CO_2-Mediated Pd-Catalyzed Stereo- and Regioselective Arylation of Free Allylamines

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Dedication: This manuscript is dedicated to the memory of Prof. Thomas H. Morton (1947-2020).

Abstract: Mizoroki-Heck couplings are a powerful method for elaborating alkene feedstocks. While selective functionalization of terminal olefins has been achieved by catalyst design, selective functionalization of internal olefins has generally required use of directing groups except in the case of Michael acceptors. Allylamine substrates have typically required protection to be suitable for these reactions, decreasing the step and atom economy of these procedures. Herein we demonstrate that the addition of CO_2 (dry ice) allows for the reproducible stereospecific arylation of both secondary and primary allylamines in the presence of a Pd^{II} catalyst. Notably, the product 3,3'-diarylallylamine motif is prevalent in a variety of biologically-relevant structures, and this method represents the most straightforward synthesis of these targets to date. Key features of the method are the ability to access relatively mild conditions that facilitate a broad substrate scope, as well as direct diarylation of terminal allylamine substrates. In addition, several complex and therapeutically-relevant molecules are included to demonstrate the utility of the transformation. Mechanistic studies point to an amine-directed reaction where CO_2 serves to protect the substrate and product from degradation.

Article: Allylamines are an important class of compounds that have seen use as antifungals,[1] antihistimines,[2] antidepressants,[3] and even as a treatment for male sexual dysfunction.[4] They have also served as useful building blocks in complex molecule synthesis.[5] As a result, there are numerous approaches to their synthesis.[6-8] However, formal C–H functionalization approaches to the synthesis of substituted allylamines are rare[9,10] – alkenes are typically reactive electrophiles that undergo hydrofunctionalization (**Figure 1a**),[11-14] difunctionalization (**Figure 1b**),[15-18] or even substitution of the amine in the case of primary allylamines (**Figure 1c**).[19] However, the rigidity of the 3,3-diaryl allylamine is a potentially valuable part of their bioactivity, and we therefore felt that accessing these directly would have great utility to rapidly access interesting lead compounds that would normally be challenging and time consuming to prepare. For this reason we set-out to achieve stereospecific and regioselective directed Mizorki-Heck (MH) coupling of primary and secondary allylamines with aryl iodides (**Figure 1d**).

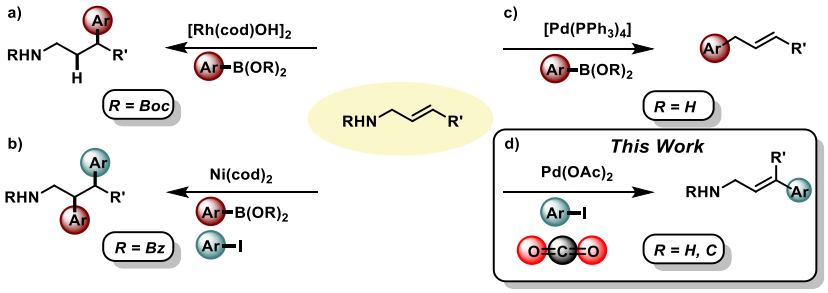


Figure 1. Transition Metal-Catalyzed Reactions of Allylamines.

Regioselective arylation of olefins has been a hot field since the pioneering work of Mizorki and Heck.[20] However, while electronic bias (*i.e.* reactions with Michael acceptors) or selectivity for terminal olefins has been thoroughly explored, regioselectivity suffers when internal olefins are used.[21,22] Achieving regioselectivity in these cases has therefore relied on chelation control through the use of a directing group.[23-26] Unfortunately, amines are generally regarded as poor directing groups for this process, and have required conversion into static

amide and carbamate-type directing groups to achieve regioselective monoarylation even of terminal alkenes[27-33] which negatively impacts both step and atom economy of these transformations. Notably, static directing groups can also be used to achieve the di-Heck coupling to form trisubstituted products, although in the absence of an appended electron withdrawing group, these can still suffer from poor regioselectivity.[34-36] Inspired by the recent popularity of transient directing groups in the field of C–H activation,[37-39] we wondered if the proposed directed MH arylation of allylamines could be realized using a transient directing group suitable for amines.[40] Notably, a nice example of a transient directing group for olefin reductive Heck coupling was disclosed while this manuscript was under preparation.[41] Our group recently developed an alternative transient directing group strategy for the C–H activation of amine substrates using carbon dioxide.[42] During this work we not only found that carbon dioxide can act as a DG, but also as a protecting group under non-supercritical conditions:[43] oxidatively sensitive secondary amines with *α*-hydrogens were *protected from oxidation* by maintaining appropriate CO_2 pressure in the reaction. MH coupling has been achieved using Boc-protected amines in the past, which suggested that a transiently generated carbamate should also be viable for directing a regioselective MH arylation of allylamines.

There were numerous potential pitfalls to an approach seeking to use CO_2 as a transient DG for the directed MH arylation of allylamines – the first being the possibility for allylic deamination as has previously been observed.[19] While homoallylic and longer chain lengths might lead to cyclization,[44] allylamines are less likely to cyclize *via* an intramolecular hydroamination pathway. However, conversion to the free carbamate, compared with a Boc-protected carbamate, would introduce a potential nucleophile that could undergo cyclization.[45,46] In addition, Pd^{II} is well known to promote C–H activation reactions, which could degrade regioselectivity for functionalization of the γ-carbon of the allylamine when sufficiently reactive sp^2 or sp^3 C–H bonds are in the molecule, while competitive C–H activation at the γ-carbon of the allylamine would lead to decreased stereoselectivity for the insertion products. Gratifyingly, after initial optimization we were able to determine conditions for the arylation of cinnamylamine substrates (see Supporting Information for discussion), using $Pd(OAc)_2$ as catalyst, AgTFA as a stoichiometric additive, aryl iodide as the arene source, acetic acid as solvent, and 10 equivalents of carbon dioxide in the form of dry ice.[47] Notably, throughout screening for this reaction many side products were observed, consistent with β-arylation, α-arylation, hydroxyarylation, and numerous deamination events, illustrating the competitive nature of other reaction pathways and the sensitivity of the desired process to changes in the reaction conditions. Interestingly, while the reaction proceeded at a temperature as low as 60 ºC in AcOH, the highest and most consistent yields were observed when the reaction was heated to 100 ºC. However, the transformation could be reliably performed at 40 ºC when TFA was used as the solvent in conjunction with AgOAc as the silver additive. Although silver is often invoked in Pd-catalyzed arylation reactions as a halide scavenger, using an alternative halide scavenger Me_4NCl[48] was not effective, suggesting that silver plays a greater role such as activating the C–I bond (see Supporting Information for details on the effects of other additives, including bases and oxidants). We compared the reaction with a variety of other potential amine-based directing groups, and found the best yield and selectivity was observed for the free amine with addition of CO_2 (see Supporting Information for details on reactions using other directing groups). However, much to our surprise, although we found that the amount of CO_2 was important for reproducible results, the control reactions gave variable yields between 0 – 40% in its absence, suggesting that its role may be more of a transient protecting group rather than as a directing group. This was surprising in that in previous examples simple application of organic acids such as AcOH or TFA as solvent were sufficient to prevent amine degradation.[49]

With these conditions in hand, we found that the scope was very broad for cinnamylamines bearing a variety of branched and linear alkyl substituents off of the nitrogen (**Table 1**, **1a** – **1h**). Various carbocycle-containing examples also worked well in the reaction (**1i** – **1m**), including both *N*-cyclopropyl (**1i**) and *N*-methylcyclopropyl (**1m**) groups. The same could be said for both saturated (**1n**) and unsaturated (**1o** and **1p**) heterocycle-containing substrates, though notably these performed better under the alternative conditions where trifluroacetic acid was employed as solvent at a reduced temperature of 40 ºC. These conditions were also preferable for arene containing substituents, and allowed electronically-neutral, rich, and poor arene-containing substrates to be used (**1q** – **1w**). Notably, the reaction could tolerate a pyridine heterocycle (**1u**), as well as S^{VI}-containing substrates (**1v** and **1w**), and was fully selective for functionalizing the γ-carbon of the allyl group despite the presence of competitive γ-C–H bonds on the side chains.

A CF_3-containing cinnamylamine was also able to participate in the reaction (**1x**). Free alcohols did not inhibit the reaction, (**1y** and **1z**), although they were protected as the acetate esters in the presence of the acetic acid solvent. We next explored amino acids, and found that a valine-derivative worked well (**1aa**). We also explored a glutamate ester, which gave the product with subsequent lactamization with the side chain after the arylation reaction (**1ab**) due to the availability of the free amine during the reaction.[50] A derivative of the dipeptide aspartame was also used in the reaction, in this case giving subsequent lactamization at the C-terminus (**1ac**). The reaction also worked on terpene-containing examples (**1ad** and **1ae**), including a more complex cedrene-containing cinnamylamine (**1af**). We could even use the reaction to selectively arylate medicinally-relevant substrates, such as cinnamylamine derivatives of colchicine (**1ag**), dehydroabiethylamine (**1ah**), and podophyllotoxin (**1ai**). Surprisingly, using *β*-substituted cinnamylamines failed to give the same products, giving alternative C–H arylation products depending on the substituent (see Supporting Information for more details).

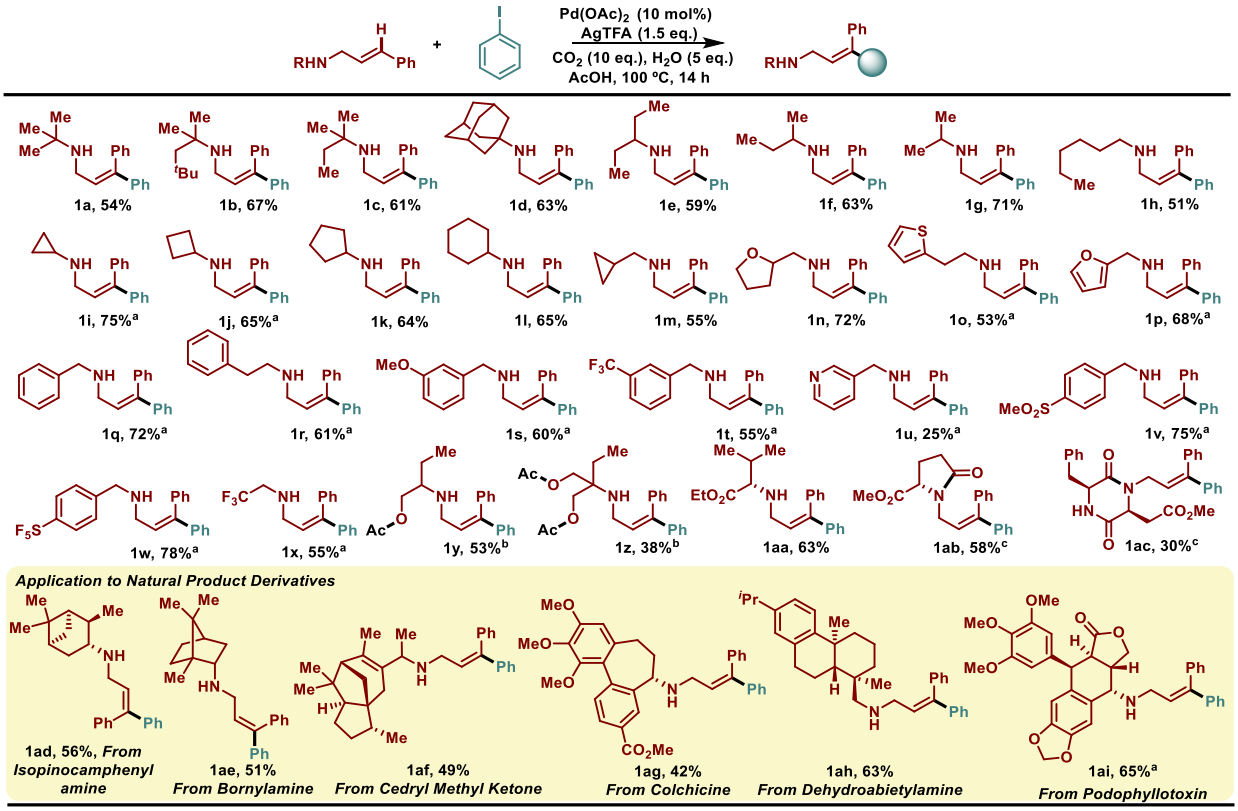


Table 1. Substrate Scope of the γ-Arylation of Cinnamylamines. All reactions were performed on 0.3 mmol scale with 2 eq. of aryl halide in 1 mL of solvent, in at least duplicate, and the average yield reported. [a] Reactions performed at 40 ºC in TFA (1 mL), AgOAc used instead of AgTFA. [b] Product obtained with concomitant esterification of the free hydroxyl group(s). [c] Product obtained with subsequent lactamization of a pendant ester group.

In addition to enjoying a broad substrate scope for amines, the reaction is also amenable to a wide array of aryl iodides (**Table 2**). Using *N-tert*-butylcinnamylamine, we could readily install arenes containing electron deficient substituents (**2a** – **2o**), including ketones (**2k** and **2m**), aldehydes (**2l**), and primary amides (**2n**), although the amide came through hydrolysis of the iodobenzonitrile starting material. While many of the products were oils, the amide product **2n** was successfully crystallized as its acetic acid salt, which confirmed the relative alkene stereochemistry and that the major products arose from a directed Heck arylation rather than a directed C–H activation. Likewise, NOESY spectroscopy of the products could be used to confirm the expected stereochemistry. The small amounts of the *Z*-stereoisomers formed might arise from a competitive C(sp^2)–H activation,[51] but could just as likely come from Pd-mediated isomerization considering the poor steric discrimination between the aryl groups. To probe this, ***E*-2a** was resubjected to the reaction conditions, however no isomerization was observed, which suggests that the *Z*-isomer comes from a competitive C–H activation pathway and not isomerization of the product.

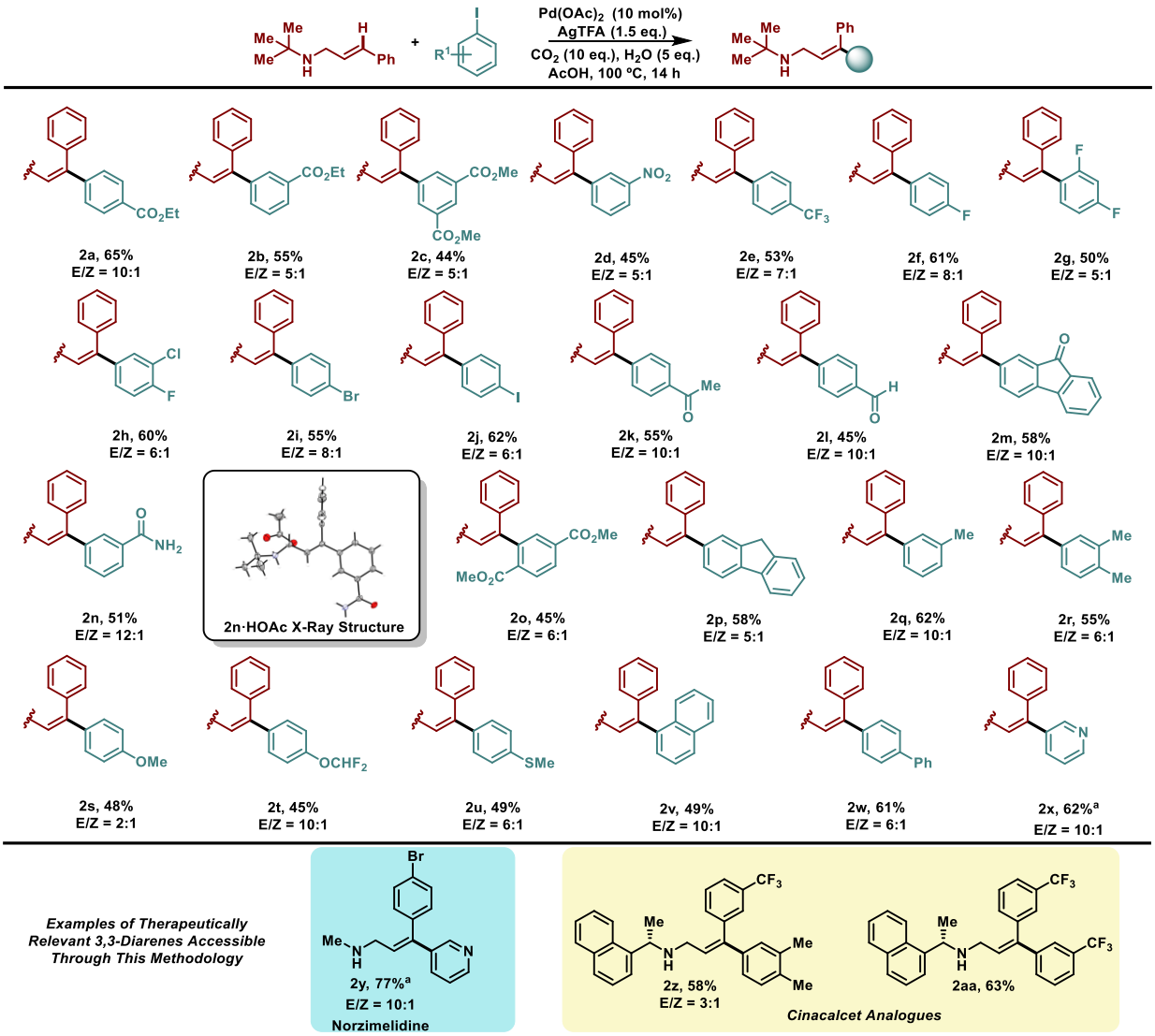


Table 2. Substrate Scope of the Aryl Iodide for the γ-Arylation of Cinnamylamines. All reactions were performed on 0.3 mmol scale with 2 eq. of aryl halide in 1 mL of solvent, in at least duplicate, and the average yield reported, with the E/Z ratio being determined from the crude mixture prior to purification. [a] Reactions performed at 70 ºC in TFA, AgOAc used instead of AgTFA (1 mL).

Electron rich groups are also tolerated (**2p** – **2w**) in the reaction, including an arylthioether that participates in the reaction without concomitant oxidation at the sulfur (**2u**). Furthermore, iodopyridine can be effectively coupled in good yield (**2x**), a common challenge in organometallic reactions with weak directing groups,[52] though notably with an elevated reaction temperature used. While we have shown a number of examples on complex substrates, we wanted to demonstrate specific synthetic targets of medicinal relevance. By starting from *N*-methyl-4-bromocinnamylamine, we were able to arylate using 3-iodopyridine, providing access to the drug Norzimelidine (**2y**) in two steps from commercially-available starting materials. We also prepared the alkene-precursor to Cinacalcet, and demonstrated that the alkene could be readily arylated to access new derivatives (**2z** and **2aa**) bearing the 3,3'-diarylmoiety.

While the selective arylation of cinnamylamines was an exciting result, we wondered whether or not the utility of the method could be extended by beginning with terminal allylamines. Notably, most directing group approaches for this transformation only give the *mono*-arylated products with high regioselectivity.[27-35] However, if successful our method could furnish symmetrical γ,γ-diarylallylamines in one pot, dramatically expediting the synthesis of this important class of drug molecules. After some additional optimization, we found

that this transformation could also be achieved (**Table 3**) by using trifluoroacetic acid as solvent, albeit at an increased temperature compared to the reaction on the secondary cinnamylamines. Simple allylamine could be diarylated effectively (**3a** – **3d**). We considered that an appropriate diiodide might give rise to an interesting carbocycle, but found perhaps unsurprisingly that under the present conditions intermolecular diarylation was faster than formation of a 14-membered ring, giving rise to the diarylated tetraester (**3e**). Secondary allylamines could also participate in the reaction (**3f** and **3g**). Impressively, when diallylamine was used as the substrate, the reaction could be performed four times simply by increasing the loading of aryl halide and silver (**3h** – **3j**).

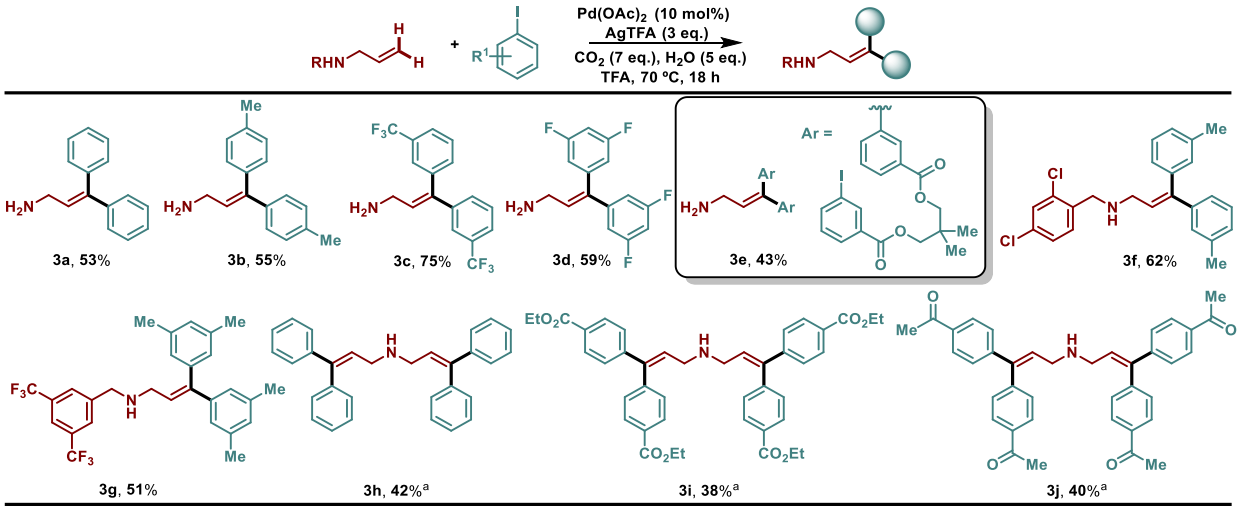
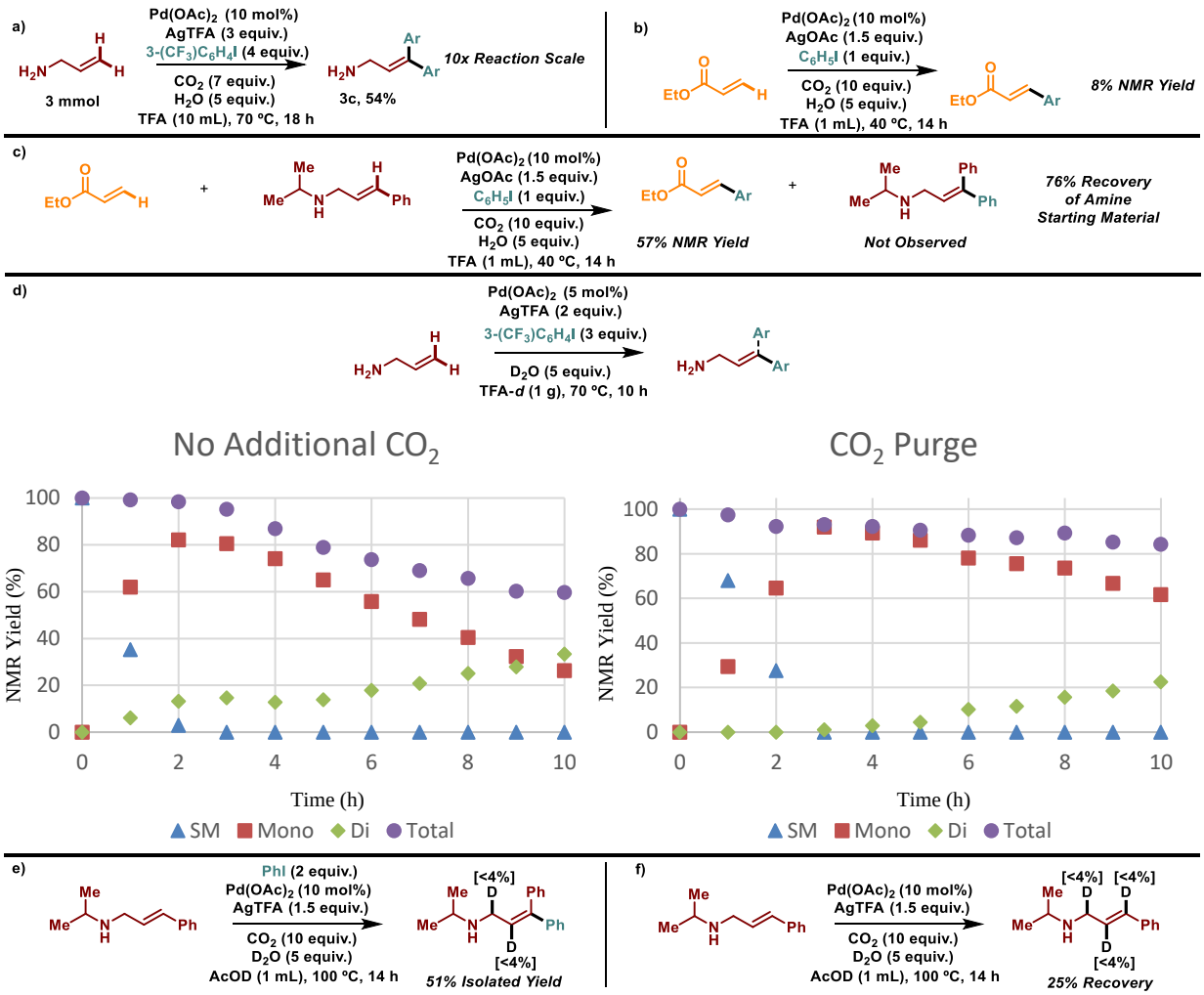


Table 3. Substrate Scope of the γ-Diarylation of Terminal Allylamines. All reactions were performed on 0.3 mmol scale with 4 eq. of aryl halide in 1 mL of solvent, in at least duplicate, and the average yield reported. [a] Reactions performed using AgTFA (4 eq.) and organohalide (12 eq.).

To ensure the utility of these reactions, we performed a scale-up on the diarylation of allylamine (**Scheme 1a**), and found that reasonable yields could still be achieved at ten times the reaction scale. We then turned our attention to better understanding the mechanism. The proposed insertion pathway would most likely occur through a Pd^0/Pd^{II} cycle, yet our optimization showed superior results when Pd^{II} precursors were used. A potential reason for this is the poor lability of the dibenzylidene acetone ligands bound to the Pd^0 precatalysts. To ensure a standard Heck mechanism could be operating, we ran the reaction but replaced the cinnamylamine substrate with ethyl acrylate (**Scheme 1b**). In this case only 8% yield of ethyl cinnamate was observed. However, when the reaction was repeated using both acrylate and cinnamyl amine with only one equivalent of aryl halide, an improved yield of 57% of ethyl cinnamate was observed with no observable amine arylation product (**Scheme 1c**). We interpret this to mean that the standard Pd^0/Pd^{II} cycle is plausible, but that the amine is critical for the success of the reaction, likely serving as a reducing agent for Pd^{II} as well as possibly a ligand, and that the traditional MH reaction on ethyl acrylate is faster than the directed MH reaction.

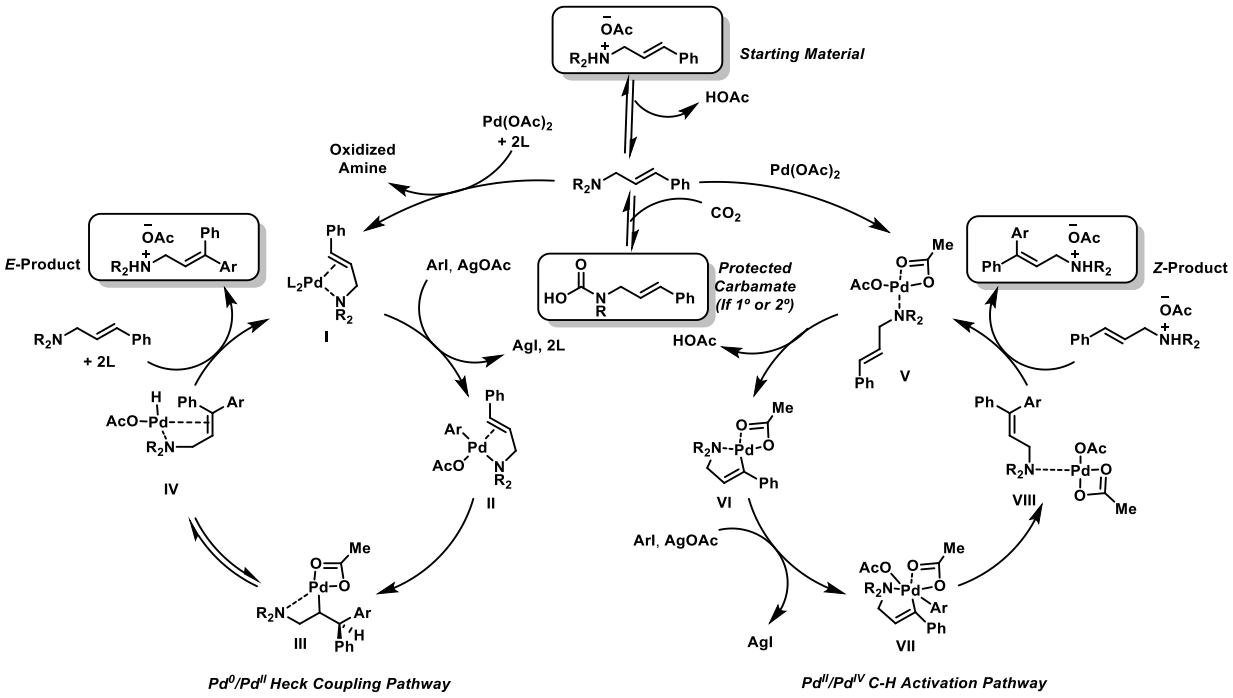
To validate the role of CO_2 in the reaction, we next explored the kinetics of the arylation of free allylamine (**Scheme 1d**). Notably, the first arylation is almost complete in two hours, even with reduced catalyst loading, but the overall recovery drops to a mere 60% after 10 hours. Meanwhile, by simply purging the reactor with CO_2, even at ambient pressure, the total amine recovery increases to over 80%. Notably, the rate of the arylation reaction is actually *slower* in the presence of extra CO_2, consistent with formation of protected carbamate to remove substrate from the catalytic cycle and thus reduce its ability to decompose. To ensure carbamate formation was actually occurring, as we predicted, AcOH was titrated into a solution of allylamine carbamate, which showed that even with excess of AcOH there was an equilibrium between free CO_2 and the carbamate (see Supporting Information for details). We therefore believe that the insertion is most likely directed by a small population of the free amine, rather than as a transient carbamate. To further substantiate the role of CO_2, we performed the reaction using the methyl carbamate and phthalimide DGs, and found no difference in the results with and without CO_2 – suggesting it is the interaction between the free amine and CO_2 that is important, rather than a consequence of modulating the pH or CO_2 interactions with other components in the reaction.

Support that the reaction is actually directed by the free amine was further implied by preparing both a 3º amine and a 4º ammonium substrate, and subjecting them to the reaction conditions. The 3º amine gave product, albeit in reduced yield, while the 4º substrate did not. Using a substituted aryl iodide, we were also able to confirm that the 3º amine product gave predominately the *E*-isomer from the MH reaction rather than the *Z*-isomer from a C–H activation reaction. Considering the 3º amine can react, while the electronically activated olefin of the 4º does not, we consider that the reaction must be amine directed rather than as a consequence of favorable electrostatics from the protonated amines or from a transient carbamate DG. An alternative explanation is that a contact ion pair forms between the ammonium and an acetate ligand on Pd, though this seems unlikely given that the 4º ammonium substrate should also be able to form this interaction, but does not give any product in the reaction. Some complexes of allylamines with Pd are known that do not involve chelation with the nitrogen at all,[53] as doing so would give a presumably less favorable four-membered metallocycle. However, because of the lack of reactivity on a 4º ammonium substrate, we reasoned the amine was still critical for the reaction. We reasoned that if amine coordination was only directing the insertion before dissociating, that the eventual β-hydride elimination could occur at either the α or γ position. Assuming that an elimination from the α-position must be reversible if it were to lead to the observed products, performing the reaction in deuterated media should lead to deuteration of the α-position. To test this hypothesis, we performed the arylation reaction of *N*-isopropylcinnamyl amine in deuterated media with phenyl iodide (**Scheme 1e**). Upon chromatographic separation no evidence for deuterium incorporation was observed by ^{1}H NMR. When the reaction was conducted in the absence of phenyl iodide, there was also no deuterium incorporation observed (**Scheme 1f**).



Scheme 1. Scale-Up and Mechanistic Experiments.

Based on our mechanistic studies, we propose the following catalytic cycles. Notably, one cycle is for an insertion-type mechanism to generate the major *E*-isomers of product, while a slower but competing C–H activation pathway gives rise to the *Z*-isomers (**Figure 2**). In acidic media the amine will primarily be protonated, however, the equilibrium will give rise to a small population of free amine. Some of this amine can enter the cycle, while we propose that CO_2 can also decrease this population, at least for 1º and 2º amine substrates, thereby slowing the rate not only of the two catalytic cycles, but also decomposition pathways. Multiple amine substrates can bind to the Pd catalyst, with at least one substrate becoming oxidized to generate a low valent Pd-intermediate (**Figure 2**, **I**). This can then undergo oxidative addition to the aryl iodide in the presence of a silver additive, giving a Pd^{II}–aryl species (**II**). This species can then undergo insertion of the Pd–Ar bond across the olefin to give **III** possessing a rare 4-membered palladacycle.[54,55] Chelation between Pd–N leads to β-hydride elimination to occur selectively from the γ-position to give **IV**. Finally **IV** undergoes ligand substitution, and base-promoted reductive elimination regenerates the active Pd^0 species. Meanwhile, coordination of the allylamine to Pd can also give a 1:1 species (**V**), which though a potential intermediate in the formation of **I** can also simply undergo concerted metalation-deprotonation to generate palladacycle **VI**. This then undergoes oxidative addition to the aryl iodide to generate a high valent Pd^{IV} intermediate (**VII**) that will readily undergo reductive elimination of a C–C bond to form the *Z*-isomer of the product (**VIII**), which is liberated by ligand exchange.



Scheme 1. Scale-Up and Mechanistic Experiments.

In conclusion, we have demonstrated that CO_2 can serve as a transient protecting group to facilitate the γ-arylation of both primary and secondary allylamines through a regio- and stereospecific olefin insertion mechanism. We have also provided evidence to support a potentially unconventional role for the amine in directing a putative four-membered insertion intermediate. Due to the lengthy and occasionally difficult syntheses required to access these 3,3-diarylallylamines, we anticipate that this method will open this class of substrates up to further scrutiny by medicinal chemists. Furthermore, the use of CO_2 as a transient protecting group under non-supercritical conditions may prove useful for improving step and atom economy in amine-based transformations. Future work will explore expanding the scope of directed olefin functionalization on this important class of substrates, as well as continued efforts to isolate reaction intermediates to better understand the mechanism of these and related transformations.

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Conflicts of Interest: M.C.Y. and M.K. hold a patent related to this work (US20190185392).

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