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

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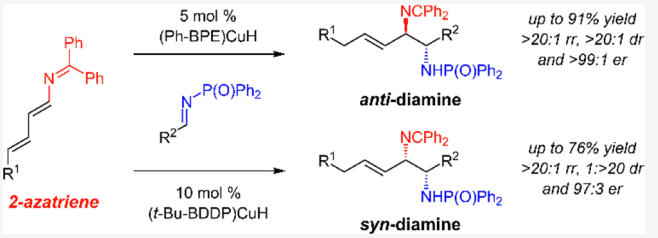
ABSTRACT: We introduce a new reagent class, 2-azatrienes, as a platform for catalytic enantioselective synthesis of allylic amines. Herein, we demonstrate their promise by a diastereodivergent synthesis of *syn*- and *anti*-1,2-diamines through their Cu−bis(phosphine)-catalyzed reductive couplings with 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, 1:>20 dr, and 97:3 er).



1. INTRODUCTION

Chiral 1,2-diols, amino alcohols, and diamines 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;[1−3] however, the invention of carbon−carbon bond-forming reactions that directly set these vicinal heteroatom-substituted stereogenic centers is underdeveloped.

A recent elegant report from the Krische group utilizes their hydrogen autotransfer 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).[4−9] Allylic amines are important structural features in numerous bioactive molecules and natural products.[10] Furthermore, the unsaturation may serve as a functional group handle for downstream transformations.[11] Although having excellent scope in the alcohol partner, the reactions were limited to terminal allenes, giving rise to terminal allyl groups; moreover, the *anti*-amino alcohol was the only stereoisomer accessible.

Our group has investigated the synthesis of both 1,2-diamines[12] (Scheme 1) and amino alcohols[13] by reductive couplings of 2-azadienes.[14,15] These transformations proceed by means of a copper−hydride[16] 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.[17]

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[18] wherein each catalyst acts cooperatively but independently to activate two reaction components individually, thereby enabling each to control stereochemistry at its respective fragment.[19,20] 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.[21] 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.[22,23] To our knowledge, no examples of diastereodivergent behavior in copper-catalyzed reductive couplings of olefins with electrophiles have been reported.[24,25]

We have developed 2-azatrienes[26] as new reagents for the synthesis of substituted allylic amines.[27] Herein, we illustrate their reductive coupling with *N*-phosphinoylimines to afford 1,2-diamines with high chemo-,[28] 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

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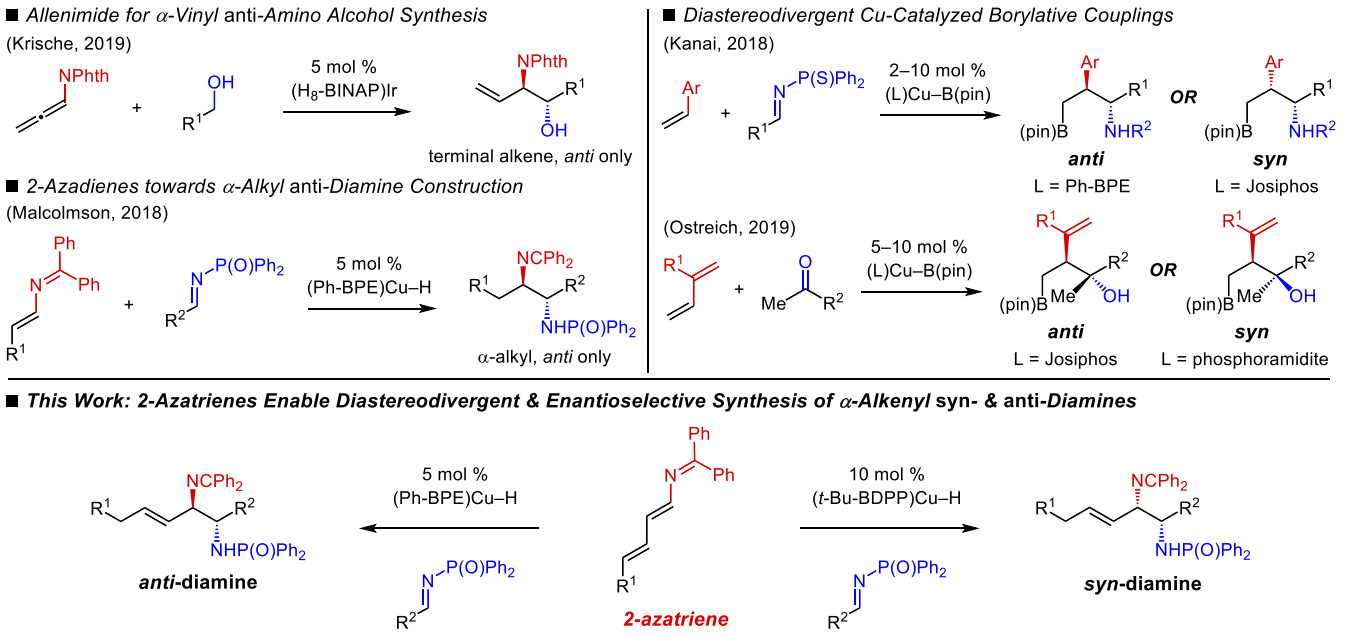
Scheme 1. Catalytic Reductive and Borylative Processes that Set Vicinal Stereogenic Centers



reductive coupling using *t*-Bu-BDPP, an uncommon ligand in catalysis,[29] to achieve good to excellent levels of diastereo- and enantioselectivity for *syn*-diamine production.[30−32]

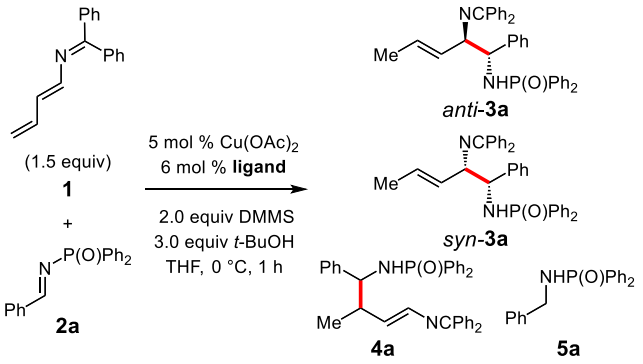
2. RESULTS AND DISCUSSION

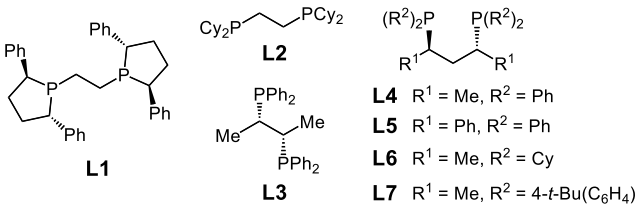
2.1. Method Development. We began by examining the coupling of terminal 2-azatriene **1** with imine **2a**, employing $Cu(OAc)_2$ and Ph-BPE (**L1**) under the conditions established for azadiene addition to these imines[12] (Table 1, entry 1). The transformation generates the *anti*-diamine **3a** with 19.5:1 dr, which was 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 that in our previous azadiene−imine coupling[12] (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 preferentially furnish the *anti*-diamine product. Although selectivity metrics were modest for DCyPE in the azatriene reaction, this result prompted us to explore whether a chiral ligand could be found that would lead to enantioselective formation of the *syn*-**3a** diastereomer.

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 (1:1.5 dr, 50:50 er) and leads to a large quantity of imine reduction (entry 5). Similarly, changing the diphenylphosphino groups to dicyclohexylphophino (**L6**) abolishes stereoselectivity (entry 6); regio- and chemoselectivity are also poor. Fortunately,

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]	*anti*:*syn*-**3a**[b]	er[c]
1	**L1**	>98 (90)[d]	86:8:4	19.5:1	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	1:8.5	94:6
9[e,f,g]	**L7**	>98 (69)[d]	81:6:12	1:12.5	97:3

[a]Reaction with 0.1 mmol imine **2a**. [b]Determined by 500 MHz ^{1}H or 162 or 202 MHz ^{31}P NMR spectroscopy of the unpurified mixture. [c]Determined by HPLC analysis of purified **3**. [d]Isolated yield of diamine **3a**. [e](**L**)$Cu(OAc)_2$ complex formed from **L**·$2BH_3$; see the Supporting Information for details. [f]2.0 equiv TMDS. [g]In CH_2Cl_2 with 10 mol % catalyst.

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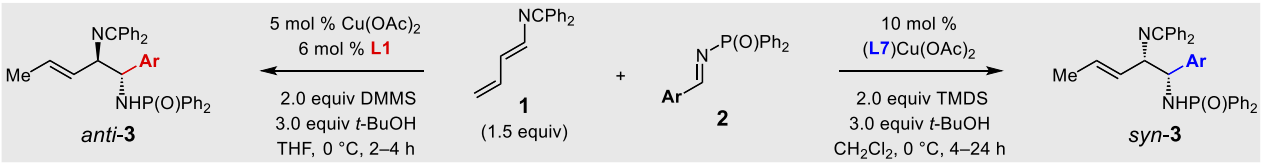
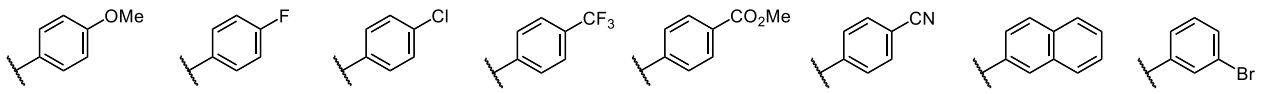
Scheme 2. Aldimine Scope in Diastereodivergent Couplings with 2-Azatriene 1[a,b]

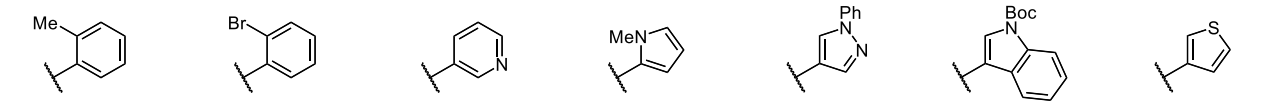


Ar =



	anti-**3b**[c]	*anti*-**3c**	*anti*-**3d**	*anti*-**3e**[e]	*anti*-**3f**	*anti*-**3g**	*anti*-**3h**	*anti*-**3i**
with **L1**	84% yield, 6.5:1 rr 7.5:1 dr, 97.5:2.5 er	77% yield, 15:1 rr >20:1 dr, 98:2 er	79% yield, >20:1 rr >20:1 dr, 99:1 er	66% yield, 19:1 rr >20:1 dr, >99:1 er	71% yield, 13:1 rr >20:1 dr, 99:1 er	56% yield, >20:1 rr >20:1 dr, 99:1 er	89% yield, >20:1 rr >20:1 dr, >99:1 er	70% yield, 15:1 rr >20:1 dr, >99:1 er
	syn-**3b**	*syn*-**3c**	*syn*-**3d**[d]	*syn*-**3e**[d]	*syn*-**3f**[d,f]	*syn*-**3g**[d,g]	*syn*-**3h**	*syn*-**3i**[d]
with **L7**	74% yield, 14:1 rr 1:11 dr, 96:4 er	63% yield, 5:1 rr 1:13 dr, 95:5 er	53% yield, 7:1 rr 1:10 dr, 94:6 er	33% yield, 5.5:1 rr 1:6.5 dr, 97:3 er	>98% conv, 1.9:1 rr 1:7 dr, er nd	77% conv, 1:1 rr 1:4.5 dr, er nd	56% yield, 7.5:1 rr 1:7.5 dr, 97:3 er	46% yield, 2.5:1 rr 1:8 dr, 97:3 er

Ar =



	anti-**3j**[h]	*anti*-**3k**[i]	*anti*-**3l**	*anti*-**3m**[k]	*anti*-**3n**	*anti*-**3o**	*anti*-**3p**
with **L1**	62% yield, 2.5:1 rr 6:1 dr, 99:1 er	>98% conv, 1:5.5 rr 6:1 dr, er nd	90% yield, >20:1 rr >20:1 dr, 99:1 er	92% yield, >20:1 rr 4:1 dr, 99:1 er	89% yield, >20:1 rr >20:1 dr, >99:1 er	88% yield, >20:1 rr >20:1 dr, >99:1 er	91% yield, 18:1 rr >20:1 dr, 99:1 er
	syn-**3j**	*syn*-**3k**[d]	*syn*-**3l**[d,j]	*syn*-**3m**[d,l]	*syn*-**3n**[m]	*syn*-**3o**	*syn*-**3p**
with **L7**	62% yield, >20:1 rr 1:>20 dr, 91:9 er	48% yield, >20:1 rr 1:>20 dr, 86.5:13.5 er	56% yield, 4:1 rr 1:13.5 dr, 97:3 er	75% yield, >20:1 rr 1:3 dr, 92:8 er	53% yield, 3:1 rr 1:3.5 dr, 92:8 er	53% yield, 13:1 rr 1:10 dr, 96.5:3.5 er	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]Regiomeric ratio (rr) is the ratio of 6,3-addition to 6,5-addition and was determined by 500 MHz ^{1}H or 162 or 202 MHz ^{31}P NMR spectroscopy of the unpurified mixture; dr, listed as *anti*:*syn*, was determined by 500 MHz ^{1}H or 162 or 202 MHz ^{31}P NMR spectroscopy of the unpurified mixture. [c]Isolated product contains 9% *syn*-**3b** and 7% **4b**. [d]3.0 eq **1**. [e]2.0 eq **1**. [f]Conversion of imine **2f**, 3:2 **3f**/**4f**:**5f**. [g]Conversion of imine **2g**, 1:1.3 **3g**/**4g**:**5g**. [h]Isolated product contains 10% *syn*-**3j** and 10% **4j**. [i]Conversion of imine **2k**; **4k** is the major product (see Figure 2). [j]Isolated product contains 7% *anti*-**3l** and 19% **4l**. [k]Isolated product contains 9% *syn*-**3m** and 20% (*Z*)-**3m**. [l]Isolated product contains 19% *anti*-**3m** and 19% (*Z*)-**3m**. [m]Isolated product contains 12% *anti*-**3n**. nd = not determined.

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 (1:6 dr), increases the proportion of diamine **3a**, and significantly improves the enantioselectivity (94:6 er). Switching the silane to TMDS further increased the quantity of *syn*-diamine **3a** (1:8.5 dr, entry 8). Finally, changing the solvent to CH_2Cl_2 and increasing the catalyst loading to 10 mol % (entry 9) allowed for *syn*-**3a** to be obtained with considerably enhanced regio- and chemoselectivity and isolated in 69% yield, 1:12.5 dr, and 97:3 er.[33]

A number of aryl aldimines of varying substitution patterns may thus be coupled with azatriene **1** to deliver either *anti*- or *syn*-diamines (Scheme 2). Diamines with a variety of arene functional groups, such as methoxy (**3b**), halide (**3c**−**d**, **3i**, **3k**), trifluoromethyl (**3e**), ester (**3f**), nitrile (**3g**), and alkyl (**3j**) were prepared. Additionally, several heterocyclic aldimines were investigated and are tolerated by the copper-based catalysts, including pyridine (**3l**), pyrrole (**3m**), pyrazole (**3n**), indole (**3o**), and thiophene (**3p**). 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.[34]

In general, the reactions we explored with Ph-BPE deliver *anti*-diamines **3** in >20:1 dr and ≥98:2 er. In contrast, 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, 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, the reaction of 2-iminopyrrole **2m** with either catalyst affords an appreciable quantity of the (*Z*)-olefin isomer[35] (ca. 2−3:1 *E*:*Z*) although only (*E*)-alkenes are obtained in all other cases.

From this initial data set, 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**−**g**, ranging from 1:4.5 to 1:13 dr), the reaction of *p*-methoxy imine **2b** in the presence of **L1** leads to only 7.5:1 dr. In contrast, *anti*-**3c**−**e** are generated in >20:1

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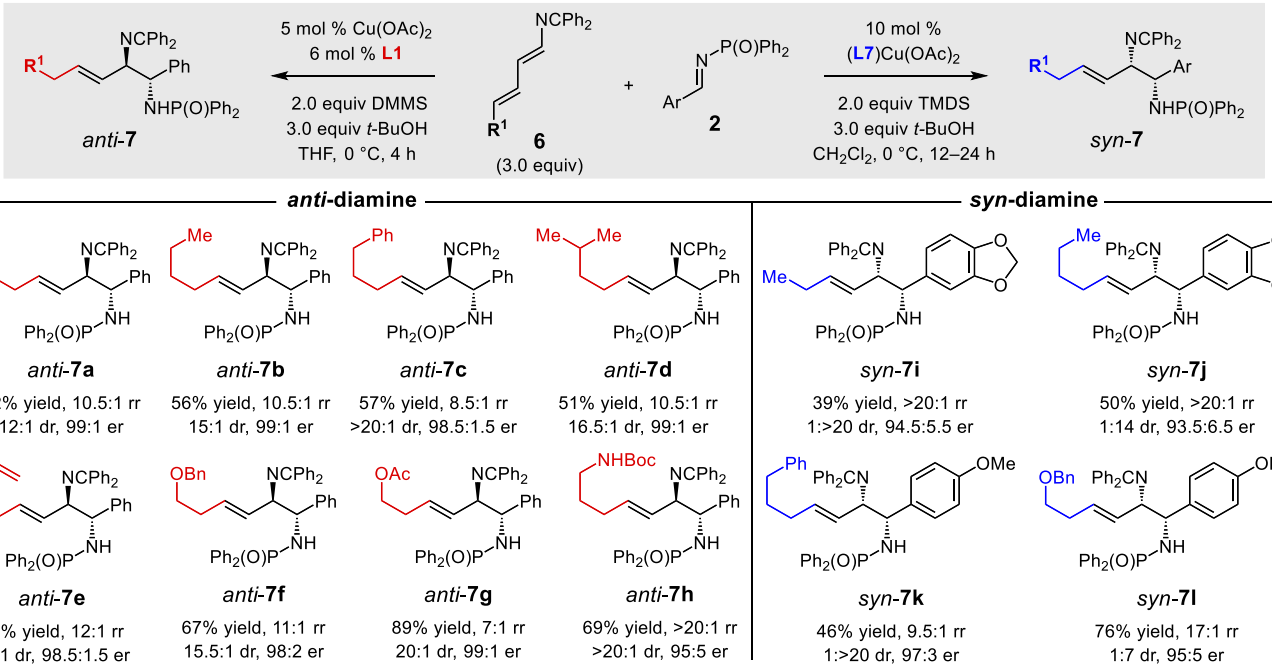
Scheme 3. Scope of 6-Substituted 2-Azatriene Couplings with Imines[a]



[a]See Scheme 2.

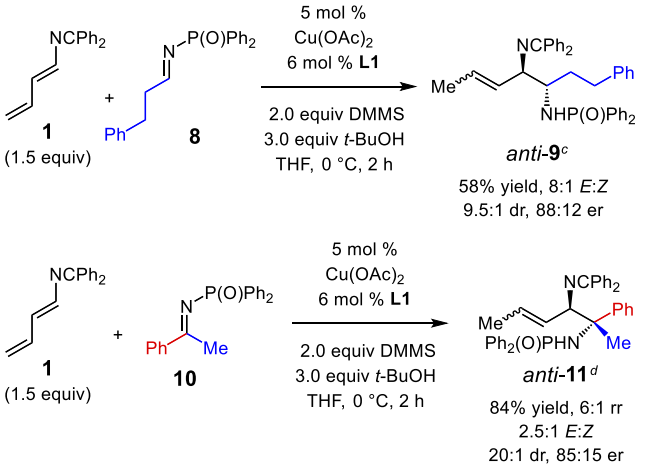
dr.[36] Likewise, regioselectivity (**3**:**4**) is greatest for reaction of **2b** versus other imines with **L7** and poorest with **L1**. Aryl aldimines bearing *ortho* substituents (**2j**–**k**) lead to perfect regio- and diastereoselectivity for *syn*-**3j**–**k** with **L7**. At the same time, this *ortho* substitution engenders the lowest enantioselectivity observed for *syn*-diamines with **L7** (91:9 er for *syn*-**3j** and 86.5:13.5 er for *syn*-**3k**). With **L1**, however, *anti*-**3j**, with its *ortho*-methyl group, is obtained in only 6:1 dr and 2.5:1 rr. *ortho*-Bromo *anti*-**3k** is the minor isomer from the reductive coupling (1:5.5 **3k**:**4k**); it is formed in only 6:1 dr and was not isolated.

2-Azatrienes bearing alkyl substituents at the 6-position (**6**) enable diamines (**7**) with longer chain olefin substituents to be obtained (Scheme 3). With the greater chemoselectivity for cross-coupling shown by Cu–Ph-BPE in azatriene couplings, *anti*-**7a**–**h** are isolated in good yields (51–89%) even with electronically neutral imine **2a**. This contrasts with transformations with substituted azadienes,[12] which required electron-rich imines to avoid reduction. Both 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 terminal azatriene **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 (Scheme 3). 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).

Ph-BPE also permits azatriene couplings with an aliphatic aldimine and a ketimine (Scheme 4). Diamine *anti*-**9** is formed with 9.5:1 dr and 88:12 er from aldimine **8** and azatriene **1**; the product was isolated as an 8:1 mixture of *E*/*Z* isomers. Ketimine **10** undergoes a highly diastereoselective addition,

Scheme 4. Cu–Ph-BPE-Catalyzed Additions of Azatriene 1 to an Aliphatic Aldimine and a Ketimine[a]



[a]See Scheme 2. [c]Ratio of 6,3:6,5-addition not determined; isolated product contains 8% *syn*-**9** and 8% (*Z*)-**9**. [d]Diamine **11** isolated as an *E*/*Z* mixture and contains 6% 6,5-addition isomer.

forming *anti*-**11** in 20:1 dr, although regio- (6:1 rr) and enantioselectivity (85:15 er) are moderate. Intriguingly, the allylation reaction leads to only 2.5:1 *E*/*Z* selectivity for the olefin within **11**. Cu–*t*-Bu-BDPP is ineffective in these couplings, generating a complex mixture of products.[35]

For preparative scale diamine synthesis, we employed lower catalyst loadings and higher reaction concentrations (Scheme 5). 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 1.2 mol % Ph-BPE. Similarly, **2a** was converted to *syn*-**3a** (61% yield) in the presence of just 3.3 mol % of the Cu–*t*-Bu-BDPP catalyst. Regio- and

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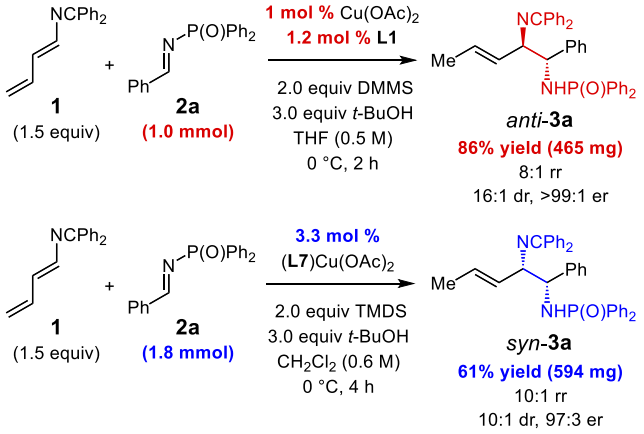
Scheme 5. Larger Scale Diamine Synthesis



stereoselectivity are largely unaffected by the scale up and modified conditions.

2.2. Mechanistic Studies. In order to gain a better understanding of factors governing the stereochemical outcome of the reductive couplings with the two optimal catalysts, we carried out a number of additional experiments. Having qualitatively observed a relationship between aryl aldimine electronics and the diastereoselectivity of diamine formation, we first initiated a more detailed study to determine if there were a true correlation and, if so, its magnitude. The results are shown as Hammett plots in Figure 1.[37]

Each ligand shows a linear dependence for the reaction diastereoselectivity upon the imine's electronic character,

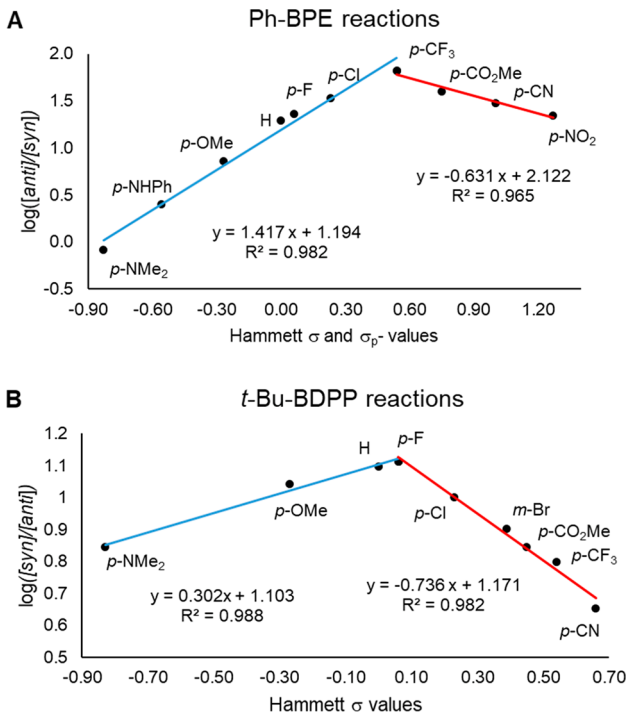
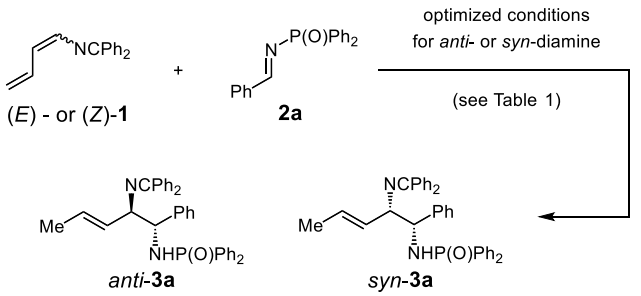


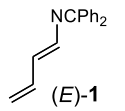
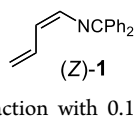
Figure 1. Hammett plots for diastereoselectivity dependence of aryl aldimine electronics with each Cu catalyst. (A) Reactions with Ph-BPE. (B) Reactions with *t*-Bu-BDPP. Diastereomer ratios measured by 500 MHz ^{1}H or 202 MHz ^{31}P NMR spectroscopy of the unpurified mixture. See the Supporting Information for additional details.

although this tie is greater for Ph-BPE (**L1**). For both ligands, the ratio of the normally observed major diastereomer to the minor isomer increases as the imine becomes more electron-deficient. With Ph-BPE, the selectivity morphs from a reaction that slightly favors the *syn*-diamine with a *p*-NMe_2 group (1:1.2 dr) to a highly *anti*-selective process (66:1 dr) with the *p*-CF_3 imine (ρ = 1.4, R^2 = 0.98, Figure 1A). For *t*-Bu-BDPP (**L7**), however, the *p*-NMe_2-substituted imine still leads to a fairly *syn*-selective reaction (1:7 dr) but the diastereoselectivity increases to a maximum of just 1:13 with a *p*-fluoro group (ρ = 0.30, R^2 = 0.99, Figure 1B). For each ligand, there is a break in the plot where diastereoselectivity then decreases as the imine becomes even more electron-poor.[38] The break is indicative of a change in the diastereodetermining step in the reactions.[39−41] For Ph-BPE, the erosion does not significantly impact the synthetic utility, with the *p*-nitro imine delivering the corresponding diamine in 22:1 dr (ρ = −0.63, R^2 = 0.97, Figure 1A); with *t*-Bu-BDPP, the *p*-cyano *syn*-diamine **3g** is modestly favored (1:4.5 dr, ρ = −0.73, R^2 = 0.98, Figure 1B).[35] It should be noted that product regioselectivity shows a poor correlation with imine electronics.

We next investigated how stereochemistry of the azatriene may play a role in the chemo-, regio-, and stereoselectivity of the imine couplings (Table 2). Under their respective

Table 2. Comparison of (*E*)- and (*Z*)-Azatrienes[a]



entry	azatriene	ligand	3a:4a:5a[b]	*anti*:*syn*-3a[b]	er *anti*-3a[c]	er *syn*-3a[c]
1	 (*E*)-1	L1	89:9:2	19.5:1	>99:1	<52:48
2		L7	83:6:11	1:12.5	42:58	97:3
3	 (*Z*)-1	L1	86:9:5	15:1	>99:1	<52:48
4		L7	84:7:9	1:12	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]Diastereomer ratios measured by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [c]Determined by HPLC analysis of purified **3a**.

optimized conditions, the copper catalysts bearing **L1** or **L7** show little difference in regio- (**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 *anti*-**3a** is formed with **L1** regardless of azatriene geometry (>99:1 er, 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 largely unaffected. We also measured the er of the minor diastereomer of the reactions. Somewhat surprisingly we discovered that it is

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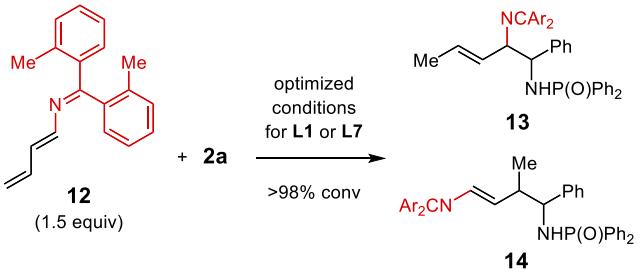
formed with poor enantioselectivity in each case. Additionally, we stopped the reactions of both (*E*)- and (*Z*)-**1** after 30 s with the Cu−Ph-BPE catalyst. There was approximately 60% conversion to *anti*-**3a** but none of the recovered azatriene had undergone stereochemical inversion in either case, suggesting CuH insertion is irreversible.

To examine the azatriene aryl groups' influence upon product distribution and stereoselectivity, we prepared *o*-tolyl containing **12** and carried out reductive coupling with imine **2a** (Table 3). In both cases, 6,5-addition product **14** is favored

Table 3. Couplings with 1,1-Di(*o*-tolyl)azatriene 12[a]



entry	ligand	13:14[b]	dr 13[b]	dr 14[b]
1	**L1**	1:2.5	1:1	4.5:1
2	**L7**	1:9.5	2.5:1	7.5:1

[a]Reaction with 0.1 mmol imine **2a**. Entry 1 was run under the conditions of Table 1, entry 1; entry 2 was run under the conditions of Table 1, entry 9. [b]Determined by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture.

over 1,2-diamine **13**, significantly so with *t*-Bu-BDPP (1:9.5 **13**:**14**, entry 2). Diamine **13** is obtained in low dr and **14** with modest selectivity.

We were able to obtain an X-ray crystal structure of the major stereoisomer of **4k** (Figure 2), which is the major

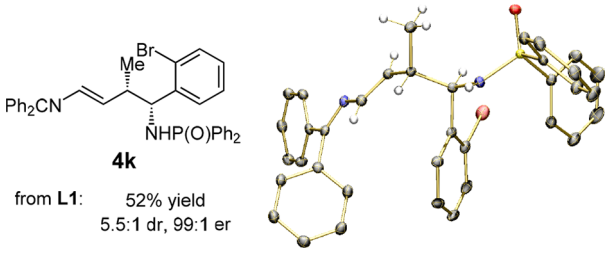


Figure 2. X-ray structure of 6,5-addition product **4k** obtained by reductive coupling with Ph-BPE (**L1**).

product of azatriene (**1**) reductive coupling with the *o*-bromo imine (Scheme 2). The observed stereochemistry indicates that the allyl−copper that leads to **4** has copper bound to the same face as that which leads to **3** and that imine facial selectivity is the same in both instances.

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 suggests a mechanistic dichotomy in the C−C bond-forming step. Furthermore, the profound diamine diastereoselectivity dependence on the imine electronics observed with the Ph-BPE-derived catalyst is significantly different from our prior azadiene additions to *N*-phosphinoyl imines with the same catalyst, where the *anti*-diamine was obtained with >20:1 dr in all cases.[12]

We propose that although both azatriene isomers **1** may undergo migratory insertion to the CuH species derived from either ligand with olefin facial selectivity, that is irrelevant as all possible stereoisomers of allyl−copper **I** can equilibrate through (*E*,*E*)-**III** via intermediates **II** (Scheme 6, left). These equilibria are likely faster than the addition of any species to the imine (Curtin−Hammett conditions) and, with the allyl−copper formation irreversible, provides the most likely explanation for the data in Table 2.

The mechanism for C−C bond formation with each catalyst is less certain. In both instances, we propose a closed transition state, and our working hypothesis is shown in Scheme 6 (right). With Ph-BPE (**L1**), we suggest that reaction takes place through O-coordination of the imine[30c] (**IV**) but with *t*-Bu-BDPP (**L7**) via coordination of the imine's nitrogen atom (**V**). Therefore, the stereochemical outcome with **L1** can be explained by α-addition of (*S*,*E*)-**II** to the imine's *Re* face (**IV**), whereas the **L7**-promoted reaction takes place by γ-addition of (*R*,*E*)-**I** to the same face of the imine (**V**).

From the phosphine ligands we have examined for this transformation, it is clear that Ph-BPE is an outlier in favoring the *anti*-diamine to any degree.[33] The product stereoisomer observed is the same as that in our previous Cu−Ph-BPE-catalyzed azadiene couplings with this class of imines, which deliver α-alkyl diamines,[12] suggesting a similar addition mode; however, in the earlier chemistry, there was no dr dependence on imine electronics. These data indicate a mechanistic pathway toward *syn*-diamines available to Cu−**L1** with azatrienes but not azadienes, likely a γ-addition mode via N-coordination of the imine (i.e., **V**). The significant, positive ρ observed at lower σ values in the Hammett plot (Figure 1A) implies that C−C bond formation is the diastereodetermining step, with addition through **IV** becoming more stabilized compared to the alternative as the imine becomes more electrophilic.[39−41] At higher σ_p− values, the negative ρ is consistent with imine coordination becoming diastereodetermining. Therefore, the most electrophilic imines become less discriminating in their coordination with and subsequent addition to the myriad allyl−copper species available.

The *t*-Bu-BDPP reactions display a similar electronic trend although the break in the plot occurs with electron-neutral imines (Figure 1B). Furthermore, although the right-hand half of the plot has a comparable negative ρ value to the Ph-BPE reactions, the correlation at small σ values shows a significantly smaller positive ρ. It may be that the *anti*-diamines formed with *t*-Bu-BDPP also arise through intermediate **IV** although several possibilities exist. For example, the path to the *anti*-diamine may not involve O-coordination of the imine but rather a different γ-addition mode, such as that from (*S*,*Z*)-**I** to an N-coordinated imine. It should be noted that since the minor diastereomer of **3** with each ligand is racemic, the stereodetermining step for the minor three stereoisomers in the coupling have similar free energies.

Further evidence in support of these two addition models can be found in the imine coupling of azadiene **15** with the Cu−*t*-Bu-BDPP catalyst (Scheme 7). Under our previously established conditions for this transformation with Ph-BPE,[12] *anti*-diamine **16** is obtained as the major isomer (5:1 *anti*:*syn*), with similar selectivity to DCyPE (3:1 *anti*:*syn*). Thus, without the possibility of N-coordination of the imine, the major

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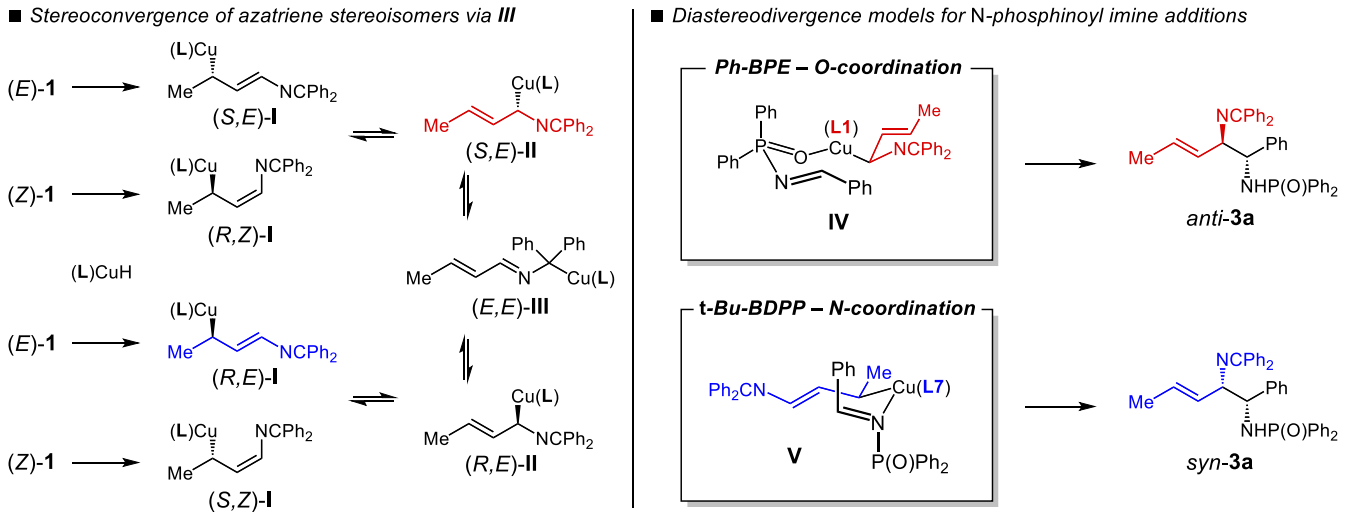
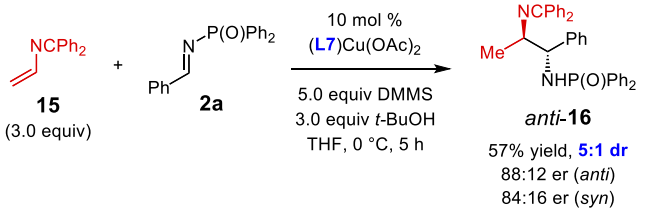
Scheme 6. Mechanistic Proposal for Azatriene−Imine Couplings



Scheme 7. *anti*-Selective Addition of Azadiene 15 to Imine 2a with the Cu−*t*-Bu-BDPP Catalyst



pathway funnels the azaallyl−copper species through an O-coordination/α-addition mode.

The majority of couplings lead to products that exclusively contain an (*E*)-alkene; however, pyrrolo imine **2m** (Scheme 2), alkyl aldimine **9** (Scheme 4), ketimine **11** (Scheme 4), and the *p*-NMe_2 and *p*-NHPh aryl aldimines utilized in the Hammett study (Figure 1) all afford measurable quantities of the (*Z*)-isomer.[35] Although the reason for alkene stereochemical erosion is unclear, the phenomenon appears to be tied to imine electrophilicity as these five partners are among the least electrophilic we examined.

The shift in regioselectivity with di(*o*-tolyl)azatriene **12** (Table 3) toward 6,5-addition product **14** with both catalysts and the poor diastereoselectivity observed for 1,2-diamine **13** implies a disruption in the allyl−copper equilibria due to added steric hindrance in **II** and **III** (Scheme 6) compared to azatriene **1**. The stereochemistry of amine **4k** (Figure 2), obtained with Ph-BPE, can be explained either by γ-addition of (*S*,*E*)-**II** to the imine (versus α-addition **IV**) or by an α-selective addition of (*S*,*E*)-**I**. The high selectivity for **14** with *t*-Bu-BDPP is somewhat puzzling as hindered *ortho*-substituted *N*-phosphinoyl imines lead to *syn*-diamines **3j−k** (Scheme 2) as the exclusive products (reaction through **V**). It may be that (*R*,*E*)-**I** is less accessible when employing **12** (versus **1**) because irreversible CuH insertion to the azatriene initially occurs to furnish (*S*,*E*)-**I**.

3. CONCLUSION

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 with 2-azatrienes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07707.

Data for **4k** (CIF) Experimental procedures, analytical data for new compounds, and NMR spectra (PDF)

Accession Codes

CCDC 2098313 contains 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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(35) See the Supporting Information.

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