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Article

Palladium-Catalyzed Regiodivergent Three-Component Alkenylamination of 1,3-Dienes with Alkyl and Aryl Amines

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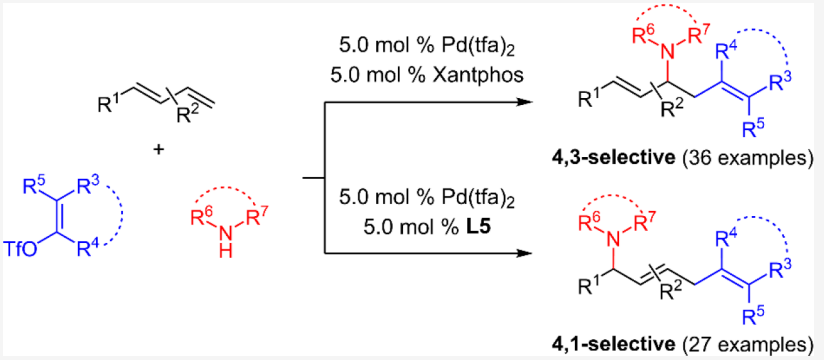

ABSTRACT: We report a palladium-catalyzed method for 4,3- or 4,1-selective alkenylamination of terminal dienes. Three-component couplings proceed with alkenyl triflates and several amines, giving vicinal carboamination with a Xantphos-supported catalyst and distal difunctionalization with a phosphoramidite ligand. A number of constitutionally different disubstituted dienes also participate in regiodivergent carboaminations. Experimental evidence indicates that selectivity in the Xantphos reactions is largely influenced by the substrate, whereas the phosphoramidite-promoted process is catalyst controlled, orchestrated by a key π-stacking interaction among the ligand, solvent, and substrate.

1. INTRODUCTION

Conjugated dienes function as a tremendous platform for a variety of nucleophilic addition reactions through their catalytic activation, leading to value-added products that retain a carbon−carbon double bond. As such, several hydro- and difunctionalization reactions of dienes have been developed with a variety of nucleophiles.[1] Three-component couplings involving dienes are a particularly attractive class of difunctionalization reactions, as they enable a rapid buildup of molecular complexity from simple, commercial or readily available materials and provide an expedient route to chemical library synthesis.[2] Yet, these transformations also come with several challenges, such as (1) avoiding possible bimolecular couplings and (2) controlling the sites of the bond formations as, in the case of terminal dienes, up to 16 isomers might be theoretically generated from the addition of the other two components. Layer in the possibility of chain walking leading to alkene migration[3] within the products and a multitude of products might be formed from this difunctionalization approach. Reports often illustrate an optimized process for the formation of only one major product isomer.[4]

Our group has had a long-standing interest in the hydrofunctionalization of acyclic dienes,[5] including hydroaminations with aliphatic amines.[6−8] Looking to expand the utility of alkyl amine−diene couplings, we sought to develop a carboamination reaction with an initial focus on alkenylation in the C−C bond-forming step to deliver skipped diene products. Three-component reactions of dienes with alkenyl reaction partners are uncommon; transformations with alkyl amines are also rare.[9]

One of the earliest reported three-component reactions with dienes involved alkenylaminations with aliphatic amines (Scheme 1). Heck and co-workers showed a 4,1-selective[10] carboamination of simple dienes, such as butadiene, isoprene, and 1,3-pentadiene, with a handful of acyclic alkenyl bromides/iodides and only two amines, morpholine and piperidine.[11−13] 1,3-Pentadiene was the only terminal diene examined. *Regioselectivity in the amination was controlled by the substrate*, where the amine attacked the least hindered carbon of the intermediate 1,3-disubstituted Pd−π-allyl complex; however, selectivity was at times poor, with some reactions being accompanied by Heck reaction (two-component coupling) and/or plagued by low product yields.

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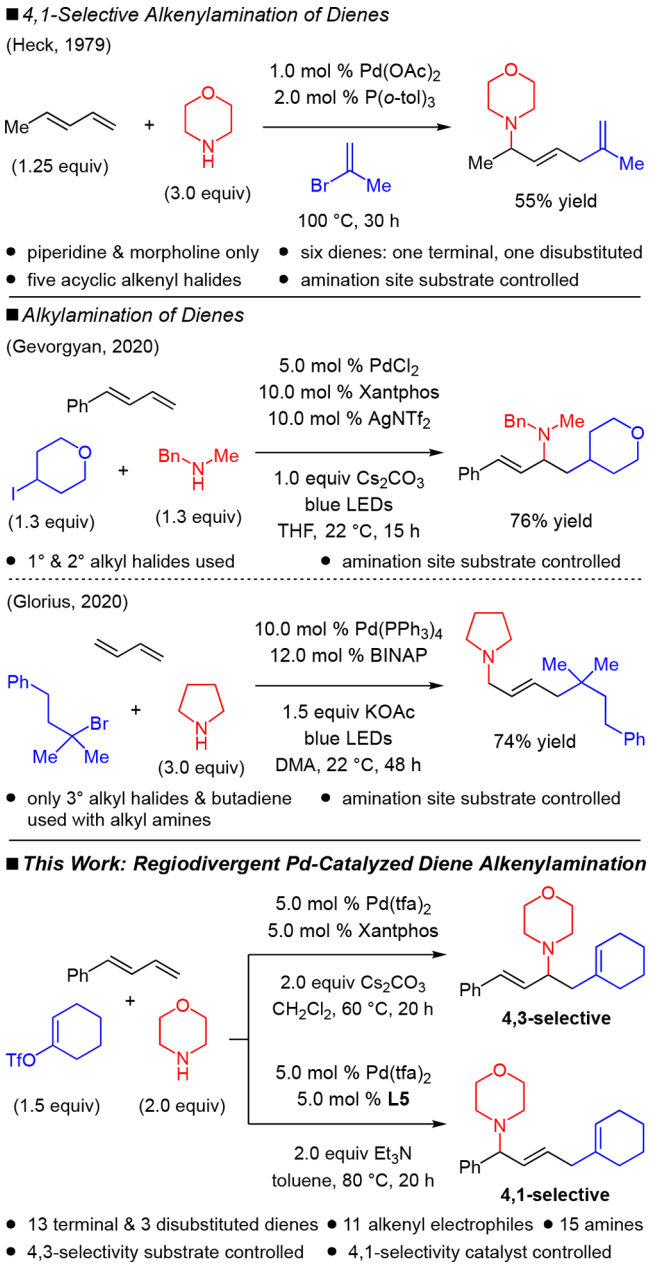
Scheme 1. Three-Component Diene Carboaminations



Relatively recently, the Gevorgyan[14] and Glorius[15] groups simultaneously described alkylaminations of dienes with aliphatic amines using Pd−phosphine catalysts under visible light irradiation.[16] In Gevorgyan's case, with primary or secondary alkyl iodides, aryl butadienes undergo selective 4,3-carboamination in the presence of a Pd−Xantphos catalyst. Substrate-controlled amination at C3 of aryl butadienes preserves olefin−arene conjugation in the product; with bulky alkyl dienes, C3 attack minimizes steric repulsion. Using Pd−BINAP as the catalyst, the Glorius group has illustrated selective 4,1-addition of tertiary alkyl bromides and aliphatic amines only with butadiene. The regioselectivity is once more controlled by the substrate sterics.

In this work, we demonstrate alkenylaminations of a broad scope of terminal and disubstituted dienes with a variety of cyclic and acyclic alkenyl electrophiles and aliphatic amines and anilines, significantly improving and going beyond the results of the Heck group (Scheme 1). Moreover, we have achieved regiodivergence in these three component couplings by the choice of ligand for palladium and gained insight into what controls the selectivity in each case. We have found that with Pd−Xantphos as the catalyst, there is nearly exclusive 4,3-addition, whereas a Pd−phosphoramidite catalyst furnishes 4,1-alkenylamination products as the major isomer.[17]

2. RESULTS AND DISCUSSION

We initiated our study by first examining P(*o*-tolyl)$_3$, as Heck had done, as the ligand for palladium (Table 1, entries 1−4) in the coupling of phenylbutadiene (**1a**, 0.15 mmol, 0.2 or 1.0 M), cyclohexenyl triflate **2a** (1.5 equiv), and morpholine (2.0 equiv) at 80 °C. In contrast to Heck's finding of exclusive 4,1-addition of morpholine (Scheme 1), we obtained a mixture of 4,3-addition (**3a**), 4,1-addition (**4a**), and Heck reaction (**5a**), regardless of the ligand/Pd ratio (compare entries 1 and 2). At higher reaction concentration (Heck did not employ solvent in his study), 4,3-addition and, particularly, Heck addition product predominate (entry 3). Addition of a substoichiometric quantity of KI (entry 4), to mimic the presence of halide as in Heck's report with alkenyl halides, drastically lowers the reactivity of the catalyst under the conditions employed. For the three-component coupling that does occur, there is only minimal regioselectivity. Thus, unlike in Heck's study with piperylene, P(*o*-tolyl)$_3$ does not provide control over product distribution in reactions of aryl diene **1a** under the handful of conditions we explored. This ligand also engenders a catalyst with an apparent lower reactivity compared to the optimal ligands we subsequently discovered for the three-component reaction (*vide infra*).

We next turned our attention to bidentate ligands, beginning with Xantphos (10 mol %) for palladium (10 mol %) with Cs_2CO_3 as the base (2.0 equiv) at 60 °C.[18] Examination of several solvents (entries 5−9) revealed that most predominantly lead to Heck addition product **5a**; however, both toluene and methylene chloride selectively afford 4,3-addition product **3a** (entries 8, 9). Lowering the reactant concentrations diminished overall conversion and increased the proportion of **5a** (entry 10), whereas increasing the concentrations only marginally improved the quantity of **3a** formed (entry 11). With a 0.5 M concentration of diene, the catalyst loading could be reduced to 5 mol % and allylic amine **3a** was isolated in 82% yield (entry 12).

Phosphoramidite ligands also lead to reactive catalysts for diene alkenylamination. With **L1** (10 mol %),[19] Pd(tfa)$_2$ (10 mol %), and triethylamine (2.0 equiv) at 60 °C, the combination of diene **1a** (0.15 mmol, 0.1 M), alkenyl triflate **2a** (1.5 equiv), and morpholine (10 equiv) generates 4,3-addition product **3a** as the major isomer but in low yield in methylene chloride (entry 13). Contrastingly, primarily 4,1-addition product **4a** is formed in toluene at 100 °C (entry 14). The structure of the phosphoramidite also impacts the selectivity. Without aryl substitution at the 3,3′-positions of the BINOL unit (**L2**, entry 15) or without an aryl amino group (**L6** or **L8**, entries 21 and 23), we obtained significant amounts of **3a** and triene **5a**. An acyclic arylamino group of the ligand similarly affords a mixture of **3a**, **4a**, and **5a** (**L7**, entry 22). Slight changes to the 3,3′-aryl groups or having an H_8−BINOL backbone has a small impact on the product distribution (**L1**, **L3**, and **L4**, entries 14, 16, and 17); however, indole-derived phosphoramidite **L5** gives a significant increase in product **4a** over all others (entry 18). This ligand also forms a more

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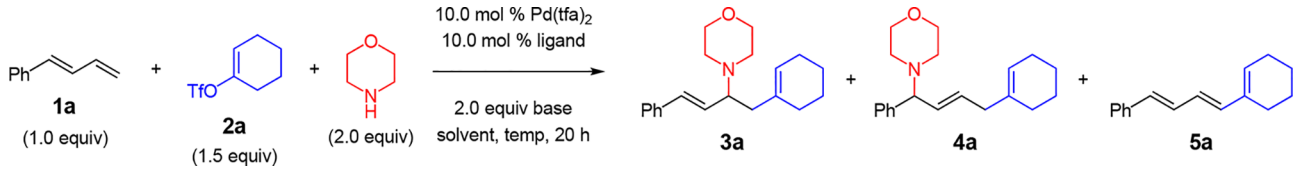
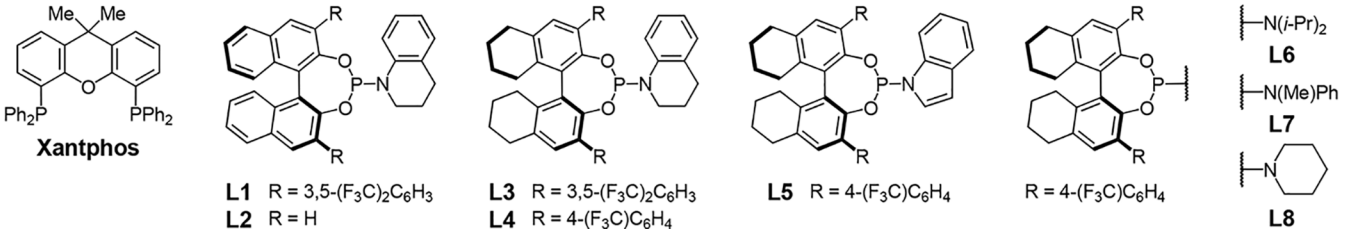
Table 1. Optimization of 4,3- and 4,1-Selective Diene Alkenylaminations[a]



entry	ligand	base	solvent ([1a])	temp (°C)	3a:4a:5a[b]	% yield 3a[c]	% yield 4a[c]
1[d]	P(*o*-tolyl)$_3$	Et_3N	toluene (0.2 M)	80	28:24:20	nd	nd
2[e]	P(*o*-tolyl)$_3$	Et_3N	toluene (0.2 M)	80	32:39:11	nd	nd
3[e]	P(*o*-tolyl)$_3$	Et_3N	toluene (1.0 M)	80	25:3:61	nd	nd
4[f]	P(*o*-tolyl)$_3$	Et_3N	toluene (0.2 M)	80	4:9:6	nd	nd
5	Xantphos	Cs_2CO_3	DMA (0.5 M)	60	<2:<2:73	na	na
6	Xantphos	Cs_2CO_3	THF (0.5 M)	60	15:<2:46	nd	na
7	Xantphos	Cs_2CO_3	CH_3CN (0.5 M)	60	20:<2:56	nd	na
8	Xantphos	Cs_2CO_3	toluene (0.5 M)	60	82:<2:11	nd	na
9	Xantphos	Cs_2CO_3	CH_2Cl_2 (0.5 M)	60	88:<2:7	87	na
10	Xantphos	Cs_2CO_3	CH_2Cl_2 (0.2 M)	60	33:<2:14	nd	na
11	Xantphos	Cs_2CO_3	CH_2Cl_2 (1.0 M)	60	83:<2:9	nd	na
12[d]	**Xantphos**	**Cs_2CO_3**	**CH_2Cl_2 (1.0 M)**	**60**	**84:<2:10**	**82**	**na**
13[g]	L1	Et_3N	CH_2Cl_2 (0.1 M)	60	17:<2:11	nd	na
14[g]	L1	Et_3N	toluene (0.1 M)	100	9:72:15	nd	72
15[g]	L2	Et_3N	toluene (0.1 M)	100	33:28:28	nd	nd
16[g]	L3	Et_3N	toluene (0.1 M)	100	15:60:20	nd	nd
17[g]	L4	Et_3N	toluene (0.1 M)	100	12:75:9	nd	nd
18[g]	L5	Et_3N	toluene (0.1 M)	100	4:87:5	nd	nd
19[d]	L5	Et_3N	toluene (0.2 M)	100	12:73:13	nd	68
20[d]	**L5**	**Et_3N**	**toluene (0.2 M)**	**80**	**9:76:10**	**nd**	**73**
21[g]	L6	Et_3N	toluene (0.1 M)	100	20:36:22	nd	nd
22[g]	L7	Et_3N	toluene (0.1 M)	100	26:53:17	nd	nd
23[g]	L8	Et_3N	toluene (0.1 M)	100	27:35:34	nd	nd



[a]Transformations run under a N_2 atmosphere with 0.15 mmol of **1a**, 2.0 equiv of morpholine, 10.0 mol % $Pd(tfa)_2$, and 10.0 mol % ligand unless otherwise noted. [b]Measured by 500 MHz ^1H NMR spectroscopy of the unpurified mixture with respect to an internal standard. [c]Yield of isolated **3a** or **4a**. [d]5.0 mol % Pd and ligand. [e]5.0 mol % Pd and 10.0 mol % ligand. [f]With 10 mol % KI. [g]10.0 equiv of morpholine. nd = not determined; na = not applicable.

reactive catalyst for 4,1-selective three-component coupling (entries 19 and 20), allowing us to lower the catalyst loading (5 mol %) and decrease the reaction temperature (80 °C) and quantity of morpholine (2.0 equiv). Under these conditions (entry 20, allyl amine **4a** is isolated in 73% yield.

With reaction conditions we considered optimized for each regioisomeric product as our starting point, we next explored the scope of both transformations with respect to each reaction component. We began with 4,3-addition product **3**, which is formed with complete selectivity over isomer **4** in each case (Scheme 2). Several aryl dienes are effective substrates for the Pd−Xantphos-catalyzed 4,3-addition. The electronics of the arene (**3b**−**g**) have little impact on reaction efficiency or selectivity, although the most electron-poor substrates lead to slightly lower yields of the allylic amines (64−73% for **3f** and **3g**). Both *meta*- and *ortho*-substitution are tolerated, with **3h** and **3i** formed in 81% and 86% yield, respectively. The transformation permits the inclusion of heteroaryl dienes such as pyridine (**3j**) and furan (**3k**). *α*-Branched alkyl dienes also allow for selective 4,3-addition with **3l** and **3m** obtained in 81−82% yield. Linear alkyl dienes generate a mixture of product isomers. Internal dienes are ineffective substrates for the reaction.

A variety of alkenyl triflates couple efficiently with phenylbutadiene and morpholine. Six-membered-ring heterocycles, a cyclohexene bearing a ketal, and a sterically hindered dihydronaphthalene take part in reactions to afford **3n**−**q** in 72−80% yield. A cyclopentenyl unit may also be installed (**3r**). The incorporation of substituted acyclic alkenes (**3s**−**u**) further widens the chemical space that may be easily accessed

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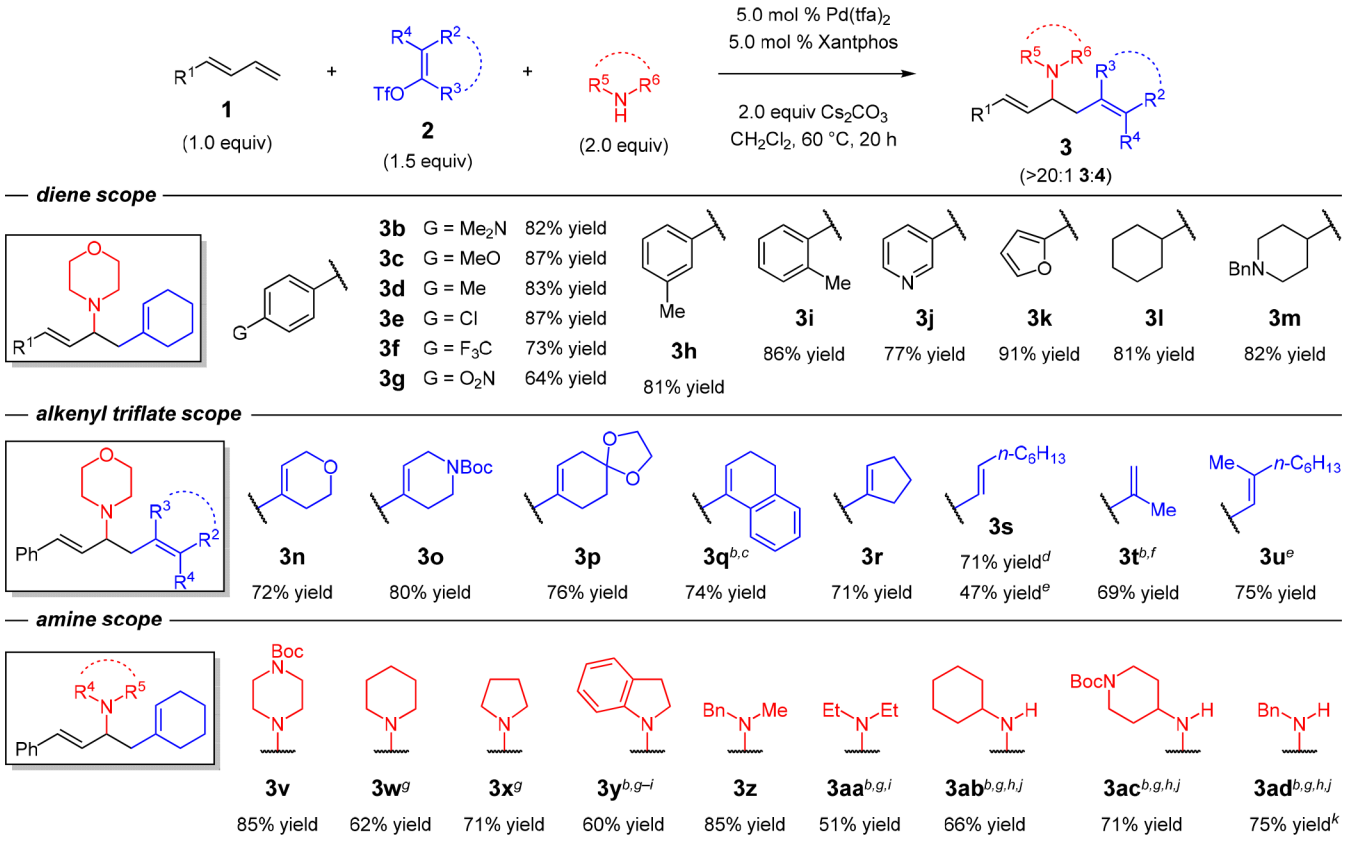
Scheme 2. Reaction Scope in the Pd−Xantphos-Catalyzed Formation of 4,3-Addition Product 3[a]



[a]Reactions under the conditions of Table 1, entry 12, unless otherwise noted; ratio of **3**:**4** as assessed by 500 MHz ^{1}H NMR spectroscopy of the unpurified reaction mixture was always >20:1. [b]Reaction temperature = 80 °C. [c]Reaction time = 50 h. [d]Alkenyl triflate **2** (0.15 mmol, 5:1 *E*:*Z*) used as the limiting reagent (1.5 equiv of **1a**); >10:1 *E*:*Z* ratio (unpurified reaction mixture and isolated) for **3s**. [e]From isomerically pure alkenyl iodide. [f]From alkenyl bromide. [g]Diene **1** concentration = 2.0 M. [h]Toluene in place of CH_2Cl_2. [i]Et_3N in place of Cs_2CO_3. [j]$NaHCO_3$ in place of Cs_2CO_3. [k]Calculated yield of **3ad**, isolated along with ca. 10 mol % of an inseparable byproduct resulting from phenyl addition to the diene instead of cyclohexenyl; see the Supporting Information for details.

through the three-component coupling. The linear 1-octenyl triflate, prepared as a 5:1 *E*:*Z* mixture, generates allylic amine **3s** in a >10:1 *E*:*Z* ratio, we presume as a result of the (*E*)-isomer of the alkenyl triflate being more reactive than the (*Z*). To support this, the corresponding (*Z*)-alkenyl iodide leads to only 6% conversion to **3s** at 80 °C under otherwise identical conditions, whereas the (*E*)-alkenyl iodide isomer, prepared and tested independently, brings about 50% conversion to (*E*)-**3s**. The formation of branched products **3t** and **3u** from the corresponding alkenyl bromide and iodide, respectively, further illustrates the compatibility of the Xantphos-promoted reaction with halides and the ability to incorporate alkenes of varying substitution pattern.

The three-component coupling is amenable to the addition of several desirable amines, including cyclic amines such as protected piperazines (**3v**), piperidine (**3w**), pyrrolidine (**3x**), and indoline (**3y**). Acyclic secondary amines (**3z** and **3aa**) and primary amines (**3ab**−**ad**) also participate. Changes to the amine structure have considerable influence over reaction efficiency and product selectivity, the most of any reaction component, and therefore required optimization on an individual basis. For instance, indoline and diethylamine addition (**3y** and **3aa**) only take place in the presence of triethylamine as the base, perhaps suggesting general base catalysis or at least the requirement for hydrogen bonding in C−N bond formation. With other bases, the Heck product is the only one formed. In this instance and for many other amines, doubling the diene concentration to 2.0 M is also needed to suppress the Heck reaction and favors three-component coupling. For primary amines, the weaker base $NaHCO_3$ in toluene as the solvent is needed to increase the fraction of 4,3-addition over Heck reaction.[20]

A variety of 4,1-selective alkenylaminations are accessible utilizing **L5** in toluene (Scheme 3).[21] Most aryl dienes deliver unconjugated product **4** as the major reaction isomer, independent of diene electronics (**4b**−**f**) or positional substitution (**4g** and **4h**); however, we discovered that the *p*-dimethylaminophenyl diene affords only a trace amount of 4,3-addition product (**3b**) but no 4,1-addition. Contrastingly, it is other more electron-rich dienes that afford higher fractions of product **4** (compare **4b**,**c** and **4g** with **4d**−**f**). Pyridine and furyl dienes function to furnish benzylic amines **4i** and **4j**, respectively, in 71% and 83% yield. As with reactions involving Xantphos as the ligand, linear alkyl dienes lead to a mixture of 4,3- and 4,1-addition with **L5**, and α-branched alkyl dienes lead to exclusive 4,3-addition (e.g., 78% yield with the cyclohexyl-substituted terminal diene), thereby highlighting a requirement for aryl substitution of the diene for achieving 4,1-addition.

Reactions of cyclic alkenyl triflates proceed uneventfully with the Pd−**L5** catalyst: skipped dienes **4k**−**o** are obtained in 74−83% yield. With 2-octenyl triflate, we also observe 4,1-addition product **4p** as the major isomer, which is isolated in 75% yield,

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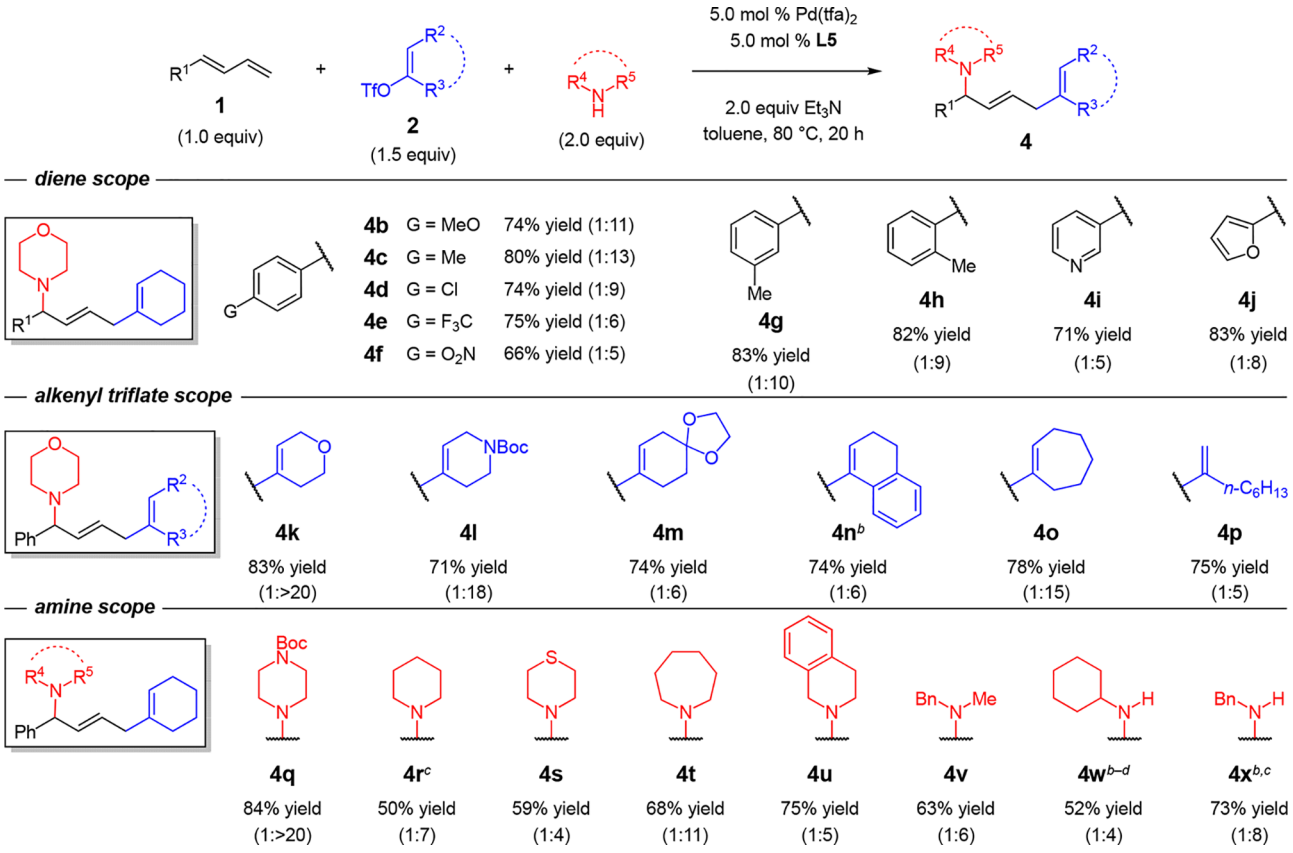
Scheme 3. Reaction Scope in the Pd–L5-Catalyzed Formation of 4,1-Addition Product 4[a]



[a]Reactions under the conditions of Table 1, entry 20, unless otherwise noted; ratio of **3**:**4** as assessed by 500 MHz ^{1}H NMR spectroscopy of the unpurified reaction mixture in parentheses. [b]Reaction temperature = 100 °C. [c]$NaHCO_3$ in place of Et_3N. [d]Reaction time = 50 h.

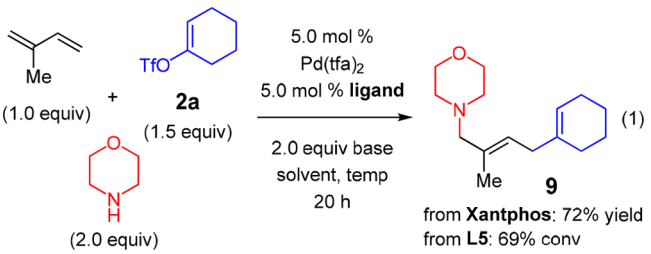
with the **L5**-based catalyst. Conversely, the corresponding alkenyl iodide predominantly leads to 4,3-addition with the same catalyst (58% yield), indicating Pd counterion-dependent regioselectivity in the amination event. Compared to this α-branched alkenyl triflate, linear substrates afford a mixture of regioisomers (ca. 1:1 **3**:**4** for 1-octenyl triflate addition).

A range of aliphatic amines are selectively added in a 4,1-fashion to generate benzylic amine products. Cyclic amines such as *N*-Boc piperazine (**4q**), piperidine (**4r**), thiomorpholine (**4s**), azepine (**4t**), and tetrahydroisoquinoline (**4u**) are reactive partners (50–84% yield). Unhindered acyclic secondary amines effectively participate in the amination (63% yield, **4v**). Primary amines can be coaxed to undergo addition but require a higher temperature (**4w** and **4x**, 100 °C) and, in the case of cyclohexylamine, a longer reaction time (50 h).

We additionally investigated alkenylaminations with more substituted dienes by studying transformations using 1-phenyl dienes bearing a methyl group at each of the four diene carbons with each catalyst (Scheme 4). Inclusion of a methyl group at C1 or C2 with the Xantphos-based catalyst facilitates the formation of allylic amines **7a** and **7b**, which contain trisubstituted alkenes. Each compound is formed as the only constitutional isomer from the reaction; amine **7a** is the only instance we have observed where an isomerically pure substrate affords any stereoisomerism (obtained as a 7:1 *E*:*Z* mixture). The inclusion of either a C3 or C4 methyl group fails to afford any discernible three-component coupling under any conditions examined (**7c** or **7d**); no Heck product can be detected in either reaction, as well, suggesting Pd–Xantphos is incapable of promoting the migratory insertion to a disubstituted double bond.

With Pd–**L5**, several allylic amines could be obtained, primarily or exclusively through benzylic attack, in the same methyl group positional scan described above. Although an internal diene (C4 methyl group, formation of **8d**) is unreactive, incorporation of the methyl group at any other carbon furnishes amines **8a–c** with good selectivity. In particular, the formation of **8a** and **8c** is notable in that benzylic addition of morpholine is the only observed pathway, regardless of whether a tetrasubstituted center is formed or not. In all cases, the products were obtained as a single olefin isomer.

We also investigated the coupling of isoprene, a feedstock chemical, under the three-component coupling conditions with each catalyst (eq 1). In this case, under our optimized



conditions for each respective ligand, both Xantphos and **L5** afford the same major product **9** (>98% *E*), resulting from

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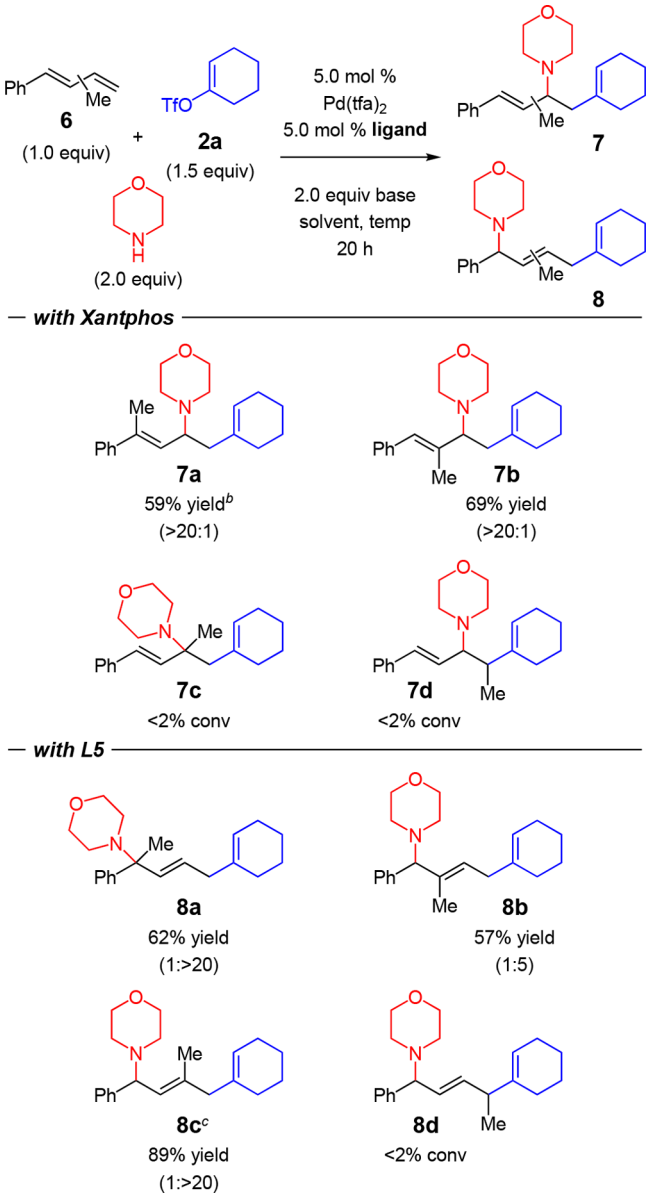
Scheme 4. Couplings with Disubstituted Dienes[a]

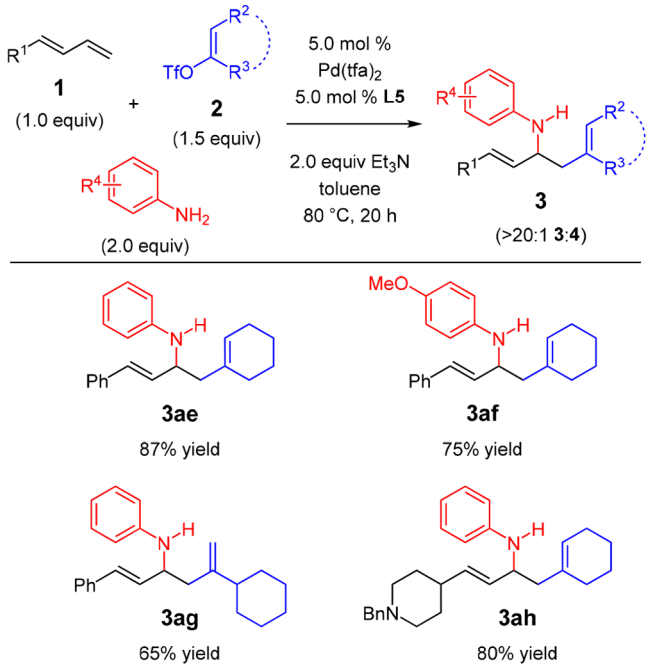


[a]Reactions with Xantphos under the conditions of Table 1, entry 12, and those with **L5** under the conditions of Table 1, entry 20; ratio of **7**:**8** listed in parentheses. [b]Obtained as a 7:1 *E*:*Z* mixture. [c]Reaction temperature = 100 °C.

insertion of the monosubstituted double bond of isoprene to the alkenyl–palladium followed by amination at the more distal carbon.

In the course of examining different amines in the three-component couplings with **L5**, we discovered that aryl amines (e.g., indoline and tetrahydroquinoline[22]) lead to exclusive 4,3-addition. Aniline addition to phenylbutadiene with cyclohexenyl triflate (Scheme 5) was a particularly efficient reaction, delivering styrenyl product **3ae** in 87% yield. Significantly, the Pd–Xantphos catalyst does not promote a three-component reaction with aniline. Thus, although affording an unexpected product constitution, phosphoramidite **L5** leads to reactivity with this important class of amine nucleophiles that is otherwise inaccessible. A more electron-rich aniline had little impact on the product yield (**3af**). 1-Cyclohexylvinyl triflate

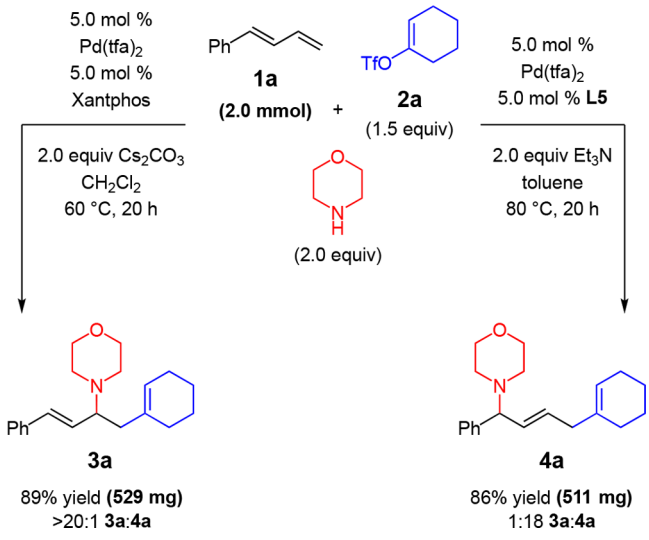
Scheme 5. Pd–L5-Catalyzed Aniline Additions Afford 4,3-Selectivity



yields 4,3-addition with aniline (**3ag**). Finally, alkyl dienes also lead to vicinal carboamination (**3ah**).

To our delight, the reactions with both catalysts were scalable. The reactions performed slightly better on a 2.0 mmol scale of diene **1a** (Scheme 6). Higher proportions of the

Scheme 6. Three-Component Carboamination Scalability



desired products were obtained in each case (**3a** in excess of Heck product **5a** for reaction with Xantphos and **4a** in excess of isomer **3a** and Heck product **5a** for reaction with **L5**).

We decided to probe the halide effect upon product selectivity further by introducing a catalytic quantity of potassium iodide to the reaction medium under the conditions that normally lead to 4,1-addition (eq 2). With just 10 mol % KI, the Pd–**L5** selectivity for 4,1-carboamination (**4a**) is completely suppressed, and 4,3-product **3a** is formed in 73% yield, accompanied by 9% Heck product **5a**. The experiment

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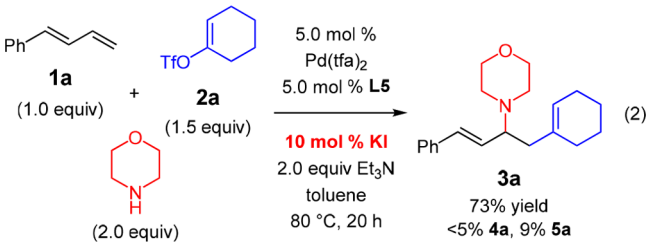


suggests the highly disruptive effect a coordinating counterion to palladium has upon product selectivity.

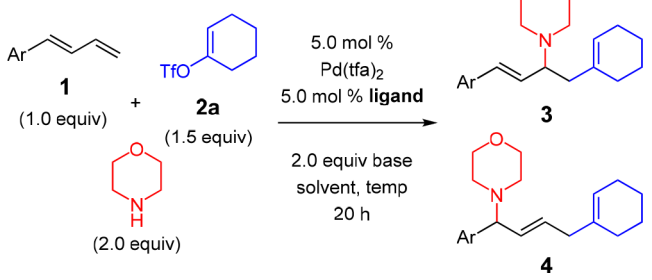
In the course of this work, we were interested in developing an enantioselective version of each carboamination. Some preliminary findings are summarized in Table 2. Most chelating ligands we investigated do not elicit three-component coupling to deliver **3a**, instead primarily delivering Heck product **5a** or a small amount of hydroamination of diene **1a** (Phox ligands).[6,20] Commercially available BoPhoz, however, selectively afforded amine **3a**, which was isolated in 64% yield and 79:21 er (entry 1). Our modifications of the BoPhoz structure did not improve upon this result.[20] Low enantioselectivity is similarly observed with phosphoramidite ligands in the formation of **4f**. Ligand **L4** gives the *p*-nitrophenyl product with the maximum 66:34 er that we have observed (entry 2), whereas our optimal ligand **L5** generates nearly racemic product (entry 4). We also find that the addition of KI to the reaction with **L5** to deliver 4,3-addition product **3a** also proceeds with low levels of enantioselectivity (entry 3). These findings contrast with related diene 4,3-arylalkylations with a derivative of **L4**, dimethyl malonate as the nucleophile, and aryl iodides that were studied by the Gong group.[19] There, reactions in MTBE as solvent led to products with >90:10 er, often >95:5.

Our findings regarding the regiodivergent behavior of Xantphos- and **L5**-based palladium catalysts for alkenylamination of dienes as well as the variables that abrogate 4,1-selectivity with **L5** to induce 4,3-addition instead led us to the following proposed models to account for the site of C−N bond formation (Scheme 7). Alkenyl−palladium migratory insertion to the diene at the least hindered position generates a π-allyl complex that may undergo amination at C1 or C3. With Xantphos, amine attack takes place at C3, the sterically least hindered position of the π-allyl and in the case of aryl dienes, the one that preserves olefin conjugation with the arene, a pathway therefore largely under the influence of the substrate.

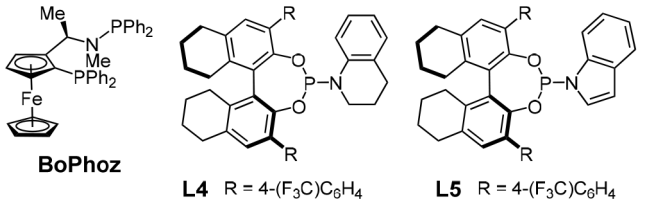
For phosphoramidite ligands, several features of the transformations to bring about amination at C1 strongly suggest that arene π-stacking is a critical organizational feature of the transition state that induces this selectivity. (1) A cyclic aryl amino substituent of the phosphoramidite ligand is a requirement. The cyclic nature of the amine restricts its rotation, further facilitating π-stacking. (2) Counterintuitively, attack occurs at C1 only for *aryl* dienes. (3) Aromatic solvents are needed to induce 4,1-selectivity.

The organization imparted by the π-stacking of the ligand, solvent, and aryl group of the π-allyl led the monodentate

Table 2. Preliminary Findings in Enantioselective Regiodivergent Three-Component Couplings[a]

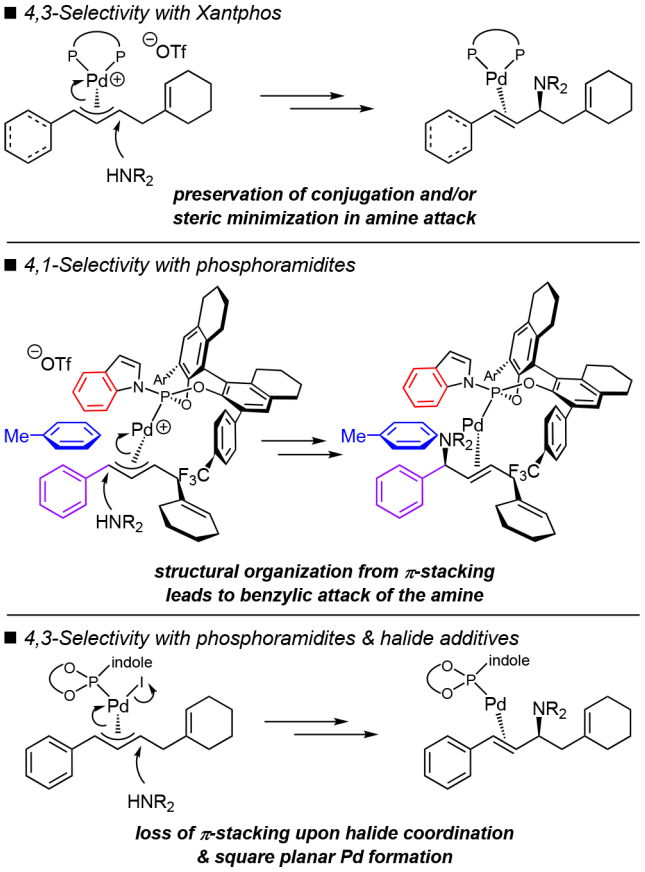


entry	diene (Ar)	ligand	3:4:5[b]	% yield 3 or 4[c]	er 3 or 4[d]
1[e]	C_6H_5	**BoPhoz**	67:<2:27	64 (**3a**)	79:21
2	4-$(O_2N)C_6H_4$	**L4**	11:63:21	57 (**4f**)	66:34
3[f]	C_6H_5	**L5**	72:4:10	69 (**3a**)	58:42
4	4-$(O_2N)C_6H_4$	**L5**	15:73:8	66 (**4f**)	55:45



[a]Reactions with BoPhoz under the conditions of Table 1, entry 8, and those with **L4** and **L5** under the conditions of Table 1, entry 20. [b]Measured by 500 MHz ^{1}H NMR spectroscopy of the unpurified mixture with respect to an internal standard. [c]Yield of isolated **3a** or **4f**. [d]Enantiomer ratios determined by HPLC with a chiral stationary phase in comparison to the authentic racemic material. [e]Reaction with 10 mol % $Pd(tfa)_2$ and 10 mol % BoPhoz. [f]Reaction with 10 mol % KI.

Scheme 7. Proposed Selectivity Models for Regiodivergence



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phosphoramidite to orient the 3-aryl substituent of the H_8–BINOL subunit toward the π-allyl. This in turn forces the C4-introduced alkenyl unit away, which if branched shields C3 from amine attack.

Other factors abolish C1 amination. The presence of a halide in solution compared to triflate likely leads to a different coordination environment at palladium by the halide becoming an inner-sphere ligand, disrupting π-stacking and thereby eliciting a C3 amine attack (Scheme 7). A lack of branching in the alkenyl triflate diminishes 4,1-selectivity as amine attack at C3 becomes more feasible. Furthermore, aryl amines, which add to C3, may also interfere with π-stacking, although their differential nucleophilicity to aliphatic amines cannot be discounted as a selectivity factor.

3. CONCLUSION

We have developed three-component regiodivergent alkenyl aminations of terminal and disubstituted dienes using aliphatic amines as the nucleophiles. Two different Pd-based catalysts lead to differential site-selectivity in the C–N bond formation step. With Xantphos as the ligand, the expected C3-amination is obtained, whereas an *N*-aryl phosphoramidite ligand leads to C1-amination, breaking olefin/arene conjugation. Several findings point to π-stacking among the ligand, solvent, and aryl group of the substrate-derived π-allyl as a key controlling factor in the latter case. Further mechanism investigations and additional three-component coupling methodologies are under study in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c09873.

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

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Notes

The authors declare no competing financial interest.

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(17) A preprint of this work was published on ChemRxiv on September 8, 2023: https://chemrxiv.org/engage/chemrxiv/article-details/64fa0964b338ec988a0fd7e8.

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(20) See the Supporting Information for greater detail.

(21) We have found that high-purity toluene (in our case 99.9% HPLC grade from Sigma-Aldrich, sparged with N_2 and passed through two successive alumina columns) is needed to achieve 4,1-selectivity. Unpurified HPLC grade toluene leads to greater quantities of 4,3-alkenylamination. See the Supporting Information for details.

(22) Cyclic aryl amines, such as indoline and tetrahydroquinoline, are capable of reacting in a 4,3-selective manner with Pd−Xantphos and also give 4,3-addition with **L5**. Under the conditions in Scheme 3, using **L5** and unoptimized for these amines, phenylbutadiene and cyclohexenyl triflate react with indoline to give 42% conversion to product and with tetrahydroquinoline to give 45% conversion to

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product. Thus, reactions with Xantphos are more efficient for these cyclic aryl amines (cf. Scheme 2).

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