CO_2 As A Transient Directing Group for the Oxidative Heck Coupling of Free Allylamines With Aryl Iodides

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

Abstract: Oxidative 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) as a transient directing group allows for the 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.

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 oxidative arylation of primary and secondary allylamines (**Figure 1d**).

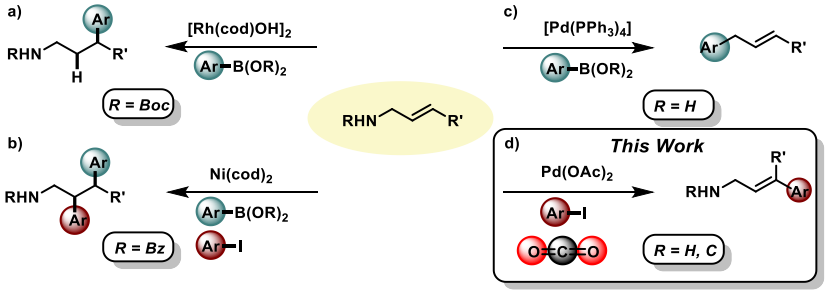


Figure 1. Transition Metal-Catalyzed Reactions of Allylamines.

Regioselective oxidative arylation of olefins has been a hot field since the pioneering work of 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. Achieving regioselectivity in these cases has therefore relied on chelation control through the use of a directing group.[21-24] Unfortunately, amines are generally regarded as poor directing groups for this process, and have required conversion into static amide and carbamate-type directing groups,[25-31] which negatively impacts both step and atom economy of these transformations. Inspired by the recent popularity of transient directing groups in the field of C–H activation,[32-

[34] we wondered if the proposed oxidative arylation of allylamines could be realized using a transient directing group suitable for amines.[35] Notably, a nice example of a transient directing group for olefin reductive Heck coupling was disclosed while this manuscript was under preparation.[36] Our group recently developed an alternative transient directing group strategy for the C–H activation of amine substrates using carbon dioxide.[37] 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:[38] oxidatively sensitive secondary amines with α-hydrogens were *protected from oxidation* by maintaining appropriate CO_2 pressure in the reaction. Notably, oxidative Heck 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 oxidative arylation of allylamines.

There were numerous potential pitfalls to an approach seeking to use CO_2 as a transient directing group for the oxidative 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,[39] allylamines are less likely to cyclize. However, conversion to the free carbamate, compared with a Boc-protected carbamate, would introduce a potential nucleophile that could still undergo cyclization.[40,41] 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. Gratifyingly, after initial optimization we were able to determine conditions for the oxidative arylation of cinnamylamine substrates (see SI for discussion), using $Pd(OAc)_2$ as catalyst, AgTFA as a stoichiometric additive (to aid oxidative addition to the C–I bond), aryl iodide as the arene source, acetic acid as solvent, and 10 equivalents of carbon dioxide in the form of dry ice.[42] Notably, product could be observed in the absence of added CO_2, but not consistently. We reasoned that perhaps advantageous uptake of CO_2 by either the substrate or solvent could be the cause. When the reaction was set-up in a glovebox with distilled amine and ampules of deuterated solvent, we found no conversion of the cinnamylamine substrate to product. This result underscores the potential for trace amounts of adventitious CO_2 to alter the course of organometallic reactions, and the importance of properly purifying and storing amine reagents. Although the desired products could be observed at 70 ºC, and reasonable yields obtained at 80 ºC, we found that performing the reaction at 100 ºC was necessary for the sake of consistency across the substrate tables. Notably, throughout screening for this reaction many side products were observed, consistent with β-arylation, α-arylation, hydroxyarylation, and numerous deamination events, suggesting the sensitivity of the reaction to relative rates.

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 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.

Though poorly nucleophilic, 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 transient nature of the DG.[43,44] 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**).

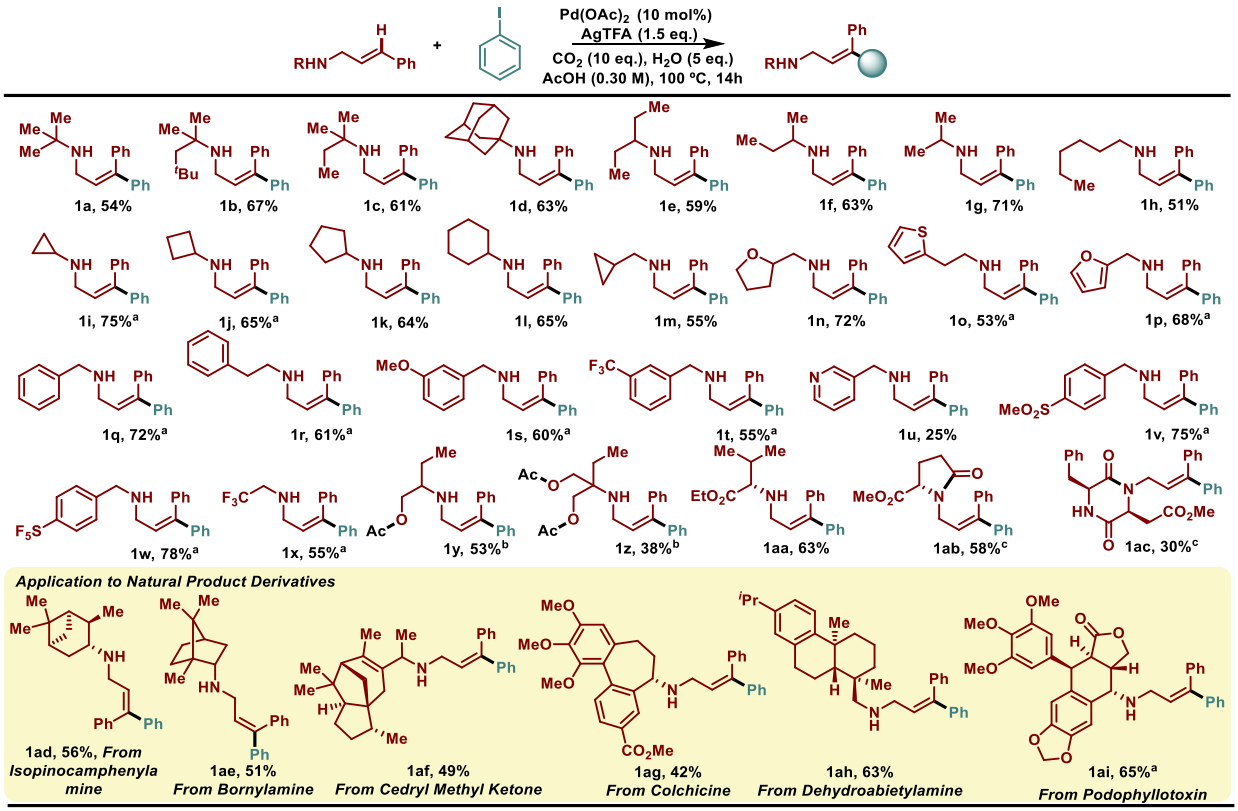


Table 1. Substrate Scope of the γ-Arylation of Cinnamylamines. All reactions were performed in at least duplicate, and the average yield reported. [a] Reactions performed at 40 ºC in TFA (1 mL), AgOAc used instead of AgTFA. [b] Product obtained with concomitant esterification of the free hydroxyl group(s). [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. Because the mechanism likely goes through directed insertion and β-hydride elimination rather than a direct C–H activation, high stereospecificity was observed for the inverted arene products. The small amounts of the *Z*-stereoisomers formed might arise from a competitive C(sp^2)–H reaction, but could just as likely come from Pd-mediated isomerization considering the poor steric discrimination between the aryl groups.[45] 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. Likewise, NOESY spectroscopy of the products could be used to confirm the expected stereochemistry.

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,[46] 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.

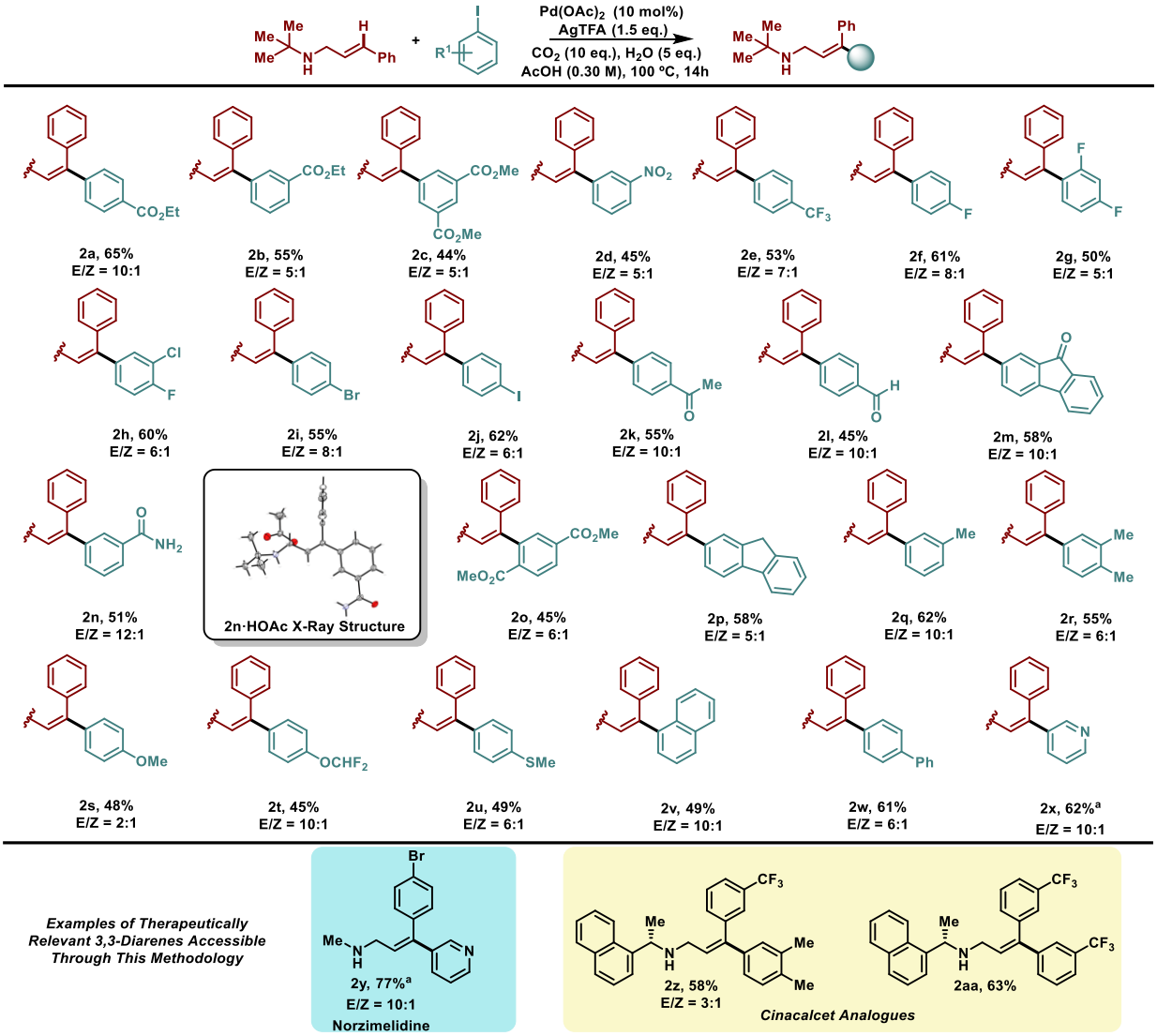


Table 2. Substrate Scope of the Aryl Iodide for the γ-Arylation of Cinnamylamines. All reactions were performed in at least duplicate, and the average yield reported, with the E/Z ratio being determined from the crude mixture prior to purification. [a] Reactions performed at 70 ºC in TFA, AgOAc used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

While the γ-C–H 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 static directing group approaches for this transformation only give the *mono*-arylated products. 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**).

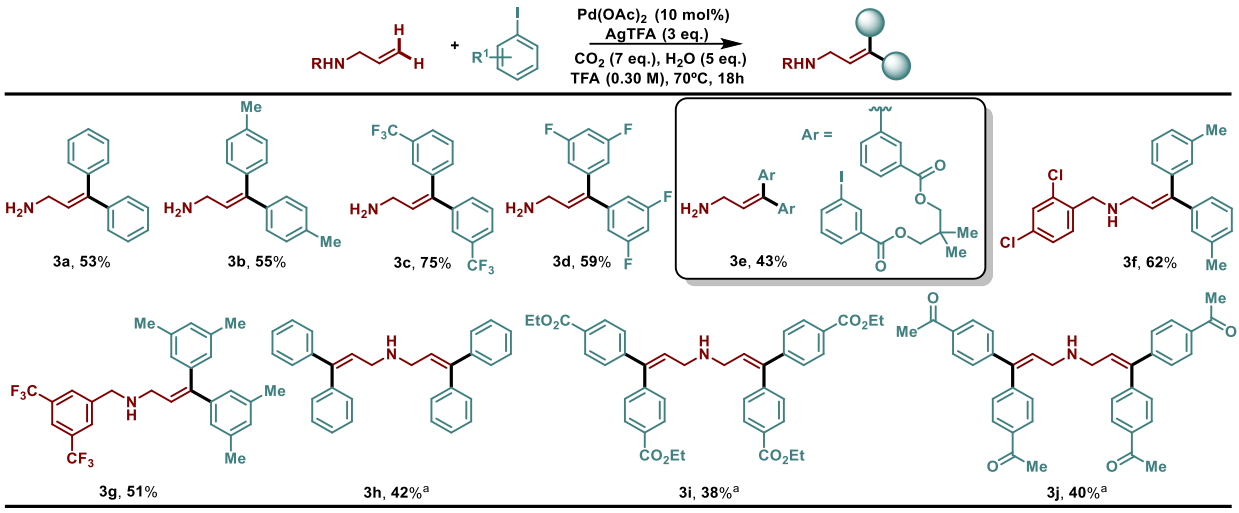
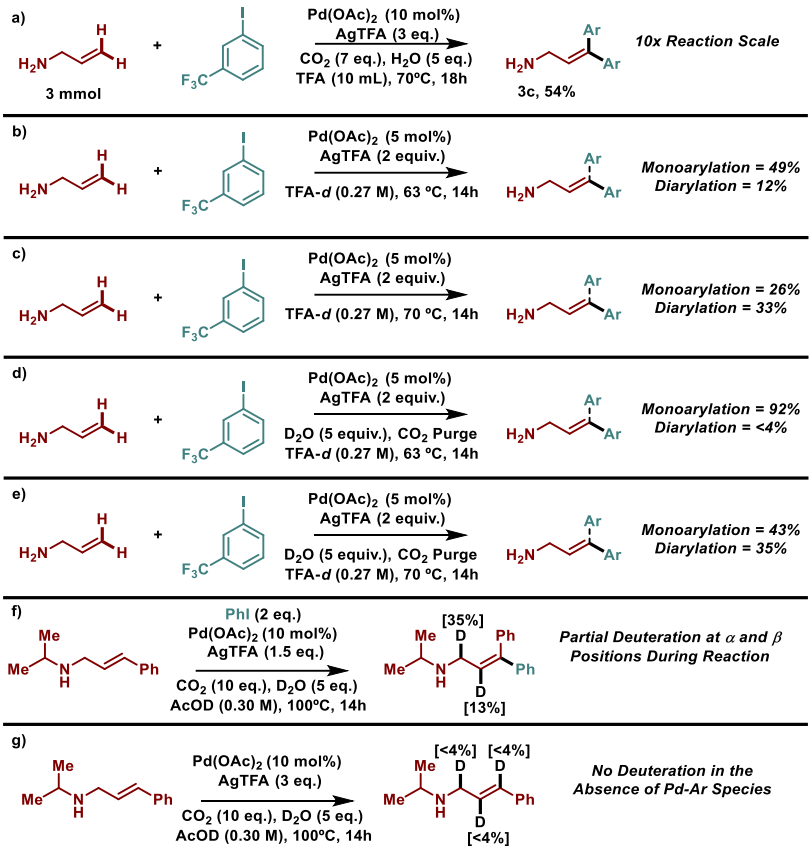


Table 3. Substrate Scope of the γ-Diarylation of Terminal Allylamines. All reactions were performed in at least duplicate, and the average yield reported. [a] Reactions performed using AgTFA (4.0 eq.) and organohalide (12.0 eq.).

To ensure the utility of these reactions, we performed a scale-up on the diarylation of allylamine (**Scheme 1a**), and found that reasonable yield could still be achieved at ten times the reaction scale. A question presented itself at this time – could the arylation be interrupted to give solely the *mono*-arylation product. To probe this, we chose to monitor the reactions in an NMR spectrometer. For ease of quantification, we lowered the equivalents of metals to facilitate shimming. Notably, when no additional CO_2 was added, the *mono*-arylation product could be achieved in up to 49% NMR yield, with a much lower amount of *di*-arylation, when the reaction was performed at 63 ºC (**Scheme 1b**). However, increasing the reaction temperature to 70 ºC increased the yield of the *di*-arylation product, but at the expense of the overall recovery due to decomposition (**Scheme 1c**). Due to the low molecular weight and volatility of the allylamine substrate, we were able to distill the compound, but it had to be measured into the experiment outside of the glovebox, and so we cannot be sure that no adventitious CO_2 was absorbed. However, addition of more CO_2 had a profound effect on the experiments – when the reaction was performed at 63 ºC, but with the addition of water and subsequent purging with CO_2, the NMR yield of the *mono*-arylation increased to 92%, with negligible *di*-arylation (**Scheme 1d**). Likely due to lower catalyst loading and lower CO_2 pressure than in the optimized conditions, running the reaction at 70 ºC did not give an appreciably higher yield of the *di*-arylation product compared to the CO_2-free reaction, however, the overall recovery was better (**Scheme 1e**). Taken together, this supports that for the primary allylamine substrates, CO_2 may be more important as a protecting group than a directing group, though for secondary amines the role of CO_2 can clearly be interpreted as being both.

Our final question revolved around addressing an outstanding mechanistic question: Is the arylation the result of solely insertion chemistry, or is there a competing C(sp^2)–H activation reaction. During the synthesis of the unsymmetrical 3,3-diarylallylamines (**Table 2**, *vide supra*), we had observed both *E* and *Z* isomers, though the *trans* isomers (from an insertion mechanism) were the major products. Because the *Z* isomers could come from isomerization, we couldn't use their presence to assess the action of a competing C–H activation mechanism. We therefore performed the arylation reaction of *N*-isopropylcinnamyl amine in deuterated media with phenyl iodide (**Scheme 1f**). The product was observed with 35% deuterium incorporation at the α-position, and 13% incorporation at the β-position. When the reaction was conducted in the absence of phenyl iodide, however, no deuterium incorporation was observed at the α-, β-, or γ-positions (**Scheme 1g**). This suggests that either no C–H activation occurs, or that if it does occur that it is irreversible under the reaction conditions.



Scheme 1. Scale-Up and Mechanistic Experiments.

In conclusion, we have demonstrated that CO_2 can serve as a transient directing group to facilitate the γ-arylation of both primary and secondary allylamines through a regio- and stereospecific olefin insertion mechanism. 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. 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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