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β-C–H Allylation of Trialkylamines with Allenes Promoted by Synergistic Borane/Palladium Catalysis

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Abstract: Functionalization of the C(sp^3)–H bonds of trialkylamines is challenging, especially for reactions at positions other than the α position. Herein, we report a method for β-C(sp^3)–H allylation of trialkylamines. In these reactions, which involve synergistic borane/palladium catalysis, an enamine intermediate is first generated from the amine via α,β-dehydrogenation promoted by $B(C_6F_5)_3$ and a base, and then the enamine undergoes palladium-catalyzed reaction with an allene to give the allylation product. Because the hydride and the proton resulting from the initial dehydrogenation are ultimately shuttled to the product by $B(C_6F_5)_3$ and the palladium catalyst, respectively, these reactions show excellent atom economy. The establishment of this method paves the way for future studies of C–H functionalization of trialkylamines by means of synergistic borane/transition-metal catalysis.

Trialkylamine groups exist in a wide variety of drugs, naturally occurring alkaloids, and agrochemicals (Figure 1a), and their presence is usually essential for the activities of these molecules.[1] Consequently, the development of methods for efficient synthesis of structurally diverse trialkylamines is highly desirable. C–H functionalization is certainly the most efficient and atom-economical approach for generating structural analogs of existing molecules of interest. However, despite the remarkable progress that has been made on amine C–H functionalization reactions over the past decades,[2] methods for C–H functionalization of trialkylamines are underdeveloped. This situation may be due in part to the tendency of electron-rich trialkylamines to decompose in the presence of metal catalysts under oxidative conditions.[3] Another possible explanation is the ineffectiveness of trialkylamines as directing groups for metal-catalyzed C–H activation: the bulk of the amines disfavors metallacycle formation. Thus far, most of the existing studies have been performed on the α-C–H bonds by harnessing their innate high reactivity resulting from the activation by the nitrogen atom.[4] Functionalizing C–H bonds at more distant positions along the alkyl chain remains a formidable challenge. The rare successes include reactions that leverage steric effects to accomplish transition-metal-catalyzed borylation and oxidation reactions at terminal carbons.[5] Moreover, installing a directing group (e.g., an amide) to control the regioselectivity is also a viable strategy.[6] It was not until 2019 that Gaunt and co-workers first successfully used trialkylamines as directing groups for palladium-catalyzed γ-C–H arylation reactions,[7] relying on an amino acid ligand to facilitate C–H activation. Nevertheless, general strategies for β-selective C–H functionalization of trialkylamines are lacking.[8]

Recently, the activity of $B(C_6F_5)_3$ to abstract hydride from α-C(sp^3)–H of tertiary amines[9] to form an iminium ion and $[B(C_6F_5)_3–H]^-$ as well as the subsequent deprotonation of the iminium ion by a base to form enamine has enabled various $B(C_6F_5)_3$-catalyzed C–H functionalization reactions of tertiary amines at either the α or β position.[10,11,12] In particular, β-selective reactions that proceed via enamines (Figure 1b) are attractive because they offer site selectivity, which is rarely achievable with existing methods. However, this strategy has

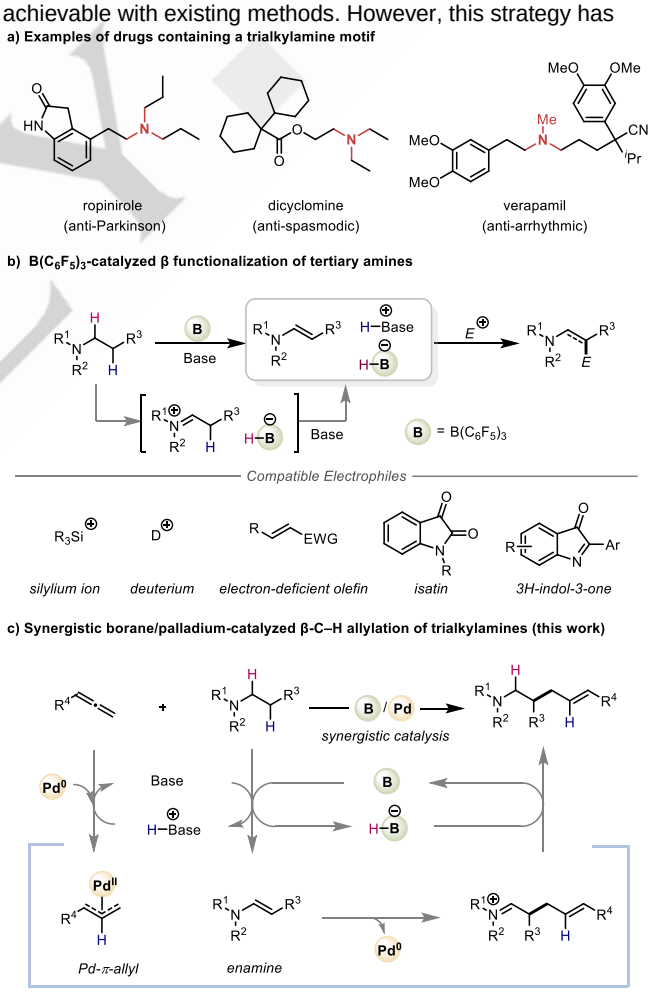

Figure 1. Development of a method for β-C–H allylation of trialkylamines.

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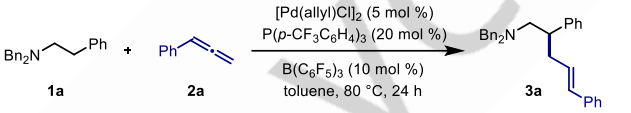
some limitations. For example, to inhibit the formation of amine–$B(C_6F_5)_3$ adducts,[13] amines are often substituted by aryl groups to decrease the basicity and increase the steric bulk,[10,11] which inversely decreases the nucleophilicity of the enamine intermediate. Although enamines generated from trialkylamines are more nucleophilic, the reactions have to deal with the low efficiency of generating the enamines. This dilemma has limited the types of electrophiles that can be used as reaction partners. To date, the compatible electrophiles for β functionalization have been confined to silylium ions (generated from hydrosilanes),[11a,d,e] a deuterium cation (generated from acetone-d_6),[11b] electron-deficient olefins,[11c,g] isatins,[11f] and 3*H*-indol-3-ones.[11h] Additionally, (3+2) cycloaddition of gold-furyl 1,3-dipoles with the enamines are feasible.[10h]

Because the properties of organometallic electrophiles, which are generated from an organic precursor and a metal catalyst, are much more tunable than those of conventional organic electrophiles, we envisaged that organometallic electrophiles with certain steric and electronic properties might be suitable for borane-catalyzed β functionalization of trialkylamines. Certainly, such reactions would require synergistic catalysis by a borane and a transition metal. We were particularly interested in Pd-π-allyl intermediates as electrophiles because they have been shown to be powerful tools for organic synthesis, and their properties can be conveniently tuned by varying the palladium catalyst.[14] Moreover, these intermediates are sufficiently electrophilic to react with enamines.[15] However, a synergistic borane/palladium catalytic system for amine functionalization has not previously been reported.

Herein, we report the accomplishment of such a synergistic catalytic system, which has been utilized for a β-C–H allylation reaction of trialkylamines with allenes (Figure 1c). In these reactions, a Pd-π-allyl intermediate is generated in situ from Pd–H and an allene;[14b,d] $B(C_6F_5)_3$ acts as a hydride shuttle; and the starting or product amine (base), together with the palladium catalyst, acts as a proton shuttle. The overall process resembles insertion of a C=C bond of the allene into the β-C–H bond of the amine.

We commenced our study by testing reactions of trialkylamine **1a** with allene **2a** to develop a synergistic catalytic system (Table 1). We were pleased to discover that the desired β-C–H allylation reaction was indeed feasible. After extensive exploration of reaction conditions, we found that reaction of 0.20 mmol of **1a** with 0.30 mmol of **2a** at 80 °C in toluene containing 5 mol % of $[Pd(allyl)Cl]_2$, 20 mol % of $P(p\text{-}CF_3C_6H_4)_3$, and 10 mol % of $B(C_6F_5)_3$ in a closed vial for 24 h gave the optimal yield of β-C–H allylation product **3a** (90%, entry 1). Under otherwise identical conditions, $Pd(OAc)_2$ failed to promote the reaction with decomposition of both substrates (entry 2). $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were inactive, resulting in recovery of unreacted **1a** (entries 3 and 4).[16] $Pd_2(dba)_3$ was a viable catalyst, giving **3a** in 83% yield (entry 5). Various phosphine ligands for the palladium catalyst were also assessed. The monodentate ligands PPh_3 and $P(p\text{-}MeOC_6H_4)_3$ and the bidentate ligand Xantphos were completely inactive or almost so (entries 6, 7 and 10), but triarylphosphines bearing an electron-withdrawing *para* or *meta* F atom were found to be active, giving **3a** in 32% and 47% yields, respectively (entries 8 and 9). That $P(p\text{-}CF_3C_6H_4)_3$ was the optimal ligand suggests that electron-withdrawing groups on the phosphine ligand might decrease the electron density of the Pd center, thereby facilitating the nucleophilic addition of the enamine to the Pd-π-allyl intermediate. Switching the Lewis acid catalyst from $B(C_6F_5)_3$ to $B(2,4,6\text{-}F_3C_6H_2)_3$, or $B(3,5\text{-}(CF_3)_2C_6H_3)_3$ shut down the reaction (entries 11 and 12), even though the two compounds are active for hydride abstraction in other C–H functionalization reactions of amines.[10g] A reaction temperature of 60 or 100 °C was less effective than 80 °C (entries 13 and 14). Furthermore, control experiments showed that the reaction did not proceed in the absence of either $B(C_6F_5)_3$ or $[Pd(allyl)Cl]_2$ (data not shown), demonstrating the necessity for synergy between the two catalysts.

Table 1. Study of reaction conditions.[a]



entry	variation from optimal conditions	yield (%)[b]
1	none	90
2	$Pd(OAc)_2$ instead of $[Pd(allyl)Cl]_2$	n.d.
3	$PdCl_2(PPh_3)_2$ instead of $[Pd(allyl)Cl]_2$	n.d.
4	$Pd(PPh_3)_4$ instead of $[Pd(allyl)Cl]_2$	n.d.
5	$Pd_2(dba)_3$ instead of $[Pd(allyl)Cl]_2$	83
6	PPh_3 instead of $P(p\text{-}CF_3C_6H_4)_3$	n.d.
7	$P(p\text{-}MeOC_6H_4)_3$ instead of $P(p\text{-}CF_3C_6H_4)_3$	<5
8	$P(p\text{-}FC_6H_4)_3$ instead of $P(p\text{-}CF_3C_6H_4)_3$	32
9	$P(m\text{-}FC_6H_4)_3$ instead of $P(p\text{-}CF_3C_6H_4)_3$	47
10	Xantphos instead of $P(p\text{-}CF_3C_6H_4)_3$	n.d.
11	$B(2,4,6\text{-}F_3C_6H_2)_3$ instead of $B(C_6F_5)_3$	n.d.
12	$B(3,5\text{-}(CF_3)_2C_6H_3)_3$ instead of $B(C_6F_5)_3$	n.d.
13	60 °C instead of 80 °C	48
14	100 °C instead of 80 °C	78

[a] Unless otherwise noted, all reactions were performed with 0.20 mmol of **1a**, 0.30 mmol of **2a**, 10 mol % Pd (or 5 mol % Pd dimer), 20 mol % phosphine ligand, and 10 mol % Lewis acid in 1.0 mL of solvent at 80 °C for 24 h. [b] NMR yields; n.d. = not detected.

With the optimal conditions in hand, we next examined the scope of this method by carrying out reactions of various tertiary amines **1** with **2a** (Table 2, top). A broad range of *N*,*N*-dibenzylphenethylamines with an electron-donating or electron-withdrawing substituent or two substituents on the benzene ring of the phenethyl group were tolerated, giving the corresponding products (**3a**–**3k**) in 31–92% isolated yields. When this benzene ring was replaced with a 3-thienyl, 3-*N*-methylindolyl, or 2-naphthyl group or a methyl or an ethyl group, the desired β-C–H allylation products (**3l**–**3p**) were still obtained in moderate to good yields. For further investigation, the phenethyl group was retained while the other two groups on the nitrogen atom (R^1 and R^2 in **1**) were varied. These experiments revealed that the reaction tolerated *N*-methyl-*N*-naphthyl, *N*-methyl-*N*-phenyl, *N*-methyl-*N*-phenethyl,[17] *N,N*-dimethyl, and *N*-methyl-*N*-benzyl groups (**3q**–**3u**). Using substrates with an *N*-methyl-*N*-benzyl moiety, we then varied the alkyl group at R^3 of **1**. A benzyl group and isopropyl,

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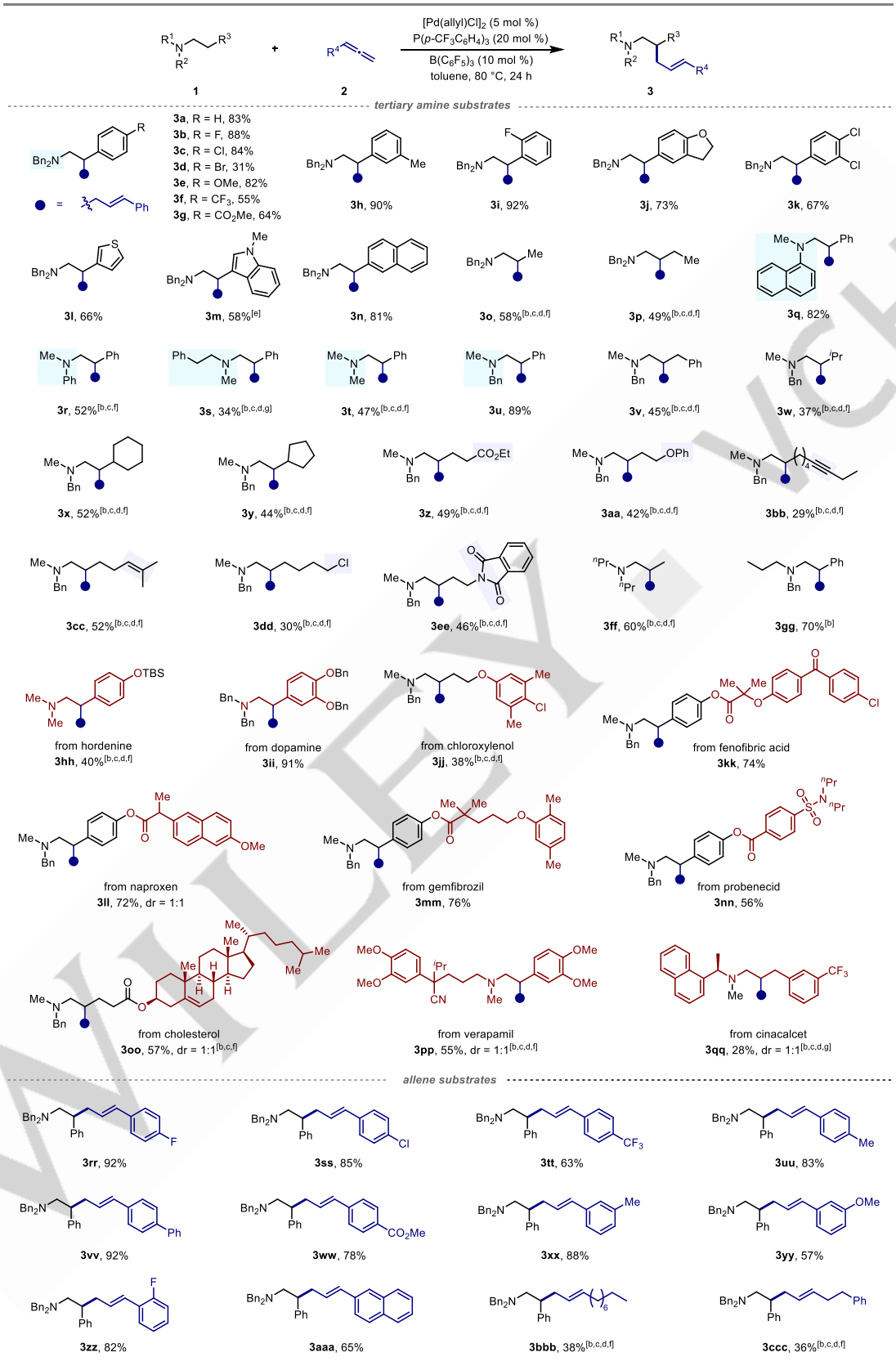
Table 2. Substrate scope. [a]



[a] Unless otherwise noted, all reactions were performed with 5 mol % $[Pd(allyl)Cl]_2$, 20 mol % $P(p\text{-}CF_3C_6H_4)_3$, 10 mol % $B(C_6F_5)_3$, 0.20 mmol of **1**, and 0.30 mmol of **2** in 1.0 mL of toluene at 80 °C for 24 h; isolated yields are provided. [b] $[Pd(\pi\text{-cinnamyl})Cl]_2$ instead of $[Pd(allyl)Cl]_2$. [c] $P(m\text{-}FC_6H_4)_3$ instead of $P(p\text{-}CF_3C_6H_4)_3$. [d] 0.40 mmol of **2**. [e] 60 °C. [f] 100 °C. [g] 120 °C.

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cyclohexyl, and cyclopentyl groups, which are more hindered, gave moderate yields of the corresponding products (**3v**–**3y**). *N*-methyl-*N*-benzyl substrates bearing an ester, phenoxyl, alkyne, alkene, halogen or amide substituent also underwent the reaction, smoothly generating products **3z**–**3ee** with retained functional groups. Tripropylamine gave **3ff** in 60% yield. Notably, when R^3 was not an aryl group, the reactions generally required more forcing conditions (2 equiv of **2a**, 100 °C); the decrease in the acidity of the β hydrogen due to the absence of the adjacent aryl group might have inhibited enamine formation, thereby decreasing the reactivity. This possibility was confirmed by the reaction of an amine bearing a propyl group and a phenethyl group on the nitrogen atom; allylation of this substrate occurred exclusively at the benzylic position to give **3gg**. We found that *N*-ethyl-substituted amines (e.g., triethylamine) were unsuitable; reactions of these substrates tended to result in elimination of the ethyl group, with the allyl group becoming attached to the nitrogen atom (for a list of incompatible amines, see the SI).

We next investigated the potential utility of this method for late-stage C–H functionalization. Gratifyingly, alkylamines derived from several natural products and pharmaceuticals (indicated in red in Table 2) underwent the desired β-allylation reactions, affording **3hh**–**3qq**, respectively, in 28–91% yields. These results demonstrate that this catalytic system could selectively target the trialkylamine moieties of structurally complex molecules regardless of other coordinative functional groups.

Next, we explored the substrate scope with respect to allene **2** by carrying out reactions with amine **1a** (Table 2, bottom). Aryl-substituted allenes bearing a fluorine (**3rr**) or chlorine (**3ss**) atom or a trifluoromethoxy (**3tt**), methyl (**3uu**), phenyl (**3vv**), or ester (**3ww**) group at the *para* position of the benzene ring delivered the desired products in good to high yields. Furthermore, *meta*-tolyl (**3xx**), *meta*-methoxyphenyl (**3yy**), *ortho*-fluorophenyl (**3zz**), and 2-naphthyl-substituted (**3aaa**) allenes were also compatible. Finally, alkyl-substituted allenes (**3bbb** and **3ccc**) were also reactive, although they gave lower yields than the arylallenes.

Notably, the mass balance of all these reactions was relatively good with respect to the amine, and those with low yields were mainly due to the presence of unreacted amine (e.g., the recovery yields of amines were 56%, 44%, 46%, and 39%, respectively, for reactions forming **3d**, **3bb**, **3qq**, and **3ccc**).

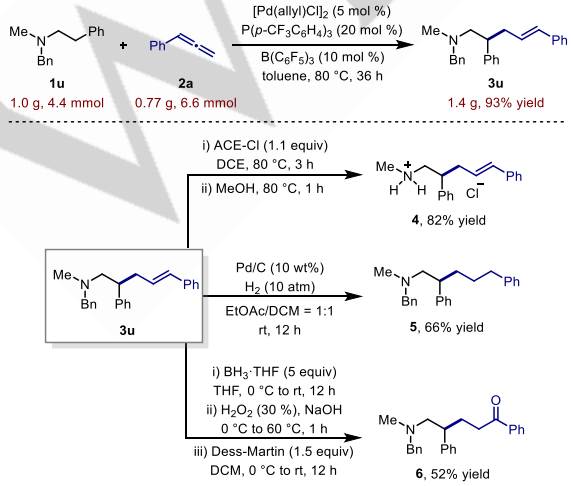

Figure 2. Gram-scale reaction and transformations of the product.

To further demonstrate the utility of this method, we performed a gram-scale reaction of **1u** with **2a**, which gave a 93% yield of **3u** (Figure 2, top). This product was then transformed in several ways (Figure 2, bottom). For example, removal of the benzyl group under acidic conditions afforded corresponding secondary amine **4** in 82% yield,[18] and in the presence a Pd/C (10 wt%) catalyst, hydrogenation with H_2 selectively reduced the C=C bond to give **5** in 66% yield without cleavage of the N–Bn bond. In addition, a hydroboration/oxidation/oxidation sequence generated carbonyl compound **6** in 52% yield.

We performed a series of control experiments to study the reaction mechanism (Figure 3). When **1a**-α-d_2 was allowed to react with allene **2a** under the standard conditions, deuterium scrambling at the α carbons of all three alkyl groups was observed in the formed product (**3a**-d_2) (Figure 3a). This result suggests that all three alkyl groups underwent reversible $B(C_6F_5)_3$-mediated α-hydride abstraction and that the two types of iminium borohydrides (formed by hydride abstraction either at the benzyl group or at the phenethyl group) could intermolecularly exchange the borohydride anion ($[B(C_6F_5)_3–H]^-$). In addition, when **1a**-α-d_6 with fully deuterated α carbons was subjected to the reaction conditions, deuterium incorporation at all the α carbons remained high in the product (**3a**-d_6) (Figure 3b), which again confirmed that hydride abstraction could occur only at the α carbons and that $[B(C_6F_5)_3–H]^-$ could add only to the iminium ion. When β-deuterated amine **1a**-β-d_2 was allowed to react with **2a** under the standard conditions, 97% deuterium incorporation at the β carbon and 78% deuterium incorporation at one of the olefin carbons were observed in the formed product (**3a'**-d_2) (Figure 3c). This result indicates that deuterium transfer from the β carbon to the allene occurred and that the scrambling at the olefin carbon might have been resulted from proton donation by residual H_2O. Next, we performed two competition experiments, between **1a**-α-d_6 and **1u** and between **1a**-β-d_2 and **1u** (Figure 3d,e). Both reactions gave the corresponding products in high yields with H/D scrambling. These results suggest that both $B(C_6F_5)_3$-mediated hydride abstraction and base-mediated proton removal were reversible and that the hydride and the proton could transfer intermolecularly.

Additionally, when 1 equiv of amine **1a** was mixed with 1 equiv of $B(C_6F_5)_3$ in toluene-d_8 at room temperature, an equilibrium was quickly reached within 5 minutes (Figure 3f); the resulting mixture contained 73% of free $B(C_6F_5)_3$ and 27% of **1a**–$B(C_6F_5)_3$ adduct, which gave distinctive sets of signals in the ^{19}F NMR spectrum. When 5 equiv of **1a** was used in the same reaction, $B(C_6F_5)_3$ was all converted to the adduct. Furthermore, we were able to observe the adduct in the mixture of a standard reaction. These results suggest that the amine-$B(C_6F_5)_3$ adduct is highly likely a resting state of $B(C_6F_5)_3$ in the allylation reaction. In contrast, when 1 equiv of **1a** was mixed with 1 equiv of the palladium catalyst, we did not observe the formation of a **1a**–palladium complex (Figure 3g); the palladium catalyst and **1a** remained free based on the ^{31}P NMR and ^1H NMR analysis.

On the basis of the above-described experimental results and existing literatures, we propose a reaction pathway involving two interconnected catalytic cycles (Figure 3h). First, the dissociation of amine-$B(C_6F_5)_3$ adduct **I** releases $B(C_6F_5)_3$. And then, $B(C_6F_5)_3$

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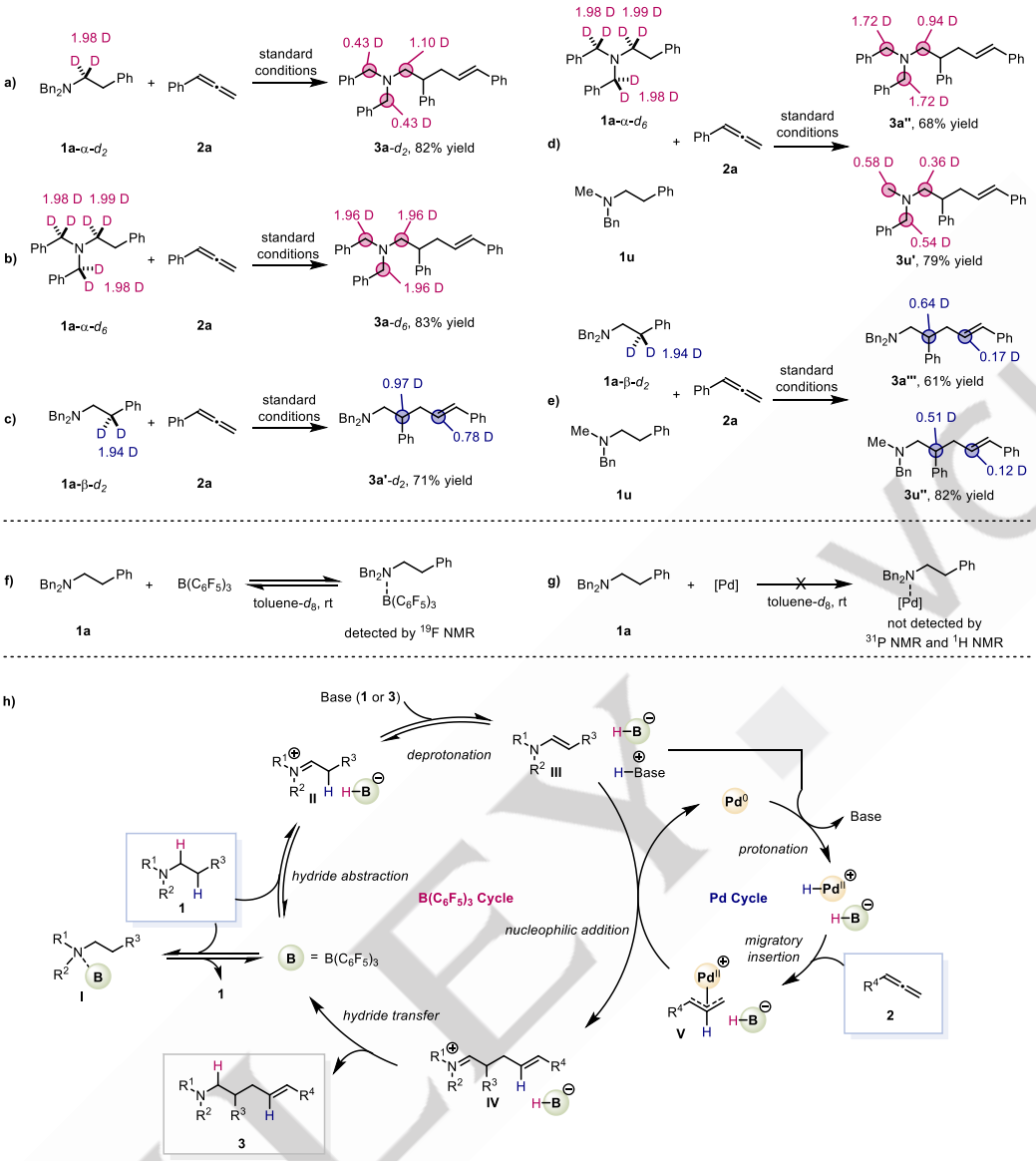

Figure 3. Mechanistic experiments and proposed mechanism.

abstracts a hydride from an *α*-C(sp^3)–H bond of amine **1** to afford iminium **II** and $[B(C_6F_5)_3–H]^-$. The iminium ion is then deprotonated by the starting amine or the product amine to afford enamine **III** and an ammonium ion. In the palladium cycle, protonation of Pd(0) by the ammonium ion forms a Pd–H species,[19] which subsequently inserts into allene **2** to provide Pd-π-allyl intermediate **V**. Next, nucleophilic addition on **V** by enamine **III** generates iminium ion **IV** and Pd(0). Finally, reduction of the iminium ion by $[B(C_6F_5)_3–H]^-$ gives the final product and releases $B(C_6F_5)_3$.

Kinetic studies of the standard reaction between **1a** and **2a** indicated a first-order dependence on $B(C_6F_5)_3$ concentration, a first-order dependence on the palladium catalyst concentration at low concentrations,[20] a zero-order dependence on the allene concentration, and a –0.49-order dependence on the amine concentration[21] (see the SI), suggesting that the protonation of Pd(0) by the ammonium ion to form Pd–H species may be involved in the rate-limiting step[19e] and that coordination of the amine to $B(C_6F_5)_3$ might have inhibited the catalytic activity of $B(C_6F_5)_3$. In addition, when amine **1a** was treated with catalytic amounts of $B(C_6F_5)_3$ (10 mol %) and the palladium catalyst (10 mol %) for 2 hours under the standard conditions without the addition of the allene, the corresponding enamine intermediate was formed in only 3% NMR yield. Therefore, the reaction of the enamine with the Pd-π-allyl intermediate is highly efficient.

In conclusion, we have developed the first method for β-C–H allylation of trialkylamines. This method demonstrates advantages of using a synergistic borane/transition-metal catalytic system for amine C–H functionalization, including no requirement of a directing group for controlling the regioselectivity, readily tunable organometallic electrophiles, and potential compatibility of other electrophiles. Currently, we are exploring

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other electrophiles generated in situ from transition-metal catalysts, as well as an enantioselective variant using a chiral catalyst.

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Keywords: boron • palladium • C–H functionalization • trialkylamine • allylation

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[16] The lack of reactivity of $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ may be due to inability of $P(p\text{-}CF_3C_6H_4)_3$ to replace PPh_3 from the Pd center because of its weaker Lewis basicity.

[17] In the reaction forming **3s**, a diastereomeric mixture of a diallylation product was also formed in 26% yield (NMR), and amine **1s** was recovered in 22% yield.

[18] CCDC 2295351 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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[20] When the concentration of the palladium catalyst increases to a certain degree, the rate stops increasing with even higher concentrations (see the SI). At this point, the rate might have been limited by the ammonium ion (H–Base$^+$), whose amount is dictated by the amount of $B(C_6F_5)_3$ used. In other words, the ammonium ion becomes saturated with the palladium catalyst.

[21] It is difficult to explain –0.49-order of amine **1a** because the amine is involved in multiple steps until the rate-limiting step. In order to get more information, the reaction of amine **1u** with **2a** was also looked at; the kinetic study indicated a –0.16-order dependence on the concentration of amine **1u**. Therefore, the rate order is also influenced by the specific amine.

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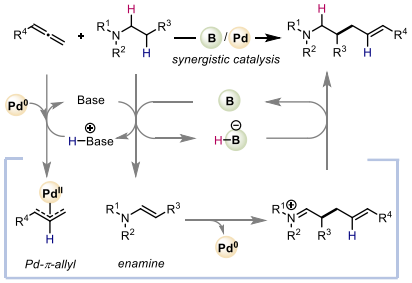

The β-C–H allylation reactions of trialkylamines with allenes were accomplished by a synergistic borane/palladium catalysis. The borane and palladium catalysts promoted the formation of an enamine intermediate from a trialkylamine and a palladium-π-allyl intermediate from an allene, respectively.