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ARTICLE

Amine-Directed Mizoroki-Heck Arylation of Free Allylamines

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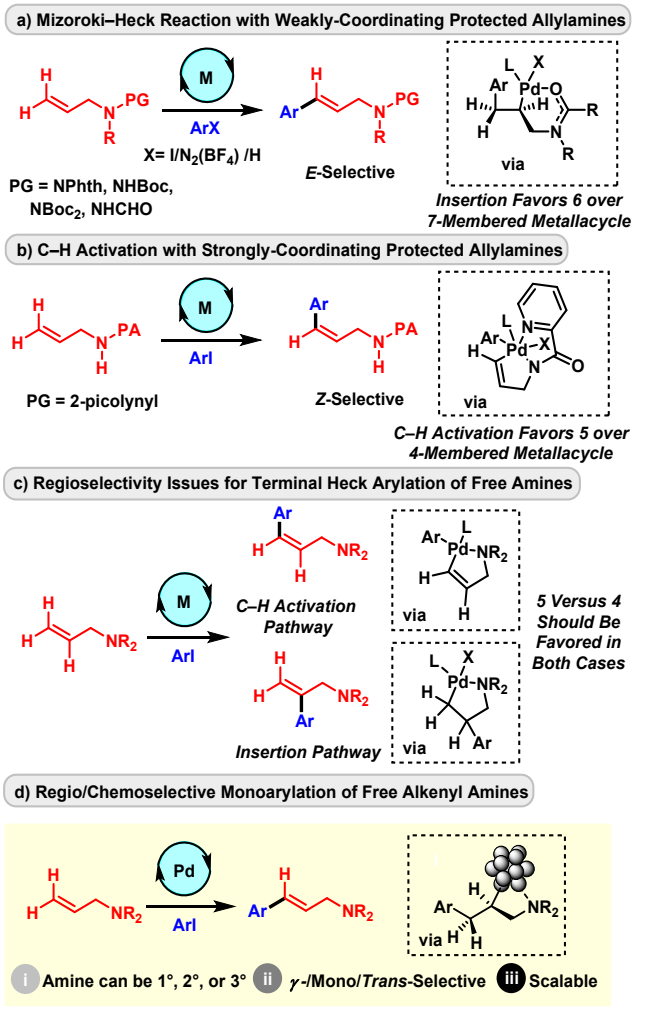
The transition metal-catalyzed Mizoroki–Heck reaction is a powerful method to synthesize C–C bonds, allowing access to several important pharmaceuticals. Traditionally free amines have not been compatible with these approaches due to oxidation of the amine by the transition metal or other side reactions. However, the functionalization of unprotected allylamines is particularly attractive due to their prevalence in various biologically active molecules. Herein we report the palladium-catalyzed selective monoarylation of free allylamines using aryl iodides. The strategy works on primary, secondary, and tertiary amines, making it very general. Our monoarylation method is scalable and works on aryl iodides with a variety of substituted arene or heterocycle motifs, including chromophoric substrates.

Introduction

Allylamines are a versatile building block in chemical synthesis, and are frequent synthetic targets which are found in various natural products and bioactive compounds.[1] Notably, cinnamylamines (3-arylallylamines) and their respective derivatives are commonly-encountered therapeutic agents. Therefore, the one-step synthesis of cinnamylamines from allylamines via a Mizoroki-Heck reaction is an attractive method to access this medicinally-important class of compounds that complements other strategies, such as hydroamination.[2] However, the use of free allylamines as substrates for this reaction can be challenging: these substrates are sensitive to oxidation through *β*-hydride elimination,[3] allylic deamination,[4] intramolecular cyclization,[5] and *N*-arylation.[6]

To circumvent these difficulties in the case of allylamines, several methods have been reported for the arylation of *protected* allylamines (**Scheme 1a**). In many examples, the coordinating ability of the protecting group is key for the regioselectivity of the insertion to form the more favorable 6-membered intermediate, while the subsequent *β*-hydride elimination favors the *trans* products.[7] The directing ability of these protected amines can also lead to more challenging double insertion reactions.[8] More strongly-coordinating protecting groups that coordinate through nitrogen can even direct a competing C–H activation pathway, which instead gives rise to the *cis* products formed through a 5-membered metallacycle (**Scheme 1b**).[9] In the case of some weaker donors or catalysts that don't coordinate, it is likely that the selectivity may be simply due to sterics, which typically favors reaction at the terminal alkene position to give the linear products.[10]



Scheme 1. Considerations and Approaches for the Synthesis of Arylated Allylamines.

Considering the need to first protect and then deprotect the substrates under these reaction protocols to access the free

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amines for subsequent biological screening or synthetic elaboration, we reasoned that there was still a need for a more step-economical approach utilizing either the free amine or a transient directing group.[11] However, the presence of a strongly coordinating amine poses the challenge that the amine is not likely to direct a γ-selective insertion reaction, and should instead promote either or both the β-selective insertion reaction or the γ-selective C–H activation reaction, both of which would proceed through a more favorable 5-membered metallacycle (**Scheme 1c**).

Notably, we had previously targeted the free-amine directed γ-C(sp^2)–H arylation of cinnamylamines.[12] In that work we found that a mixture of γ-arylated products were formed, but arose through competing insertion and C–H activation pathways. Despite the use of CO_2, which served as an *in situ*-protecting group for the amine substrates,[13] we rationalized that the selectivity for the insertion reaction came from a nanoparticle-catalyzed insertion that obviated the challenge of forming a 4-membered metallacycle that would be expected from a mononuclear catalyst.[14] Inspired by the ability to achieve γ-insertion reactions to form trisubstituted alkenes, we also demonstrated that we could perform symmetrical diarylation of terminal olefins in one step.

At the time we could not determine conditions to achieve the selective monoarylation reaction of the terminal allylamines, which as mentioned would give rise to the important class of cinnamylamines. In addition, while we had a good handle on the competing mechanisms for the arylation of cinnamylamines to form the 3,3-diarylallylamines, we lacked a similar understanding of how the first arylation occurred – did it also come from a competition between C–H activation (followed by possible isomerization)[15] and γ-selective Mizoroki-Heck coupling, or could the terminal alkene be directly arylated without the involvement of the amine, which under acidic conditions would be protonated.[16] The goal of this work was therefore to determine conditions that would allow us to access cinnamylamines directly, and to address some of the outstanding questions regarding the mechanism of the first arylation.

Results and Discussion

We began our study on the monoselective Mizoroki–Heck reaction of unprotected allylamines using a slight excess of allylamine and 3-Iodobenzotrifluoride as model substrates (see ESI for complete optimization details). In the presence of $Pd(OAc)_2$, AgOAc, CO_2, and TFA at 50 °C for 14 h, product **1a** was obtained in 88% yield. Surprisingly (based on our previous report),[12] we did not observe any diarylation product under the optimized conditions for the monoarylation. The increased monoselectivity is most likely due to the significantly different ratio of aryl iodide:amine substrate (the amine is now in slight excess) as well as using generally milder reaction temperatures. While trace Pd (*a.k.a.* dirty stir bars) could lead to trace product,[17] we only found product formation with Pd salts, and not other metals relevant to alkene functionalization such as Ni,[18] Co,[19] Mn,[20] Ir,[21] Re,[22] or W.[23] The use of acid was postulated to help protect the amine from degradation,[16] though we also found a small but reproducible affect from adding CO_2. On the basis of our previous work, we suggest that the ability to form transient carbamates during the reaction further slows degradation of the amine substrates.[12]

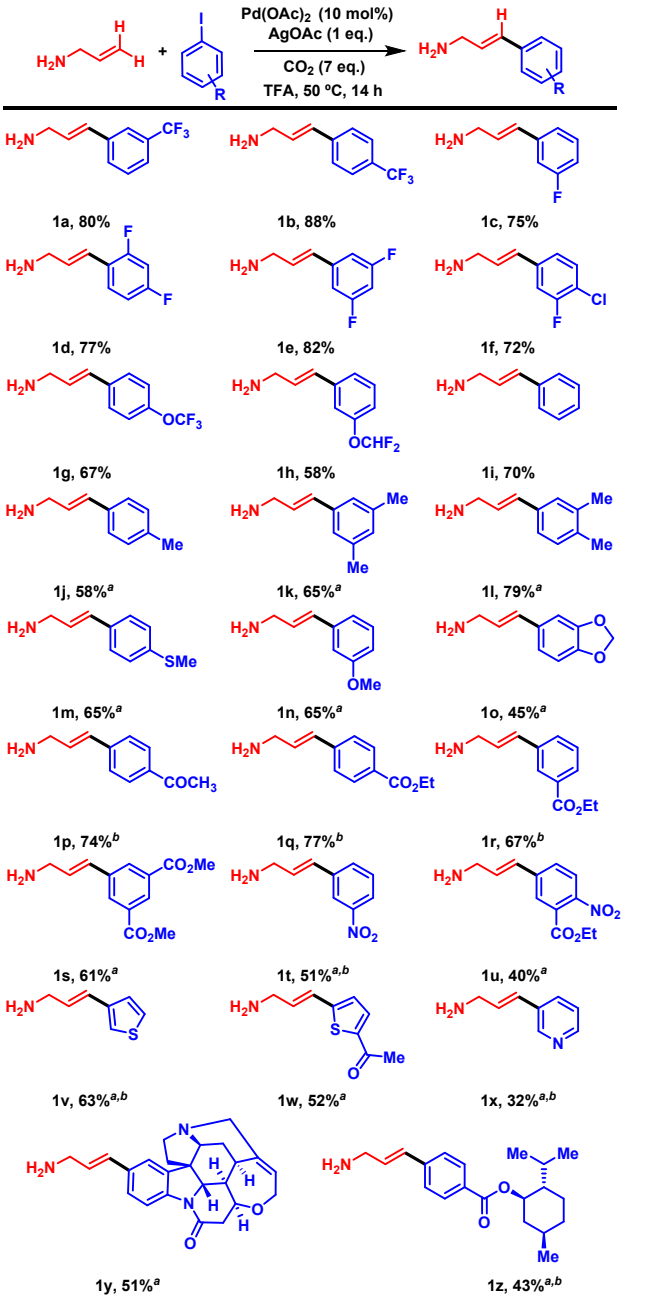


Table 1. Substrate Scope for Aryl Iodides. Reaction conditions: allylamine (0.36 mmol), aryl iodide (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), CO_2 (7 eq.) and TFA (1 mL), heated at 50 °C for 14 h and isolated as HCl salt. Reactions performed in triplicate and the average yield reported. [a] AcOH at 70 °C. [b] Isolated as the Bz protected product.

With our optimized reaction conditions in hand, we next investigated the scope of the mono γ-arylation of allylamine

with various iodoarenes (**Table 1**). Notably, while pursuing this study we found that many of the cinnamylamine products, most of which are oils, would rapidly solidify after aqueous work-up, purification, and isolation. These solids were generally insoluble in $CDCl_3$, but upon redissolution in aqueous mineral acid, freebasing, and re-extraction returned the cinnamylamine oils. Solidification was completely inhibited when the products were stored in a desiccator. On the basis of these observations and the spectral data (see ESI), we propose that these solids are a mixture of ammonium carbonate/bicarbonate/carbamate species which are formed from the reaction with ambient water and CO_2. As a result, we opted to isolate many of the arylated allylamines as their HCl salts (or in limited cases as the Bz-protected amides) to facilitate handling and storage.

Fluorine-functionalized iodoarenes were viable substrates under the reaction conditions (**1a** – **1h**). While an *ortho*-fluoro substituent was tolerated (**1d**), other groups such as methyl, methoxy, and flanking nitro and carboxylate groups were unreactive (see ESI). Simple iodobenzene also worked well under the optimized TFA conditions (**1i**). However, we found that the majority of non-fluorinated aryl iodides were not as effectively coupled using these conditions. Modified conditions using AcOH as solvent at 70 °C, worked better for disubstituted iodoarenes containing weak electron donors (**1k** and **1l**), still with complete *E*-selectivity. 4-Iodothioanisole was effectively coupled with allylamine without any oxidation at sulphur, and afforded the corresponding product **1m** in 65% yield.

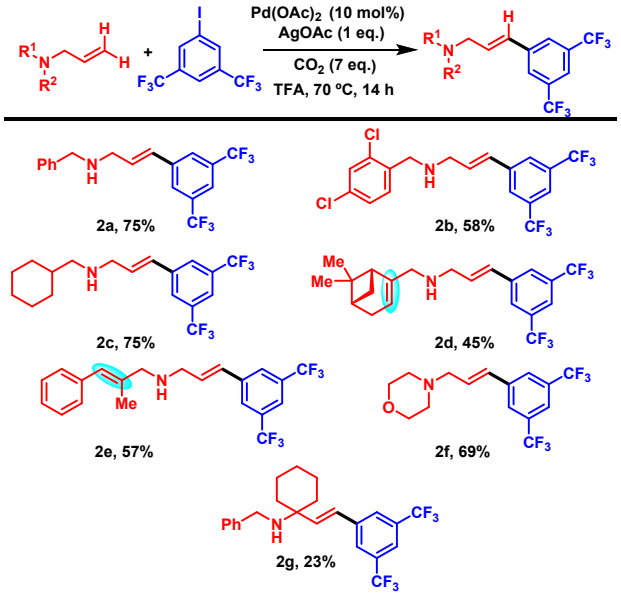


Table 2. Substrate Scope for Amines. Reaction conditions: allylamine (0.36 mmol), aryl iodide (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), CO_2 (7 eq.) and TFA (1 mL), heated at 70 °C for 14 h.

The revised reaction conditions were also compatible with ethereal groups (**1n** and **1o**). Reactions with moderate-to-strongly electron withdrawing groups such as ketone, ester, and nitro groups on the aryl iodide also proceeded in good yields (**1p** – **1u**). To our delight, thiophenes and pyridines also successfully gave product under the reaction conditions in moderate to good yields (**1v** – **1x**), despite the challenges that these types of substrates typically present in Pd catalysis.[24] Gratifyingly, 2-iodostrychnine was readily coupled with allylamine, affording the product **1y** in 51% yield despite the presence of amide, allylic ether, and tertiary amine functional groups. Finally, a mentholate ester was also tolerated under the reaction conditions (**1z**).

Next, we focused on exploring the scope of the reaction for secondary and tertiary amines (**Table 2**) using 1-iodo-3,5-bis(trifluoromethyl)benzene as the coupling partner. The reaction works with benzylic and carbocyclic substrates (**2a** – **2c**). Apart from monoarylation, no sp^2 C–H arylation products were observed via C–H activation pathways.[25] A terpenoid-functionalized allylamine showed complete regioselectivity for the terminal olefin, albeit in fair yield (**2d**). α-Methyl cinnamyl substrates have been observed to undergo diarylation through a chain walking mechanism,[26] and we wondered if we could achieve selective monoarylation in the presence of these functional groups. In this case monoarylation was observed exclusively at the terminal olefin to give the product in moderate yield (**2e**). To expand the reaction scope, we next carried out a reaction with a tertiary amine substrate, which afforded the monoarylated product in good yield (**2f**). In this reaction, we observed the same yield of product in the presence/absence of CO_2, presumably because tertiary amines do not react directly with CO_2. Surprisingly, no reaction was observed with a β-methylallylamine, although using our previously published conditions the expected γ,γ'-diarylation product could be determined (see ESI).[26a] Meanwhile, a sterically hindered α,α-disubstituted amine could participate in the reaction, albeit with relatively low yield (**2g**), with 46% recovery of the starting amine material.

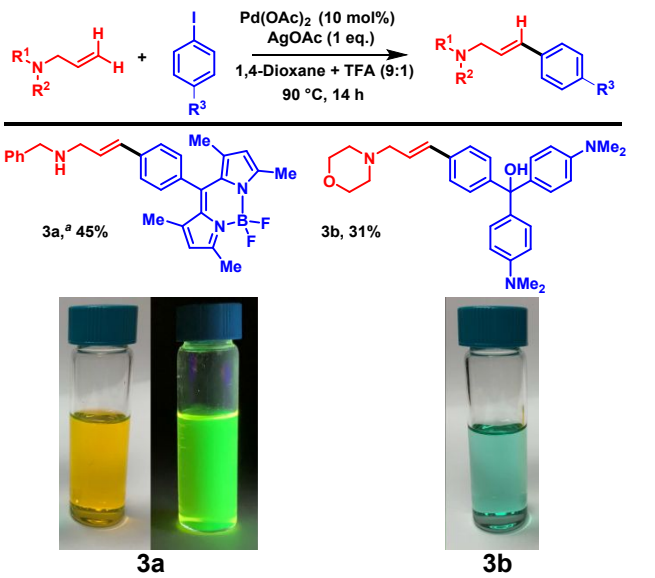
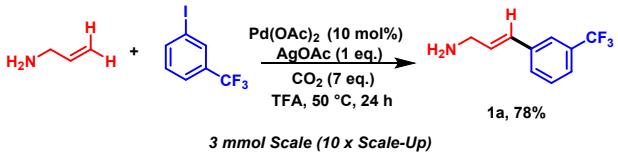


Table 3. Substrate Scope for Amines. Reaction conditions: allylamine (0.36 mmol), aryl iodide (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), and 9:1 dioxane and TFA (1 mL), heated at 90 °C for 14 h. [a] CO_2 (7 eq.) were added during the reaction.

We next hoped to demonstrate the applicability of this method towards the synthesis of chromophore-labelled molecules. Chromophoric and fluorophoric molecules are important probes in *in vivo* biological applications[27] and chemical sensing.[28] The major challenge to coupling organic molecules to chromophores via organometallic processes is the sensitive nature of the coupling partners under sometimes harsh conditions.[29] Considering that our methodology works on otherwise sensitive free amine substrates, we believed that our method should be able to overcome this limitation. However, under our optimized conditions, none of our dye coupling partners worked. After screening several different conditions, we eventually settled on a 9:1 mixture of 1,4-dioxanes and TFA at 90 °C as a suitable solvent mixture (**Table 3**). A BODIPY was easily coupled with a secondary amine in fair yield (**3a**). Notably, the fluorescence was retained in the coupled product, despite containing a free amine. We could also take a derivative of malachite green and couple it to generate a green chromophoric amine (**3b**). Regrettably, we were unable to find conditions during this study for the conjugation of these dye molecules to simple allylamine.

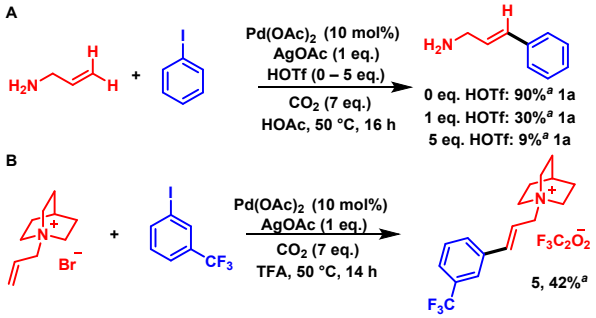
Given the potential utility of this reaction for the straightforward manufacture of cinnamylamine derivatives for therapeutic applications, we have also studied the scalability of this catalytic protocol (**Scheme 2**). The present palladium-catalyzed monoarylation was performed for the model reaction at ten times the scale. We were delighted to find that the product **1a** was obtained in 78% isolated yield. Notably, no diarylated product was observed under the scaled-up conditions either, obviating potentially challenging purification.



Scheme 2. Scale-Up Reaction conditions: allylamine (3.6 mmol), 3-iodobenzotrifluoride (3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (3 mmol), CO_2 (7 eq.) and TFA (1 mL), heated at 50 °C for 24 h.

Considering that under the present conditions perhaps no Pd nanoparticles were forming, we attempted to determine if a mononuclear or nanoparticle catalyst system was responsible for the monoarylation (note: the second arylation was already confirmed to be due to *in situ*-formed nanoparticles).[12] Our first piece of evidence that nanoparticles were forming came when we attempted to perform kinetics reactions, and found the initial rates to be variable. When we performed a mercury drop test, the reaction progress halted. Taken together, this still implied *in situ*-formation of the active Pd catalyst, which would be expected to facilitate formation of the terminal-functionalized product even if the amine is directing the reaction.

To further address the role of the amine, we considered that while trifluoroacetic acid or acetic acid solvents would lead to significant protonation of the amine, there would be expected a small equilibrium to the free amine which could then be providing a directing effect.[30] However, a stronger acid added would be expected to further drive the equilibrium of free amine down, which should inhibit the reaction if the amine is involved.[31] We therefore ran the reaction with varied concentrations of trifluoromethylsulfonic (triflic) acid (**Scheme 3a**). As may be expected for an amine-directed reaction, as the concentration of triflic acid was increased, the overall efficiency of the reaction decreased.



Scheme 3. Interrogating the Directing Ability of Free Amines. A) Affect of Added Strong Acid on Reaction Efficiency: Allylamine (0.36 mmol), iodobenzene (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), CO_2 (7 eq.), HOTf (0, 1, or 5 eq.), and TFA (1 mL), heated at 50 °C for 14 h. B) Functionalization of a Quarternary Allylammonium Substrate: *N*-allylquinuclidinium bromide (0.36 mmol), 3-iodobenzotrifluoride (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (0.3 mmol), CO_2 (7 eq.) and TFA (1 mL), heated at 50 °C for 14 h.

We simultaneously explored a covalent strategy for tying up the amine by preparing several protected amines with various directing abilities, including some *in situ*-formed transient directing groups,[32] and found that the yields were either decreased, the selectivity was decreased, or both (see ESI for details). One notable exception is when we prepared *N*-allylquinuclidinium bromide and subjected it to the reaction conditions. Perhaps surprisingly considering the previous experiments, under these conditions the arylated product was formed in 42% NMR yield with complete selectivity for *γ*-monoarylation, and 12% recovery of starting material (**Scheme 3b**). From these experiments we conclude that while the reaction may not require the amine as a directing group, the free amine can accelerate the reaction in this system.

Conclusions

We have disclosed a versatile and efficient method for selective monoarylation of allylamines employing a palladium catalyst. The present methodology has a broad substrate scope for amines and iodoarenes. The present strategy is highly selective and can easily be scaled up. The current approach has been utilized to effectively synthesize amines incorporating fluorophore/chromophores for potential biological applications.

Author Contributions

Conceptualization was performed by V.G.L. and M.C.Y. Investigation, methodology, and validation was performed by all authors. Writing – original draft was performed by V.G.L., T.A.M., and M.C.Y., while writing – review & editing was performed by V.G.L., A.L.B., F.L., and M.C.Y.

Conflicts of interest

There are no conflicts to declare.

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