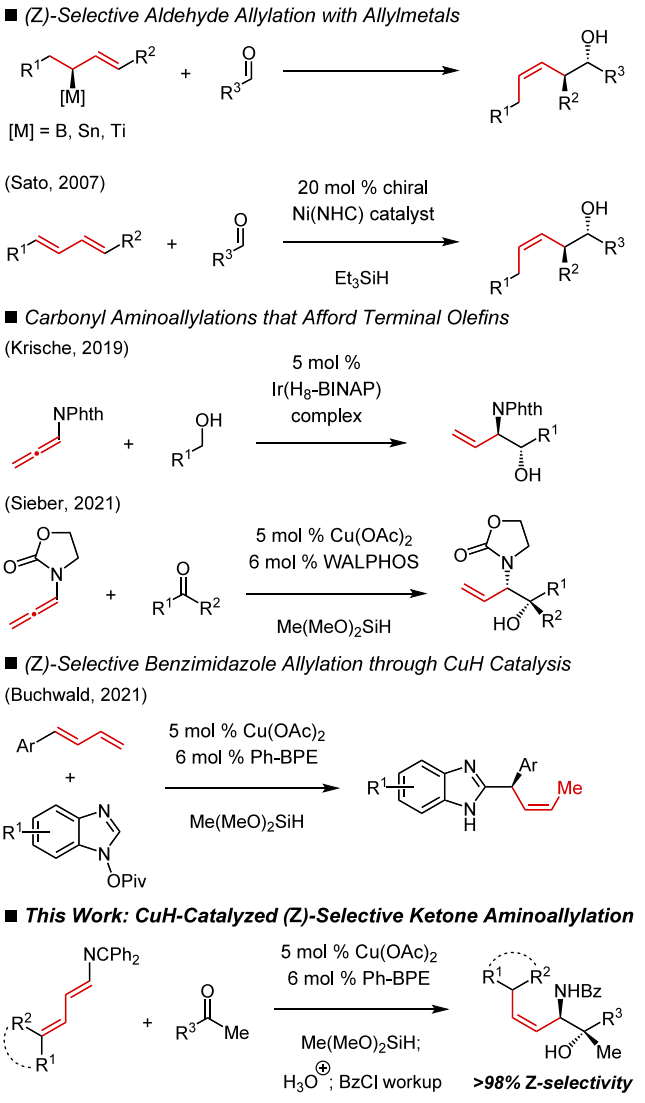
Scheme 1. Stoichiometric Carbonyl and Catalytic Enantio- and (Z)-Selective Allylation Reactions

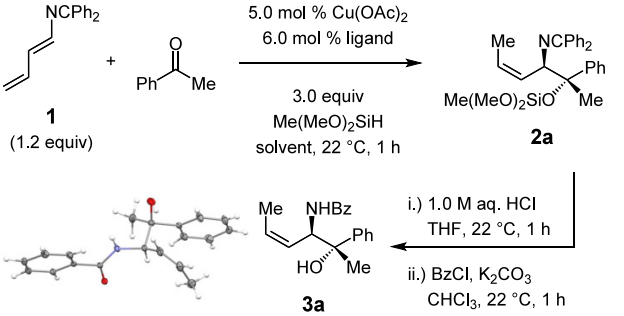


alizations of the products, including those that take advantage of the amino alcohol's nearby (Z)-alkene, highlight the synthetic utility of this method.

2. RESULTS AND DISCUSSION

2.1. Method Development. We first explored the feasibility of ketone aminoallylation by reductive coupling of azatriene **1** with acetophenone under conditions similar to our previously reported azatriene−imine couplings that afford *anti*-1,2-diamines bearing an (*E*)-alkene (Table 1, entry 1).[16] Compared to those reactions with Cu(Ph-BPE) as the catalyst, in THF, the ketone addition furnishes imino silyl ether **2a** with >98% (*Z*)-selectivity as a 13:1 mixture of diastereomers favoring the *anti*-isomer. For ease of handling and isolation, the imine and ether of **2a** were hydrolyzed to the corresponding hydroxy ammonium salt, which was converted to its benzamide derivative to afford **3a** (70% isolated yield, 99:1 er). The stereoisomer identity was confirmed by X-ray crystallography. We examined other solvents to improve the diastereoselectivity (entries 2−4). Although most solvents do lead to formation of the amino alcohol as a single diastereomer, they lower the reactivity of the catalyst; however,

Table 1. Optimization of (Z)-Selective Ketone Aminoallylation[a]



entry	ligand	solvent	% conv[b]	Z:E[c]	dr[c]	er[d]
1	Ph-BPE	THF	83 (70)[e]	>20:1	13:1	99:1
2	Ph-BPE	Et_2O	68	>20:1	>20:1	nd
3	Ph-BPE	CyH	72	>20:1	>20:1	nd
4	Ph-BPE	toluene	83 (72)[e]	>20:1	>20:1	98:2
5	BINAP	toluene	73	>20:1	>20:1	95:5
6	SEGPHOS	toluene	65	5:1	>20.1	98:2
7[f]	DTBM-SEGPHOS	toluene	52	1:4	3:1	40:60
8	BDPP	toluene	90	1:1	17:1	nd
9	SL-J001−1	toluene	83	3:1	7:1	nd
10	SL-J002−1	toluene	89	1:2	4:1	nd

[a]Transformations run under N_2 with 0.2 mmol acetophenone; see the Supporting Information for experimental details. [b]Consumption of acetophenone as analyzed by 500 MHz 1H NMR spectroscopy with an internal standard. [c]Analysis for **2a** as determined by 500 MHz 1H NMR spectroscopy of the unpurified mixture. [d]Determined by HPLC analysis of purified (Z)-**3a**. [e]Isolated yield of **3a**. [f](E)-**2a** formed in >20:1 dr; 22.5:77.5 er of (E)-**3a**. nd = not determined.

toluene affords similar conversion and yield of **3a** (72% yield) as THF while improving diastereoselectivity (>20:1 dr) and maintaining perfect (*Z*)-selectivity (entry 4). As the enantioselectivity was only slightly diminished (98:2 er) compared to THF, we elected to move forward with the entry 4 conditions as our optimized reaction parameters. Notably, the minor diastereomer of **3a** is also formed with high enantioselectivity (97:3 er), another significant departure from Cu(Ph-BPE)-catalyzed reductive couplings of azatrienes and imines, where the minor diastereoisomer was nearly racemic. This finding further indicates a significant mechanistic difference in imine and ketone additions with this catalyst.[18]

Intriguingly, most other phosphine ligands lead to low selectivity for olefin stereochemistry, at best moderately favoring the (*Z*)- or (*E*)-alkene (Table 1, entries 6−10). We did discover, however, that BINAP was a considerably effective ligand for promoting the azatriene−acetophenone reductive coupling (entry 5), with the amino alcohol being formed as a single diastereomer in 95:5 er. Although reactivity and enantioselectivity are slightly lower with BINAP − the primary reason we did not proceed with BINAP as our ligand of choice for developing reaction scope − the lower cost of BINAP compared to Ph-BPE[19] and its good performance level should be considered by those wishing to apply this methodology in synthesis.

We subsequently examined the addition of azatriene **1** to several ketones, beginning with variation of the arene within aryl/alkyl ketones (Scheme 2). The reductive coupling works well with methyl ketones whose aryl group bears a number of substitution patterns and spans a range of electronically

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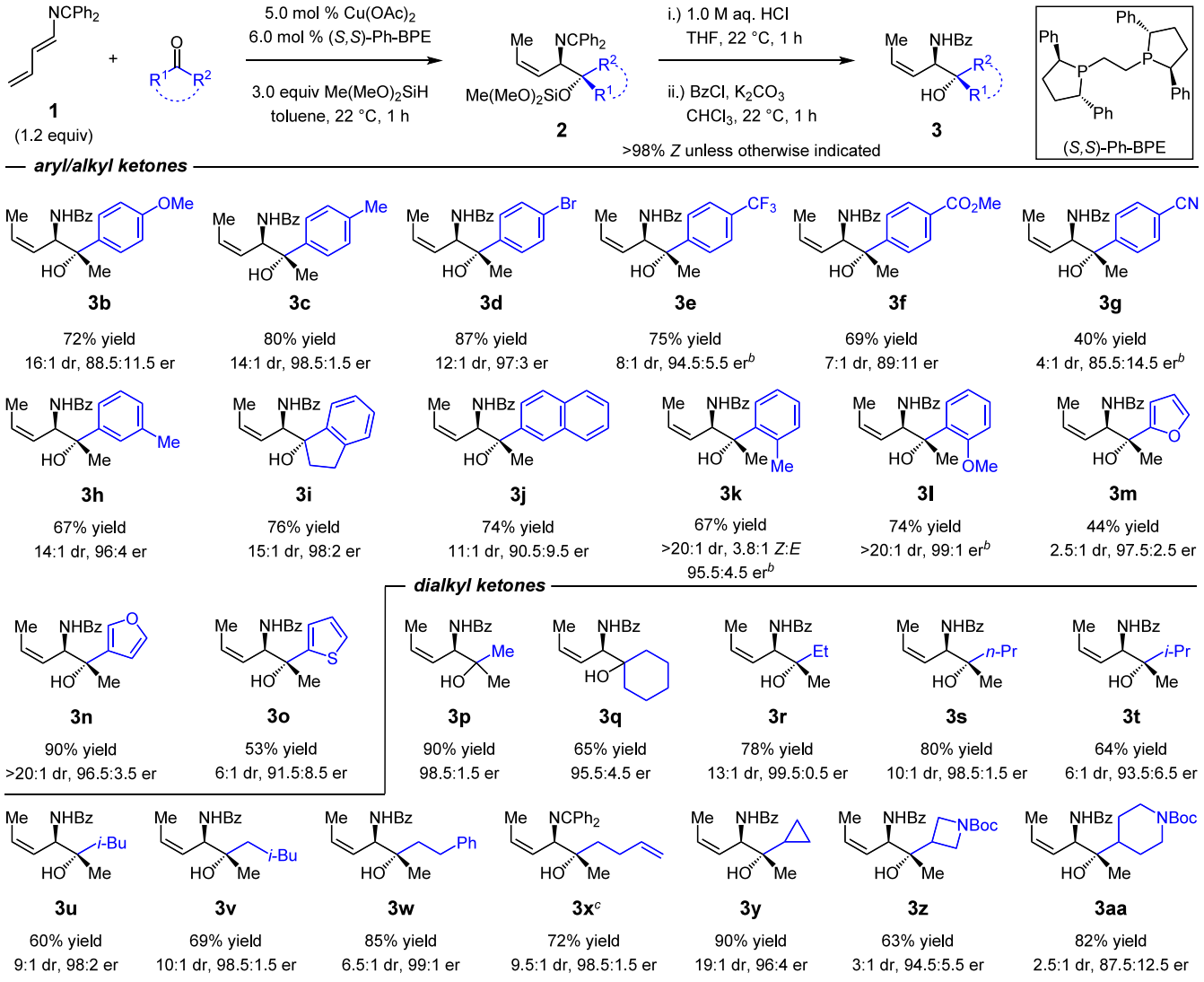
Scheme 2. Ketone Scope in (*Z*)-Selective Reductive Aminoallylations with Azatriene 1a[a]



[a]Diastereromeric ratios determined for compound **2** prior to purification; enantiomeric ratios determined for compound **3** after purification. Yields reported are for a mixture of diastereomers in the majority of cases; see the Supporting Information for details. [b]Overlap of minor peaks in the HPLC trace may impact the er determination. [c]Instead of the standard workup, the silyl group was cleaved with a solution of NH_4F in methanol while retaining the imino protecting group.

activating and deactivating groups (**3b**–**l**); however, more electron-poor ketones engender lower conversion to product due to competitive ketone reduction (**3g**). Stereoselectivities are often high although they are affected by the ketone's electronics with both diastereoselectivity and enantioselectivity maximizing for the more electron-neutral ketones. Electron-rich ketones often lead to high diastereoselectivity as well but lower enantioselectivity (16:1 dr, 88.5:11.5 er for **3b**) whereas more electron-poor ketones lead to lowering of both stereoselectivity metrics (compare **3d**–**g**). Although the trends seem clear that diastereo- and enantioselectivity both decrease as the ketones become more electron-rich or electron-poor from acetophenone, compared to our (*E*)-selective azatriene reductive couplings with aldimines,[16] where enantioselectivity was uniformly high but diastereoselectivity modulated similarly with respect to electrophile electronics, the linear free energy correlations with these ketone data are moderate.[20]

Reaction of *m*-methyl acetophenone furnishes tertiary alcohol **3h** with 14:1 dr and 96:4 er, and a naphthyl ketone affords **3j** in 11:1 dr and 90.5:9.5 er. The *o*-methoxyphenyl-containing **3l** is obtained as a single diastereomer in 99:1 er, whereas its *o*-tolyl counterpart (**3k**) is formed in 7:1 dr with slightly lower enantioselectivity; the steric hindrance of this ketone also interestingly leads to an appreciable quantity of (*E*)-alkene isomer (3.8:1 *Z*:*E*). The cyclic ketone 2-indanone allows for amido alcohol **3i** to be isolated in 15:1 dr and 98:2 er. In comparison, acyclic ketones that are comprised of alkyl groups larger than methyl are poorly reactive. For example, propiophenone undergoes only 40% conversion to the desired amino alcohol, which is formed in a 2:1 *Z*:*E* ratio. Benzophenone addition affords only the (*E*)-alkene of the amido alcohol (57% yield), further substantiating that the sterics of the ketone impact *Z*/*E*-selectivity.

Heteroaryl ketones can be coupled with azatriene **1** (amido alcohols **3m**–**o**). The position of the acetyl group on the heterocyclic ring can have a profound effect. The 3-furyl ketone addition is both highly diastereo- and enantioselective (>20:1 dr, 96.5:3.5 er for **3n**) but the coupling with the 2-furyl

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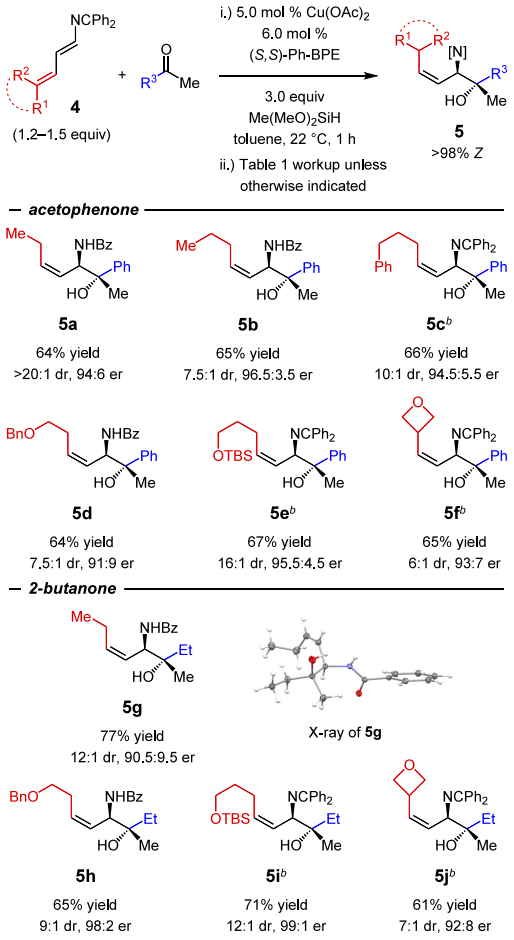
ketone leads to lower diastereoselectivity (2.5:1 dr, 97.5:2.5 er for **3m**).

We then investigated reactions with dialkyl ketones (Scheme 2). Transformations of this ketone class were largely unsuccessful in our prior Cu-catalyzed azadiene reductive couplings, with only acetone participating after extensive reaction reoptimization over the aryl/alkyl ketone conditions.[21] Work from the Sieber laboratory has also illustrated the challenge imposed by aminoallylations of dialkyl ketones.[12] We were thus pleased to find that addition of acetone and cyclohexanone proceeded smoothly under identical conditions to acetophenone coupling, affording amido alcohols **3p** and **3q** in 98.5:1.5 and 95.5:4.5 er, respectively; the reactions occur with complete (*Z*)-selectivity for the olefin. Myriad other ketones that give rise to a second stereogenic center also undergo aminoallylation efficiently and with moderate to excellent diastereo- and enantioselectivities (**3r**−**aa**). For instance, 2-butanone yields tertiary alcohol **3r**, where the catalyst has effectively differentiated between the methyl and ethyl groups of the ketone to deliver high stereoselectivity (13:1 dr and >99:1 er). Alkyl chains longer than ethyl and those that are branched also deliver good enantioselectivity of the amido alcohol products (93.5:6.5 to 99:1 er, **3s**−**x**) but diastereoselectivity is diminished largely as a function of size (*vide infra*). Ketones with α-cycloalkanes take part in the aminoallylation, and the reaction is tolerant of nitrogen heterocycles such as azetidines and piperidines (**3y**−**aa**). As with isopropyl methyl ketone (**3t**), the α-branching leads to modest diastereoselectivity but reasonable to good enantioselectivity. One fairly different and obvious exception is cyclopropyl methyl ketone, whose aminoallylation affords **3x** with excellent stereoselectivity (19:1 dr, 96:4 er).

We next turned our attention to the azatriene scope for reductive couplings with both acetophenone and 2-butanone that would yield amino alcohols bearing (*Z*)-alkenes with several different alkyl substituents (Scheme 3). Linear (**5a**−**e**) azatrienes couple with acetophenone to give reasonable yields and stereoselectivities of the amino alcohol products. Benzyl (**5d**) and silyl ethers (**5e**) are tolerated. Geminal substitution at the azatriene's 6-position is permissible in the form of a cyclic moiety if reductive coupling is accompanied by a significant decrease in angle strain; oxetane-containing **5f** was obtained in 6:1 dr and 93:7 er. Substituted azatrienes also undergo couplings with 2-butanone (**5g**−**j**) with amino alcohols furnished in good stereoselectivities. In each case, the olefin is generated exclusively as the (*Z*)-isomer. X-ray crystallographic analysis of **5g** confirmed that substituted azatrienes **4** and dialkyl ketones couple to afford the same major stereoisomer as acetophenone additions to terminal azatriene **1**.

2.2. Synthetic Utility of Amino Alcohol Products. The synthetic value of the (*Z*)-allylic 1,2-amino alcohol derived products is illustrated in Scheme 4 in a number of ways. First, the (*Z*)-stereochemistry of the olefin unit enables diastereoselective functionalizations through minimization of allylic strain. Although epoxidation of amido alcohol **3a** with *m*-CPBA affords **7** in 58% yield and 5.5:1 dr, conversion of the hydroxyl group to its trimethylsilyl ether (**6**), subsequent treatment with *m*-CPBA, and desilylation (NH_4F) allows for installation of the epoxide with 13:1 diastereoselectivity (81% yield of **7** over three steps). We speculate that competing directing effects from the amide and the hydroxyl group in **3a** diminish diastereoselectivity and that direction occurs solely

Scheme 3. Azatriene Scope in Additions to Acetophenone and 2-Butanone[a]



[a]Diastereromeric ratios determined for product of the reaction, prior to workup and purification; enantiomeric ratios determined for compound **5** after purification. Yields reported are for a mixture of diastereomers; see the Supporting Information for details. [b]Silyl group cleaved with a solution of NH_4F in methanol.

from the carbonyl of amide **6**.[22,23] Bromocyclization of **3a** takes place with high efficiency, delivering oxazoline **8** in 97% yield (6.5:1 dr).

Preparation of oxygen heterocycles or carbocycles bearing vicinal amino alcohols is also readily achieved. Dihydropyran **9** is generated in 64% yield (two steps) from amido alcohol **3a** by formation of the requisite allyl ether and treatment with the Hoveyda−Grubbs second generation catalyst (**Ru**−**I**). Cyclohexene **10** can be formed in 74% yield from a similar ring-clsoing metathesis of imino alcohol **3x**.

Finally, treatment of amido alcohol **3a** with thionyl chloride allows for cyclization to form oxazoline **11** with stereochemical inversion at the carbinol (70% yield),[12,24,25] providing a pathway to access (*Z*)-allylic *syn*-amino alcohols. In total, the transformations in Scheme 4 are illustrative of the potential the (*Z*)-allylic amino alcohol products hold for the preparation of complex fragments for downstream synthesis.

2.3. Computational and Experimental Investigations of Reaction Mechanism. We next sought to gain a better understanding of the factors contributing to the unusual (*Z*)-selectivity and other stereochemical aspects of the reaction. We imagined the most likely scenario for (*Z*)-selective allylation

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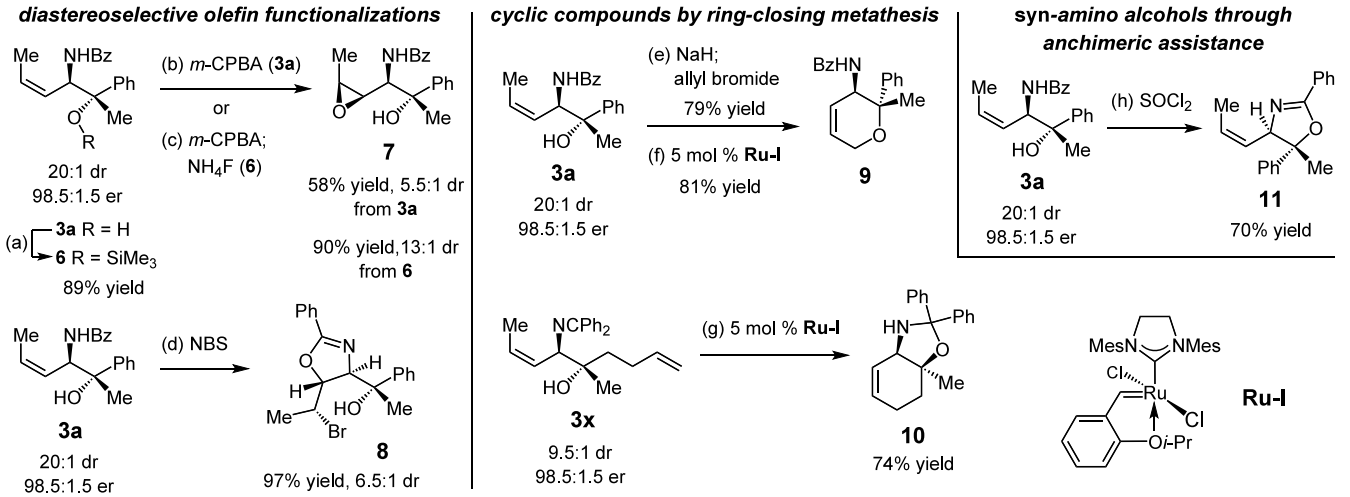
Scheme 4. Synthesis Potential of (*Z*)-Allylic Amino Tertiary Alcohols



[a]1.5 equiv Me_3SiOTf, 2.1 equiv 2,6-lutidine, CH_2Cl_2, 22 °C, 2 h. [b]1.1 equiv *m*-CPBA, 1.1 equiv $NaHCO_3$, CH_2Cl_2, 22 °C, 24 h. [c]1.1 equiv *m*-CPBA, 1.1 equiv $NaHCO_3$, CH_2Cl_2, 22 °C, 24 h; NH_4F, MeOH, 22 °C, 1 h. [d]1.2 equiv NBS, CH_2Cl_2, − 78 °C, 4 h. [e]10 equiv NaH, 2.0 equiv allyl bromide, THF, reflux, 4 h. [f]5.0 mol % **Ru−I**, benzene, 22 °C, 10 h. [g]5.0 mol % **Ru−I**, CH_2Cl_2, 22 °C, 18 h. [h]1.2 equiv $SOCl_2$, CH_2Cl_2, 0 to 22 °C, 10 h.

would involve a closed transition state for carbonyl addition wherein the *cis* olefin would arise from a pseudoaxial alkyl group of the allylcopper. Accordingly, we envisioned the catalytic cycle illustrated in Figure 1. Hydrocupration of

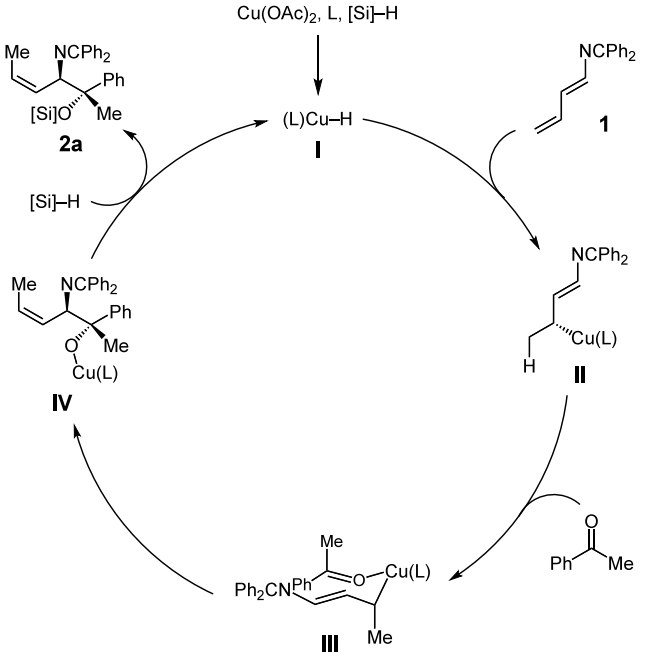


Figure 1. Proposed catalytic cycle for enantio-, diastereo-, and (*Z*)-selective ketone aminoallylation.

azatriene **1** with the chiral CuH catalyst **I** leads to iminoallylcopper **II** (**IN-9** in Figure 2 below). Complexation of acetophenone to **II** then affords **III** with its pseudoaxial methyl group. Zimmerman−Traxler-like addition (transition state shown in Figure 3A below) furnishes copper alkoxide **IV**, which may turn over with silane to deliver product **2a** and regenerate CuH **I**.

We first investigated this proposal computationally, which revealed that Curtin−Hammett kinetics are operative in the ketone aminoallylation with Cu−Ph-BPE (Figures 2 and 3). The calculations show that hydrocupration of azatriene **1** is highly exergonic and selective for insertion to the terminal double bond's *Si*-face (compare **IN-1** to **IN-2** via **TS-1−2** and **IN-10** to **IN-9** via **TS-9−10**, Figure 2); however, the facial selectivity for this step is irrelevant due to rapid equilibration of the two allylcopper stereoisomers via copper migration along the hydrocarbon chain. Copper 1,3-shifts, such as **IN-2** to **IN-3** via Cu−π-allyl transition state **TS-2−3**, take place, which ultimately put the metal at the benzhydryl position (**IN-5** and **IN-6**). This occurrence effectively erases the catalyst differentiation of the azatriene stereotopic faces in the hydrocupration step by ablating stereochemistry in the hydrocarbon chain: **IN-5** and **IN-6** are connected by a simple rotation about the C−N bond (**TS-5−6**), enabling a facial switch of copper along the azaallyl chain. A series of similar, diastereomeric 1,3-shifts allow copper migration to **IN-9**, which has nearly identical free energy to **IN-2**. Thus, our proposal that azatriene hydrocupration could generate iminoallylcopper **II** (Figure 1) is plausible but the stereoisomer depicted is neither formed kinetically nor is it thermodynamically favored.

It is notable that a slightly alternative pathway appears to be energetically accessible. Rather than 1,3-shift from **IN-3** to benzhydryl copper **IN-5** through **TS-3−5** (−14.0 kcal·mol^{-1}), a 1,2-shift to azomethine ylide **IN-4** via **TS-3−4** (−14.8 kcal·mol^{-1}) may proceed followed by a barrierless 1,2-shift to **IN-5**. The reciprocal barrier **TS-7−8** to afford azomethine ylide **IN-7** from **IN-6** is more favorable (−17.0 kcal·mol^{-1}) than the corresponding 1,3-shift of **IN-6** to **IN-8** through **TS-6−8** (−14.1 kcal·mol^{-1}).

All told, this dynamic equilibrium has a highest calculated barrier of 12.6 kcal·mol^{-1} (**IN-2** to **TS-5−6**). Significantly, the transition state energy for **TS-5−6** (−10.8 kcal·mol^{-1}) is far less than the lowest energy transition state for the addition of any hydrocupration intermediate to acetophenone (Figure 3), making the conversion of allylcopper **II** to copper alkoxide **IV** via addition mode **III** conceivable (Figure 1).

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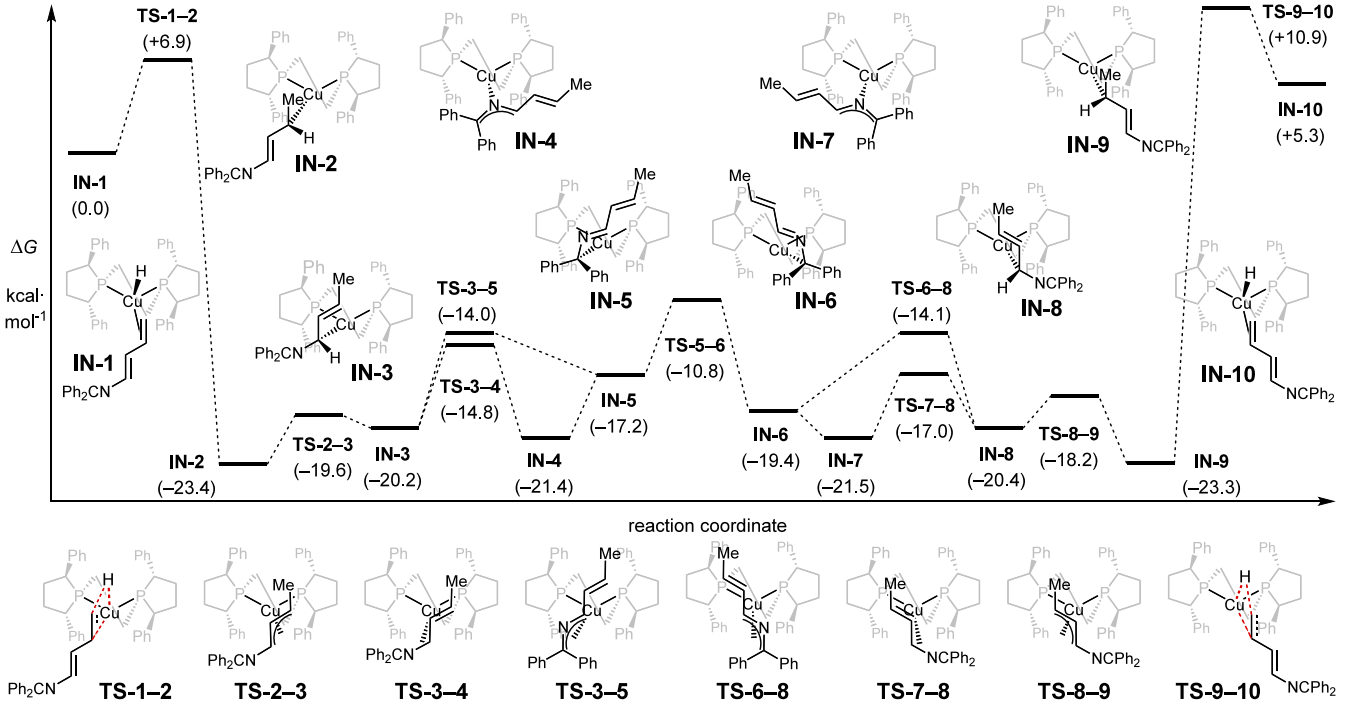

Figure 2. Calculated pathway for (Ph-BPE)CuH migratory insertion to azatriene **1** and subsequent copper migration.

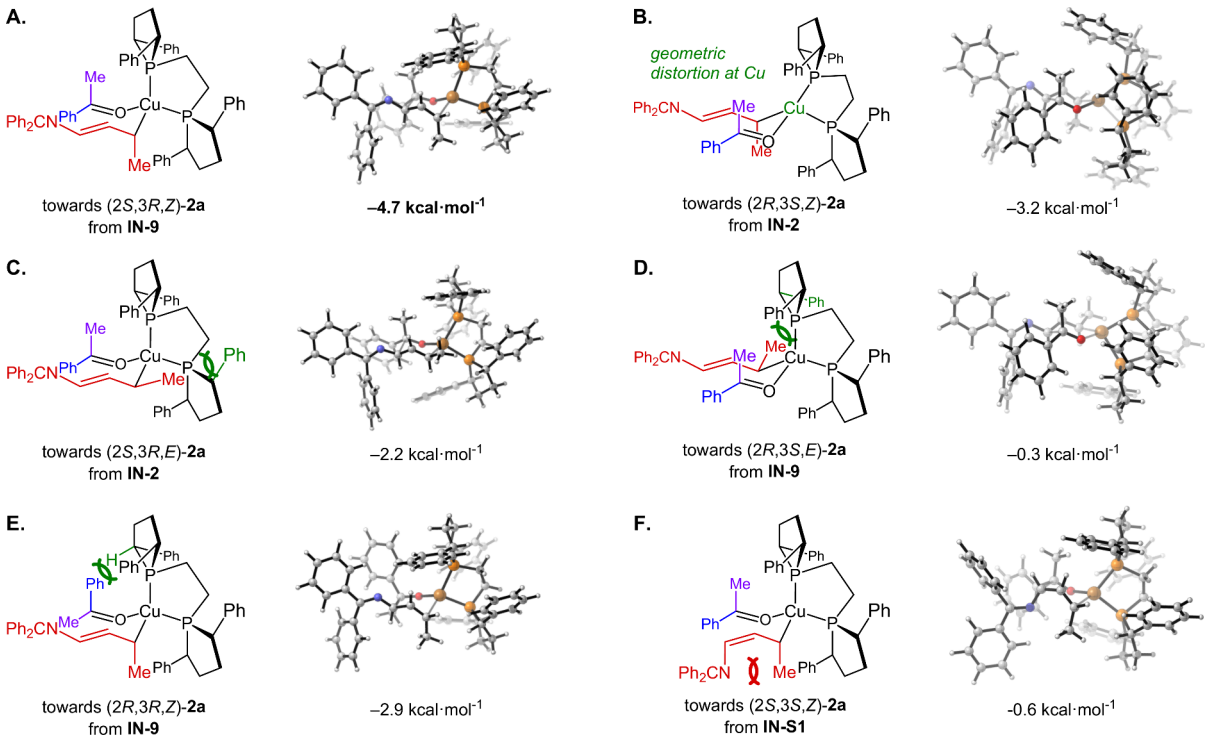

Figure 3. Calculated transition states for aminoallylation of acetophenone. (A) Energetically favored pathway that delivers the observed product major isomer. (B) Toward the enantiomer of the major product. (C–D) Generation of *anti*-diastereomer enantiomers of (*E*)-**2a**. (E–F) Formation of *syn*-diastereomers of (*Z*)-**2a**.

We then considered several possible ketone addition models from the various intermediates in Figure 2 and many others, including direct stereoretentive or stereoinvertive additions from alkenyl isomers of α-iminocopper species (e.g., the *E* isomer of **IN-3**), γ-aminoallylations from **IN-5**, and open transition states such as from the (*Z*)-alkenyl isomer of azomethine ylide **IN-4**. All proved to be higher energy than a closed γ-aminoallylation from either **IN-2** or **IN-9**. A number of the most relevant such transition structures for the C–C bond-forming step are illustrated in Figure 3.[26]

The identified major stereoisomer of the coupling product **2a**, determined by X-ray crystallography of its benzamide derivative **3a** (Table 1), is correctly predicted by the transition structure in Figure 3A, wherein **IN-9** binds the ketone, placing

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its aryl group in the pseudoequatorial position. With the imino group also occupying a pseudoequatorial position, the methyl group at the stereogenic carbon is disposed pseudoaxally to avoid negative steric interactions with the ligand (Figure 3D), thereby affording the (*Z*)-olefin of the product ($\Delta G^{\ddagger}$ = −4.7 kcal·mol^{-1}). The transition state leading to the observed enantiomer of (*Z*)-**2a** from **IN-2** is higher in energy possibly due to the distorted tetrahedral geometry at copper, which may lessen unfavorable steric interactions (Figure 3B). Enantiomer formation is still calculated to be lower compared to *E* isomer synthesis, as the pseudoequatorial group clashes with one of the phenyl groups (green) of the ligand (H−H distance of 2.14 Å, Figure 3C); the transition state leading to its enantiomer has a similar steric interaction (H−H distance of 2.15 Å, Figure 3D). Related transition states that afford the *syn*-diastereomers of **2a**, either epimeric at the carbinol (repulsion of the ketone's aryl group and a phospholane proton, Figure 3E) or amino center (allylic strain, Figure 3F) are also disfavored.

A notable aspect of this method is the high reaction efficiency and enantioselectivity that is possible for aminoallylation of alkyl methyl ketones, and our studies indicate that there is a significant free energy relationship in the ratio of diastereomers formed with the sterics of the variable alkyl group within the electrophile (Figure 4). Utilizing the Charton

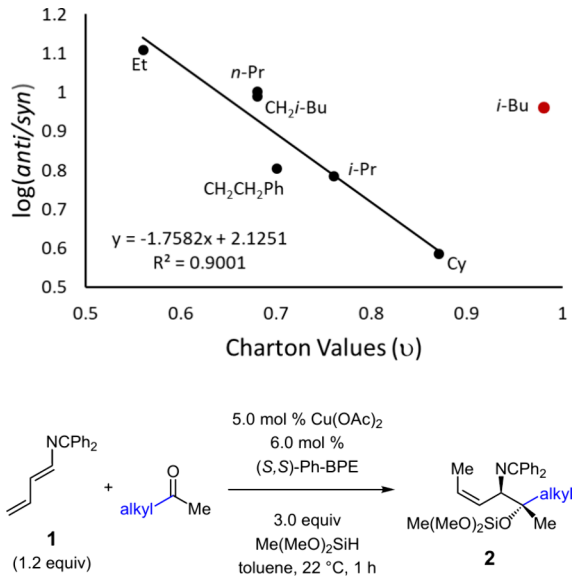

Figure 4. Diastereoselectivity−sterics free energy relationship in reductive couplings of azatriene **1** with alkyl methyl ketones.

parameter as a measure of sterics,[27] which defines the size of an alkyl group by its van der Waals radius, we observe a strongly negative correlation (φ = −1.76), wherein the relative rate of formation of the two diastereoisomers decreases as the alkyl group becomes larger. For example, dr goes from just under 13:1 for the ethyl ketone (υ = 0.56) to slightly less than 4:1 for cyclohexyl methyl ketone (υ = 0.87). The majority of the data for dialkyl ketones in Scheme 2 are in harmony with this established relationship. Other than the cyclopropyl ketone, which brings about a significantly higher diastereoselectivity (19:1 dr, **3y**) than its Charton value (υ = 1.06) would predict, there is one other significant outlier. The isobutyl ketone diastereoselectivity (9:1 dr, **3u**) is also higher than expected (υ = 0.98), perhaps indicating that β-branching of the alkyl group reinforces one mode of addition over another. Our attempts to reconcile these data with our computational model have thus far been unsuccessful, and the identity of the competing transition state that leads to stereochemical erosion for larger alkyl groups is unclear at the moment.

3. CONCLUSIONS

We have developed an enantio- and diastereoselective Cu−Ph-BPE-catalyzed reductive coupling of azatrienes and ketones that prepares vicinal amino tertiary alcohols with a (*Z*)-alkene. This aminoallylation strategy constitutes a rare example of carbonyl allylation to set two stereogenic centers in a catalytic enantioselective manner while simultaneously delivering a *cis* olefin; it is the first example of such a ketone allylation. The addition delivers the valuable amino alcohol pharmacophore, whose neighboring unsaturation allows for hetero- and carbocycle construction and diastereoselective olefin functionalization, controlled by allylic strain minimization.

Calculations illustrate that after azatriene hydrocupration, Curtin−Hammett kinetics are operative in dynamically shifting the copper along the aminoallyl chain and inverting the allylcopper stereochemistry prior to predicted turnover-limiting ketone addition. The calculations support a closed transition state for this aminoallylation step, leading to the (*Z*)-olefin through pseudoaxial disposition of the alkyl group of the iminoallylcopper and affording *anti*-amino alcohols. Although the *anti*-diastereomer is the major product stereoisomer, the corresponding *syn*-amino alcohols may be generated through stereochemical inversion of the carbinol with anchimeric assistance from the neighboring amide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c05637.

Experimental procedures, analytical data for new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 2347012 and 2347013 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) The *syn*-stereoisomer of **3d** is also found to be 97:3 er, the same enantiomeric ratio as the *anti*-diastereomer.

(19) For a comparison, 2.0 g of Ph-BPE from Strem Chemicals costs 1140 USD ($288,762/mol) while 5.0 g of BINAP costs 288 USD (ca. $35,867/mol); prices accessed from www.strem.com on February 10, 2024.

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