

A Diastereodivergent and Enantioselective Approach to *syn*- and *anti*-Diamines: Development of 2-Azatrienenes for Cu-Catalyzed Reductive Couplings with Imines that Furnish Allylic Amines

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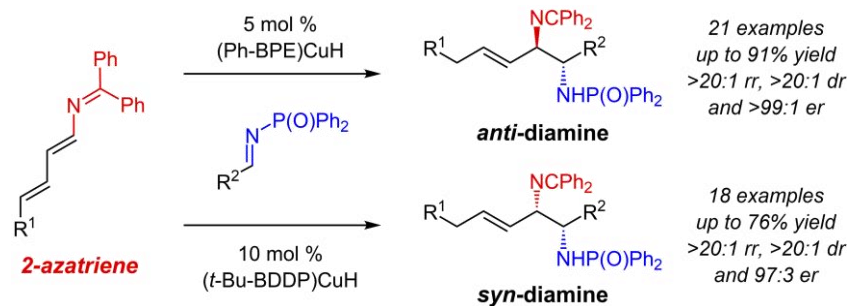
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Abstract: We introduce a new reagent class, 2-azatrienes, as a platform for catalytic enantioselective synthesis of allylic amines. Herein, we demonstrate their promise by a diastereodivergent synthesis of *syn*- and *anti*-1,2-diamines through their Cu–bis(phosphine)-catalyzed reductive couplings with imines. With Ph-BPE as the supporting ligand, *anti*-diamines are obtained (up to 91% yield, >20:1 dr, and >99:1 er), and with the rarely utilized *t*-Bu-BDPP, *syn*-diamines are generated (up to 76% yield, >20:1 dr, and 97:3 er).

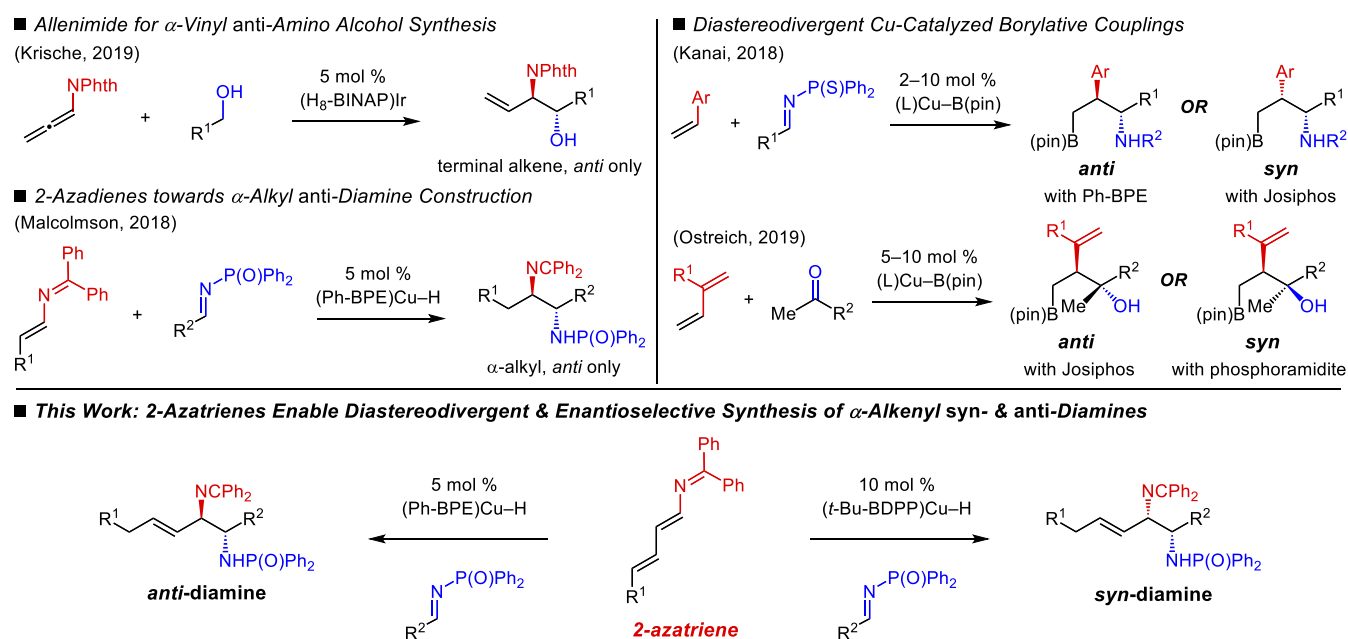
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TOC graphic:



Chiral 1,2-diols,^[1] amino alcohols,^[2] and diamines^[3] are important targets for organic synthesis as these motifs are ubiquitous in natural products and drugs, as ligands for metal-based catalysts, and as catalysts themselves. Several approaches to these scaffolds have been established; however, the invention of carbon–carbon bond-forming reactions that directly set these vicinal heteroatom-substituted stereogenic centers is underdeveloped.

A recent elegant report was disclosed by the Krische group, utilizing their hydrogen auto-transfer technology to couple an allenimide with a primary alcohol-derived aldehyde to afford 1,2-amino alcohols where the amino group is allylic (Scheme 1).^[4–6] Allylic amines are important structural features in numerous bioactive molecules and natural products.^[7] Furthermore, the unsaturation may serve as a functional group handle for downstream transformations.^[8] Although having excellent scope in the alcohol partner, the reactions were limited to terminal allenenes, giving rise to terminal allyl groups; moreover, the *anti*-amino alcohol was the only stereoisomer accessible.



Scheme 1. Access to Vicinal Stereogenic Centers by Catalytic Processes

Our group has investigated the synthesis of both 1,2-diamines^[9] (Scheme 1) and amino alcohols¹⁰ by reductive couplings of 2-azadienes.^[11,12] These transformations proceed by means of a copper–hydride^[13] intermediate with the bis(phospholane) Ph-BPE as the ligand. In both cases, the product amines bear an α -alkyl group. Furthermore, the diamines were generated solely as the *anti* diastereomer in every case.

These examples highlight an often encountered situation in enantioselective reactions that afford more than one stereogenic center: the ability to access only one diastereoisomer. One strategy that addresses this shortcoming is a dual catalyst approach^[14] wherein each catalyst acts cooperatively

but independently to activate two reaction components individually, thereby enabling each to control stereochemistry at its respective fragment.^[15,16] An alternative is the use of two related single catalysts for transformations that individually afford opposite diastereomers with high enantioselectivity. Such an approach has recently been illustrated in copper–phosphine-catalyzed borylative couplings (Scheme 1). Shimizu, Kanai, and co-workers demonstrated Cu–B(pin) addition to styrene followed by coupling with *N*-thiophosphinoylimines.^[17] β -Arylamines are obtained as the *syn*-isomer with a Josiphos ligand whereas Ph-BPE delivers the *anti*-diastereomer. Similarly, the Ostreich group discovered that 2-substituted dienes yield homoallylic alcohols as the *anti*-diastereomer with Josiphos but the *syn*-diastereomer with a phosphoramidite ligand.^[18,19] To our knowledge, no examples of diastereodivergent behavior in copper-catalyzed reductive couplings of olefins with electrophiles have been reported.^[20,21]

We have developed 2-azatrienes as new reagents for the synthesis of substituted allylic amines. Herein we illustrate their reductive coupling with *N*-phosphinoylimines to afford 1,2-diamines with high chemo-,^[22] regio-, diastereo-, and enantioselectivity (Scheme 1). Cu–Ph-BPE promotes the formation of *anti*-diamines. Unexpectedly, and in stark contrast to our findings with azadiene reagents, we discovered that several other ligands enable the cross-coupling and favor the *syn*-diamine product. We disclose the first examples of reductive coupling using *t*-Bu-BDPP, an uncommon ligand in catalysis,^[23] to achieve good to excellent levels of diastereo- and enantioselectivity for *syn*-diamine production.^[24–26]

We began by examining the coupling of terminal 2-azatriene **1** with imine **2a**, employing Cu(OAc)₂ and Ph-BPE (**L1**) under the conditions established for azadiene addition to these imines^[9] (Table 1, entry 1). The transformation generates the *anti*-diamine **3a** as the sole stereoisomer, isolated in 90% yield and 99:1 er. Regioselectivity for the 6,3-addition product over the isomeric azadiene **4a** (6,5-addition) is excellent. Furthermore, chemoselectivity for reductive coupling over imine reduction (**3a/4a:5a** >20:1) is considerably greater than in our previous azadiene–imine coupling^[9] (coupling/reduction = 5:1), which might be attributed to the LUMO-lowering effect of extra conjugation in **1** plus its decreased sterics over an azadiene (cf. Scheme 1).

Unexpectedly, we discovered that *syn*-diamine **3a** is the major product (1:3.5 *anti:syn-3a*) with achiral DCyPe (**L2**, entry 2) when attempting to prepare the authentic racemic material for entry 1. This finding stands in contrast to azadiene reductive couplings with imine **2a**, where Ph-BPE and DCyPE both furnish the *anti*-diamine product. Although selectivity metrics were modest for DCyPE in the azatriene coupling, this result prompted us to explore whether a chiral ligand could be found that would lead to enantioselective formation of the *syn-3a* diastereomer.

Table 1. Ligand Choice in CuH-Catalyzed Coupling of 2-Azatriene **1** and Imine **2a** Leads to Diastereodivergence^[a]

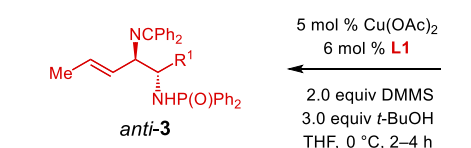
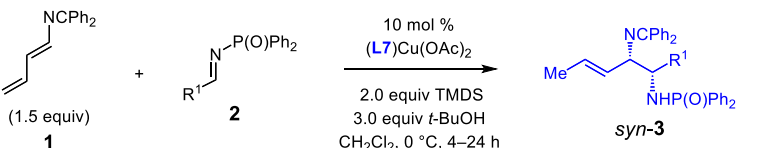
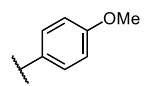
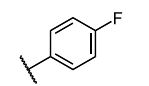
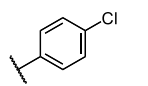
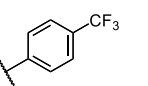
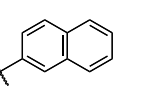
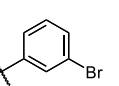
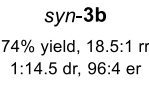
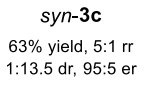
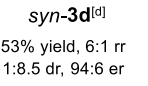
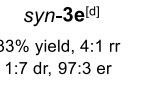
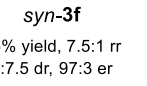
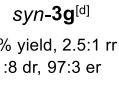
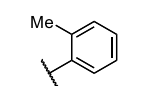
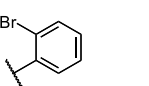
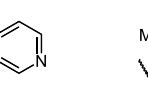

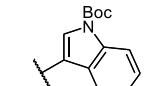
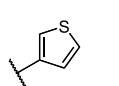
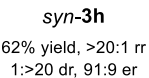
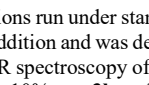
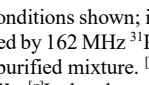
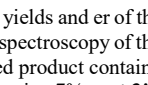
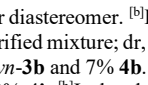
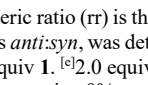
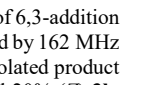
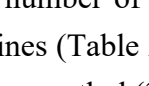
entry	ligand	conv of 2a (%) ^[b]	3a:4a:5a ^[b]	<i>anti:syn-3a</i> ^[b]	er ^[c]
1	L1	>98 (90) ^[d]	86:8:4	>20:1	99:1
2	L2	>98	75:13:12	1:3.5	—
3	L3	80	58:14:28	1:2.5	50:50
4	L4	>98	60:18:22	1:6	83:17
5 ^[e]	L5	>98	28:6:66	1:1.5	50:50
6 ^[e]	L6	>98	27:31:42	1:1	52:48
7 ^[e]	L7	>98	64:12:24	1:6	94:6
8 ^[e,f]	L7	>98	66:12:22	1:10	94:6
9 ^[e,f,g]	L7	>98 (69) ^[d]	81:6:12	1:10	97:3

^[a]Reaction with 0.1 mmol imine **2a**. ^[b]Determined by 162 MHz ³¹P NMR spectroscopy of the unpurified mixture. ^[c]Determined by HPLC analysis of purified **3**. ^[d]Isolated yield of diamine **3**. ^[e](**L**)Cu(OAc)₂ complex formed from **L**·2BH₃; see the Supporting Information for details. ^[f]2.0 equiv TMDS. DMMS = Me(MeO)₂SiH; TMDS = [(Me)₂HSi]₂O.

With Chiraphos (**L3**), the reaction is reasonably efficient but poorly selective in all categories, generating *syn-3a* as a racemate (entry 3). In contrast, spacing the phosphino groups farther apart by turning to BDPP (**L4**) leads to markedly improved stereoselectivity (1:6 *anti:syn-3a*, 83:17 er, entry 4). Replacing the methyl groups of BDPP with phenyl substituents (**L5**) significantly erodes stereoselectivity (1.5:1 dr, 50:50 er) and leads to a large quantity of imine reduction (entry 5). Similarly, changing the diphenylphosphino groups to dicyclohexylphosphino (**L6**) abolishes stereoselectivity (entry 6); regio- and chemoselectivity are also poor. Fortunately, modification of the aryl groups of the phosphine within the BDPP structure proved more fruitful. Introduction of a *tert*-butyl group at the arene's *para* position (herein called *t*-Bu-BDPP, **L7**, entry 7) restores diastereoselectivity (6:1 dr), increases the proportion of diamine **3a**, and significantly improves the enantioselectivity (94:6 er). Switching the silane to TMDS further increased the proportion of *syn*-diamine **3a** (1:10 dr, entry 8). Finally, changing the solvent to CH₂Cl₂ and increasing the

catalyst loading to 10 mol % (entry 9) allowed for *syn*-**3a** to be obtained with considerably enhanced regio- and chemoselectivity and finally isolated in 69% yield and 97:3 er.

Table 2. Aldimine Scope in Diastereodivergent Couplings with 2-Azatriene **1**^[a,b]

			
$R^1 =$			
 anti-3b ^[c] <div>with L1</div> 84% yield, 7.5:1 rr 9:1 dr, 97.5:2.5 er		 anti-3c 77% yield, 15:1 rr >20:1 dr, 98:2 er	
 anti-3d 79% yield, >20:1 rr >20:1 dr, 99:1 er		 anti-3e ^[e] 66% yield, 19:1 rr >20:1 dr, >99:1 er	
 anti-3f 89% yield, >20:1 rr >20:1 dr, >99:1 er		 anti-3g 70% yield, 15:1 rr >20:1 dr, >99:1 er	
 syn-3b <div>with L7</div> 74% yield, 18.5:1 rr 1:14.5 dr, 96:4 er		 syn-3c 63% yield, 5:1 rr 1:13.5 dr, 95:5 er	
 syn-3d ^[d] 53% yield, 6:1 rr 1:8.5 dr, 94:6 er		 syn-3e ^[d] 33% yield, 4:1 rr 1:7 dr, 97:3 er	
 syn-3f 56% yield, 7.5:1 rr 1:7.5 dr, 97:3 er		 syn-3g ^[d] 46% yield, 2.5:1 rr 1:8 dr, 97:3 er	
$R^1 =$			
 anti-3h ^[f] <div>with L1</div> 62% yield, 2.5:1 rr 6:1 dr, 99:1 er		 anti-3i 52% yield, >20:1 rr 5.5:1 dr, 99:1 er	
 anti-3j 90% yield, >20:1 rr >20:1 dr, 99:1 er		 anti-3k ^[h] 92% yield, >20:1 rr 4:1 dr, 99:1 er	
 anti-3l 89% yield, >20:1 rr >20:1 dr, >99:1 er		 anti-3m 88% yield, >20:1 rr >20:1 dr, >99:1 er	
 anti-3n 91% yield, 18:1 rr >20:1 dr, 99:1 er			
 syn-3h <div>with L7</div> 62% yield, >20:1 rr 1:>20 dr, 91:9 er		 syn-3i ^[d] 48% yield, >20:1 rr 1:>20 dr, 86.5:13.5 er	
 syn-3j ^[d,g] 56% yield, 4:1 rr 1:13.5 dr, 97:3 er		 syn-3k ^[d,i] 75% yield, >20:1 rr 1:3 dr, 92:8 er	
 syn-3l ^[j] 53% yield, 3:1 rr 1:3.5 dr, 92:8 er		 syn-3m 53% yield, 13:1 rr 1:10 dr, 96.5:3.5 er	
 syn-3n 64% yield, 5.5:1 rr 1:19 dr, 95.5:4.5 er			

^[a]Reactions run under standard conditions shown; isolated yields and er of the major diastereomer. ^[b]Regiomer ratio (rr) is the ratio of 6,3-addition to 6,5-addition and was determined by 162 MHz ³¹P NMR spectroscopy of the unpurified mixture; dr, listed as *anti*:*syn*, was determined by 162 MHz ³¹P NMR spectroscopy of the unpurified mixture. ^[c]Isolated product contains 9% *syn*-**3b** and 7% **4b**. ^[d]3.0 equiv **1**. ^[e]2.0 equiv **1**. ^[f]Isolated product contains 10% *syn*-**3h** and 10% **4h**. ^[g]Isolated product contains 7% *anti*-**3j** and 19% **4j**. ^[h]Isolated product contains 9% *syn*-**3k** and 20% (*Z*)-**3k**. ^[i]Isolated product contains 19% *anti*-**3k** and 19% (*Z*)-**3k**. ^[j]Isolated product contains 12% *anti*-**3l**.

A number of aldimines may thus be coupled with azatriene **1** to deliver either *anti*- or *syn*-diamines (Table 2). Several arene functional groups, such as methoxy (**3b**), halide (**3c–d**, **3g**, **3i**), trifluoromethyl (**3e**), and alkyl (**3h**) with various substitution patterns were prepared. Additionally, a variety of heterocyclic aldimines were investigated and are tolerated by the copper-based catalysts, including pyridine (**3j**), pyrrole (**3k**), pyrazole (**3l**), indole (**3m**), and thiophene (**3n**). Yields range from 33% to 91% for the major diastereomer of any isolated product, demonstrating the broad potential of the method to prepare both vicinal diamine diastereomers with a diverse chemical landscape.

Several differences in trends in reaction metrics from transformations involving Ph-BPE (**L1**) and *t*-Bu-BDPP (**L7**) are notable. Whereas more electron-rich aldimines lead to greater diastereoselectivity when **L7** is employed (compare *syn*-**3b–e**, ranging from 1:7 to 1:14.5 dr), the reaction of *p*-methoxy imine **2b** in the presence of **L1** leads to only 9:1 dr. In contrast, *anti*-**3c–e**

are generated in >20:1 dr. Likewise, regioselectivity (**3:4**) is greatest for reaction of **2b** with **L7** and poorest with **L1**. Aryl aldimines bearing *ortho* substituents (**2h–i**) lead to perfect regio- and diastereoselectivity for *syn*-**3h–i** with **L7**; however, **L1** affords *anti*-**3h–i** in only ca. 6:1 dr but with 99:1 er. Comparatively, the *ortho* substitution engenders the lowest enantioselectivity observed for *syn*-diamines with **L7** (91:9 er for *syn*-**3h** and 86.5:13.5 er for *syn*-**3i**).

In general, reactions we explored with Ph-BPE deliver *anti*-diamines **3** in >20:1 dr and ≥98:2 er. Contrastingly, stereoselectivity for *syn*-diamine formation with *t*-Bu-BDPP is considerably more variable, showing a wide range of both dr (1:3 to 1:>20) and er (86.5:13.5 to 97:3). Still, the vast majority of couplings favor *syn*-diamines over the *anti*-isomers and with good enantioselectivity (≥7:1 *syn:anti* and ≥94:6 er for the *syn*). Regioselectivity for the allylic diamine is also greater with Ph-BPE as the supporting ligand (≥15:1 rr in most cases) and more variable with *t*-Bu-BDPP (3:1 to >20:1 rr), which is one factor in the higher yields obtained for the *anti* diastereomer. Chemoselectivity for reductive coupling versus imine reduction is tied to imine electronics with both catalysts: more electron-rich imines deliver a higher proportion of C–C bond formation. The copper complex derived from *t*-Bu-BDPP was more greatly influenced in this regard. For example, *p*-chloro *syn*-**3d** is obtained in 53% yield but *p*-CF₃ *syn*-**3e** in just 33% yield despite the reactions having similar regio- and diastereoselectivity. Intriguingly, reaction of 2-iminopyrrole **2k** with either catalyst affords an appreciable quantity of the (*Z*)-olefin isomer (ca. 2–3:1 *E:Z*) although only (*E*)-alkenes are obtained in all other cases.

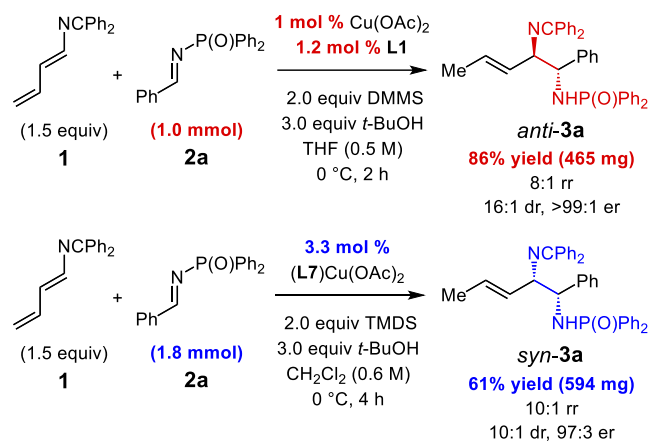
2-Azatrienes bearing alkyl substituents at the 6-position (**6**) enable diamines (**7**) with longer chain olefin substituents to be obtained (Table 3). With the greater chemoselectivity for cross-coupling shown by the Cu–Ph-BPE catalyst, *anti*-**7a–h** are isolated in good yields (51–89%) even with an electronically neutral imine (**2a**, Table 3, left). Both the diastereo- and enantioselectivity are excellent (12:1 to >20:1 dr and 95:5 to 99:1 er), but in most cases regioselectivity is more modest than with **1** (7:1 to 12:1 rr for *anti*-**7a–g**). Triamine *anti*-**7h**, however, is formed as a single regioisomer.

The Cu–*t*-Bu-BDPP catalyst is more prone to imine reduction, and with the greater sterics of substituted azatrienes **6**, more electron-rich imines are required to achieve appreciable yields of *syn*-diamines (Table 3, right). Within these confines, a number of azatriene–imine combinations afford *syn*-diamines in good yields (39–76% for **7i–l**). Diastereo- and regioselectivity are good (1:7 to 1:>20 dr and 9.5:1 to >20:1 rr) and enantioselectivity remains high (93.5:6.5 to 97:3 er).

Table 3. Scope of 6-Substituted 2-Azatriene Couplings with Imines^[a,b]

<i>anti</i> -diamine			<i>syn</i> -diamine		
<p> 6 (3.0 equiv) + 2a (1.0 mmol) </p> <p> 5 mol % Cu(OAc)_2 6 mol % L1 2.0 equiv DMMS 3.0 equiv <i>t</i>-BuOH THF, 0 °C, 4 h </p> <p><i>anti</i>-7</p>			<p> 6 (3.0 equiv) + 2 (R^2) </p> <p> 10 mol % $(\text{L7})\text{Cu(OAc)}_2$ 2.0 equiv TMDS 3.0 equiv <i>t</i>-BuOH CH_2Cl_2, 0 °C, 12–24 h </p> <p><i>syn</i>-7</p>		
<p><i>anti</i>-7a</p> <p>72% yield, 10.5:1 rr 12:1 dr, 99:1 er</p>	<p><i>anti</i>-7b</p> <p>56% yield, 10.5:1 rr 15:1 dr, 99:1 er</p>	<p><i>anti</i>-7c</p> <p>57% yield, 8.5:1 rr >20:1 dr, 98.5:1.5 er</p>	<p><i>syn</i>-7i</p> <p>39% yield, >20:1 rr 1:>20 dr, 94.5:5.5 er</p>	<p><i>syn</i>-7j</p> <p>50% yield, >20:1 rr 1:14 dr, 93.5:6.5 er</p>	
<p><i>anti</i>-7d</p> <p>51% yield, 10.5:1 rr 16.5:1 dr, 99:1 er</p>	<p><i>anti</i>-7e</p> <p>62% yield, 12:1 rr 13:1 dr, 98.5:1.5 er</p>		<p><i>syn</i>-7k</p> <p>46% yield, 9.5:1 rr 1:>20 dr, 97:3 er</p>	<p><i>syn</i>-7l</p> <p>76% yield, 17:1 rr 1:7 dr, 95:5 er</p>	
<p><i>anti</i>-7f</p> <p>67% yield, 11:1 rr 15.5:1 dr, 98:2 er</p>	<p><i>anti</i>-7g</p> <p>89% yield, 7:1 rr 20:1 dr, 99:1 er</p>	<p><i>anti</i>-7h</p> <p>69% yield, >20:1 rr >20:1 dr, 95:5 er</p>			

^[a,b]See Table 2.



Scheme 2. Larger Scale Diamine Synthesis

For preparative scale diamine synthesis, we employed lower catalyst loadings and higher reaction concentrations (Scheme 4). Excellent yields of the two diamine diastereomers are thereby obtained within a few hours. For instance, *anti*-**3a** was generated in 86% yield with just 1.0 mol

% copper. Similarly, **2a** was converted to *syn*-**3a** (61% yield) in the presence of just 3.3 mol % of the **L7**-copper catalyst. Regio- and stereoselectivity are largely unaffected by the scale up and modified conditions.

We next sought to understand how stereochemistry of the azatriene might play a role in the chemo-, regio-, and stereoselectivity of the imine couplings (Table 4). Under their respective optimized conditions, the copper catalysts bearing **L1** or **L7** show little difference in regioselectivity (**3a:4a**) or chemoselectivity (**3a/4a:5a**) for the addition of either (*E*)-**1** or (*Z*)-**1** to imine **2a** (compare entry 1 with 3 and entry 2 with 4). The same major enantiomer of the *anti*-diastereomer is formed with **L1** regardless of azatriene geometry (>99:1 er for *anti*-**3a**, entries 1 and 3). Likewise, the **L7**-derived catalyst leads to 97:3 er in favor of the same major enantiomer of *syn*-**3a** beginning with either azatriene stereoisomer (entries 2 and 4). Diastereoselectivity is also unaffected. We also measured the er of the minor diastereomer from each combination of ligand and azatriene stereoisomer. Somewhat surprisingly we discovered that the minor diastereomer is formed with poor enantioselectivity in each case. Additionally, we stopped the reaction of both (*E*)- and (*Z*)-**1** after 30 seconds with the Cu-Ph-BPE catalyst. There was approximately 60% conversion to *anti*-**3a**, but none of the recovered azatriene had undergone stereochemical inversion in either case, suggesting that the CuH insertion event is irreversible.

Table 4. Comparison of (*E*)- and (*Z*)-Azatrienes^[a]

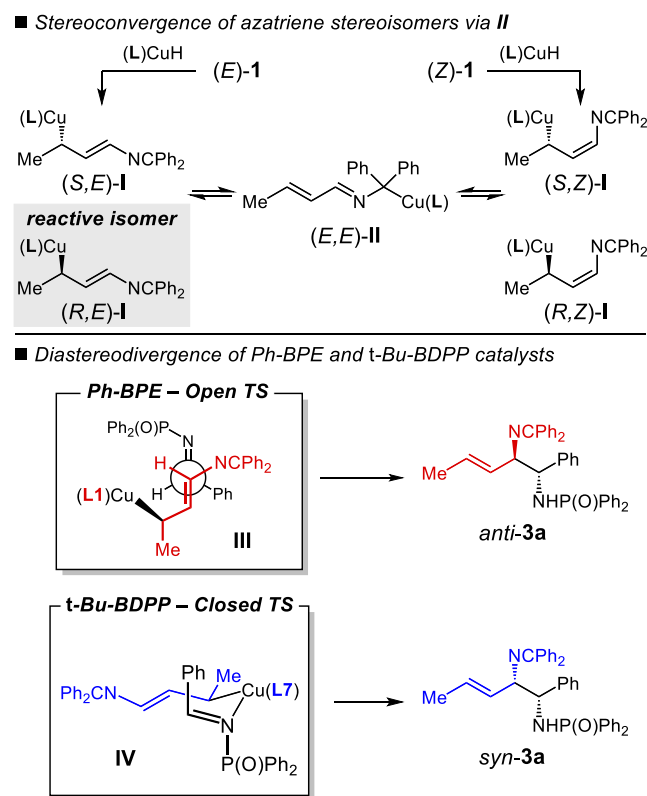
optimized conditions for *anti*- or *syn*-diamine (see Table 1)

entry	azatriene	ligand	3a:4a:5a ^[b]	<i>anti:syn</i> - 3a ^[b]	er <i>anti</i> - 3a ^[c]	er <i>syn</i> - 3a ^[c]
1		L1	89:9:2	>20:1	>99:1	<52:48
2		L7	83:6:11	1:15.5	42:58	97:3
3		L1	86:9:5	>20:1	>99:1	<52:48
4		L7	84:7:9	1:13	44:56	97:3

^[a]Reaction with 0.1 mmol imine **2a**. Entries 1 and 3 run under the conditions of Table 1, entry 1; entries 2 and 4 run under the conditions of Table 1, entry 9. ^[b,c]See Table 1.

The stereoconvergence of the (*E*)- and (*Z*)-azatriene isomers with each catalyst might be explained by several mechanistic possibilities, while the diastereodivergence observed for the two

catalysts clearly indicates a mechanistic dichotomy in the C–C bond-forming step. Our working hypothesis to explain these phenomena is outlined in Scheme 3. Both azatriene isomers **1** may undergo migratory insertion to the CuH species derived from either ligand. This process may occur with olefin facial selectivity but that is irrelevant as all possible stereoisomers of allylic copper **I** may equilibrate through (*E,E*)-**II**. We propose that with the enantiomer of each catalyst utilized in this study, addition to the imine is funneled through (*R,E*)-**I**. With Ph-BPE, ^{24a} reaction may proceed through an open transition state (**III**), possibly due to imine coordination to the copper being hindered by the bulky phospholane ligand. In contrast, the transformation with *t*-Bu-BDPP might occur through a closed transition state (**IV**).



Scheme 3. Mechanistic Proposal for Azatriene–Imine Couplings

We have developed the first examples of Cu-catalyzed diastereodivergent and enantioselective reductive coupling reactions. Through the use of a new umpolung reagent, 2-azatrienes, we have successfully prepared both *syn*- and *anti*-diamines through addition to *N*-phosphinoylimines. The synthesis of the *syn*-isomers was enabled by the bis(phosphine) *t*-Bu-BDPP, the first use of this ligand in CuH processes. Ongoing work is dedicated to uncovering more details of the mechanism of this reaction and to the development of other transformations of 2-azatrienes.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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