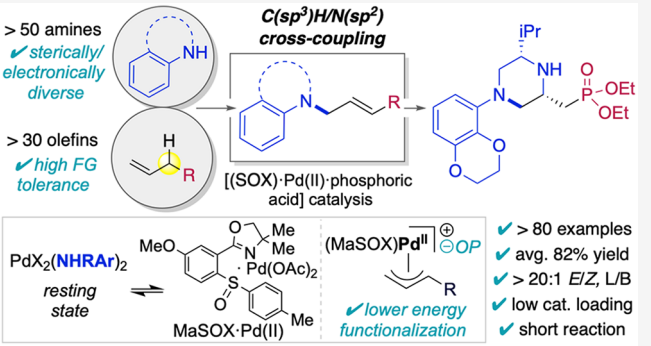
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

C(sp^3)H/N(sp^2) Cross-Coupling Reaction for the Synthesis of Tertiary Arylamines via Fluxional SOX·Pd(II) Catalysis

Brenna G. Budaitis, Zachary M. Firestein, Andrew C. Yue, and M. Christina White*

Cite This: J. Am. Chem. Soc. 2025, 147, 32786−32798
Read Online

ABSTRACT: *N*-alkyl arylamines are important structural motifs in pharmaceuticals, yet traditional alkylating methods rely on the nucleophilicity of the amine and make access to such compounds with valuable bioproperties challenging. While metal-mediated reactions may alleviate these limitations, they often encounter amine-metal interactions that can hinder catalysis or lead to deleterious pathways. Herein, we report a palladium(II) [Pd(II)]/sulfoxide-oxazoline(SOX)/phosphoric acid-mediated C(sp^3)H/N-(sp^2) cross-coupling of 53 arylamine nucleophiles and 39 terminal olefins to furnish >80 diverse tertiary (3°) arylamines in excellent yields (average 82%) and selectivities (>20:1 *E*/*Z*, >20:1 linear/branched). The reaction furnishes electron-deficient and sterically bulky arylamines as well as those housing alkyl/aryl halides, epoxides, carbonyls, epimerizable centers, carboxylic acids, and *N*-triflyl/tosyl alkylamines, showcasing orthogonal scope to existing aminations. The generality of this reaction enables facile synthesis of six pharmaceuticals and derivatives (e.g., zafirlukast) and five late-stage drug fragment couplings (e.g., flutamide-duloxetine). Whereas spectroscopic studies identify a catalytically inactive bis(arylamine)·Pd(II) complex **4** as the resting state, the reaction proceeds with high efficiencies (short reaction times, low catalyst loadings). Mechanistic studies reveal that the SOX ligand **L1** [(±)-MeO-SOX = MaSOX)] establishes a dynamic equilibrium with **4** to generate the active catalyst. Phosphoric acids promote the reaction by affording a significant increase in the functionalization rate, rendering a lower energy allylic C−H cleavage as the rate-determining step. We anticipate that this reaction will find broad use in the discovery of complex and medicinally relevant *N*-alkyl arylamines and that the mechanistic insights will be leveraged to improve efficiencies of other metal-catalyzed aminations.



INTRODUCTION

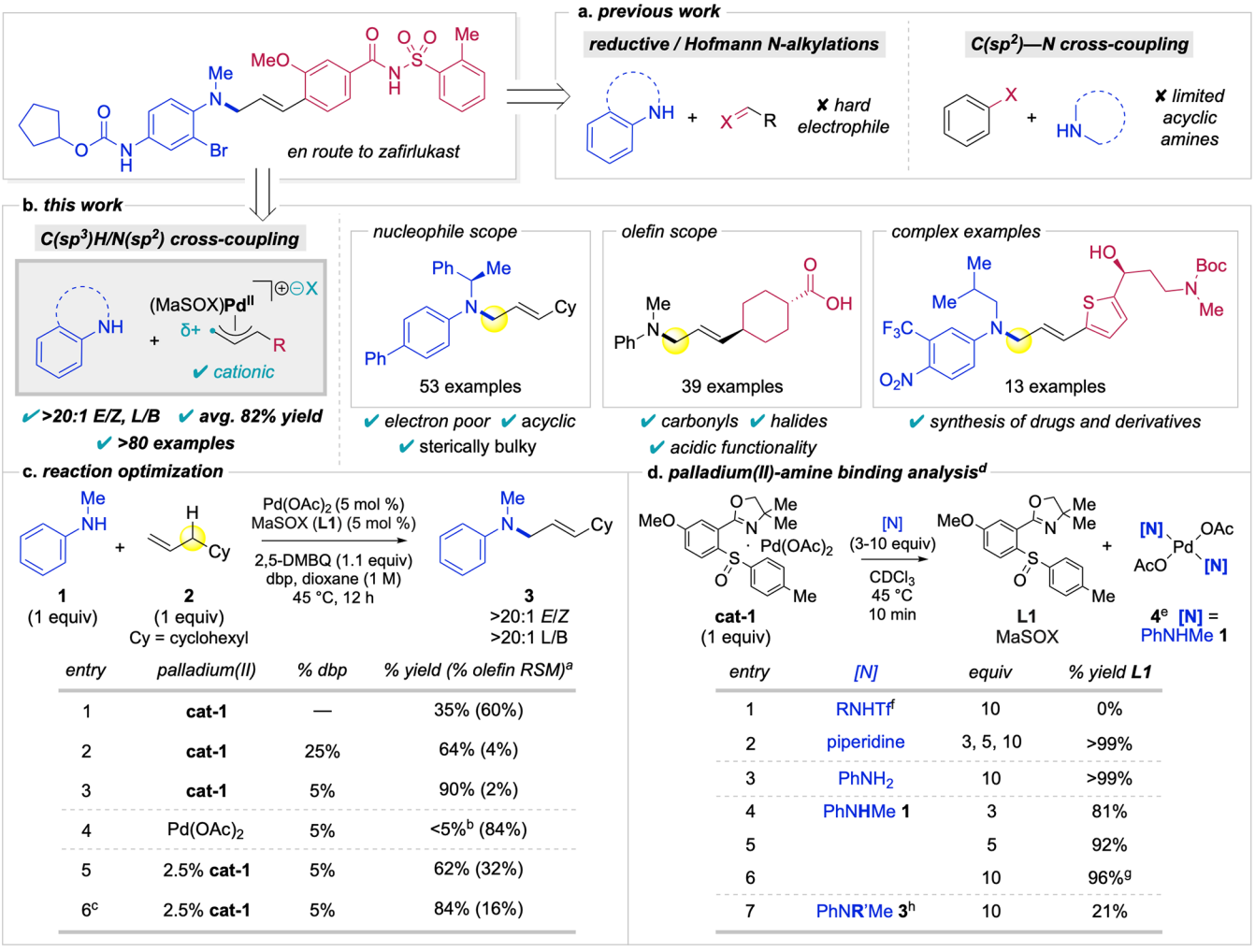
The modularity of the phenyl moiety paired with the physiological properties of nitrogen atoms makes arylamines attractive motifs that are found in one-third of medicinal compounds.[1−3] Traditional approaches to furnish *N*,*N*-dialkylated tertiary (3°) arylamines—reductive and Hofmann *N*-alkylations—face reactivity challenges because they rely on coupling polarizable, "soft" arylamine nucleophiles with "hard" preoxidized electrophiles (e.g., alkyl halides, carbonyls; Figure 1a).[4] Electron-deficient and sterically bulky 3° arylamines—structural modifications that may improve a drug's bioproperties (e.g., metabolic stability), enhance lipophilicity, and prevent undesired oxidation pathways[3]—are the most challenging to synthesize with these methods and generally require excess electrophile, forcing conditions, or substrate-specific modifications.

Nucleophilic aromatic substitutions[1,5] provide an orthogonal synthesis of 3° arylamines that cross-couple aryl halides and secondary (2°) amines. Advances in copper and palladium-catalyzed C(sp^2)−N aminations[2,6−9] have enabled broad applicability and streamlined the synthesis of cyclic *N*,*N*-dialkylated arylamines (Figure 1a). The coupling of acyclic 2° amines, however, remains challenging due to their steric bulk and/or propensity to undergo metal-mediated *β*-hydride elimination processes.[6,7] Additionally, the strongly basic conditions commonly utilized may result in compatibility limitations with acidic functionality, potentially leading to catalyst deactivation or undesired side reactions.[10]

A C(sp^3)−H cross-coupling of terminal olefins with 2° arylamines under mildly acidic conditions affords an analogous retrosynthetic disconnection to *N*-alkylations that may be more facile due to good polarity matches between the arylamine nucleophile and the *π*-allyl-Pd(II) electrophile (Figure 1b). Reported intermolecular Pd(II)-catalyzed allylic C−H aminations have demonstrated limited scope using specialized arylamines (e.g., diphenylamine) and/or activated

Received: May 26, 2025
Revised: August 4, 2025
Accepted: August 8, 2025
Published: August 28, 2025

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798



entry	palladium(II)	% dbp	% yield (% olefin RSM)[a]
1	**cat-1**	—	35% (60%)
2	**cat-1**	25%	64% (4%)
3	**cat-1**	5%	90% (2%)
4	$Pd(OAc)_2$	5%	<5%[b] (84%)
5	2.5% **cat-1**	5%	62% (32%)
6[c]	2.5% **cat-1**	5%	84% (16%)

entry	[N]	equiv	% yield **L1**
1	RNHTf[f]	10	0%
2	piperidine	3, 5, 10	>99%
3	$PhNH_2$	10	>99%
4	PhNHMe **1**	3	81%
5		5	92%
6		10	96%[g]
7	PhNR'Me **3**[h]	10	21%

Figure 1. Reaction Development. [a]Olefin recovered starting material (RSM) yield. [b]Yield was determined by crude ^{1}H NMR analysis using benzotrifluoride as an internal standard. Wacker oxidation (ca. 9%) observed with trace **3** (ca. 2%) likely results from an aza-Wacker pathway. Yield of **3** at 24 h ca. 4% with reduced olefin RSM (70%). [c]A solution of **1** in dioxane was added via a slow addition. [d]Yield of **L1** was determined by ^{1}H qNMR using 1,3,5-trimethoxybenzene as an internal standard. [e]**4** is formed as a mixture of diastereomers. [f]R = CH_2CH_2Ph. [g]Experiment with 1 equiv of dbp and 10 equiv of **1** yielded 94% **L1**. [h]R′ = $CH_2CH{=}CHC_6H_{11}$.

olefins (e.g., allylarenes and dienes) in excess amounts (2−7 equiv).[11,12] Pd(0)-catalyzed allylic substitutions of preoxidized olefins also have a narrow scope and in some cases poor selectivities [*E*/*Z*, L/B (linear/branched)].[13,14] This precedent suggested to us that binding of arylamines to Pd(II) to form catalytically inactive bis(arylamine)·Pd(II) complexes may make C−H cleavage and/or functionalization challenging. We hypothesized that the high affinity of SOX (sulfoxide-oxazoline) ligands for Pd(II)[15] and the sterically hindered nature of 2° arylamines may enable productive catalysis.

Herein, we report that Pd(II)/SOX/phosphoric acid catalysis enables a general C(sp^3)H/N(sp^2) cross-coupling of electronically and sterically diverse 2° arylamines with complex terminal olefins to furnish over 80 acyclic and cyclic 3° arylamine products in high regio- and stereoselectivities (>20:1 *E*/*Z*, >20:1 L/B). The amination proceeds under fragment coupling conditions (1 equiv) with broad scope and the highest average yields (82%), shortest reaction times (ca. 12 h), and lowest catalyst loadings (5 mol %) of any reported allylic C−H functionalization to date. This method is orthogonal to reductive amination and Hofmann *N*-alkylation reactions, efficiently furnishing electron-deficient and sterically hindered tertiary arylamines bearing epimerizable carbonyls, alkyl halides, epoxides, and aldehydes. Moreover, substrates containing functionality that pose challenges in palladium-catalyzed aminations—including acyclic 2° arylamines, acidic functionality such as *N*-tosyl (Ts) and *N*-triflyl (Tf) amines, indoles, alcohols, and carboxylic acids—are well-tolerated. While this reaction proceeds with notable efficiency, ^{1}H NMR studies suggest that the majority of Pd(II) is sequestered as an inactive bis(arylamine)·Pd(II) species and that trace SOX·Pd(II) catalyst is present during catalysis. The key to efficient reactivity is the ability for SOX to competitively bind to Pd(II) and undergo ligand exchange with the arylamine, thereby promoting C−H cleavage and functionalization. The fluxional binding of SOX to Pd(II) demonstrates that static ligand binding is not essential for efficient, selective catalysis when amine binding is reversible. The typically high barrier for π-allyl-Pd(II) functionalization is lowered with phosphoric acid additives, shifting the rate-determining step to a lower energy C−H cleavage.

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

RESULTS AND DISCUSSION

Reaction Development. We previously reported (±)-MeO-SOX (MaSOX)·Pd(OAc)$_2$ (**cat-1**) catalyzed allylic C−H amination cross-couplings of terminal olefins with both nonbasic *N*-Tf protected 1° alkylamines[16] and basic 2° alkylamines,[17] in which MaSOX ligand **L1** is critical for catalysis.[18,19] Whereas high concentrations of basic amines bind to electrophilic Pd(II) catalysts and irreversibly displace **L1**, BF_3/HBF_4 2° alkylamine salts were discovered to undergo a catalyst-regulated slow release of free amine nucleophiles at concentrations tolerated in catalysis. Unlike alkylamines (pK_{aH} ∼ 10), less basic arylamines (pK_{aH} ∼ 4) do not undergo full complexation to generate *N*-alkyl phenylamine·BF_3/HBF_4 salts. Attempts at in situ generation resulted in poor reactivity and low mass balance due to unproductive olefin reaction pathways (see the Supporting Information). Significantly, examining free 2° *N*-methyl phenylamine **1** with unactivated allylcyclohexane **2** furnished 3° arylamine product **3** in an encouraging yield (35%) and excellent mass balance (95%) (Figure 1c, entry 1). Primary (1°) phenylamine, however, furnished no observable allylic amination product and poor conversion (Supporting Information).

Phosphoric acid additives have been demonstrated to improve reactivity in allylic C−H aminations with 2° aliphatic amines by acting as noncoordinating counteranions and effecting Coulombic activation of the cationic π-allyl-MaSOX·Pd(II)(X) electrophile (where X = phosphate) (Figure 1b).[17,20] Introducing dibutyl phosphate (dbp) to the catalytic reaction with *N*-methyl phenylamine **1** afforded a substantial increase in reactivity (from 35% to 64% yield, Figure 1c, entry 2) whereas 1° phenylamine still furnished only trace product (see the Supporting Information). Phosphoric acids are additionally excellent H-bond donors and acceptors;[21] for example, the acceptor properties of phosphate counteranions were shown to accelerate *cis*-SOX·Pd(II)-catalyzed allylic C−H etherifications involving H-bond-donating alcohol nucleophiles.[22] In this reaction with H-bond-accepting nucleophiles, we questioned whether excess dbp was hydrogen-bond donating to the arylamine and reducing the active nucleophile's concentration in solution. ^{1}H and ^{31}P NMR analysis of 2° arylamine **1** with high dbp loadings (25 and 50 mol %) revealed shifts consistent with hydrogen-bond donation and/or protonation (see the Supporting Information).[23] Lowering dbp loadings to match the upper limit of the electrophile in the catalytic cycle (5 mol %) further improved yield (from 64% to 90% yields, entry 3). Collectively, these experiments showed that excess acid may deactivate the arylamine nucleophile and support that dbp's main role is to electrostatically activate the π-allyl-MaSOX·Pd(II)(X) electrophile by promoting counterion exchange.

In order to evaluate if MaSOX ligand **L1** undergoes ligand exchange with excess amines, representative of catalysis, MaSOX·Pd(OAc)$_2$ **cat-1** was exposed to amine nucleophiles used in allylic C−H aminations.[16,17] Nonbasic amine nucleophile *N*-Tf phenethylamine afforded no observable free MaSOX **L1**, even at 10 equiv (Figure 1d, entry 1). Basic 2° amine nucleophile piperidine, which requires BF_3/HBF_4 protection for catalysis, fully displaced the MaSOX ligand at 3−10 equiv (>99% free **L1**, entry 2). Significant ligand displacement was observed with 1° phenylamine even at low concentrations (92% **L1** with 3 equiv of amine, see the Supporting Information), and MaSOX was fully displaced at 10 equiv (>99% free **L1**, entry 3). Strong binding to Pd(II) may, in part, account for why 1° arylamines are generally not effective nucleophiles under these conditions (Supporting Information). In contrast, *N*-methyl phenylamine **1** did not fully displace the ligand, however, substantial amounts of free ligand were observed at 10 equiv (96% free **L1**, entry 6) with formation of (PhNHMe)$_2$·Pd(OAc)$_2$ **4** as the major palladium species in solution. Addition of 1 equiv of dbp with respect to **cat-1** did not significantly alter the amount of free ligand **L1** generated (94% free **L1**), indicating that the phosphoric acid does not significantly influence ligand exchange. Whereas these studies support a MaSOX·Pd(II) ligand **L1** exchange with arylamines, importantly, no catalysis was observed without MaSOX **L1** (Figure 1c, entry 4).

Tertiary arylamine product **3** did not displace MaSOX **L1** as readily as the corresponding 2° arylamine nucleophile **1** (21% versus 96% **L1** with 10 equiv amine, Figure 1d entries 7 versus 6). We hypothesized that product formation decreases the concentration of 2° arylamine nucleophile and shifts the equilibrium toward active MaSOX·Pd(II) catalyst. Consistent with this, lowering **cat-1** loadings (2.5 mol %) afforded a diminished yield of 3° phenylamine **3** (Figure 1c, entry 5), however, decreasing the concentration of 2° amine **1** in solution via slow addition of **1** restored the yield (entry 6). In contrast, neither doubling the **cat-1** loadings (10 mol %) nor slow addition of the 1° phenylamine nucleophile significantly improved the yields of allylated 2° phenylamine (7% and 11%, respectively; see the Supporting Information), suggesting that 1° arylamine binding to Pd(II) is less reversible and may more strongly sequester the catalyst.

Nucleophile Scope. We first assessed the reactivity of electronically and sterically diverse *N*-methyl arylamines with unactivated allylcyclohexane **2** under MaSOX·Pd(OAc)$_2$ **cat-1**/dbp catalysis under conditions open to air and moisture (Figure 2a). Spectroscopic interrogation of 4-nitro-*N*-methyl phenylamine with **cat-1** showed decreased bis(arylamine)·Pd(II) complexation relative to *N*-methyl phenylamine **1** (14% **L1** with 10 equiv of amine), whereas only free MaSOX **L1** was observed with electron-rich 4-methoxy-*N*-methyl phenylamine (99% **L1** with 10 equiv of amine). Reflective of this, electron-deficient and -neutral amines underwent amination under the standard conditions (**5**−**7**, **9**), whereas 4-methoxy-*N*-methyl phenylamine required either 10 mol % **cat-1** or slow addition of the amine under standard conditions to achieve high yields (**8**). These trends contrast with classic *N*-alkylations, where the attenuated nucleophilicities of electron-deficient arylamines require more forcing conditions than electron-rich ones. Consistent with challenging functionalization, longer reaction times (48 h) paired with increased dbp loadings (15 mol %) were needed for preparative reactivity of sterically hindered 2,6-disubstituted *N*-methyl arylamines. 2,6-dihalogen analogue, a prominent moiety in drugs like clenbuterol, was furnished in 72% yield (**10**). Additional modifications (10 mol % **cat-1**) were needed to couple highly sterically encumbered 2,6-diisopropyl-*N*-methyl phenylamine in useful yield (**11**). Current methods to alkylate these sterically hindered amines require harsh conditions, such as formal amine deprotonations with strong bases and/or elevated temperatures.[4f]

N-methyl arylamines decorated with diversifiable functionalities allow streamlined access to attractive synthetic intermediates. Substrates housing aryl bromide and aryl boronic ester moieties, classic electrophiles and nucleophiles in Pd(0)-mediated cross-coupling reactions, underwent ami-

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

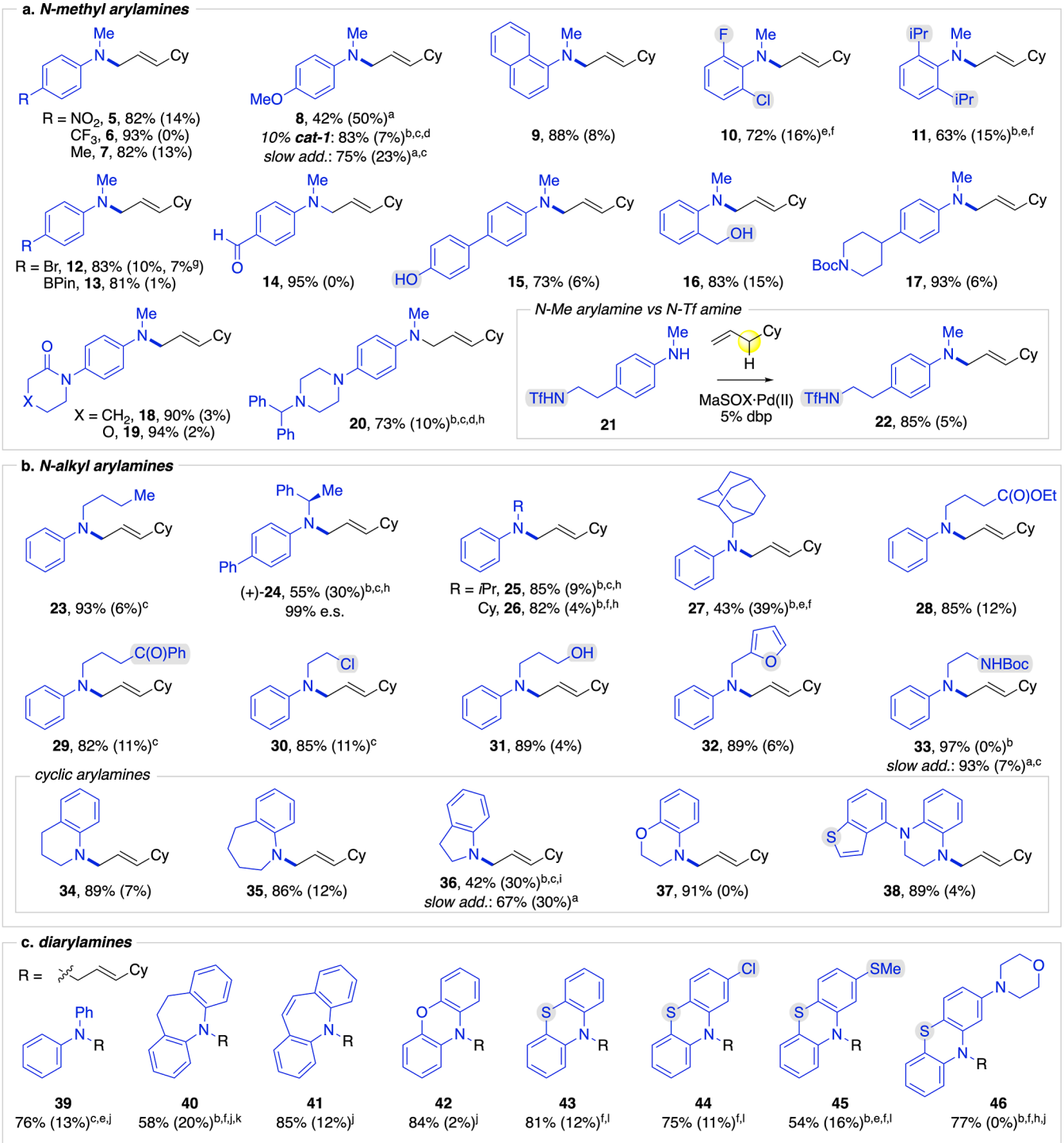


Figure 2. Nucleophile Scope. Unless otherwise noted, all reactions were run under the standard conditions: amine and olefin (1 equiv), $Pd(OAc)_2$ (5 mol %), MaSOX (5 mol %), 2,5-dimethylbenzoquinone (2,5-DMBQ) (1.1 equiv), and dibutyl phosphate (dbp) (5 mol %) in dioxane (1 M) and stirred for 12 h at 45 °C under ambient conditions; olefin RSM (shown in parentheses) was determined by crude ^{1}H NMR analysis; reported yields are the average isolated yields of three experiments. All products were formed in >20:1 *E*/*Z* and >20:1 L/B selectivity. [a]2 repeats. [b]10 mol % **cat-1**. [c]24 h. [d]0.9 equiv 2,5-DMBQ was used for ease of purification. [e]15 mol % dbp. [f]48 h. [g]Recovered starting amine. [h]10 mol % dbp. [i]5 mol % **cat-1** for 48 h afforded 15% yield (42% olefin RSM). [j]Toluene. [k]50 mol % dbp. [l]1,2-dichloroethane.

nation under these oxidative conditions (**12**, **13**). 4-(methylamino)benzaldehyde, containing a traditional electrophile for reductive aminations, afforded **14** in 95% yield. MaSOX·Pd(II) catalysis shows orthogonal reactivity to base-mediated processes that do not tolerate unprotected phenols[4g,10] and that effect benzylic alcohol oxidations;[24] amine nucleophiles containing these functionalities successfully afforded the 3° allylic arylamines **15** and **16** in excellent yields.

Nonbasic *N*-heterocyclic functionality like Boc-protected piperidine as well as piperidinone and morpholinone, found in drugs like apixaban and rivaroxaban, were well-tolerated in *N*-methyl arylamine derivatives (**17**–**19**). Although 3° aliphatic

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

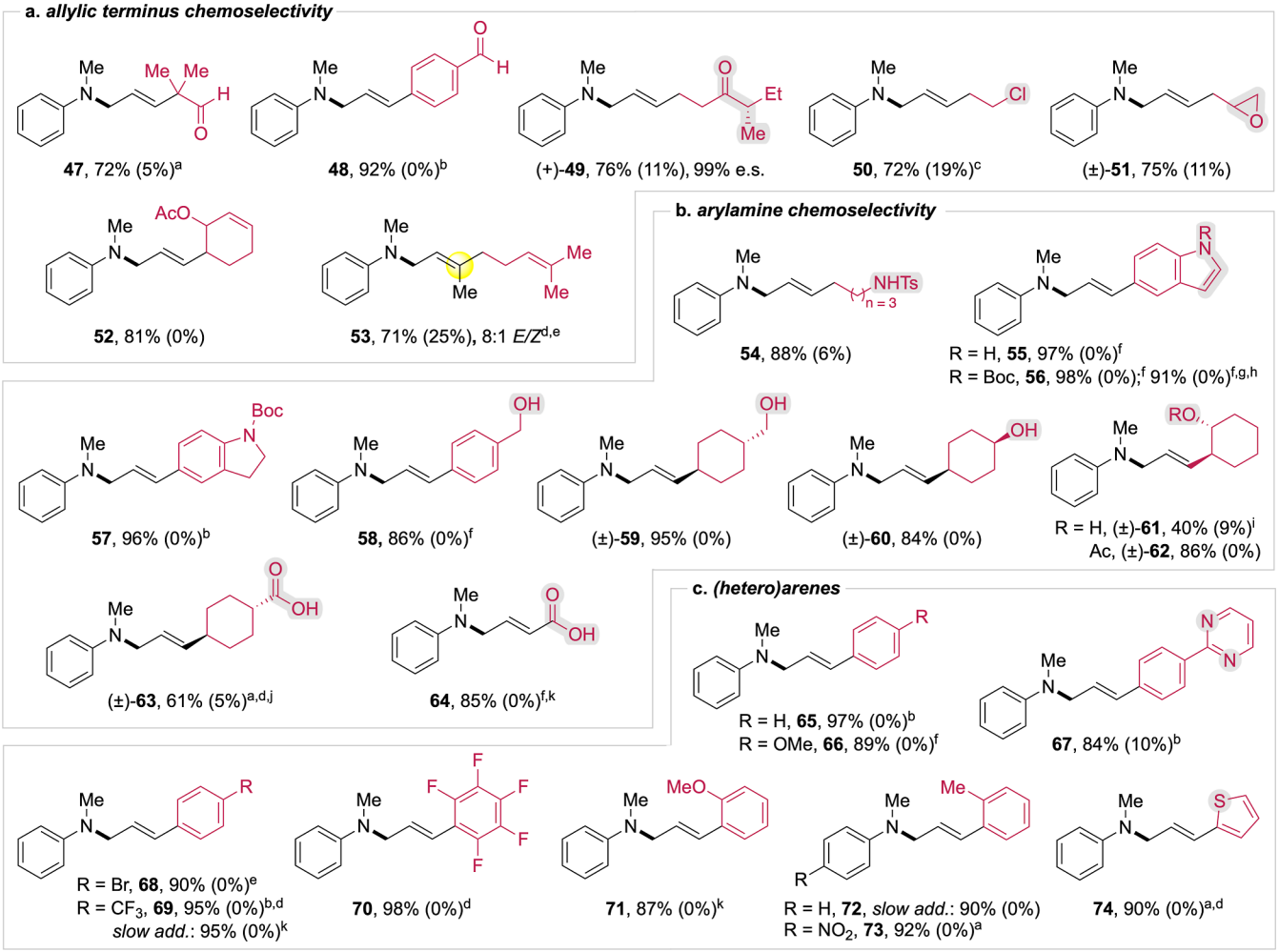


Figure 3. Electrophile Scope. Unless otherwise noted, all reactions were run and analyzed using the standard conditions (Figure 2) and all products were formed in >20:1 *E*/*Z* and >20:1 L/B selectivity. Olefin RSM is reported in parentheses. [a]24 h. [b]3 h. [c]10 mol % dbp. [d]10 mol % **cat-1**. [e]48 h. [f]2.5 mol % **cat-1**. [g]1.2 g, **56**. [h]2 repeats. [i]Reaction run in the absence of **1** afforded 49% recovered olefin with unidentifiable byproducts (see the Supporting Information). [j]20 mol % dbp. [k]4 h.

amines are generally not tolerated due to their high affinity for electrophilic Pd(II), the sterically encumbered *N*-benzhydryl functionality was compatible (**20**). *N*-methyl arylamine substrate **21** housing an acidic *N*-Tf alkylamine reacted under C(sp^3)H/N(sp^2) cross-coupling conditions to furnish allylic arylamine **22** in 85% yield with no observed *N*-Tf alkylamine coupling. Running the reaction under the previously reported nonacidic conditions for *N*-Tf alkylamine C−H allylic amination (10 mol % **cat-1**, 72 h, 0% dbp)[16] furnished a diminished yield of **22** (44%), with poor conversion (40% olefin recovered starting material (RSM)) and no observed *N*-triflyl amine allylation product (see the Supporting Information).

A diverse scope of *N*-alkyl arylamine nucleophiles, which present steric challenges and greater susceptibility for *β*-hydride elimination,[6,7] were evaluated (Figure 2b). *N*-butyl phenylamine as well as chiral (*R*)-*N*-(1-phenylethyl)arylamine derivative were each cross-coupled to afford **23** and **24** in high yields, with high enantiospecificity (99% e.s.) and no imine or acetophenone byproducts detected for the latter (see the Supporting Information). These results signify that C(sp^3)H/N(sp^2) cross-coupling likely proceeds via C−N bond formation outside the sphere of the metal and/or with neutral arylamines,[13a] as palladium-alkylamido intermediates are known to undergo *β*-hydride elimination and racemization pathways. A series of sterically bulky *N*-methine substituted derivatives (isopropyl, cyclohexyl (Cy), and adamantyl) furnished preparative yields of 3° allylic arylamines **25**−**27**, underscoring the high steric tolerance for this reaction.

N-alkylated arylamines appended with ester, ketone, and alkyl-chloride functionalities, classical electrophiles in *N*-alkylations, afforded **28**−**30** with no detected byproducts from competitive condensation, substitution, or elimination pathways. *N*-propanol phenylamine housing a 1° unprotected alcohol afforded **31** in 89% yield under this oxidative protocol, with no observed ether[22] or carbonyl[24] byproducts. Heteroatoms tethered by a two-carbon linker can act as strong bidentate ligands to palladium and inhibit catalysis. Whereas a furan functionality was well-tolerated under the standard conditions (**32**), an *N*-Boc amine gave recovered starting material. Highlighting the capacity for MaSOX·Pd(OAc)$_2$ conditions to be readily modified to overcome inhibitory substrate binding, 10 mol % **cat-1** or nucleophile slow addition furnished **33** in 97% and 93% yields, respectively.

Cyclic alkyl arylamine heterocycles were also proficient nucleophiles. Tetrahydroquinoline and tetrahydrobenzoaze-

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

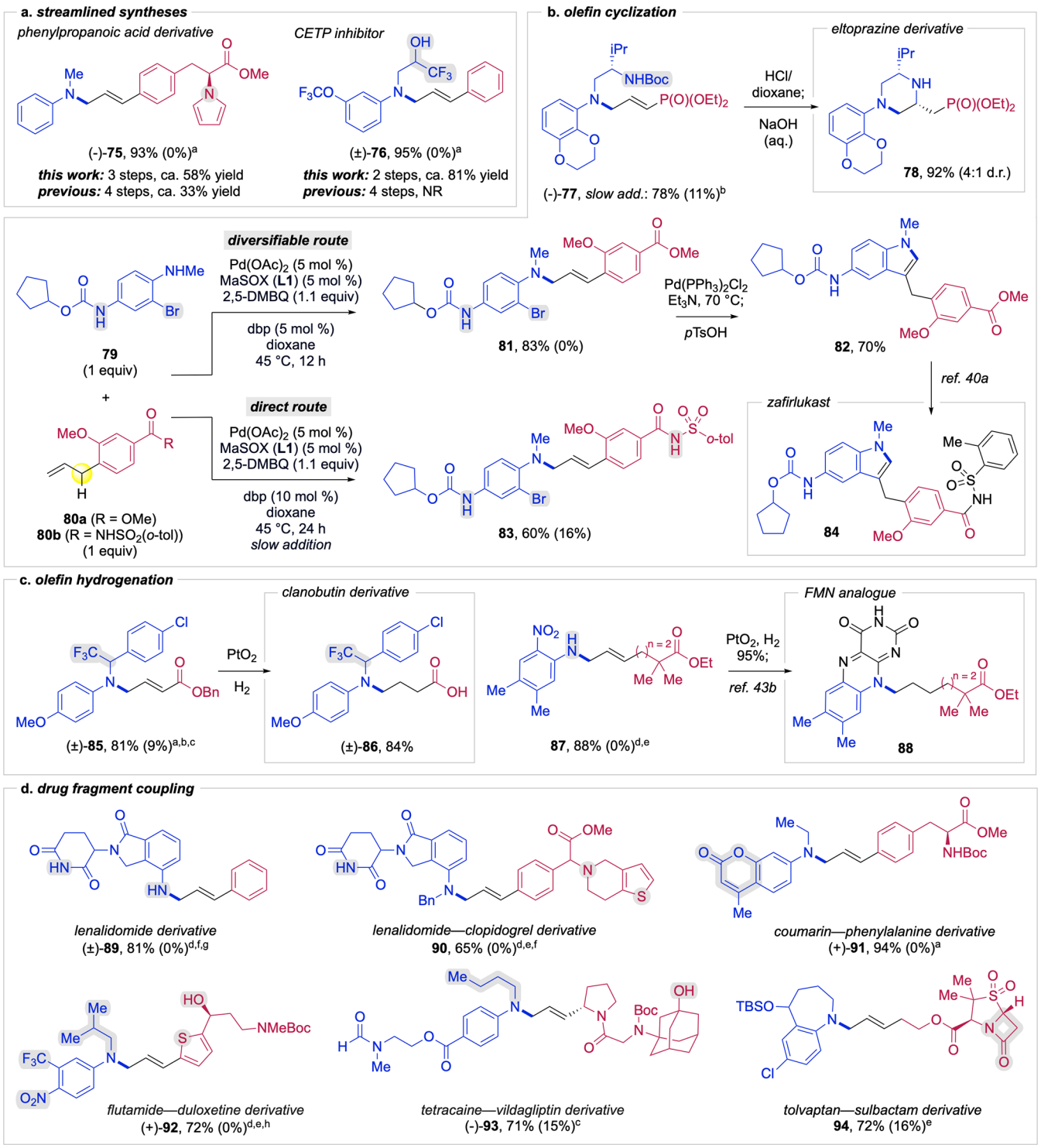


Figure 4. Complex Examples. Unless otherwise noted, all reactions were run and analyzed using the standard conditions (Figure 2) and all products were formed in >20:1 *E*/*Z* and >20:1 L/B selectivity. Olefin RSM is reported in parentheses. [a]2.5 mol % **cat-1**. [b]Room temperature. [c]24 h. [d]10 mol % **cat-1**. [e]10 mol % dbp. [f]72 h. [g]1,2-dichloroethane. [h]48 h.

pine afforded products in excellent yields under the standard conditions (**34**, **35**), however, indoline afforded trace cross-coupled product **36** with poor mass-balance (see the Supporting Information). Consistent with indoline's higher basicity,[3,25] spectroscopic studies revealed more MaSOX **L1** displacement relative to *N*-methyl phenylamine **1** (97% versus 81% **L1** at 3 equiv of amine) as well as the formation of indole side products.[26] Slow addition of indoline at 5 mol % **cat-1** gave cross-coupled product **36** in 67% yield with restored mass-balance. Arylamine-derived morpholine and piperazine, bearing a pendent benzothiophene, were also suitable cyclic nucleophiles and furnished densely functionalized 3° amines **37** and **38**.

Diarylamines, broadly represented in pharmaceuticals and natural products, are challenging nucleophiles due to their electron-deficient and sterically encumbered nature. Consistent

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

with this, catalyst deactivation via amine binding was not problematic; evaluation of **cat-1** with diphenylamine (10 equiv) resulted in only 8% free **L1**. While modest reactivity was observed under the standard conditions (see the Supporting Information), increasing catalyst and/or phosphoric acid loadings afforded significant improvements. This reactivity enhancement was likely due to higher concentrations of the electrophilic π-allyl-MaSOX·Pd(II) intermediate, thereby promoting functionalization. Under such conditions, the C(sp^3)H/N(sp^2) cross-coupling of allylcyclohexane with diphenylamine or cyclic dihydrodibenzazepine, problematic under reductive amination conditions,[4a] afforded allylated products **39** and **40** in 76% and 58% yields, respectively (Figure 2c). Diarylamines like iminostilbene, phenoxazine, and 2-H/Cl phenothiazine—having a more puckered conformation that partially releases the nitrogen lone pair from resonance delocalization[27]—underwent amination at 5 mol % **cat-1** (**41**−**44**). Phenothiazines—generally strong binders to Pd(II)—are common cores in psycholeptic drugs, and ones housing thioether and morpholine functionalities afforded *N*-allylated products **45** and **46** in useful yields at higher **cat-1** and dbp loadings.[4b,28,29]

Electrophile Scope. We explored coupling *N*-methyl phenylamine with diverse olefins, many bearing functionality not tolerated in known aminations (Figure 3a). Underscoring this method's orthogonality to reductive aminations, olefins containing classically reactive aliphatic and benzylic aldehydes afforded allylic 3° arylamine products **47** and **48** as the only observed products. Whereas enolizable α-substituted ketones are prone to epimerization under basic amination conditions,[8] a stereodefined sec-butyl ketone olefin underwent functionalization in 76% yield (**49**) with 99% e.s. under these mildly acidic conditions. Olefins housing an alkyl chloride and a terminal epoxide, electrophiles for Hofmann *N*-alkylations, were maintained to afford aminated products **50** and **51** in good yields and with excellent mass balance. An allylic acetate moiety, employed as electrophiles in Pd(0)-catalyzed allylic substitutions,[13] was well-tolerated in this oxidative Pd(II) amination to furnish **52** in preparative yield. Consistent with previous reports of sulfoxide·$Pd(OAc)_2$ catalysis, allylic C−H cleavage was highly selective for terminal olefins in the presence of internal ones.[15−17,22] In a geraniol-derived diene, C−H cleavage occurred selectively at the terminal olefin on a hindered 3° center to afford trisubstituted **53** in a useful yield. Interestingly, the *E*/*Z* selectivity remained preparative (8:1 *E*/*Z*) and was substantially higher than Pd(0)-mediated allylic substitution of a geraniol allylic alcohol with arylamine nucleophiles (1:1.6 *E*/*Z*), suggesting a faster functionalization step.[30]

We evaluated the selectivity for arylamine functionalization on olefins bearing nucleophiles precedented to react under Pd(II) catalysis (Figure 3b). A substrate appended with a remote *N*-Ts amine—a classic nucleophile for aza-Wacker reactions[31] but not allylic C−H aminations—afforded the linear allylic arylamine product **54** in a good yield (88%). Indole, an ambident nucleophile for C2- and *N*-alkylation in Pd(II)-mediated olefin functionalizations,[32] was well-tolerated in the electrophile in both the N−H and *N*-Boc forms to furnish **55** and **56**, respectively (**56**, 1.2 g, 91%). Indoline, a nucleophile for this reaction (e.g., **36**), was well-tolerated on the olefin in its protected form (**57**). Primary and 2° alcohols, recently reported nucleophiles under *cis*-SOX·Pd(II)/phosphoric acid catalysis,[22] were maintained on the olefin coupling partner in this allylic amination (**58**−**60**). Interestingly, 2-allyl cyclohexanol, housing an alcohol positioned for intramolecular functionalization, afforded a diminished yield of aminated product (**61**, 40%) with poor olefin recovery (9%). Introduction of an acetate protecting group restored productive reactivity to afford **62** in 86% yield. Remarkably, arylamines reacted preferentially to carboxylic acids, well-precedented nucleophiles in Pd(II)-catalyzed allylic C−H esterifications,[33] to furnish products **63** and **64** in preparative yields.

Cinnamyl-derived olefins are typically more reactive in allylic C−H functionalizations due to more activated C−H bonds and more electrophilic π-allyl-Pd(II) intermediates.[12] Electron-rich and -neutral allylbenzenes, including *N*-heterocycles, reacted with reduced reaction times (3 h) or 2.5 mol % **cat-1** loadings (**65**−**67**, Figure 3c). We explored electron-deficient and/or sterically hindered olefins that may compete poorly with arylamines for Pd(II)-binding required for C−H cleavage. Electron-deficient allylbenzenes were effective coupling partners using longer reaction times (48 h), higher catalyst loadings (10 mol %), or the slow addition protocol under standard conditions (**68**−**70**). For example, whereas 4-trifluoromethyl allylbenzene did not react under standard conditions, either 10 mol % **cat-1** or slow addition of *N*-methyl phenylamine **1** at 5 mol % **cat-1** furnished **69** in 95% yield. *Ortho*-methoxy aryl substitution afforded 87% yield of **71** under standard conditions, whereas bulkier methyl substitution afforded **72** in good yield by using the slow addition protocol. Consistent with a competitive arylamine/olefin Pd(II)-binding scenario, exchange of **1** with 4-nitro-*N*-methyl phenylamine—a nucleophile that binds poorly to **cat-1** (14% free **L1**, see Supporting Information)—afforded **73** in excellent yield under the standard conditions. 2-Allylthiophene, containing a sulfur that may additionally compete for Pd(II)-coordination, reacted with **1** at higher catalyst loadings (10 mol %) to afford preparative yield of **74**.

Complex Examples. We investigated whether the broad scope and robust conditions of this C−H amination enable a platform for late-stage fragment coupling to furnish pharmaceuticals and their derivatives. Antidiabetic experimental drug **75** was furnished via coupling of a pyrrolyl allylphenylalanine derivative with *N*-methyl phenylamine at low catalyst loadings and short reaction times (2.5% **cat-1**, 12 h) in ca. a 2-fold increase in overall yield relative to the previous hydrozirconation/borylation route (58% versus 33%) (Figure 4a).[34] Hofmann alkylations with sterically hindered and/or electron-deficient arylamines proceed under strongly basic conditions that require protecting group manipulations of competing nucleophilic functionality. Highlighting the notable reactivity and chemoselectivity of MaSOX·$Pd(OAc)_2$ catalysis, the cross-coupling of a hindered, electron-deficient 2-arylamino ethanol derivative with allylbenzene at 2.5% **cat-1** afforded experimental cholesteryl ester transfer protein (CETP) inhibitor **76**. By eliminating alcohol protection/deprotection steps, the C−H amination route proceeded in half the steps relative to a Hofmann sequence.[35]

The *E*-allylic arylamines generated via this C(sp^3)H/N(sp^2) cross-coupling are versatile intermediates for the construction of diversely functionalized *N*-heterocycles (Figure 4b). The coupling of Boc-L-valine-derived arylamine with diethyl allyl phosphate afforded **77** in preparative yield; subsequent intramolecular aza-Michael cyclization[36] provided rapid access to synthetically challenging,[28,37] nonsymmetrical C3- and C5-

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

substituted piperazine **78**, the core of serotonergic drug eltoprazine. *E*-allylic amines generated from readily available 2-bromo arylamines can be directly taken into the Mori−Ban reaction, providing a diversifiable route to indoles, the sixth most frequent heterocycle in pharmaceuticals.[38,39] Using the 4-carbamoyl-*N*-methyl arylamine fragment **79**, selective cross-coupling of the more electron-rich nitrogen with the allylbenzene fragment **80a** furnished *E*-allylic amine **81** as one regio- and stereoisomer. The *ortho*-bromine functionality was maintained under these oxidative conditions and further utilized in the Mori−Ban reaction[39] to afford known indole precursor **82** to zafirlukast **84**, an FDA-approved antiasthma medication, in two steps with excellent yields and selectivities.[40] An alternative route to **84** would be a late-stage cross-coupling with sulfonyl benzamide olefin **80b** followed by the Mori−Ban reaction. No allylic amination was observed using **80b**, however, (trimethylsilyl)ethyoxymethyl (SEM) protection of the sulfonyl benzamide restored catalytic reactivity (see Supporting Information). We postulated that accumulation of an anionic olefin sulfonyl benzamide nitrogen in **80b** (N−H $pK_a \sim 5$) generated from deprotonation by the arylamine **79** deactivated **cat-1**. In agreement with this, the slow addition of arylamine **79** to **80b** afforded **83** in preparative yield (60%).

A C(sp^3)H/N(sp^2) cross-coupling, olefin hydrogenation sequence provides a rapid route to *N*-alkyl 3° arylamine drug derivatives traditionally challenging to access using direct alkylation (Figure 4c). A sterically encumbered α-trifluoromethyl (CF_3) arylamine—an amide bioisostere[41]—was effectively coupled with benzyl butenoate to furnish **85** in 81% yield. Global hydrogenation of the olefin and benzyl ester furnished clanobutin derivative **86**. Although 1° arylamines are generally not viable nucleophiles in this reaction (see the Supporting Information), some electron-deficient and/or sterically hindered 1° arylamines can afford 2° allylic arylamines in preparative yields. 2-nitro arylamine, a common precursor for quinoxaline derivatives, underwent amination to afford **87** in 88% yield. No diallylated product was observed, likely because of a deactivating intramolecular hydrogen-bonding interaction between the N−H and *ortho*-nitro group in the 2° arylamine product.[42] Subsequent hydrogenation of the olefin and nitro functionalities afforded the known diamine intermediate for the synthesis of flavin mononucleotide (FMN) derivative **88**.[43]

Amines tethered via flexible carbon linkers to other functionalities are a common structural feature in medicines and molecular recognition moieties (Figure 4d). Proteolysis-targeting chimera (PROTAC)—a heterobifunctional molecule with a linker that connects an E3 ubiquitin ligase to a protein of interest—is a promising protein degradation therapeutic-strategy.[44] Functionally dense lenalidomide, a known E3 ubiquitin ligand, presents challenges in the installation of small molecules via Hofmann *N*-alkylations due to competitive generation of arylamine- and imide-alkylated products.[4c] Under MaSOX·Pd(OAc)$_2$/dbp catalysis, lenalidomide and its benzylated derivative were cross-coupled with allylbenzene and an allylated clopidogrel derivative, bearing a tetrahydrothienopyridine, to afford monoallylated 2° arylamine **89** and 3° arylamine **90**. Although ca. 10% diallylated product (see the Supporting Information) was seen in cross-coupling of the 1° arylamine, no detected imide-alkylation was observed for either **89** or **90**. Tertiary arylamine coumarins are used as small-molecule fluorescent probes in environmental and medicinal applications.[45] This amination provides a convenient approach for tethering small molecules to the arylamine core, as demonstrated in the cross-coupling of a coumarin-derived *N*-ethyl arylamine with an amino-acid olefin analogue (**91**, 94% yield).

Late-stage C(sp^3)H/N(sp^2) cross-coupling of drug fragments furnishes complex arylamines housing biologically relevant functionality. An *N*-alkyl arylamine flutamide analogue, showcasing a sterically and electronically challenging nucleophile, was cross-coupled with an allylated duloxetine derivative, housing a thiophene-core and an unprotected benzylic alcohol, to afford **92** in 72% yield. An allylated derivative of antidiabetic vildagliptin underwent amination with the sterically demanding *N*-butyl arylamine tetracaine analogue to furnish **93** in high yield. Whereas benzylic alcohols and tetrahydrobenzoazepines were individually well-tolerated in this allylic C−H amination (e.g., **16**, **35**, **58**, **92**), modest yields were observed in the cross-coupling of a tolvaptan fragment containing a free benzylic alcohol with an allylated sulbactam fragment (33% yield, see the Supporting Information). Silyl protection of the alcohol, however, restored reactivity to furnish tolvaptan-sulbactam derivative **94** in 72% yield.

Mechanistic Investigations. Palladium catalyst deactivation via ligand displacement and formation of off-cycle bis(amine)·Pd complexes is a central challenge in C−N cross-couplings.[46] Fluxional ligand binding was previously observed in bis-sulfoxide·Pd(II) catalyzed allylic C−H functionalizations and as a result, these reactions required the use of specialized, electron-deficient nucleophiles (e.g., *N*-Ts carbamates) for effective catalysis.[33b,47] Previous MaSOX·Pd(II) allylic C−H aminations also used electron-deficient amines (*N*-Tf alkylamines)[16] or diverted this challenge with basic 2° alkylamines using a slow-release strategy with BF_3/HBF_4 amine salts.[17] Mechanistic studies were conducted to understand the basis for the remarkably high generality and efficiency of this C(sp^3)H/N(sp^2) cross-coupling despite only trace amounts of the active MaSOX·Pd(II) catalyst present during the reaction.

We hypothesized that the efficiency of this allylic C−H amination is attributed to the aptitude of MaSOX ligand **L1** to establish a dynamic equilibrium with inactive bis(arylamine)·Pd(II) **4** as well as Pd complexes throughout the catalytic cycle. Complex **4** was not effective as a catalyst for C(sp^3)H/N(sp^2) amination (Figure 5a, entry 1) and agrees with the results observed without MaSOX **L1** (vide supra, Figure 1c, entry 4). However, combining both **L1** and **4** in the reaction restored the reactivity (Figure 5a, entry 2), supporting the proposed equilibrium scenario and necessity of MaSOX for catalysis. Precedented C−N cross-couplings often require elevated temperatures (>80 °C) and/or the development of modified ligand scaffolds to access sufficient concentrations of active catalyst.[46] In contrast, this C(sp^3)H/N(sp^2) cross-coupling achieves high reactivity under mild reaction conditions (45 °C) and with one SOX ligand (**L1**). This underscores the facile reversibility between inactive bis(arylamine)·Pd(II) **4** and active MaSOX·Pd(II) **cat-1**.

To directly probe the effects of MaSOX **L1** and phosphoric acid on functionalization, four stoichiometric π-allyl-Pd(II) complexes were synthesized with either acetate (***OAc***) or phosphate (***OP***) counterions with or without the MaSOX ligand (**L1**). The reactivity and initial rates of functionalization were evaluated with *N*-methyl phenylamine **1** or *N*-Tf phenethylamine under mock-catalytic conditions (20 equiv of

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

amine relative to 1 equiv of palladium) (Figure 5b). Reaction profiles revealed an induction period for functionalization of ***OP*** and [***OP***(**L1**)] complexes only with arylamine **1**, and initial rates were measured afterward. ^{1}H NMR analysis of complexes ***OAc***(**L1**) and ***OP***(**L1**) in the presence of arylamine **1** showed chemical shift changes that suggests altered **L1** binding, however, free MaSOX **L1** was not observed (see the Supporting Information).

Evaluation of π-allyl-Pd(II)X/$_2$ (X = acetate or phosphate) complexes in the absence of MaSOX **L1** (***OAc*** and ***OP***) with *N*-methyl phenylamine **1** showed no reactivity from ***OAc*** but product **3** formation from ***OP*** (see the Supporting Information). Given that catalysis does not happen in the absence of MaSOX **L1**, this suggests that the ligand is required for allylic C−H cleavage but not for functionalization under the phosphoric acid conditions. However, MaSOX-bound complex ***OP***(**L1**) afforded a ca. 35-fold increase in the rate of functionalization relative to that of ***OP***, indicating that catalysis likely proceeds via a MaSOX-bound π-allyl-Pd(II) intermediate. Consistent with the beneficial effect of dbp on reactivity with arylamines (Figure 1c, entries 1−3), the rate of functionalization of electrostatically activated π-allyl-MaSOX·Pd(II)[OP(O)(OBn)$_2$] ***OP***(**L1**) with *N*-methyl phenylamine **1** proceeded ca. 7-fold faster, after the induction period, than the corresponding acetate complex ***OAc***(**L1**).

Whereas phosphoric acid additives had a negligible effect on C−H amination with acidic *N*-Tf amine nucleophiles when used in equimolar amounts relative to **cat-1**, at higher dbp loadings—where full exchange of acetate for phosphate counteranion occurs—significantly diminished yields of **96** were observed (see the Supporting Information). Stoichiometric π-allyl rate studies of *N*-Tf phenethylamine with complex ***OP***(**L1**) showed a ca. 6-fold decrease in the rate relative to ***OAc***(**L1**) (Figure 5b). The acetate counteranion may serve an important role in deprotonating acidic *N*-Tf amine nucleophiles, thereby facilitating functionalization. Consistent with this, under the standard C(sp^3)H/N(sp^2) reaction conditions, the yield of *N*-Tf amine product **96** was significantly lower than that of arylamine **3** (28% versus 90%, respectively; see the Supporting Information and Figure 1c, entry 3). However, functionalization rate studies and parallel reactions with each nucleophile in the absence of phosphoric acid suggested that *N*-Tf amines should be competitive with *N*-arylamine nucleophiles (Figure 5b,c). Interestingly, analogous to the intramolecular competition results (Figure 2, **21**), an intermolecular competition between *N*-methyl phenylamine and *N*-Tf phenethylamine under dbp-free conditions afforded 3° arylamine **3** as the major product (Figure 5c). This suggests that arylamines have an inhibitory effect on functionalization of less basic nucleophiles previously demonstrated under (SOX)·Pd catalysis.[16,22,33] Collectively, these effects may strongly contribute to the high chemoselectivity for arylamine functionalization in this reaction.

Under previous intermolecular allylic C−H cross-couplings, functionalization is either entirely rate-determining or contributes significantly to the reaction rate.[16,22] The high efficiency of this reaction may partially arise by shifting the rate-determining step from a high-energy functionalization to a lower energy C−H cleavage step. Consistent with this, parallel rate and intramolecular KIEs of *N*-methyl phenylamine **1** under the optimal reaction conditions with 5 mol % dbp matched (4.95 ± 0.06 and 5.05 ± 0.02, respectively), signifying that C−H cleavage is rate-determining and that functionaliza-

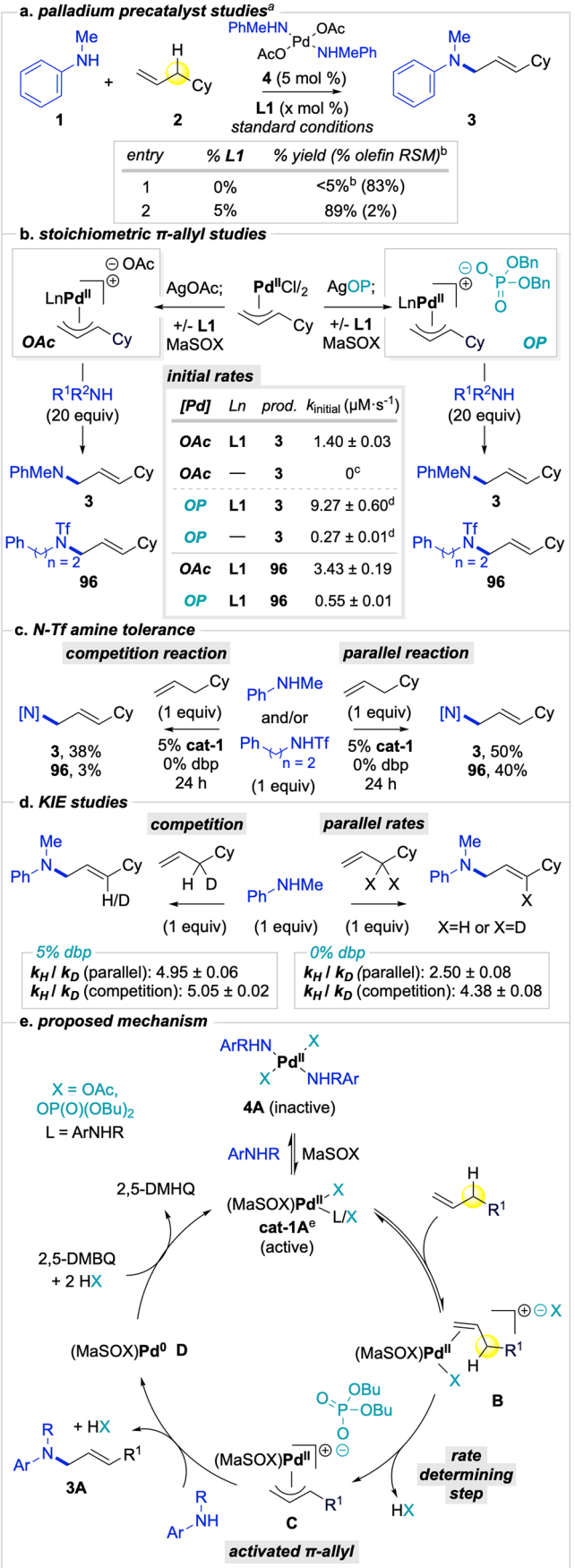


Figure 5. Mechanistic Investigations. [a]Reactions were run under standard conditions (Figure 2) with complex **4** as the Pd(II)-source

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

Figure 5. continued

and 0.9 equiv of **1**. [b]Determined by ^{1}H NMR analysis. [c]No product **3** observed. [d]$k_{initial}$ measured after an induction period. [e]Complex **cat-1A** is cationic if L is coordinated to the Pd(II) center.

tion is facile (Figure 5d). In contrast, parallel rate measurements in the absence of phosphoric acid showed a lower intermolecular KIE (2.50 ± 0.08) than that of the innate intramolecular KIE (4.38 ± 0.08), indicating that functionalization plays a prominent role in the amination rate. These latter KIEs are comparable to those previously observed with the *N*-Tf phenethylamine nucleophile where allylic C−H amination is less efficient, requiring higher catalyst loadings and longer reaction times (10 mol % **cat-1**, 24−72 h).[16]

Guided by these mechanistic studies, a proposed mechanism for C(sp^3)H/N(sp^2) cross-coupling amination is shown in Figure 5e. Bis(arylamine)·Pd(II) **4A** is an inactive Pd(II) resting state that is in a dynamic equilibrium with catalytically active MaSOX·Pd(II) **cat-1A** (Figure 1). Rate-determining heterolytic C−H cleavage from MaSOX·Pd(II) olefin complex **B** affords π-allyl-MaSOX·Pd(II)[OP(O)(OBu)$_2$] **C** that undergoes ligand- and counterion-accelerated functionalization to give 3° arylamine product **3A**. Although not explicitly shown, interactions of arylamine with Pd(II) complexes **B** and **C** are likely occurring. Arylamine functionalization of **C** via an amine-Pd(II) binding and soft deprotonation pathway is not supported by the results observed with acyclic *N*-alkyl arylamines that do not undergo epimerization or β-hydride elimination—processes typically associated with palladium-alkylamido mechanisms (Figure 2b, **24**).[6,7] The greater steric hindrance of 3° arylamine product **3A** relative to the 2° arylamine nucleophile makes it less competitive for Pd(II)-binding, thereby driving the reaction forward via a Le Chatelier effect (Figure 1d, entries 6 and 7). Quinone-mediated Pd(0) reoxidation of complex **D** generates hydroquinone and reestablishes the active **cat-1A**.

In conclusion, a general and efficient MaSOX·Pd(OAc)$_2$/phosphoric acid catalyzed C(sp^3)H/N(sp^2) amination is presented that cross-couples complex 2° arylamines and complex terminal olefins to furnish diverse acyclic and cyclic 3° *N*,*N*-dialkylated arylamines in preparative yields and high selectivities. This fragment-coupling method showcases an orthogonal scope to both classic and palladium-mediated aminations. Mechanistic studies revealed that MaSOX **L1** undergoes ligand exchange with neutral arylamines to furnish MaSOX·Pd(II) complexes that effectively promote C−H cleavage and functionalization. Moreover, the barrier for functionalization can be lowered using precise amounts of phosphoric acids. These findings underscore the ability to access both efficient and highly selective reactivity under transition-metal catalysis without the requirement for static ligand binding. We anticipate that this reaction will find broad use in the synthesis of medicinally relevant, complex arylamines and that the mechanistic studies will inform the development of other metal-catalyzed aminations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c08883.

Experimental section including characterization data (PDF)

NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

M. Christina White − *Roger Adams Laboratory, Department of Chemistry, University of Illinois Urbana−Champaign, Urbana, Illinois 61801, United States;* orcid.org/0000-0002-9563-2523; Email: mcwhite7@illinois.edu

Authors

Brenna G. Budaitis − *Roger Adams Laboratory, Department of Chemistry, University of Illinois Urbana−Champaign, Urbana, Illinois 61801, United States;* Present Address: AbbVie, Inc. North Chicago, Illinois 60064, United States

Zachary M. Firestein − *Roger Adams Laboratory, Department of Chemistry, University of Illinois Urbana−Champaign, Urbana, Illinois 61801, United States*

Andrew C. Yue − *Roger Adams Laboratory, Department of Chemistry, University of Illinois Urbana−Champaign, Urbana, Illinois 61801, United States;* Present Address: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States.

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c08883

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This manuscript is the result of funding in whole or in part by the National Institutes of Health (NIH). It is subject to the NIH Public Access Policy. Through acceptance of this federal funding, NIH has been given a right to make this manuscript publicly available in PubMed Central upon the Official Date of Publication, as defined by NIH. Financial support for this work was provided by the National Institute of General Medical Sciences (GMS) Maximizing Investigators' Research Award (MIRA R35GM122525). The Bruker 500 MHz NMR spectrometer was obtained with financial support from the Roy J. Carver Charitable Trust.

Notes

The authors declare the following competing financial interest(s): The University of Illinois has a patent (US10,266,503B1) on sulfoxide-oxazoline ligands for Pd(II)-catalyzed allylic CH functionalizations. The authors declare no other competing interests.

■ ACKNOWLEDGMENTS

We thank the SCS NMR lab, Dr. L. Zhu, and Dr. D. Olson for helpful discussion on NMR spectroscopy. We further thank H. Way for checking procedures and repeating the amination to furnish **14**.

■ REFERENCES

(1) Roughley, S. D.; Jordan, A. M. The medicinal chemist's toolbox: An analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **2011**, *54*, 3451−3479.

(2) Ruiz-Castillo, P.; Buchwald, S. L. Applications of palladium-catalyzed C—N cross-coupling reactions. *Chem. Rev.* **2016**, *116*, 12564−12649.
(3) Rappoport, Z. *The Chemistry of Anilines*; Wiley: New York, 2007; Vol. *1*.
(4) (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures. *J. Org. Chem.* **1996**, *61*, 3849−3862. (b) Karicherla, V.; Phani, K.; Bodireddy, M. R.; Prashanth, K. B.; Gajula, M. R.; Pramod, K. A simple and commercially available process for improved yields of Metopimazine, a dopamine D_2-receptor antagonist. *Org. Process Res. Dev.* **2017**, *21*, 720−731. (c) Qiu, X.; Sun, N.; Kong, Y.; Li, Y.; Yang, X.; Jiang, B. Chemoselective synthesis of lenalidomide-based PROTAC library using alkylation reaction. *Org. Lett.* **2019**, *21*, 3838−3841. (d) Righi, M.; Bedini, A.; Piersanti, G.; Romagnoli, F.; Spadoni, G. Direct, one-pot reductive alkylation of anilines with functionalized acetals mediated by triethylsilane and TFA. Straightforward route for unsymmetrically substituted ethylenediamine. *J. Org. Chem.* **2011**, *76*, 704−707. (e) Link, J. T.; Sorensen, B. K.; Patel, J.; Emery, M.; Grynfarb, M.; Goos-Nilsson, A. Discovery of novel nonsteroidal glucocordicoid receptor modulators. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2209−2212. (f) Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. Intramolecular "hydroiminiumation and -amidiniumation" of alkenes: A convenient, flexible, and scalable route to cyclic iminium and imidazolinium salts. *J. Org. Chem.* **2007**, *72*, 3492−3499. (g) Greten, F.; Denk, D.; Andreux, P.; Dugi, K. A.; Rinsch, C. L. Therapeutic uses of urolithin derivatives. WO 2024/025953 A2, 2024.
(5) Brown, D. G.; Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: Where have all the new reactions gone? *J. Med. Chem.* **2016**, *59*, 4443−4458.
(6) For reviews, see: (a) Muci, A. R.; Buchwald, S. L.; Miyaura, N. Practical Palladium Catalysts for C—N and C—O Bond Formation. In *Cross-Coupling Reactions. Topics in Current Chemistry*; Springer, 2002; pp 131−209. (b) Hartwig, J. F. Carbon-heteroatom bond formation catalysed by organometallic complexes. *Nature* **2008**, *455*, 314−322.
(7) For examples with acyclic amine coupling partner challenges, see: (a) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. Palladium-catalyzed amination of aryl bromides: Use of phosphinoether ligands for the efficient coupling of acyclic secondary amines. *J. Org. Chem.* **1997**, *62*, 1568−1569. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. Palladium-catalyzed coupling of optically active amines with aryl bromides. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.
(8) For an example with enolizable ketone challenges, see: De Borggraeve, W.; Aigret, B.; Jacobs, J.; Van Meervelt, L. Asymmetric synthesis of 1-aza-4-deoxypicropodophyllotoxin. *Synlett* **2013**, *24*, 1097−1100.
(9) Ley, S. V.; Thomas, A. W. Modern synthetic methods for copper-mediated C(aryl)—O, C(aryl)—N, and C(aryl)—S bond formation. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.
(10) Harris, M. C.; Huang, X.; Buchwald, S. L. Improved functional group compatibility in the palladium-catalyzed synthesis of aryl amines. *Org. Lett.* **2002**, *4*, 2885−2888.
(11) Shimizu, Y.; Obora, Y.; Ishii, Y. Intermolecular aerobic oxidative allylic amination of simple alkenes with diarylamines catalyzed by the $Pd(OCOCF_3)_2$/NPMoV/O_2 system. *Org. Lett.* **2010**, *12*, 1372−1374.
(12) (a) Jin, Y.; Jing, Y.; Li, C.; Li, M.; Wu, W.; Ke, Z.; Jiang, H. Palladium-catalysed selective oxidative amination of olefins with Lewis basic amines. *Nat. Chem.* **2022**, *14*, 1118−1125. (b) Liu, R.; Shen, M.-L.; Fan, L.-F.; Zhou, X.-L.; Wang, P.-S.; Gong, L.-Z. Palladium-catalyzed branch- and *Z*-selective allylic C—H amination with aromatic amines. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202211631.
(13) For asymmetric allylic substitutions with 1° arylamines, see: (a) Pàmies, O.; Margalef, J.; Cañellas, S.; James, J.; Judge, E.; Guiry, P. J.; Moberg, C.; Bäckvall, J.-E.; Pfaltz, A.; Pericàs, M. A.; Diéguez, M. Recent advances in enantioselective Pd-catalyzed allylic substitution: From design to applications. *Chem. Rev.* **2021**, *121*, 4373−4505. (b) Moreno-Mañas, M.; Morral, L.; Pleixats, R. Palladium(0)-catalyzed allylation of highly acidic and nonnucleophilic anilines. The origin of stereochemical scrambling when using allylic carbonates. *J. Org. Chem.* **1998**, *63*, 6160−6166. (c) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. (π-allyl)palladium complexes bearing diphosphinidenecyclobutene ligands (DPCB): Highly active catalysts for direct conversion of allylic alcohols. *J. Am. Chem. Soc.* **2002**, *124*, 10968−10969. (d) Ghosh, R.; Sarkar, A. Palladium-catalyzed amination of allyl alcohols. *J. Org. Chem.* **2011**, *76*, 8508−8512. (e) Guo, W.; Martínez-Rodríguez, L.; Kuniyil, R.; Martin, E.; Escudero-Adán, E. C.; Maseras, F.; Kleij, A. W. Stereoselective and versatile preparation of tri- and tetrasubstituted allylic amine scaffolds under mild conditions. *J. Am. Chem. Soc.* **2016**, *138*, 11970−11978. For allylic substitutions using bis-sulfoxide·Pd(II), see: (f) Yurino, T.; Saito, S.; Ichihashi, M.; Ohkuma, T. Aerobic allylic amination catalyzed by a $Pd(OAc)_2$/$P(OPh)_3$ system with low catalyst loading. *J. Org. Chem.* **2022**, *87*, 2864−2872.
(14) For iridium and rhodium catalyzed allylic substitutions with 1° arylamines to give branched products, see: (a) Shu, C.; Leitner, A.; Hartwig, J. F. Enantioselective allylation of aromatic amines after in situ generation of an activated cyclometalated iridium catalyst. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797−4800. (b) Kim, S. W.; Schwartz, L. A.; Zbieg, H. R.; Stivala, C. E.; Krische, M. J. Regio- and enantioselective iridium-catalyzed amination of racemic branched alkyl-substituted allylic acetates with primary and secondary aromatic and heteroaromatic amines. *J. Am. Chem. Soc.* **2019**, *141*, 671−676. (c) Arnold, J. S.; Nguyen, H. M. Rhodium-catalyzed dynamic kinetic asymmetric transformations of racemic tertiary allylic trichloroacetimidates with anilines. *J. Am. Chem. Soc.* **2012**, *134*, 8380−8383.
(15) For examples of chiral-SOX ligands promoting high levels of asymmetric induction, see: (a) Liu, W.; Ali, S. Z.; Ammann, S. E.; White, M. C. Asymmetric allylic C—H alkylation via palladium(II)/*cis*-ArSOX catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 10658−10662. (b) Ammann, S. E.; Liu, W.; White, M. C. Enantioselective allylic C—H oxidation of terminal olefins to isochromans by palladium(II)/chiral sulfoxide catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 9571−9575.
(16) Ma, R.; White, M. C. C—H to C—N cross-coupling of sulfonamides with olefins. *J. Am. Chem. Soc.* **2018**, *140*, 3202−3205.
(17) Ali, S. Z.; Budaitis, B. G.; Fontaine, D. F. A.; Pace, A. L.; Garwin, J. A.; White, M. C. Allylic C—H amination cross-coupling furnishes tertiary amines by electrophilic metal catalysis. *Science* **2022**, *376*, 276−283.
(18) For other allylic C—H aminations using electron deficient nitrogen nucleophiles, see: (a) Park, Y.; Kim, Y.; Chang, S. Transition metal-catalyzed C—H amination: Scope, mechanism, and applications. *Chem. Rev.* **2017**, *117*, 9247−9301. (b) Ide, T.; Feng, K.; Dixon, C. F.; Teng, D.; Clark, J. R.; Han, W.; Wendell, C. I.; Koch, V.; White, M. C. Late-stage intermolecular allylic C—H amination. *J. Am. Chem. Soc.* **2021**, *143*, 14969−14975. (c) Lei, H.; Rovis, T. A site-selective amination catalyst discriminates between nearly identical C—H bonds of unsymmetrical disubstituted alkenes. *Nat. Chem.* **2020**, *12*, 725−731. (d) Knecht, T.; Mondal, S.; Ye, J.-H.; Das, M.; Glorius, F. Intermolecular, branch-selective, and redox-neutral Cp^*Ir^{III}-catalyzed allylic C—H amidation. *Angew. Chem., Int. Ed.* **2019**, *58*, 7117−7121. (e) Teh, W. P.; Obenschain, D. C.; Black, B. M.; Michael, F. E. Catalytic metal-free allylic C—H amination of terpenoids. *J. Am. Chem. Soc.* **2020**, *142*, 16716−16722. (f) Lescot, C.; Darses, B.; Collet, F.; Retailleau, P.; Dauban, P. Intermolecular C—H amination of complex molecules: insights into the factors governing the selectivity. *J. Org. Chem.* **2012**, *77*, 7232−7240. (g) Burman, J. S.; Blakey, S. B. Regioselective intermolecular allylic C—H amination of disubstituted olefins via rhodium/π-allyl intermediates. *Angew. Chem., Int. Ed.* **2017**, *56*, 13666−13669. (h) Bao, H.; Tambar, U. K. Catalytic enantioselective allylic amination of unactivated terminal olefins via an

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

ene reaction/[2,3]-rearrangement. *J. Am. Chem. Soc.* **2012**, *134*, 18495−18498.
(19) For other allylic C—H aminations using aliphatic amines, see: (a) Pak Shing Cheung, K.; Fang, J.; Mukherjee, K.; Mihranyan, A.; Gevorgyan, V. Asymmetric intermolecular allylic C—H amination of alkenes with aliphatic amines. *Science* **2022**, *378*, 1207−1213. (b) Li, M.; Jin, Y.; Chen, Y.; Wu, W.; Jiang, H. Palladium-catalyzed oxidative amination of unactivated olefins with primary aliphatic amines. *J. Am. Chem. Soc.* **2023**, *145*, 9448−9453. (c) Cheng, Q.; Chen, J.; Lin, S.; Ritter, T. Allylic amination of alkenes with iminothianthrenes to afford alkyl allylamines. *J. Am. Chem. Soc.* **2020**, *142*, 17287−17293. (d) Wang, D. J.; Targos, K.; Wickens, Z. K. Electrochemical synthesis of allylic amines from terminal alkenes and secondary amines. *J. Am. Chem. Soc.* **2021**, *143*, 21503−21510.
(20) Osberger, T. J.; White, M. C. *N*-Boc amines to oxazolidinones via Pd(II)/bis-sulfoxide/Brønsted acid co-catalyzed allylic C—H oxidation. *J. Am. Chem. Soc.* **2014**, *136*, 11176−11181.
(21) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568.
(22) Kaster, S. H. M.; Zhu, L.; Lyon, W. L.; Ma, R.; Ammann, S. E.; White, M. C. Palladium-catalyzed cross-coupling of alcohols with olefins by positional tuning of a counteranion. *Science* **2024**, *385*, 1067−1076.
(23) Milic, M.; Targos, K.; Tellez Chavez, M.; Thompson, M. A. M.; Jennings, J. J.; Franz, A. K. NMR quantification of hydrogen-bond-accepting ability for organic molecules. *J. Org. Chem.* **2021**, *86*, 6031−6043.
(24) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-promoted palladium-catalyzed aerobic oxidation reactions. *Chem. Rev.* **2018**, *118*, 2636−2679.
(25) Zakrzewska, A.; Gawinecki, R.; Kolehmainen, E.; Ośmiałowski, B. ^{13}C-NMR based evaluation of the electronic and steric interactions in aromatic amines. *Int. J. Mol. Sci.* **2005**, *6*, 52−62.
(26) Kuehne, M. E.; Hall, T. C. Oxidation of primary amines and indoline with palladium dichloride and gold trichloride. *J. Org. Chem.* **1976**, *41*, 2742−2746.
(27) (a) Ionescu, M.; Mantsch, H. Phenoxazines. *Adv. Heterocycl. Chem.* **1967**, *8*, 83−113. (b) McDowell, J. J. H. The crystal and molecular structure of phenothiazine. *Acta Crystallogr.* **1976**, *B32*, 5−10.
(28) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.
(29) Filip, I. H.; Gál, E.; Lupan, I.; Perde-Schrepler, M.; Lönnecke, P.; Surducan, M.; Găină, L. I.; Hey-Hawkins, E.; Silaghi-Dumitrescu, L. Tunning the coordination properties of phenothiazine by regioselective introduction of diphenylphosphanyl groups. *Dalton Trans.* **2015**, *44*, 615−629.
(30) Gumrukcu, Y.; de Bruin, B.; Reek, J. N. H. Hydrogen-bond-assisted activation of allylic alcohols for palladium-catalyzed coupling reactions. *ChemSusChem* **2014**, *7*, 890−896.
(31) (a) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. Palladium(II)-catalyzed cyclization of olefinic tosylamides. *J. Org. Chem.* **1996**, *61*, 3584−3585. (b) Kotov, V.; Scarborough, C. C.; Stahl, S. S. Palladium-catalyzed aerobic oxidative amination of alkenes: Development of intra- and intermolecular aza-Wacker reactions. *Inorg. Chem.* **2007**, *46*, 1910−1923.
(32) (a) Ferreira, E. M.; Stoltz, B. M. Catalytic C—H bond functionalization with palladium(II): Aerobic oxidative annulations of indoles. *J. Am. Chem. Soc.* **2003**, *125*, 9578−9579. (b) Luzung, M. R.; Lewis, C. A.; Baran, P. S. Direct, chemoselective *N-tert*-prenylation of indoles by C—H functionalization. *Angew. Chem., Int. Ed.* **2009**, *48*, 7025−7029.
(33) (a) Chen, M. S.; White, M. C. A sulfoxide-promoted, catalytic method for the regioselective synthesis of allylic acetates from monosubstituted olefins via C—H oxidation. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347. (b) Chen, M. S.; Narayanasamy, P.; Labenz, N. A.; White, M. C. Serial ligand catalysis: A highly selective allylic C—H oxidation. *J. Am. Chem. Soc.* **2005**, *127*, 6970−6971. (c) Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. Allylic C—H acetoxylation with a 4,5-diazafluorenone-ligated palladium catalyst: a ligand-based strategy to achieve aerobic catalytic turnover. *J. Am. Chem. Soc.* **2010**, *132*, 15116−15119. (d) Malik, H. A.; Taylor, B. L. H.; Kerrigan, J. R.; Grob, J. E.; Houk, K. N.; Du Bois, J.; Hamann, L. G.; Patterson, A. W. Non-directed allylic C—H acetoxylation in the presence of Lewis basic heterocycles. *Chem. Sci.* **2014**, *5*, 2352−2361.
(34) Casimiro-Garcia, A.; Bigge, C. F.; Davis, J. A.; Padalino, T.; Pulaski, J.; Ohren, J. F.; McConnell, P.; Kane, C. D.; Royer, L. J.; Stevens, K. A.; Auerbach, B. J.; Collard, W. T.; McGregor, C.; Fakhoury, S. A.; Schaum, R. P.; Zhou, H. Effects of modifications of the linker in a series of phenylpropanoic acid derivatives: Synthesis, evaluation as PPARα/γ dual agonists, and X-ray crystallographic studies. *Bioorg. Med. Chem.* **2008**, *16*, 4883−4907.
(35) Sikorski, J. A.; Durley, R. C.; Mischke, D. A.; Reinhard, E. J.; Fobian, Y. M.; Tollefson, M. B.; Wang, L.; Grapperhaus, M. L.; Hickory, B. S.; Massa, M. A.; Norton, M. B.; Vernier, W. F.; Parnas, B. L.; Promo, M. A.; Hamme, A. T.; Spangler, D. P.; Rueppel, M. L. Substituted *N,N*-disubstituted diamino compounds useful for inhibiting cholesterol ester transfer protein activity. U.S. Patent 2002/0120011 A1, 2002.
(36) (a) Sánchez-Roselló, M.; Escolano, M.; Gaviña, D.; del Pozo, C. Two decades of progress in the asymmetric intramolecular aza-Michael reaction. *Chem. Rec.* **2022**, *22*, No. e202100161. (b) Yu Rulev, A. Aza-Michael reaction: A decade later − is the research over? *Eur. J. Org Chem.* **2023**, *26*, No. e202300451.
(37) Ye, Z.; Gettys, K. E.; Dai, M. Opportunities and challenges for direct C—H functionalization of piperazines. *Beilstein J. Org. Chem.* **2016**, *12*, 702−715.
(38) Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An update on the nitrogen heterocycle compositions and properties of U.S. FDA-approved pharmaceuticals (2013−2023). *J. Med. Chem.* **2024**, *67*, 11622−11655.
(39) (a) Humphrey, G. R.; Kuethe, J. T. Practical methodologies for the synthesis of indoles. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Mori, M.; Chiba, K.; Ban, Y. The reactions and syntheses with organometallic compounds. V. A new synthesis of indoles and isoquinolines by intramolecular palladium-catalyzed reactions of aryl halides with olefinic bonds. *Tetrahedron Lett.* **1977**, *18*, 1037−1040. (c) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. A novel and general synthetic pathway to strychnos indole alkaloids: total syntheses of (−)-tubifoline,(−)-dehydrotubifoline, and (−)-strychnine using palladium-catalyzed asymmetric allylic substitution. *J. Am. Chem. Soc.* **2003**, *125*, 9801−9807. (d) Hong, W.-X.; Chen, L.-J.; Zhong, C.-L.; Yao, Z.-J. Bidirectional synthesis of the central amino acid of chloptosin. *Org. Lett.* **2006**, *8*, 4919−4922.
(40) (a) Goverdhan, G.; Reddy, A. R.; Sampath, A.; Srinivas, K.; Himabindu, V.; Reddy, G. M. An improved and scalable process for zafirlukast: an asthma drug. *Org. Process Res. Dev.* **2009**, *13*, 67−72. (b) Howard, K. C.; Gonzalez, O. A.; Garneau-Tsodikova, S. Second generation of zafirlukast derivatives with improved activity against the oral pathogen *Porphyromonas gingivalis*. *ACS Med. Chem. Lett.* **2020**, *11*, 1905−1912.
(41) Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. Amide bond bioisosteres: Strategies, synthesis, and successes. *J. Med. Chem.* **2020**, *63*, 12290−12358.
(42) Omelchenko, I. V.; Shishkin, O. V.; Gorb, L.; Hill, F. C.; Leszczynski, J. Properties, aromaticity, and substituents effects in poly nitro- and amino-substituted benzenes. *Struct. Chem.* **2012**, *23*, 1585−1597.
(43) (a) Vicens, Q.; Mondragón, E.; Reyes, F. E.; Coish, P.; Aristoff, P.; Berman, J.; Kaur, H.; Kells, K. W.; Wickens, P.; Wilson, J.; Gadwood, R. C.; Schostarez, H. J.; Suto, R. K.; Blount, K. F.; Batey, R. T. Structure-activity relationship of flavin analogues that target the flavin mononucleotide riboswitch. *ACS Chem. Biol.* **2018**, *13*, 2908−2919. (b) Dixon, B. R.; Blount, K. F.; Berman, J.; Coish, P. D. G.;

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798

Osterman, D.; Harpreet, K.; Kells, K.; Wickens, P.; Wilson, J.; Wu, J. Flavin derivatives. WO 2010/019208 A1, 2010.
(44) (a) Békés, M.; Langley, D. R.; Crews, C. M. PROTAC targeted protein degraders: The past is prologue. *Nat. Rev. Drug Discovery* **2022**, *21*, 181−200. (b) Li, Y.; Yang, J.; Aguilar, A.; McEachern, D.; Przybranowski, S.; Liu, L.; Yang, C.-Y.; Wang, M.; Han, X.; Wang, S. Discovery of MD-224 as a first-in-class, highly potent, and efficacious proteolysis targeting chimera murine double minute 2 degrader capable of achieving complete and durable tumor regression. *J. Med. Chem.* **2019**, *62*, 448−466.
(45) Cao, D.; Liu, Z.; Verwilst, P.; Koo, S.; Jangjili, P.; Kim, J. S.; Lin, W. Coumarin-based small-molecule fluorescent chemosensors. *Chem. Rev.* **2019**, *119*, 10403−10519.
(46) (a) Wagaw, S.; Buchwald, S. L. The synthesis of aminopyridines: A method employing palladium-catalyzed carbon-nitrogen bond formation. *J. Org. Chem.* **1996**, *61*, 7240−7241. (b) McCann, S. D.; Reichert, E. C.; Arrechea, P. L.; Buchwald, S. L. Development of an aryl amination catalyst with broad scope guided by consideration of catalyst stability. *J. Am. Chem. Soc.* **2020**, *142*, 15027−15037.
(47) (a) Reed, S. A.; White, M. C. Catalytic intermolecular linear allylic C—H amination via heterobimetallic catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 3316−3318. (b) Liu, G.; Yin, G.; Wu, L. Palladium-catalyzed intermolecular aerobic oxidative amination of terminal alkenes: Efficient synthesis of linear allylamine derivatives. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733−4736. (c) Reed, S. A.; Mazzotti, A. R.; White, M. C. A catalytic, Brønsted base strategy for intermolecular allylic C—H amination. *J. Am. Chem. Soc.* **2009**, *131*, 11701−11706.

https://doi.org/10.1021/jacs.5c08883
J. Am. Chem. Soc. 2025, 147, 32786−32798