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Selective C–H Activation of Unprotected Allylamines by Control of Catalyst Speciation

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SUMMARY

An outstanding challenge in the Pd-catalyzed functionalization of allylamines is the control of stereochemistry. Terminal alkenes preferentially undergo Heck-type reactions, while internal alkenes may undergo a mixture of Heck and C–H activation reactions that give mixtures of stereochemical products. In the case of unprotected allylamines, the challenge in achieving C–H activation is that facile *in situ* formation of Pd nanoparticles leads to preferential formation of *trans* rather than *cis*-substituted products. In this study we have demonstrated the feasibility of using mono-protected amino acid (MPAA) ligands as metal protecting groups to prevent aggregation and reduction, allowing the selective synthesis of free *cis*-arylated allylamines. This method complements Heck-selective methods, allowing complete stereochemical control over the synthesis of cinnamylamines, an important class of amine that can serve as therapeutics directly or as advanced intermediates. To highlight the utility of the methodology, we have demonstrated rapid access to mu opioid receptor ligands.

Amines • Organometallics • Organic Synthesis • Drug Discovery • Opioids • Biological Activity

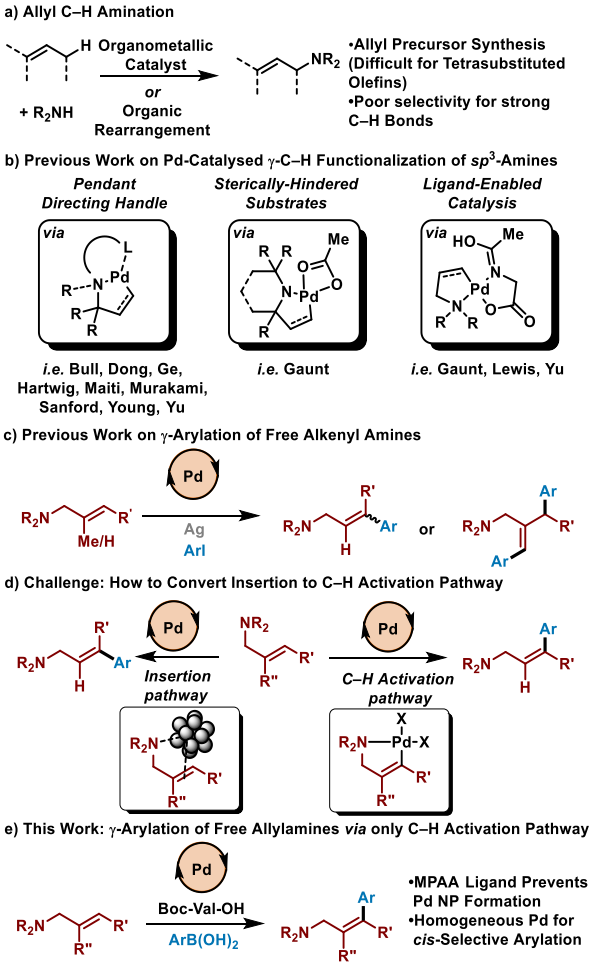
INTRODUCTION

Over 40% of approved drugs contain at least one amine group.[1] As a result, methods to access new chemical space around this functional group are important for developing new therapeutics. Of particular interest are functionalized allylamines given their utility in G-protein coupled receptor (GPCR)-based therapeutics, including antihistamines,[2] vasoconstrictors,[3] opioid analgesics,[4] antidepressants,[5] as well as treatments for sexual dysfunction.[6] Several methods have been developed to synthesize allylamines that involve forming the C–N bond by substitution on allylic systems, either through simple S_N2 reactions[7] or through many recent and elegant approaches to allylic C–H amination.[8-11] However, these methods require the pre-synthesis of the allyl fragment, which means the majority of these methods have only been used for disubstituted alkene products, or trisubstituted alkenes where the 1,1-groups are the same, due to the challenge of accessing more complex allyl substrates (**Scheme 1a**). Meanwhile, methods that make use of the amine as a structural feature to facilitate further elaboration have generally been limited to protected amine substrates.[12-14] We were particularly interested in how the use of C–H activation could enable rapid access to substitution of the alkene from simple precursors, rather than relying on low-yielding and multistep reaction sequences to prepare unsymmetrical 3,3-disubstituted allylamines.[15]

THE BIGGER PICTURE

Controlling the selectivity of organometallic reactions on substrates that can generate multiple reaction products is a valuable area of research for expanding access to new chemical space and to rapidly access established chemical space, both important for UN SDG 3: Good Health and Well-Being. In terms of developing methods to access new therapeutic compounds, control of chemo, regio, and stereoselectivity is paramount for the biological function of the target molecules. 3-Aryl and 3,3-diarylallylamines represent a particularly important subset of therapeutic amines, however, methods to synthesize these using transition metals almost exclusively give Heck products and not the C–H activation products. This precludes the development of high throughput methods for library synthesis due to the inability to access the other isomer from common starting materials. These insertion methods are also not viable on cyclic alkenes. We show herein that by controlling catalyst speciation through specific choice of ligand, we can prevent the formation of Pd nanoparticles during an allylamine functionalization reaction, and subsequently enable favorable selective C–H activation reactions. The application of this approach to the rapid construction of some tramadol analogues is subsequently demonstrated. Overall this provides an alternative to allylic substitution, allylic C–H amination, or Heck coupling, and will complement these other techniques in terms of scope and limitations.

Scheme 1. Progress Towards a General C-H Arylation Strategy for Allylamines



Although C–H activation/functionalization of a number of substrate classes has been achieved using directing groups,[16-20] unactivated alkene substrates are often challenging to engage in C(sp^2)–H activation reactions, and more commonly participate in allylic C–H functionalization[21,22] or insertion-type mechanisms.[23,24] In the case of protected allylamines[25-29] and allyl alcohols,[30,31] the most commonly observed reactions are Heck-type reactions, while C–H activation is more favorably when the directing group is more remote.[32-34] In addition, the application of Pd-catalyzed C–H activation strategies to γ-arylation of benzylic amines[35] or δ-arylation of homobenzylic amines and anilines[36] has been achieved on free amine substrates; however, primary aliphatic and allylic amines have traditionally required protection of the amine to prevent decomposition and control speciation (limitation of catalytically-inactive dimers).[37] To circumvent the need for a protecting group, primary amines have been functionalized by applying transient directing groups,[38] either through the formation of imines,[39-44] through the use of deactivating acids,[45-48] or CO_2 (**Scheme 1b**).[49, 50] Meanwhile, free secondary amines can be functionalized either by exploiting bulky amines (controlling catalyst speciation by limiting dimerization) with no oxidizable α-C–H bonds,[51, 52] while CO_2 has also been used for less sterically-hindered amines with some success.[49, 50] With regard to tertiary amines, the current state of the art requires the use of secondary coordination sites,[53, 54] or the use of ligands for Pd that effectively shut down β-hydride elimination pathways, thus allowing C–H activation to outcompete substrate oxidation.[55, 56]

Based on our previous work, we envisioned that the use of CO_2 would be the simplest method to facilitate the desired C–H activation of allylamines. When we applied these techniques to allylamines, however, we found the Heck-type reactions dominated (**Scheme 1c**).[57-59] What is particularly noteworthy about these reactions is that rather than being catalyzed by mono or dinuclear Pd species, evidence supported that all of these Heck-type processes were being promoted by *in situ*-formed Pd nanoparticles. These particles gave high yields of the insertion products, with only sluggish background C–H activation which was attributed to smaller homogeneous species. However, as a result of these two competing reactions, reactions yielded mixtures of the *trans* (from the Heck-type reaction) and *cis* (from the C–H activation pathway) products (**Scheme 1d**). The product mixtures were not always easily separable as prepared, which presented a problem in terms of assessing the biological activity since each stereoisomer of the alkene will have different biological activity.[60] Subsequently, we developed an oxidative Heck reaction which had improved *trans* selectivity (often >20:1).[61] The key to achieve the *trans* products selective was to shut down the background C–H activation process by using a coupling partner which could be engaged under milder conditions that precluded the rate-determining C–H activation step.

Conversely, shutting down the Mizoroki–Heck reaction of free allylamines is not as straightforward. The observation from our previous work is that free amines are readily degraded by Pd^{II} salts, especially under harsh reaction conditions, giving rise to catalytically-active metal nanoparticles. One way to stymie this pathway would be to find an appropriate protecting group/directing group modification of the amine. This could allow the amine to engage in the reaction without being as quickly degraded, but these methods are generally only applicable to one of primary, secondary, or tertiary amines, and usually not to the other two. We reasoned therefore that a broader free amine-based approach was desirable. Inspired by the use of mono-protected amine acid ligands for C(sp^3)–H activation of amines,[62-64] we sought to exploit this approach to essentially protect the metal from direct reduction by the amine, thus facilitating the selective γ-C–H activation of unprotected allylamines (**Scheme 1e**).

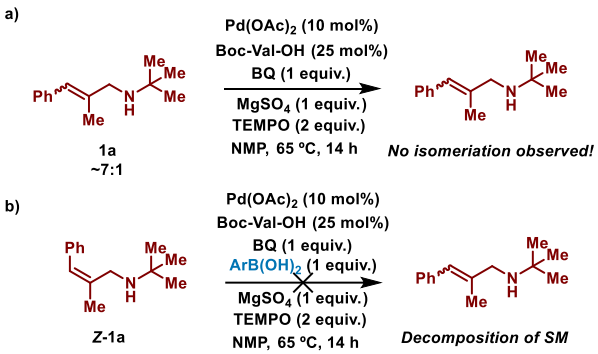
RESULTS AND DISCUSSION

Based on previous reports, we initiated this study using 4-(trifluoromethyl)benzene boronic acid as an arene source and $Pd(OAc)_2$ as the catalyst, along with various bases, but no C–H activation products were observed during the initial screening regiment with any simple 1°, 2°, or 3° cinnamylamines. However, addition of a subsituent at the β-position of the allyl fragment led to the desired C–H activation product when *N*-*tert*-butyl β-methylcinnamylamine was used as the amine, and the $Pd(OAc)_2$ was combined with Ac-Val-OH in HFIP,[65] though in low overall yield. After successive rounds of screening, the best results were obtained when the reaction was performed in *N*-methylpyrrolidinone (NMP) as solvent at 65 °C with Boc-Val-OH as a ligand, as well as $MgSO_4$ as a base, giving the desired product in 72% isolated yield (**Table 1**, **3a**). Quite surprisingly, the addition of TEMPO during reaction screening was found to be important, increasing the yield in the optimized conditions by ~20%. Notably, the reaction can be completed in a relatively short time period, giving the desired product **3a** in 72% isolated yield after 3 h. Due to the paramagnetic nature of the crude reaction mixtures, NMR yields were not useful, and we were forced to rely on isolated yields for our conclusions. If the reaction is left for a longer time, the substrate begins to decompose, even with protection by the ligand, leading to a decreased yield. Gratifyingly, the optimized reaction conditions were also found to be free of added silver, a common additive required to achieve high yields on similar transformations.[66] Notably, after determining optimized conditions, we found that arylation did occur also on substrates without a β-substituent, but only in trace yield with the majority of the substrate having decomposed.

The amine substrate **1a** contains approximately 12% of the *cis* isomer as an impurity (this is a carryover from the aldehyde starting material). The alkene stereoisomer is not easily purified, either at the aldehyde or the amine stage, to obtain a single stereoisomer of the olefin. Notably, in our optimized conditions we generally find complete conversion of the substrate. Based on work from the Engle group,[67] we hypothesized that perhaps the *cis* isomer could interconvert with the *trans* isomer during the reaction, leading all of the starting material to engage in a productive reaction. To test this we subjected the starting material

1a to the reaction conditions, except without the aryl boronic acid present. In this case the *E*/*Z* ratio was observed to be the same, suggesting that the incorrect isomer is simply decomposed in the reaction (**Scheme 2a**). The major observed side products come from oxidation of the amine and subsequent hydrolysis to give α-methylcinnamaldehyde, as well as what is expected to be an oxidation/hydrolysis/*retro*-aldol sequence to give benzaldehyde. Overall this leads to easier purification of the amine product, and is considered a sort of kinetic resolution in which one isomer reacts to form product, while the other simply gets degraded. We also isolated a small amount of the enriched ***Z*-1a** to test it in the reaction. When ***Z*-1a** was subjected to the reactoin conditions it was found to decompose fully during the reaction without any desired arylated product being detected (**Scheme 2b**). The major observed products are again the α-methylcinnamaldehyde as well as the homo-coupling product of the aryl boronic acid.

Scheme 2. Importance of Starting Isomer of Allylamine on Reaction Progress

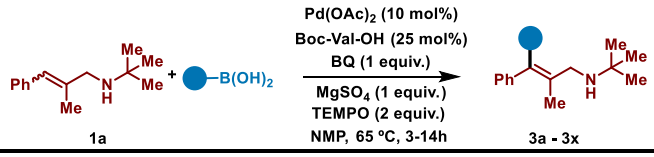


With the optimized conditions in hand, the substrate scope of the boronic acid coupling partner was investigated. Halogenated substrates, including those decorated with CF_3, fluoride, and bromide (**3a** – **3f**) were tolerated in the reaction. Simple phenyl boronic acid participated in the reaction (**3g**), as did more electron rich tolyl and xylylboronic acids (**3h** and **3i** respectively). Methoxy groups could also be installed on the product without significant side reactions (**3j** – **3l**), as well as simple aryl substituents, including a phenyl-substituted (**3m**) and a 2-naphthyl-substituted (**3n**) benzene. Regarding more potentially-sensitive substrates, arenes with both trimethylsilyl (**3o**) as well as nitrile (**3p**) groups could be installed. Thanks to the acid-free conditions, the nitrile group was preserved, rather than undergoing hydrolysis.[59] Other carbonyl derivatives could also be used in the reaction, including an aldehyde (**3q**), ketone (**3r**), and an ester (**3s**), all without significant observed side reactions between the amine and the carbonxyl. Heterocycles could also be used, including a morpholine-derivative (**3t**) and a carbazole-derivative (**3u**).

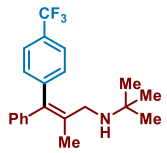
Based on the successful incorporation of carbazole, an electron donor triphenylamine group (**3v**) was also found to be viable in the reaction. Meanwhile, pyridine-containing substrates could also be installed (**3w** and **3x**). Surprisingly, the use of simple 3-pyridine boronic acid was unsuccessful under the same reaction conditions, suggesting that the bulky *ortho*-substitutent may be playing a role in limiting coordination with the pyridine ring. Although a thiophene substrate could not be coupled, the analogous 3-furanyl group was amenable to the reaction conditions (**3y**).

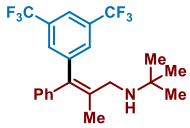
To ensure that the reaction would be useful to the synthetic community, we sought to study the bounds of the reaction scale. We first increased the scale by a factor of 10 using 4-methylphenyl boronic acid. Under these conditions, it was found that the reaction time needed to be increased, but after 24 h the product **3h** could be isolated in 59% yield (**Scheme 3**). Meanwhile, at 20 times scale using 3,5-bis(trifluoromethyl)phenyl boronic acid, the product **3b** could be isolated in 39% yield after 24 h reaction time. This supports the use of these reactions in more complex circumstances, such as in target-oriented synthesis with additional reoptimization at the larger scale.

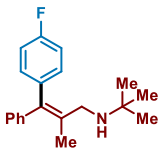
Table 1. Substrate Scope of Arylboronic Acid Coupling Partners

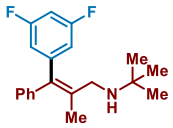


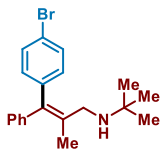
1a → 3a - 3x

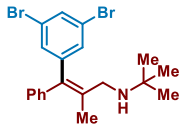

3a, 72%

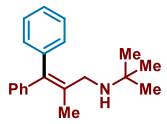

3b, 61%

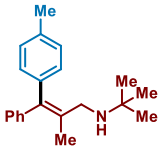

3c, 61%

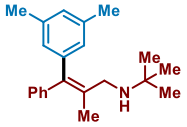

3d, 71%

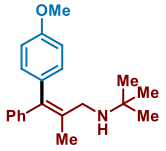

3e, 49%

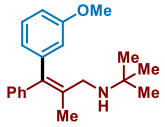

3f, 32%

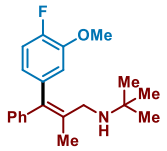

3g, 65%

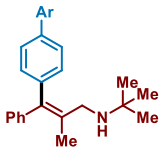

3h, 77%

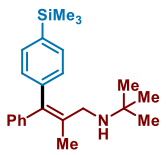

3i, 75%

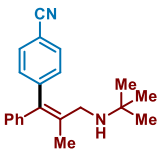

3j, 62%

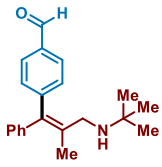

3k, 65%

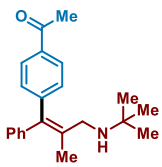

3l, 46%

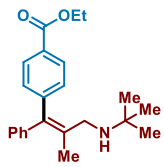

Ar = Ph, 3m, 66%
Ar = 2-Napth, 3n, 51%

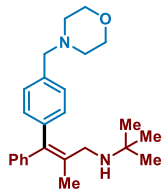

3o, 71%

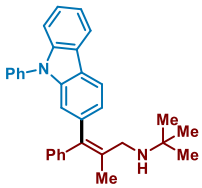

3p, 60%

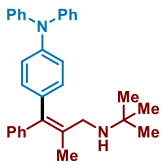

3q, 63%

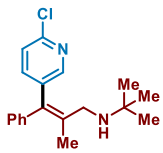

3r, 58%

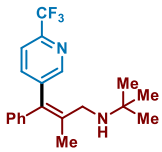

3s, 71%

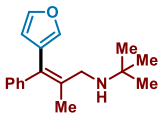

3t, 60%


3u, 63%


3v, 52%

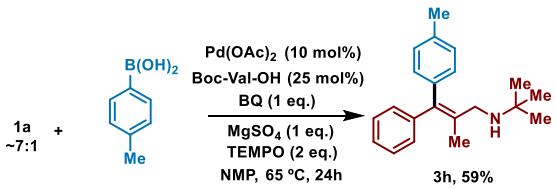

3w, 55%


3x, 41%

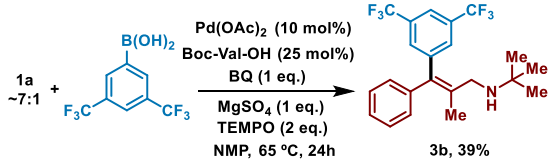

3y, 48%

[a] Reaction conditions: **1a** (0.30 mmol), boronic acid (0.60 mmol), $Pd(OAc)_2$ (10 mol%), Boc-Val-OH (25 mol%), benzoquinone (0.30 mmol), magnesium sulfate (0.30 mmol), and TEMPO (0.60 mmol) in NMP (1 mL), heated at 65 °C. All reactions were performed in triplicate and the isolated yield reported as an average of the three runs.

Scheme 3. Reaction Scale-Up



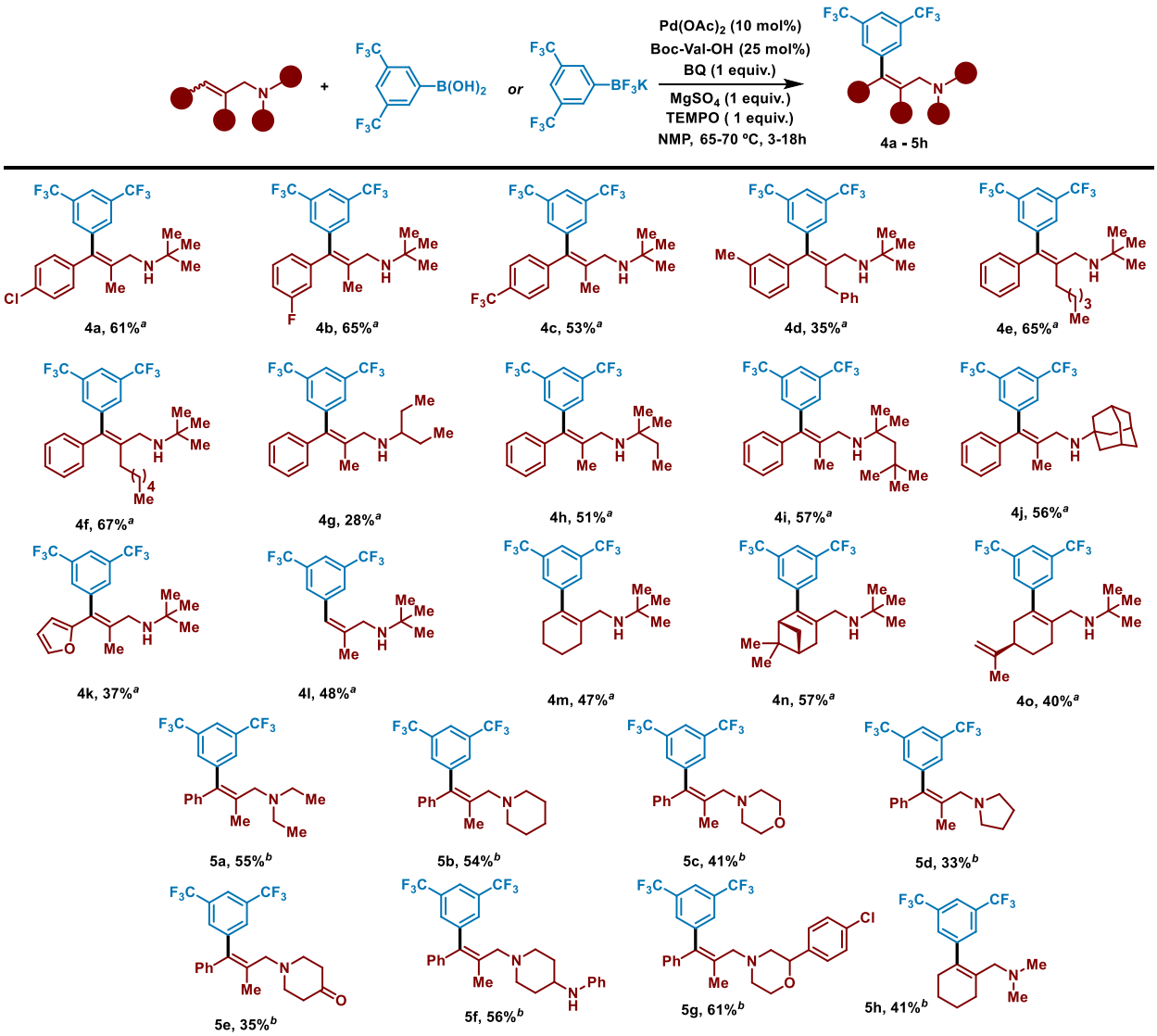
3 mmol Scale (10 x Scale-Up)



6 mmol Scale (20 x Scale-Up)

Regarding the amine scope, addition of functional groups on the cinnamyl arene were reasonably tolerated (**Table 2, 4a – 4c**). Although it was found that a substituent was required at the β-position, benzylic or longer alkyl chains were also tolerated in the reaction (**4d – 4f**). We anticipated that the reason a substitutent at the β-position was required was to promote a favorable conformation between C1 and C2 for the C–H activation. Other α-secondary and α-tertiary secondary allylamines were also competent substrates for the reaction (**4g – 4j**), although bulkier α-secondary centers were required on the amine substituent side to achieve the desired reactions, also likely due to comformational biasing. This is interesting, as C–H activation, although slow, was possible on much less sterically-encumbered substrates under our previous harsher conditions.

Table 2. Substrate Scope of Secondary and Tertiary Amines



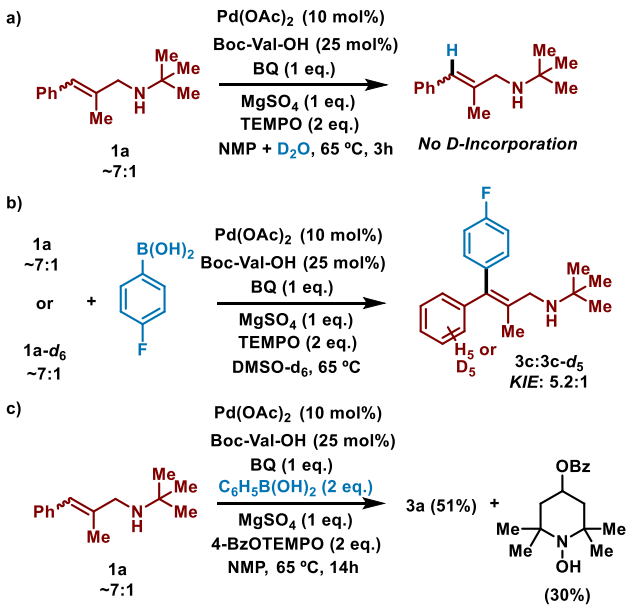
[a] Reaction conditions: amine (0.30 mmol), boronic acid (0.60 mmol), $Pd(OAc)_2$ (10 mol%), Boc-Val-OH (25 mol%), benzoquinone (0.30 mmol), magnesium sulfate (0.30 mmol), TEMPO (0.60 mmol) in NMP (1 mL), heated at 65 °C for 3-14 h. [b] Reaction conditions: amine (0.30 mmol), potassium aryltrifluoroborate (0.60 mmol), $Pd(OAc)_2$ (10 mol%), Boc-Val-OH (25 mol%), benzoquinone (0.30 mmol), magnesium sulfate (0.30 mmol), TEMPO (0.60 mmol) in NMP (1 mL), heated at 70 °C for 14-18 h. All reactions were performed in triplicate and the isolated yield reported as an average of the three runs.

The reaction was also found to occur if the γ-arene was replaced with a heterocycle (**4k**), or even if it were removed entirely (**4l**). These two results suggested that terpene-based substrates should also be amenable to the reaction, and subsequently several cyclohexene-based carbocycles were demonstrated as viable substrates, including a simple cyclohexenyl-derived substrate (**4m**) as well as myrtenal- and perillaldehyde-derived substrates (**4n** and **4o**). Although the perillaldehdye-derived substrate possesses a 1,1-disubtituted alkene in addition to the allylamine moiety, the undirected Mizoroki–Heck reaction at this alternative alkene site was not observed.

Considering the sensitivity of the current system to substitution around the amine, we expected that using a less hindered primary amine might be difficult. Indeed, although we have shown that primary allylamines are suitable for directing insertion reactions, they were not functionalized under the current protocol. Tertiary amines on the otherhand could direct the C–H activation reaction suitably, and various acyclic (**Table 2**, **5a**) and common cyclic (**5b** – **5d**) amines were studied in the reaction. A key change that was required for these more substituted amines was the need to use the Molander trifluoroborate salts instead of the boronic acid. These salts are easily prepared by fluoride addition to the parent boronic acid followed by simple filtration.[68] More elaborately-functionalized cyclic amine substrates were also tested, including a piperidinone (**5e**), diamine (**5f**), and a substituted morpholine (**5g**).[69] Given the success in achieving C–H activation on the cyclohexenyl-substrates, we expected that a simple tertiary amine should also give rise to products on these cyclic scaffolds. Gratifyingly, 1-dimethylaminomethyl-cyclohex-1-ene was a suitable substrate, giving the arylated product in fair yield (**5h**).

Having established the general reaction scope, we also explored the mechanism. While we have previously been able to demonstrate reversible C–H activation of similar substrates under acidic conditions,[58] in the present reaction the process seems to be irreversible. When the reaction is performed without aryl boronic acid with 0.1 mL of D_2O added, the starting amine is recovered with no significant incorporation of deuterium at the γ-position as judged by both ^1H and ^2H NMR (**Scheme 4a**). As expected, there is a reasonable kinetic-isotope effect observed when the rate of a protio and deutero substrate (prepared from benzaldehyde-d_6) are compared (**Scheme 4b**). We were able to follow the reaction kinetics by ^{19}F NMR, which due to the greater base line separation in peaks was sufficient to identify the starting material and product despite the increased paramagnetism of the reaction mixtures.

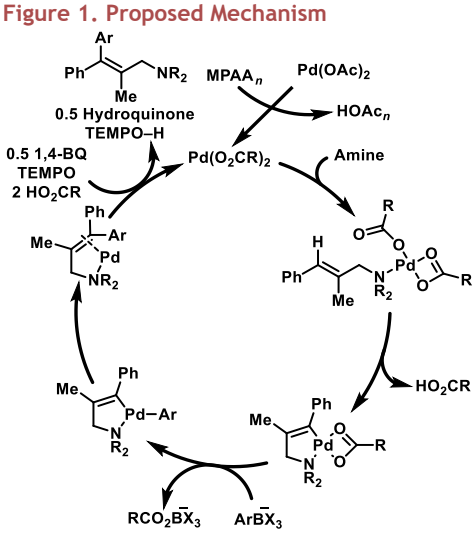
Scheme 4. Mechanistic Studies



Considering the role of TEMPO, our hypothesis was that it was simply serving as a one-electron oxidant during the reaction cycle.[70] While it was difficult to isolate TEMPO by-products from the reaction mixture, the similarly-reactive 4-BzO-TEMPO allowed us to isolate and unambiguously characterize reduced hydroxylamine, consistent with TEMPO's role as a co-oxidant during the reaction (**Scheme 4c**). The exact role of the MPAA ligand was also investigated, but contrary to several reports about the role of MPAA in other systems as a bidentate dianionic ligand for the Pd,[71,72] NMR titration showed that the N–H proton of the MPAA ligand broadens but does not disappear during Pd/MPAA titration experiments. This is more consistent with the intermediates proposed by Lewis and Stahl.[73] Instead of forming doubly-deprotonated complexes, the MPAA likly gives a mixture of $Pd_x(OAc)_y(O\text{-}Val\text{-}Boc)_z$ species that nevertheless make C–H activation more favorable than β-hydride elimination. Even when we prepared $Pd_n(O\text{-}Val\text{-}Boc)_{2n}$, we did not observe evidence of the N–H bond becoming deprotonated.

Based on these results, we propose a standard Pd^{II}-Pd^{0} cycle (**Figure 1**). $Pd(OAc)_2$ will undergo some level of substitution with the MPAA. This may happen to give $Pd(Boc\text{-}Val\text{-}O)_2$ or a mixture of carboxylates. In any case, the MPAA is expected to only be bound via the carboxylate. It is also possible that rather than being mononuclear in nature that the MPAA carboxylates may be bridging between different Pd centers. Coordination to the amine positions the target C–H bond in proximity to the catalyst. Aided by the presence of the MPAA, the cyclopalladation can occur more quickly, thereby preventing the competing β-hydride elimination. Once cyclometalated, transmetalation furnishes an aryl substituted Pd center, which can undergo reductive elimination to give the reduced Pd-center and the arylated product. At this point reoxidation by a mixture of TEMPO and benzoquinone allows liberation of the product and regeneration of the active Pd^{II} catalyst.

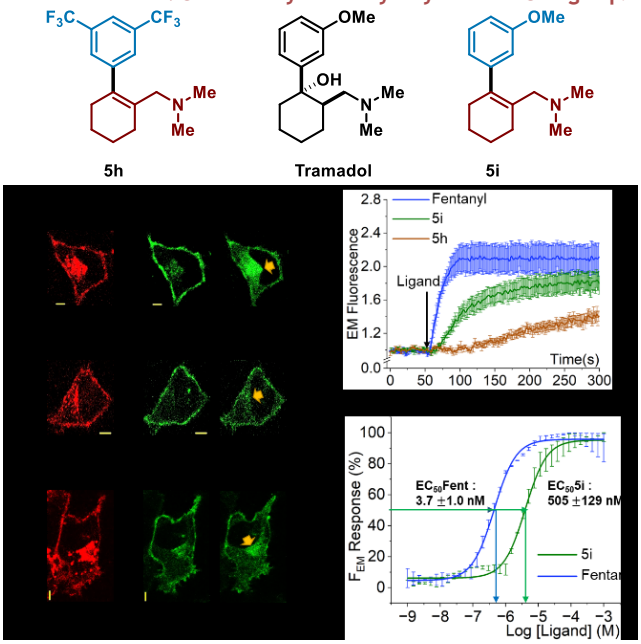
Figure 1. Proposed Mechanism



One of our longstanding goals is to leverage these allylamine compounds as new therapeutic agents to improve human health. Opioids are one of the major groups of analgesic compounds frequently used in clinical practices, which act on a group of GPCRs known as Opioid receptors. Opioids are often necessary to treat pain, with an estimated 17% of Americans receiving at least one prescription for opioid pain medications in 2017.[74] There are three primary opioid receptors, namely mu (γ) opioid receptors (MOR), kappa (κ) opioid receptors (KOR), and delta (δ) opioid receptors (DOR).[75] Opioids can be agonists, antagonists, or partial agonists, depending on how they interact with receptors. Most clinically approved opioids for analgesia interact with MORs in the central and peripheral nervous systems. Fentanyl, morphine, oxycodone, and hydrocodone are widely used clinical opioids. Opioid use disorders and fatal opioid overdoses cost the United States over one

trillion USD annually.[76] High acute toxicity, chronic toxicity, and potential for addiction are three major challenges associated with current opioid therapies. We therefore considered the utility of this methodology to access novel opioids.

Figure 2. Examination of MOR Activity of 3-Arylallylamines Using a γ9 Assay



MOR-mCh and γ9 distribution in HeLa cells expressing Venus-γ9 pre-ligand addition and post-ligand addition. Note the gradual reduction of Venus intensity on the PM (Plasma Membrane) and concurrent accumulation in EMs upon ligand addition. [b] Activation kinetics (baseline normalized EM fluorescence change over time) (n = 25) (mean ± SEM). [c] Activation DoseResp $\{y = A_1 + (A_2 - A_1)/[1 + (10^{(\log x_0 - x)p}]\}$ function fitted to the experimental data to calculate the EC_{50}(concentration for half response) value (here, A_1 is the initial response, A_2 the final response, x the logarithm of the agonist dose, x_0 the center of the curve (EC_{50}), and p the Hill coefficient).

Since most clinically used opioids and substances driving opioid use disorders (OUD) interact with MORs, we used MOR to examine the MOR pharmacology of the newly-synthesized compounds **3a** to **5h**. MOR is an inhibitory G protein (Gi/o)-coupled GPCR.[77] Therefore, we used a well-established G protein γ9 translocation assay to examine the activation of the receptor upon ligand addition.[78] Upon Gi/o-GPCR activation, Gγ9 shows a robust translocation from the plasma membrane to the endomembranes (Golgi and Endoplasmic Reticulum-ER), which reverses upon receptor activity termination.[79,80] As a control, we used Fentanyl, a potent MOR agonist. To examine ligand-dependent activation of MOR, HeLa cells co-expressing MOR-mCherry (MOR-mCh) and Venus-γ9 were treated with 500 nM Fentanyl hydrochloride. After MOR activation by Fentanyl, γ9 subunits translocated from the plasma membrane to the endomembranes until an equilibrium was reached. Using confocal time-lapse imaging, Venus-γ9 dynamics in cells we captured at 1 Hz frequency using a 63x, 1.49 NA oil immersion objective (**Figure 2a**).

Using a similar approach, we examined the ability of individual members of the compound library to activate MOR. While the other compounds had no appreciable activity in the assay, we observed minor MOR activity upon cell exposure to **5h** (**Figure 2a** – **b**). Considering that **5h** has an analogous structure to Tramadol, a known opioid analgesic, we synthesized **5i**. Gratifyingly, **5i** gave significantly enhanced MOR activity (**Figure 2a** – **b**). We next determined the EC_{50} for Fentanyl and **5i** using the same translocation assay. For Fentanyl an EC_{50} of 3.7 ± 1.0 nM was observed (**Fig. 1c**). Interestingly, this was even lower than the previously reported EC_{50} for fentanyl determined from mini-Gi and β-arrestin recruitment assays, indicating the suitability of the γ9 assay.[65] For **5i**, the γ9 assay provided an EC_{50} of 505

± 129 nM (**Figure 2c**). For reference, the potency of **5i** is comparable to morphine with an EC_{50} of 430 nm.[81]

CONCLUSION

In conclusion, we have demonstrated how simple mono-protected amino acid ligands can be used to protect allylamines from rapid decomposition, which in turn protects the Pd catalyst, thereby allowing a reaction that had previously given *trans*-addition products through a directed Mizoroki–Heck reaction to become selective for *cis*-addition through a directed C–H activation pathway. This technology allows for a variety of unprotected 2° and 3° allylamine substrates to be derivatized directly, including carbocyclic alkenes, which were not previously accessible with other processes. We applied this approach to the synthesis of two new tramadol derivatives, and will in the future use this chemistry to access more synthetic analogues which were not readily accessible with classical techniques.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Michael Young (michael.young8@utoledo.edu)."

Materials availability

All materials generated in this study are available from the lead contact. Compounds have been prepared and stored as HCl salts for ease of future library screening.

SUPPLEMENTAL INFORMATION

Document S1. Supplemental experimental procedures, Figures *S*-1–*S*-115, and Tables *S*-1–*S*-3.

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AUTHOR CONTRIBUTIONS

Conceptualization was performed by V. G. L., A. K., and M. C. Y. Data curation was performed by all authors. Formal analysis was performed by V. G. L., A. K., and M. C. Y. Investigation was performed by all authors. Writing – original draft was performed by V. G. L. and M. C. Y. Writing – review & editing was performed by all authors. Funding acquisition was performed by A. K. and M. C. Y.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

One or more of the authors of this paper self-identifies as a gender minority in their field of research. One or more of the authors of this paperself-identifies as living with a disability. One or more of the authors of this paper received support from a program designed to increase minority representation in their field of research. While citing references scientifically relevant for this work, we also actively worked to promote gender balance in our reference list.

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