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Preparation of Chiral Allenes through Pd-Catalyzed Intermolecular Hydroamination of Conjugated Enynes: Enantioselective Synthesis Enabled by Catalyst Design

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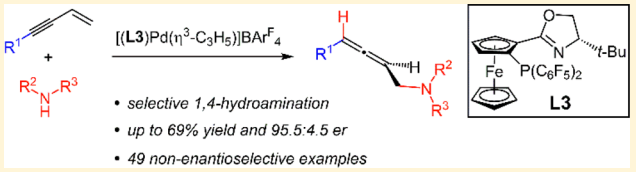
Supporting Information

ABSTRACT: In this study, we establish that conjugated enynes undergo selective 1,4-hydroamination under Pd catalysis to deliver chiral allenes with pendant allylic amines. Several primary and secondary aliphatic and aryl-substituted amines couple with a wide range of mono- and disubstituted enynes in a nonenantioselective reaction where DPEphos serves as the ligand for Pd. Benzophenone imine acts as an ammonia surrogate to afford primary amines in a two-step/one-pot process. Examination of chiral catalysts revealed a high degree of reversibility in the C−N bond formation that negatively impacted enantioselectivity. Consequently, an electron-poor ferrocenyl-PHOX ligand was developed to enable efficient and enantioselective enyne hydroamination.



1. INTRODUCTION

The development of new transformations for the installation of amine functionality is critically important for the preparation of new medicines, agrochemicals, and natural products. Intermolecular hydroamination[1] provides an atom economical way of generating chiral amines from readily available unsaturated hydrocarbons via C−N bond formation. Catalytic enantioselective reactions involving alkynes,[2] allenes,[3] cyclic[4] and acyclic[5] 1,3-dienes, vinylarenes,[6] cyclopropenes,[7] and simple α-olefins[8] have been disclosed.[9]

In contrast to these numerous examples are the paucity of reports detailing hydroamination of conjugated enynes. Recently, Barrett, Hill, and co-workers have demonstrated a single, nonenantioselective Sr-catalyzed hydroamination of an enyne that delivers an aminomethyl-substituted allene (Scheme 1).[10] The Yamamoto laboratory has shown that 3-substituted enynes undergo Pd−bis(phosphine)-catalyzed double addition of aliphatic amines to yield 2-butenyl-1,4-diamines.[11] These reactions were suggested to take place by the intermediacy of an aminomethyl-substituted allene. To our knowledge, there are no reported examples of enantioselective hydroamination of nonpolarized enynes.[12,13] In general, intermolecular couplings of unactivated enynes with nucleophiles are rare, especially in a catalytic enantioselective fashion.[14]

In fact, the majority of late transition-metal-catalyzed enyne hydrofunctionalizations have concerned reductive couplings with aldehydes or ketones as *electrophiles*.[15] Interestingly, reactions that take place by initial metal−hydride insertion[16] (Ru-, Ir-, or Cu-based catalysts) generally do so at the alkene, forming a propargyl metal species that is in equilibrium with an allenyl metal. It should be noted that Cu-catalyzed enyne hydroboration[17] delivers chiral allenes through the direct σ-bond metathesis of the metal for boron in the allenyl metal intermediate.[18]

In part inspired by Yamamoto's proposal that enyne diaminations occur by initial formation of an aminomethyl allene,[11] we hypothesized that under milder reaction conditions and with the appropriate catalyst, Pd-catalyzed hydroamination of enynes might lead to allene products (Scheme 1). Although Pd−H insertion could occur at the olefin, this cannot lead to a stable π-allyl complex for amine addition. Instead, alkyne insertion would lead to η^1-butadienyl−Pd **I**, which could then lead to the η^3-butadienyl−Pd **II**. Nucleophilic attack at the least hindered electrophilic carbon would then afford the allene product.[19] Such a π-allyl complex has been invoked as an intermediate in several Pd-catalyzed allylic substitution and related reactions.[20]

Yet even if this site-selectivity could be achieved for hydroamination, several questions remained with regard to the enantio- and chemoselectivity of the Pd-catalyzed process. (1) To achieve high enantioselectivity, a chiral catalyst would have to control the direction of the 90° single bond rotation of dienyl **I** in forming π-allyl **II** or, alternatively, nucleophilic attack upon **II** or its diastereomer would have to be under Curtin−Hammett control.[20] Although there was some precedent in allylic substitution with malonate,[20a,b,d] amine,[20b,c] and amide nucleophiles,[20c−e] would this be possible in hydroamination? (2) Even if kinetic control of enantioselectivity could be achieved, would reaction reversibility via C−N bond ionization and reformation of **I** erode it over the course of the reaction? (3) Would the optimal catalyst for controlling site-selectivity and enantioselectivity also selectively lead to allene formation without further reaction to produce a

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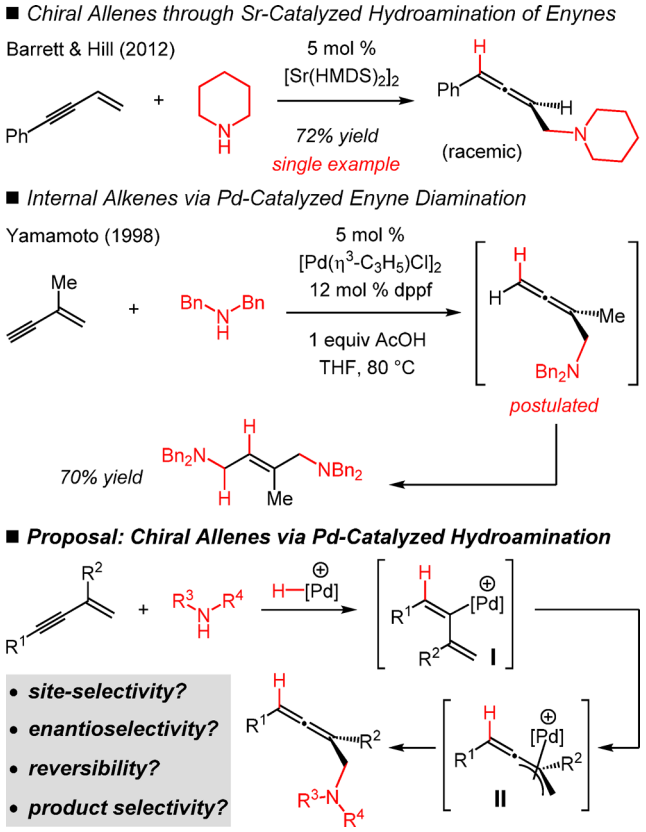
Scheme 1. Hydroaminations of Enynes

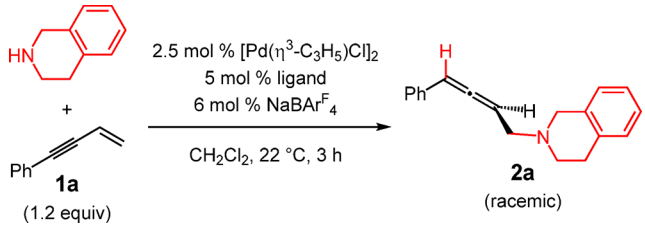


diamine?[11] In this work, we illustrate the successful realization of an enyne 1,4-hydroamination process to prepare myriad racemic aminomethyl-substituted allenes with DPEphos-ligated Pd as the catalyst. Through the design and development of a new PHOX ligand, we demonstrate the principles needed for enantioselectivity control in this transformation.

2. RESULTS AND DISCUSSION

2.1. Development of Nonenantioselective Enyne Hydroamination with Alkyl Amines, Aryl-Substituted Amines, and Benzophenone Imine. We began our study by investigating the nonenantioselective addition of tetrahydroisoquinoline (THIQ) to phenyl-substituted enyne **1a** (Table 1). Catalyst was generated in situ from 2.5 mol % $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 6 mol % $NaBAr^F{}_4$ with 5 mol % of several achiral bis(phosphine) ligands. No matter the phosphine identity, allene **2a** was obtained selectively after 3 h at ambient temperature in CH_2Cl_2. Other product regioisomers and diamination of the enyne were not observed. The efficiency of the reaction was correlated with the natural bite angle of the phosphine (entries 1−6).[21,22] This phenomenon could perhaps be attributed to an increased rate of nucleophilic attack upon the Pd-π-allyl with wider bite angle ligands.[22] As DPEphos and Xantphos gave roughly equivalent results, we opted to continue with the former. $NaBF_4$ in place of $NaBAr^F{}_4$ gave nearly the same result as well (entry 7) although having a noncoordinating counterion was important for reaction efficiency.[23] The isolated Pd complex (**Pd-1**) behaved similarly to that formed in situ (entry 8), and so for exploration of reaction scope, we employed isolated **Pd-1**. Under the optimized conditions, allene **2a** was obtained in 88% yield.

Table 1. Role of Ligand Bite Angle on Efficiency of the Nonenantioselective Pd-Catalyzed Process[a]



entry	ligand	bite angle	yield of **2a** (%)[b]
1	dppe	86°	14
2	dppp	91°	44
3	dppb	94°	62
4	dppf	99°	63
5	DPEphos	104°	84
6	Xantphos	108°	83
7[c]	DPEphos	104°	86
8[d]	DPEphos	104°	88

[a]Reactions under N_2 with 0.2 mmol of tetrahydroisoquinoline (0.8 M). [b]Isolated yield of **2a** after purification. [c]$NaBF_4$ instead of $NaBAr^F{}_4$. [d]Reaction with isolated $[(DPEPhos)Pd(\eta^3\text{-}C_3H_5)]BF_4$ (**Pd-1**).

Numerous readily accessible enynes couple with a wide range of commercially available amines for 1,4-hydroamination with **Pd-1** (Table 2). A variety of aryl-substituted enynes are effective partners in transformations with THIQ (**2b−k**, 63−92% yield). Substrate electronics have little obvious effect on reaction efficiency, and several aryl substituents are compatible with the hydroamination process, including functionality with acidic protons (**2c**), aryl bromides (**2d**), and aldehydes (**2e**). *ortho*-Substituted arenes afford products with only slightly diminished yields (**2j−k**). A naphthyl group (**2l**) and heteroaromatic rings (**2m−n**), including a Lewis basic pyridyl substituent, are tolerated.

Alkyl-substituted enynes and a silyl-substituted enyne undergo efficient hydroamination with THIQ[24] as well (Table 2, **2o−u**, 52−86% yield). The functional group tolerance is again impressive, a testament to the mild reaction conditions for this catalytic process. A propargylic phthalimido group (**2q**) and a primary tosylate (**2s**) remain intact. A free hydroxyl group (**2r**) does not interfere in the process. With extended reaction times, steric hindrance imposed at the alkyne by a TBS (**2t**) or cyclohexyl (**2u**) group can also be overcome by the Pd-based catalyst.

The amine scope is similarly broad (Table 2), with both phenyl-substituted enyne **1a** and phenethyl-containing enyne **1o**; the atom economic reactions generate allenes **2v−am** in 51−92% yield. Several amines, including the more Lewis basic piperidine (**2w** and **2af**) and pyrrolidine (**2x** and **2ah**) that may at times prove challenging to late transition metal catalysts, couple in good yields. Additionally, azepane (**2y**) and a ketal-containing piperidine (**2ag**), which may serve as an ammonia surrogate,[25] are also effective partners. Aryl-substituted amines, such as tetrahydroquinoline and indoline, afford allenes **2z** and **2ai** in 59% and 70% yields, respectively. Acyclic secondary amines such as *N*-methylbenzylamine (**2aa** and **2aj**) and sterically hindered diethylamine (**2ab** and **2ak**) add smoothly to enynes. Primary amines are also capable of participating in the enyne hydroamination (**2ac−ad** and **2al−am**) although the transformations require 10 mol % **Pd-1** and

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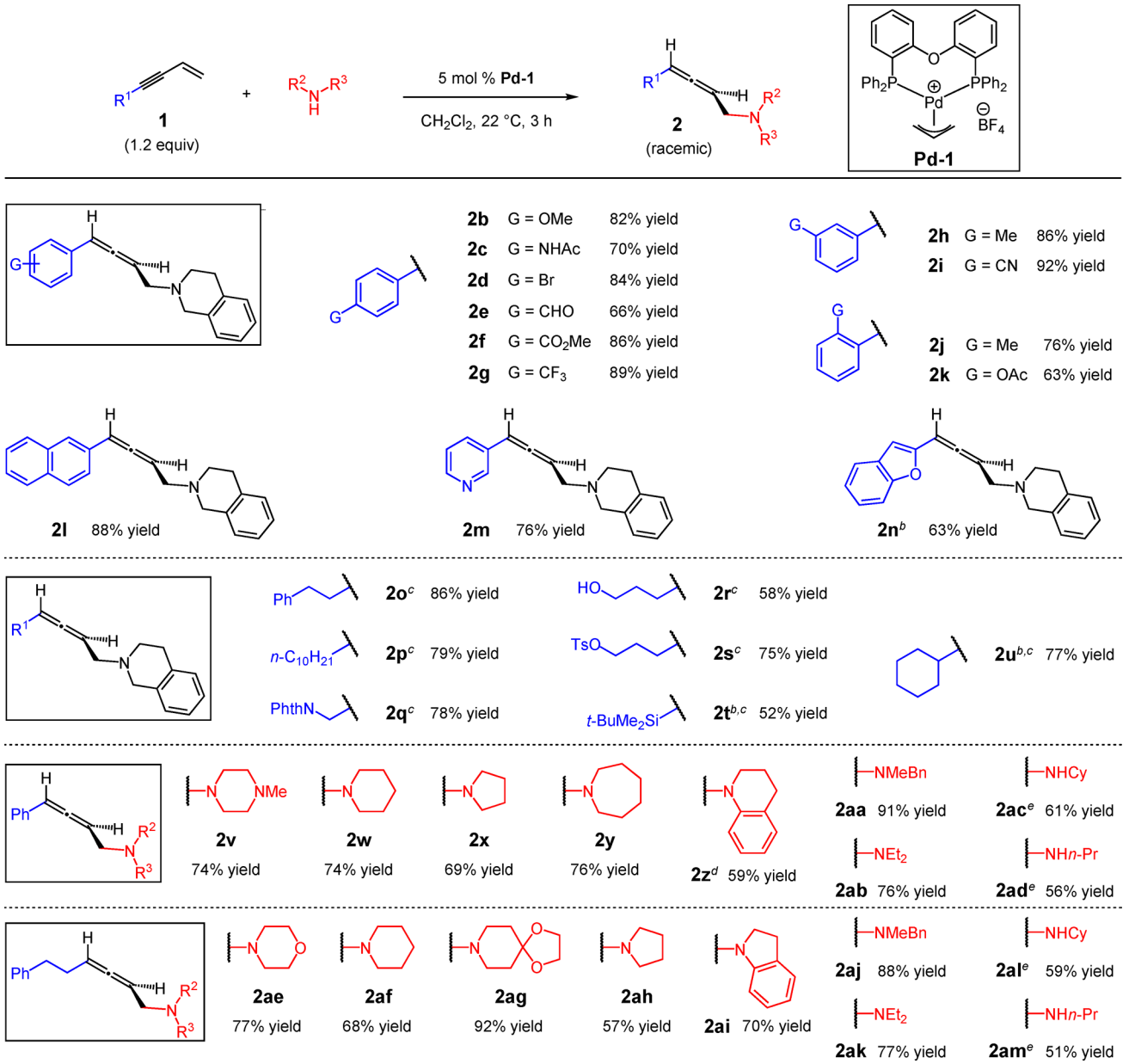
Table 2. Scope of Nonenantioselective Enyne Hydroamination To Prepare Disubstituted Allenes[a]

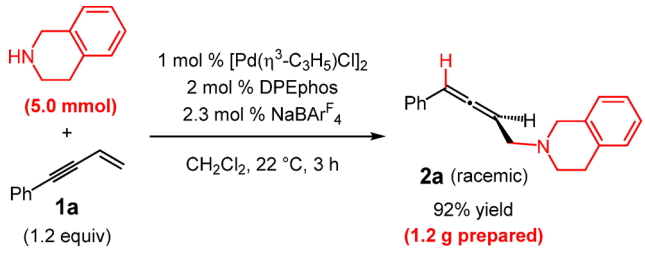


[a]Reactions under N_2 with 0.2 mmol of amine (0.8 M) and 5 mol % **Pd-1** for 3 h unless otherwise noted. Isolated yields of purified products. [b]15 h reaction. [c]Catalyst prepared in situ with $NaBAr^F_4$. [d]20 h reaction. [e]10 mol % **Pd-1**.

catalyst turnover is low (51−61% yield). The 1,4-hydroamination of enyne **1a** is readily scalable (5.0 mmol scale) and can be carried out with as little as 2 mol % Pd catalyst, prepared in situ with $NaBAr^F_4$ (Scheme 2). Under these conditions, 1.2 g of the THIQ adduct **2a** was obtained in 92% yield.

We were also pleased to find that benzophenone imine,[3i] which serves as a surrogate for ammonia, undergoes facile addition to enynes **1** with 5 mol % **Pd-1** in the presence of Et_3N as a proton shuttle (Table 3). Selective 1,4-addition occurs to afford **3** after 24 h. The imine may be isolated or hydrolyzed in the workup under mildly acidic conditions to form the corresponding primary amine **4**. For example, reaction with enyne **1a** leads to allene **3** in 86% yield, but addition to naphthyl-substituted enyne **1l** and in situ hydrolysis of the resulting imine delivers primary amine **4a** in 65% yield.

Scheme 2. Scalability of Nonenantioselective Hydroamination with Tetrahydroisoquinoline



Alkyl-substituted enynes also react with benzophenone imine to form allenes **4b−c** after hydrolysis. Thus, through the 1,4-hydroamination process, myriad chiral allenes that contain

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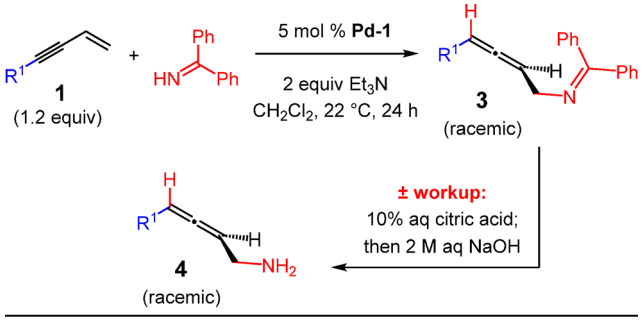
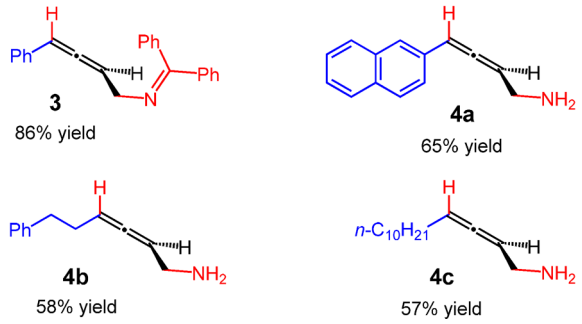
Table 3. Enyne Hydroamination with Benzophenone Imine as an Ammonia Surrogate[a]



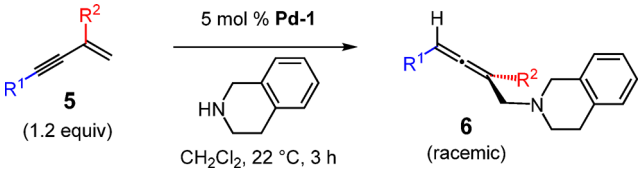


[a]Reactions under N_2 with 1.0 mmol benzophenone imine (0.8 M).

tertiary, secondary, and primary amines may be obtained in racemic form.

Furthermore, we have investigated the addition of THIQ to a handful of 1,3-disubstituted enynes **5** (Table 4). Selective

Table 4. 1,3-Disubstituted Enyne Scope for Trisubstituted Allene Synthesis[a]



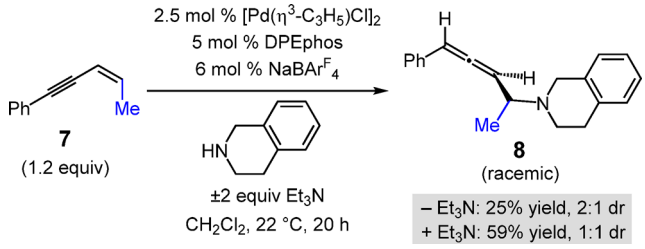
entry	product, R^1, R^2	yield (%)[b]
1	**6a**, Ph, Me	60
2	**6b**, Ph, *n*-C_6H_{13}	66
3	**6c**, Ph, Cy	51
4	**6d**, Ph, CF_3	60
5	**6e**, Cy, Me	82

[a]Reactions under N_2 with 0.2 mmol of tetrahydroisoquinoline (0.8 M). [b]Isolated yields of purified products.

1,4-addition, catalyzed by **Pd-1**, enables the isolation of trisubstituted allenes **6** in 51−82% yield. With a phenyl substituent at C1, several groups are tolerated at the 3-position, including methyl (**6a**), linear alkyl (**6b**), α-branched cyclohexyl (**6c**), and a trifluoromethyl group (**6d**). An enyne bearing alkyl groups at both the 1- and 3-positions furnishes trialkyl-containing allene **6e** in 82% yield; however, with aryl substitution at both positions, the enyne proved too unstable to allow for study.

We additionally examined the addition of THIQ to 1,4-disubstituted enyne (Z)-**7** (Scheme 3). Compared to reactions with the 1,3-disubstituted congeners, the transformation is markedly less efficient in the absence of Et_3N. After 20 h with

Scheme 3. THIQ Addition to a 1,4-Disubstituted Enyne

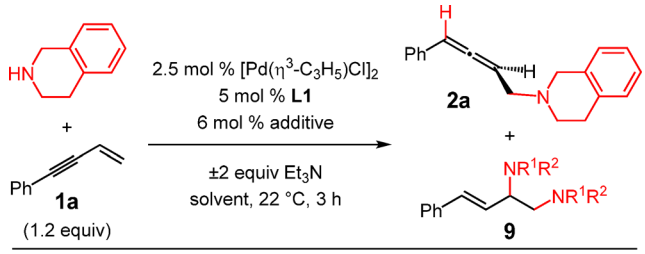


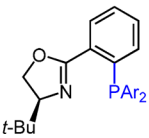
[Pd(DPEphos)]BAr^F_4, aminoethyl allene **8** is isolated in 25% yield as a 2:1 mixture of diastereomers. The stereochemical configuration of the major isomer was not determined. In the presence of Et_3N, allene **8** is isolated in 59% yield (1:1 dr).

2.2. Development of Enantioselective Enyne Hydroamination with Pd(PHOX) Catalysts. Having established the feasibility of transforming conjugated enynes to chiral allenes by site-selective 1,4-addition of amines with an achiral Pd catalyst, we next sought to develop an enantioselective variant. With our previous successes in 1,3-diene hydrofunctionalization reactions with Pd(PHOX) catalysts,[5b,c,26] we once again turned to ligand **L1**, containing an electron-deficient phosphine (Table 5), for enyne hydroamination.

However, we quickly discovered numerous differences between the Pd(DPEphos)- and Pd(PHOX)-catalyzed processes. First, in situ generation of the catalyst derived from **L1** and $NaBF_4$ fails to generate allene **2a** from enyne **1a** and THIQ (entries 1 and 3). Contrastingly, 5 mol % isolated [(η^3-C_3H_5)Pd(**L1**)]BF_4 delivers a 4:1 mixture of allene **2a** and

Table 5. Initial Examination of Conditions for Enantioselective Enyne Hydroamination[a]





L1 Ar = 3,5-$(F_3C)_2C_6H_3$

entry	additive	Et_3N (Y/N)	solvent	yield of **2a** (%)[b]	**2a**:**9**[c]	er of **2a**[d]
1	$NaBF_4$	N	CH_2Cl_2	<2	–	–
2[e]	$NaBF_4$	N	CH_2Cl_2	56	4:1	53.5:46.5
3	$NaBF_4$	Y	CH_2Cl_2	<2	–	–
4[e]	$NaBF_4$	Y	CH_2Cl_2	71	19:1	63:37
5[e]	$NaBArF_4$	N	Et_2O	73	13:1	69.5:30.5
6	$NaBArF_4$	Y	Et_2O	48−73[f]	>20:1	<52:48−74:26[f]
7	$NaBArF_4$	Y	CH_2Cl_2	65−70[f]	>20:1	54:46−82:18[f]

[a]See Table 1. [b]Isolated yield of **2a** (single data point unless otherwise noted). [c]Determined by 400 MHz ^1H NMR analysis of the unpurified mixture. [d]Determined by HPLC analysis (single data point unless otherwise noted). [e]Performed with isolated catalyst; see the Supporting Information. [f]Range for three experiments.

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diamine **9** in 56% yield (entry 2). The observation of diamine **9**, which likely arises from hydroamination of allene **2a**,[11] is another departure from reactions promoted by DPEphos, which result in complete selectivity for the allene. The second amine addition can be largely suppressed by the inclusion of 2.0 equiv of Et_3N (entry 4, 19:1 **2a**:**9**), but enantioselectivity remains poor. With the catalyst bearing **L1** and a BAr^F_4 counterion, the allene could also be selectively obtained even without Et_3N (entry 5, 13:1 **2a**:**9**). The collective data in Table 4 (entries 2 and 4−5) suggest that the identity of the ammonium salt that serves as the acid source during the reaction is critical to suppressing overamination. Triethylammonium with either BF_4 or BAr^F_4 as the counterion selectively leads to proton transfer when Pd is bound to the alkyne of **1a** rather than the allene of product **2a**. Comparatively, the ammonium salt of THIQ shows significantly different selectivity profiles depending on its counterion. Thus, the inclusion of Et_3N in the reaction mixture seemed likely to be beneficial for product selectivity in the eventual expansion of the reaction to other amine nucleophiles beyond THIQ.

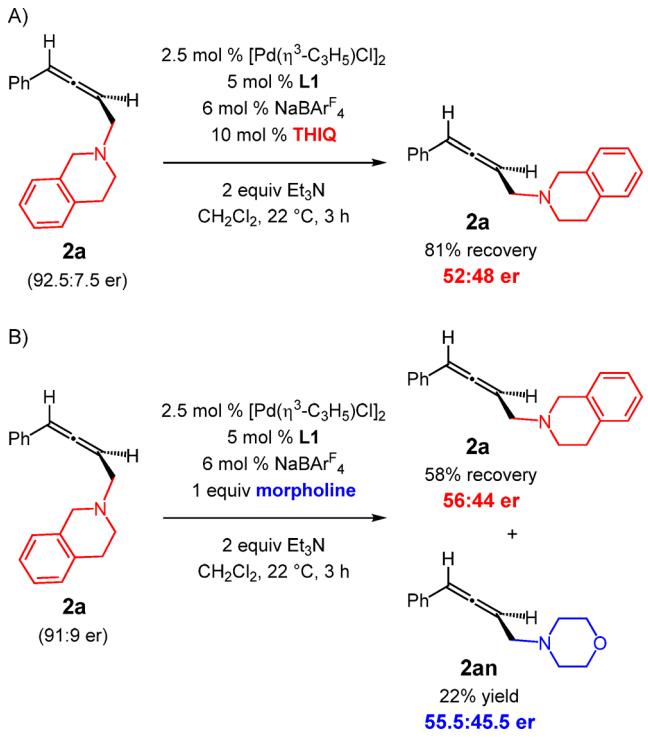
Switching to $NaBAr^F_4$ as the additive also allows for the in situ preparation of an active catalyst (entries 6−7) perhaps due to its faster formation of NaCl. With the $NaBAr^F_4$ additive and Et_3N, only the desired allene was observed; however, the product yield and especially the enantioselectivity of the transformation proved highly variable under several conditions. In a number of identical experiments, the enantiopurity of **2a** ranged from 82:18 er to nearly racemic.[23]

We thought that the variability in enantioselectivity might be due to reaction reversibility. Erosion of enantiopurity over time has been previously observed in Pd-catalyzed 1,3-diene hydroamination by such a process,[27] including Pd(PHOX) catalysts.[5c] Indeed, subjection of highly enantioenriched **2a** (92.5:7.5 er) to the Pd(**L1**) catalyst with 10 mol % THIQ leads to rapid racemization of the allene (Scheme 4A). Futhermore, the addition of 1 equiv of morpholine to enantioenriched **2a** (91:9 er) and the Pd(**L1**) catalyst results in 58% recovery of **2a** in only 56:44 er and 22% yield of morpholine adduct **2an** in equally low enantiopurity (Scheme 4B). Although both **2a** and **2an** were nearly racemic after 3 h, determination of the equilibrium ratio of the two allenes by employing the Pd(PHOX) catalyst was thwarted by formation of diamine products from **2a** after extended reaction times. However, the same process with achiral Pd(DPEphos) affords a 1.3:1 **2a**:**2an** mixture within 3 h.[23]

Although we cannot rule out other mechanisms[28] at this time, the racemization pathway likely proceeds by ionization of the C−N bond in Pd(0)−allene complex **III** (Scheme 5A) to regenerate π-allyl−Pd **II**. Isomerization to the diastereomeric complex **IV** via alkenyl−Pd **I** then leads to **V** after C−N bond formation. Dissociation of the Pd(PHOX) catalyst from **III** and **V** leads to allene enantiomers.

Since the ionization of the ammonium group in **III** or **V** is at the heart of the racemization process, we rationalized that redesigning the catalyst to slow this event by minimizing the trans effect of the phosphine ligand within complex **III**/**V** could lead to more reproducible results and potentially higher enantioselectivity. Reasoning that an even more electron-deficient phosphine might accomplish this goal, perhaps also disfavoring allene coordination to the catalyst compared to an enyne, led us to prepare ligands **L2** and **L3** (Scheme 5B) containing a bis(perfluorophenyl)phosphino group. We were heartened to find that, consistent with our hypothesis, the

Scheme 4. Reaction Reversibility and Transamination Studies



enantiomerization rate was significantly retarded with **L2** (Scheme 5C): the combination of **2a** (91:9 er), Pd(**L2**) catalyst, and 10 mol % THIQ allows for allene **2a** to be recovered in 72:28 er after 3 h (cf., Scheme 4A).

Importantly, addition of THIQ to **1a** with the Pd(**L2**) catalyst allows for a high degree of reproducibility (Table 6, entry 1) with **2a** formed in ca. 70% yield and 82:18 er at room temperature in CH_2Cl_2 after 3 h. Ferrocenyl-PHOX **L3** gave slightly higher enantioselectivity (entry 2), and so we chose to optimize further with this ligand.[23] Impressively, even in CH_2Cl_2 as a polar solvent, which we have observed in diene hydroamination to increase the enantiomerization rate compared to reactions in Et_2O,[5c] enantioselectivity only decreases to 82.5:17.5 er after 19 h at room temperature (entry 3). After the reaction was cooled to 4 °C, allene **2a** was obtained in 63% yield and 92.5:7.5 er (entry 4).

The addition of THIQ to several aryl-substituted enynes **1** proceeds with moderate reaction efficiency but good levels of enantioselectivity in the presence of 5 mol % Pd catalyst formed from **L3** (Table 7, Condition A: CH_2Cl_2, 4 °C, 20 h). Both electron-rich and electron-poor enynes react with roughly equal efficiency: anisole **2b** is isolated in 64% yield (91:9 er), and benzoate **2f**, in 57% yield (94:6 er). An aryl bromide is tolerated in the coupling, with **2d** formed in 52% yield and 94.5:5.5 er. An *ortho*-tolyl group leads to lower enantioselectivity (86:14 er), but **2j** is still generated in 57% yield. Although a pyridyl substituent had little impact on hydroamination with the Pd(DPEphos) catalyst, the heterocycle significantly impedes the **L3**-derived catalyst: allene **2m** is obtained in 91:9 er but only 32% yield.

Whereas addition of THIQ to enynes required a 5 mol % catalyst loading to obtain allenes in good yields,[23] other amines couple efficiently with enyne **1a** with only 2 mol % of the catalyst formed from **L3** (Table 7, Condition B: Et_2O, 4 °C,

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Scheme 5. Design of a Chiral PHOX Ligand To Minimize Erosion of Allene Enantiopurity

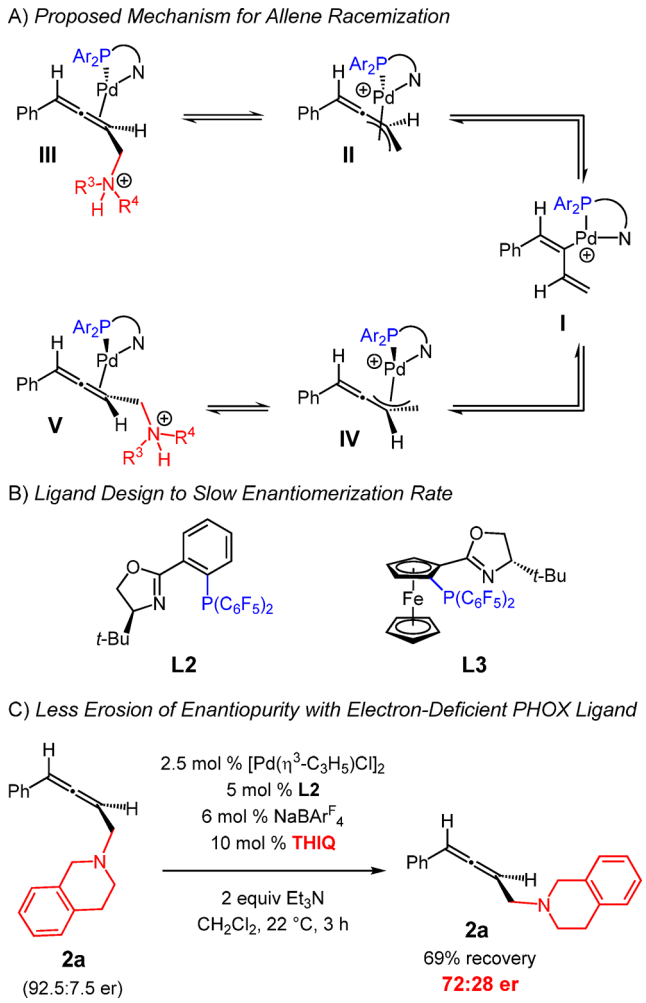
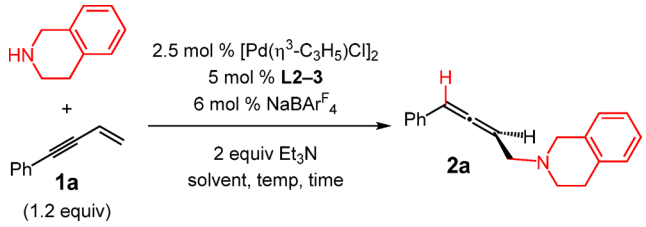


Table 6. Improved Enantioselectivity with Electron-Deficient PHOX Ligands[a]

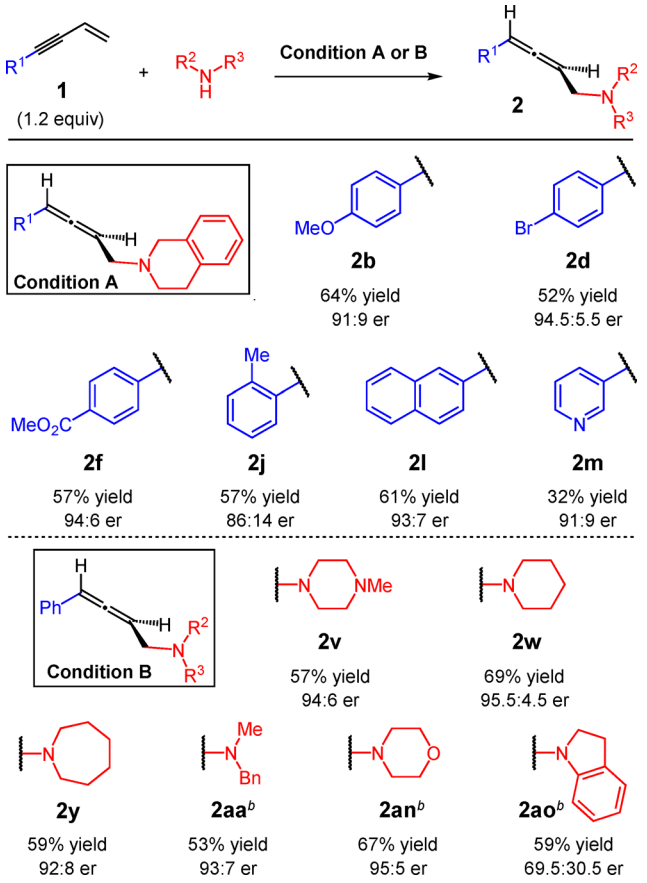


entry	ligand	solvent	temp (°C)	time (h)	yield of **2a** (%)[b]	er of **2a**[c]
1	**L2**	CH_2Cl_2	22	3	67–73[d]	82:18–82.5:17.5[d]
2	**L3**	CH_2Cl_2	22	3	66	86.5:13.5
3	**L3**	CH_2Cl_2	22	19	78	82.5:17.5
4	**L3**	CH_2Cl_2	4	19	63	92.5:7.5

[a]See Table 1. [b]Isolated yield of **2a** (average of 2–3 experiments unless otherwise noted). [c]Determined by HPLC analysis (average of 2–3 experiments unless otherwise noted). [d]Range for three experiments.

3 h). These optimal conditions enable allene products to be isolated with greater enantiopurity. As a result, cyclic amines (**2v**, **2w**, **2y**, and **2an**) are isolated in 92:8 to 95.5:4.5 er (57–

Table 7. Scope of Enantioselective Enyne Hydroamination[a]



[a]Reactions run under N_2 with 0.2 mmol of amine (0.8 M). Condition A: 2.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 5 mol % **L3**, 6 mol % NaBAr$^F_4$, 2 equiv of Et_3N, CH_2Cl_2, 4 °C, 20 h. Condition B: 1 mol % [Pd(η^3-C_3H_5)Cl]$_2$, 2 mol % **L3**, 2.5 mol % NaBAr$^F_4$, 2 equiv of Et_3N, Et_2O, 4 °C, 3 h. [b]5 h reaction.

69% yield). Acyclic alkyl-substituted amines are also tolerated: **2aa** is obtained in 53% yield and 93:7 er. Despite displaying similar reaction efficiency as aliphatic amines, indoline addition to **1a** leads to allene **2ao** with only 69.5:30.5 er (59% yield). The lower enantioselectivity is not due to more rapid product enantiomerization but rather to lower kinetic selectivity; in fact, the enantiopurity of **2ao** remains constant throughout the course of the reaction with the **L3**-derived catalyst.[23]

The addition of THIQ to alkyl-substituted enynes as promoted by the Pd(**L3**) catalyst, however, occurs with low enantioselectivity,[23] perhaps suggesting that ionization of the C–N bond of the product is competitive with ligand exchange of the allene for another alkyl-substituted enyne substrate at the Pd(0) center (displacement of the allene within **III**, Scheme 5A, for enyne). The more substituted enynes **5** and **7** (Table 4 and Scheme 3, respectively) are relatively unreactive with the Pd(PHOX) catalyst; benzophenone imine also does not add to enyne **1a**.[23]

2.3. Reaction Mechanism Investigations. Our proposed mechanism for the enyne 1,4-hydroamination proceeds through η^3-butadienyl–Pd **II** (Scheme 6), itself formed from η^1-butadienyl–Pd **I**, the product of alkyne insertion to a palladium hydride species **VI**.[29] This pathway mirrors that suggested by Yamamoto[11] in a related process and is also based on prior work in Pd–bis(phosphine)-catalyzed hydroamina-

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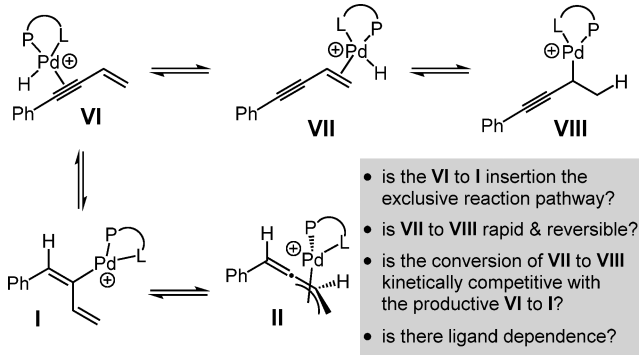
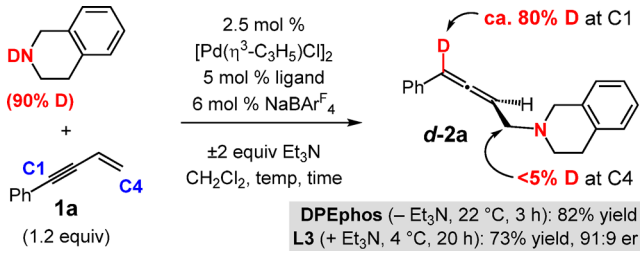
Scheme 6. Possible Reaction Pathways in the Course of Pd-Catalyzed Enyne Hydroamination



tion of dienes and styrene,[22] which have been shown to proceed through outer-sphere addition of the amine to a π-allyl–Pd or π-benzyl–Pd complex, respectively. Alkene insertion to the palladium hydride in complex **VII** might also occur to generate propargylic Pd species **VIII**. Although **VIII** cannot collapse to a stable π-allyl–Pd complex, we wondered if alkene insertion were a competitive process or if alkyne insertion (**VI** to **I**) were the exclusive reaction pathway. We also questioned whether DPEphos- and **L3**-derived Pd catalysts might show different kinetic site-selectivity profiles for migratory insertion.

To investigate these site-selectivity questions, we employed N-deuterated THIQ (90% labeled) in a reaction with enyne **1a** (Scheme 7). With either bis(phosphine) or PHOX ligand, the

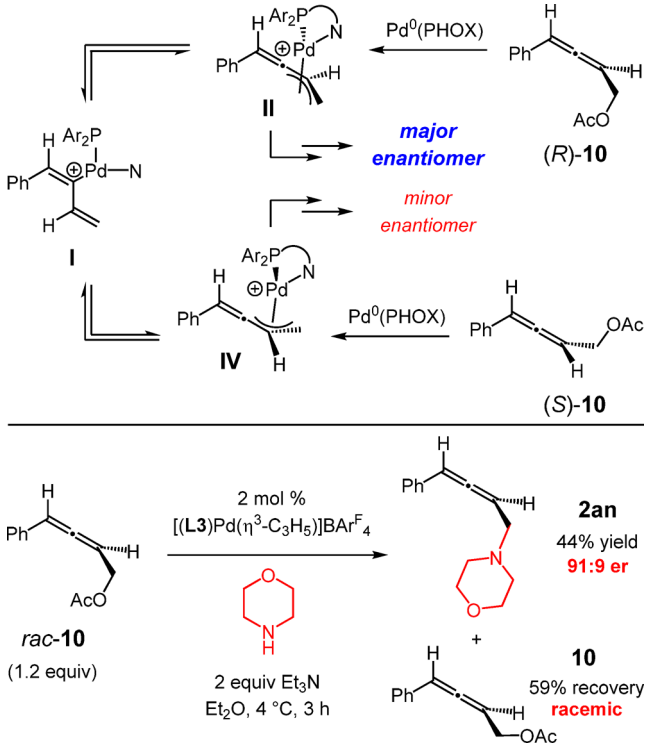
Scheme 7. Deuterium Labeling Reveals Kinetic Selectivity for Alkyne Insertion to Pd–H



deuterium label is confined to C1 in ***d*-2a** (80% labeled) with <5% incorporation at the allylic C4 position. No deuterium label was detected in the recovered enyne **1a**. Therefore, we can conclude that insertion of the alkyne to the palladium hydride is significantly faster than olefin insertion.

Having determined that Pd–H migratory insertion occurs kinetically at the alkyne to furnish η^1-butadienyl–Pd **I**, we next examined the origin of high enantioselectivity in enyne hydroamination. Two possibilities seemed likely, the first being selective collapse of **I** to η^3-butadienyl–Pd **II** followed by faster attack of the amine (Scheme 8). The second option is that **II** might be in rapid equilibrium with diastereomeric complex **IV**, with amine attack upon **II** being faster than addition to **IV** (Curtin–Hammett kinetics). Recognizing that the Trost laboratory[20b] has observed a Curtin–Hammett situation in allylic aminations involving allene substrates that share common intermediates **II** and **IV**, we investigated the allylic amination of racemic allylic acetate **10**. Addition of morpholine to *rac*-**10** with the Pd(**L3**) catalyst under the conditions for enyne hydroamination affords aminomethyl-

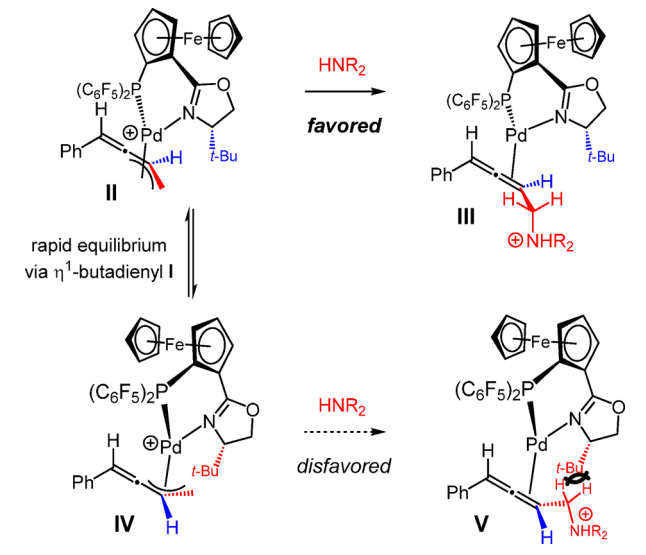
Scheme 8. Allylic Substitution Suggests Curtin–Hammett Kinetics Operative in Enyne Hydroamination



substituted allene **2an** in 44% yield and 91:9 er (cf. 95:5 er from enyne hydroamination) with the (*R*)-enantiomer still as the major isomer (Scheme 8). Allene **10** is recovered as the racemate, illustrating enantioconvergence in the reaction (i.e., not kinetic resolution). The data indicate that allylic amination with Pd(**L3**) is under Curtin–Hammett control and strongly suggests that enyne hydroaminations are as well.

The preferential attack of the amine upon η^3-butadienyl **II** compared to **IV** can be rationalized in terms of the transition states leading to allene–Pd complexes **III** and **V**, respectively (Scheme 9). In both π-allyl–Pd complexes **II** and **IV**, the

Scheme 9. Proposed Stereochemical Model for Enyne Hydroamination



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phosphine lies *trans* to the allyl ligand's methylene carbon, which undergoes attack by the amine (trans effect). The C−N bond formation causes rehybridization at this carbon, which leads to steric clash with the *tert*-butyl group of the oxazoline en route to **V**. Comparatively there is less interaction between these substituents in the amine addition to **II** that leads to **III**.

3. CONCLUSION

In this study, we have demonstrated the selective 1,4-addition of aliphatic amines, aryl-substituted amines, and benzophenone imine to deliver chiral aminomethyl-substituted allenes. Several tertiary, secondary, and primary amines can be obtained in racemic form with a Pd(DPEphos) catalyst. The enyne scope is equally broad with several 1-substituted and 1,3-disubstituted enynes amenable to the reaction.

Furthermore, we have demonstrated the first examples of catalytic enantioselective intermolecular addition of nucleophiles to nonpolarized 1,3-enynes. Transformations take place in good yield and enantioselectivity with a Pd(PHOX) catalyst that bears an electron-poor bis(perfluorophenyl)phosphino group. With the electron-deficient Pd catalyst, reaction reversibility is slowed significantly, thereby preserving the stereochemistry set in the initial C−N bond-forming step. Still, these studies highlight future areas for improvement, including hydroamination with alkyl-substituted enynes, disubstituted substrates, and reactions of benzophenone imine. Likely success in these objectives will require further catalyst development.

Initial mechanistic investigations indicate that, unlike enyne reductive couplings with electrophiles that proceed via Rh−H, Ir−H, or Cu−H insertion at the olefin, Pd−H insertion in enyne hydroamination takes place exclusively at the alkyne with both Pd(DPEphos) and Pd(PHOX) catalysts. Additionally, comparison with known allylic substitutions indicates that enantioselectivity in the Pd(PHOX)-catalyzed enyne hydroaminations likely takes place under Curtin−Hammett kinetics involving rapid equilibration of diastereomeric π-allyl−Pd complexes.

1,4-Addition of nucleophiles to conjugated enynes provides a new avenue for the synthesis of multisubstituted chiral allenes. Studies directed toward the catalytic enantioselective addition of other nucleophiles to 1,3-enynes are underway in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b02637.

Experimental procedures, analytical data for new compounds (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(23) For additional details, see the Supporting Information.

(24) Transformations involving THIQ addition to alkyl-substituted enynes lead to small inseparable quantities of a byproduct, tentatively assigned as benzylic oxidation of the N-heterocycle of the desired product, affording a lactam. This process is unique to reactions of THIQ with alkyl-substituted enynes and was discovered to be mitigated by in situ generation of the catalyst.

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