Carbon Dioxide-Mediated C(sp^2)–H Arylation of Primary and Secondary Benzylamines

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ABSTRACT: C–C bond formation by transition metal-catalyzed C–H activation has become an important strategy to fabricate new bonds in a rapid fashion. Despite the pharmacological importance of *ortho*-arylbenzylamines, however, effective *ortho*-C–C bond formation of free primary and secondary benzylamines using Pd^{II} remains an outstanding challenge. Presented herein is a new strategy for constructing *ortho*-arylated primary and secondary benzylamines mediated by carbon dioxide (CO_2). The use of CO_2 with Pd is critical to allowing this transformation to proceed under relatively mild conditions, and mechanistic studies indicate that it (CO_2) is directly involved in the rate determining step. Furthermore, the milder temperatures furnish free amine products that can be directly used or elaborated without the need for deprotection while tolerating a reasonably broad substrate scope (74 examples). In cases where diarylation is possible, an interesting chelate effect is shown to facilitate selective monoarylation.

Amines are a ubiquitous functional group, being especially important in polymers[1-3] and pharmaceuticals.[4, 5] Despite many classical[6-8] and modern[9-12] approaches to their synthesis, however, new methods are still in demand to access new chemical space surrounding these functional groups.[13] One strategy for preparing amines that has recently been gaining traction has been to functionalize C–H bonds through C–H activation[14-17] and C–H functionalization[18-20] methods. These approaches can allow rapid access to compounds that were either inaccessible with conventional synthetic methods, or required more lengthy synthetic routes, thereby expediting and improving drug library synthesis.[21] Although primary and secondary aliphatic amines often require pre-functionalization with *static* directing groups to facilitate C–H bond activation and prevent undesirable substrate oxidation under palladium-catalyzed protocols,[22-28] aromatic C–H bonds have generally been more easily targeted. For this reason free homobenzylamines[29, 30] have been widely used as substrates for a variety of palladium-catalyzed C–H activation reactions without the need to pre-functionalize the amine. It is therefore interesting to note that there was until recently no example in the literature whereby free primary *ortho*-aryl benzylamines could be directly accessed via C–H arylation, and there is still no method for the same transformation on free secondary benzylamine substrates or any method to do either transformation while preserving the chirality of the starting amine.[31] Because of the importance of the biaryl moiety in a number of biologically-active molecules (Figure 1),[32-34] we considered that the ability to directly access free primary and secondary *ortho*-aryl benzylamines directly under mild conditions would have utility to the synthetic community.

Ortho-aryl benzylamines are generally prepared directly from biaryl nitriles via reduction[35, 36] or an azidation/reduction sequence, also from a pre-formed biaryl species.[37] Alternatively, they can be prepared from *protected* benzylamines via Suzuki-Miyaura cross-coupling[38, 39] or directed C–H arylation.[40] However, it was not until 2006 that Daugulis was able to show the first example of Pd-catalyzed *ortho*-arylation utilizing free primary and secondary benzylamines as substrates.[41] Though the arylation strategy was successful, the harsh conditions led to partial protection of the substrate and product acetamides, which led to the need to fully protect the amines for isolation. Furthermore, the substrate scope of secondary amines was limited to those *without* β-hydrogens. Subsequent strategies have emerged for C–H arylation,[42, 43] carbonylation,[44] olefination,[45] and even a Catellani-type reaction[46] of tertiary benzylamines using Pd as a catalyst, as well as one example of the carbonylation/lactamization of free primary benzylamines,[47] yet no improvements have been made on C–H arylation of secondary benzylamines, and only one report has improved on the arylation of primary benzylamines.[31]

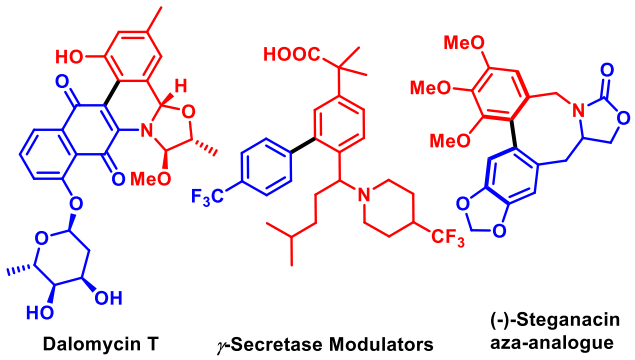


Figure 1. Examples of Biologically Active *ortho*-Aryl Benzylamines.

Recent efforts in the field of C–H activation field have moved towards use of *transient* directing groups that can be formed *in situ*.[48] Though more frequently applied to aldehyde[49-51] and ketone[52-54]-based substrates, this has also been achieved more recently using amine substrates combined with aldehyde-based directing groups.[31, 55-59] Inspired by this and the use of CO_2 as a traceless directing group for C–H activation of phenols,[60, 61] we recently developed a different approach, and showed that γ-arylation of aliphatic amines could be achieved in the presence of carbon dioxide.[62] Mechanistic experiments

surrounding that work supported the idea of a *transient carbamate* serving as a directing as well as protecting group, thereby facilitating the desired C–H activation step. We therefore considered that carbon dioxide might facilitate the realization of a C–H activation strategy towards free primary and secondary *ortho*-arylbenzylamines.

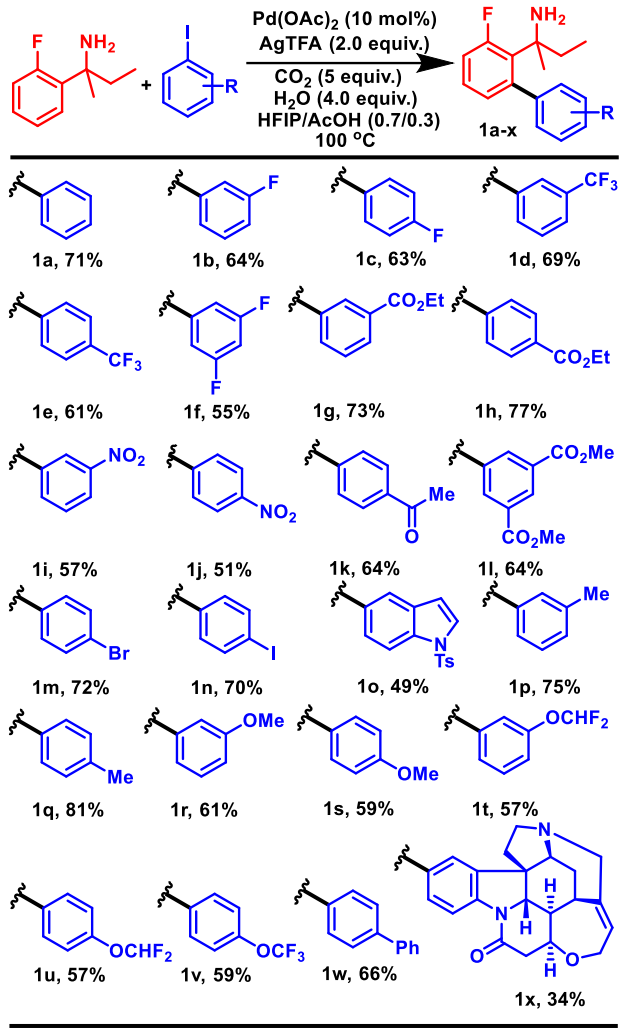


Table 1. Aryl Iodide Scope of the γ-C(sp^2)–H Arylation of 2-(2-fluorophenyl)butan-2-amine.

To investigate the feasibility of utilizing carbon dioxide to facilitate the γ-C(sp^2)–H arylation of benzylamines, we focused on the substrate 2-(2-fluorophenyl)butan-2-amine. We were delighted to find that our previously reported conditions for aliphatic amines, using $Pd(OAc)_2$ as pre-catalyst, AgTFA as an additive, and acetic acid as solvent, gave product albeit in only modest yield. The reactions were performed in 2 dram reaction vials by combination of the reagents and solvent, followed by addition of carbon dioxide in the form of dry ice.[63] Despite numerous examples in our previous report where C(sp^3)–H arylation was exclusively observed for secondary benzylamines (presumably due to possessing a more favorable conformation),[64] only C(sp^2)–H arylation was observed in the current example. After significant screening, we established that the optimal reaction conditions involved using $Pd(OAc)_2$ as pre-catalyst, with AgTFA as an additive, along with a mixture (7:3) of HFIP (hexafluoroisopropanol):acetic acid as solvent, in the presence of approximately 5 eq of CO_2 added in the form of dry ice (See Supporting Information for more detail). Although Ag salts are sometimes used simply as halide scavengers,[65] less than one turnover was achieved when silver trifluoroacetate was omitted, suggesting more than one role in this transformation. Unsurprisingly, omission of palladium completely shut down the reaction. Consistent with our hypothesis, the reaction is greatly enhanced by CO_2, and only 9% yield was obtained in the absence of additional CO_2.

With the optimized conditions in hand, we next set-out to explore the substrate scope of the transformation with regard to aryl halides (**Table 1**). Using the optimized conditions, the standard product was isolated in 71% yield (**1a**). The reaction could be performed on a number of fluorinated aryl iodides (**1b** – **1f**), as well as those with more electron deficient groups such as esters (**1g** and **1h**), nitro groups (**1i** and **1j**), ketones (**1k**), and even multiple electron deficient groups (**1l**). It is noteworthy that neither the ketone nor the isophthalate groups show signs of condensation or substitution with the amine under the reaction conditions. Reactions with either bromoiodobenzene (**1m**) or diiodobenzene (**1n**) could be performed without reactivity at the second halogen. Electron rich aryl iodides bearing indole rings (**1o**), methyl groups (**1p** and **1q**), methoxy groups (**1r** and **1s**), both difluoro and trifluoromethoxy groups (**1t** – **1v**), and even an arene with extended conjugation (**1w**) were also tolerated during the reaction. Surprisingly, 2-iodostrychnine[66] can be used in the reaction (**1x**) despite the presence of a tertiary amine that can also react with CO_2. Furthermore, the conditions are mild enough to preserve both the amide and allylic ether groups.

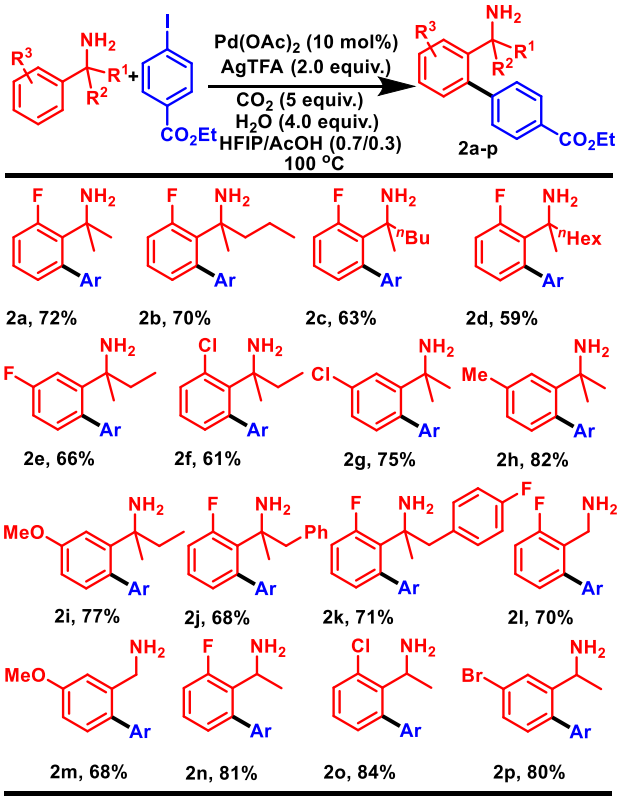


Table 2. Primary Benzylamine Scope of the γ-C(sp^2)–H Arylation with Aryl Halides.

We next focused on the scope of the reaction with respect to the amine substrates. Short to medium length aliphatic chains could be tolerated, all with excellent selectivity for C(sp^2)–H arylation (**Table 2**, **2a** – **2d**). Moving the position of the fluoro

substituent on the benzylamine (**2e**) as well as using substrates bearing either an *o*- or *m*-chloro group (**2f** and **2g**) all gave good yields. More electron rich benzylamines with methyl (**2h**) and methoxy (**2i**) substituents were also tolerated in the reaction. Amines with both benzylic and homobenzylic sites showed complete selectivity for γ-arylation on the benzyl rather than δ-arylation on the homobenzylic chain (**2j** and **2k**), presumably due to a faster rate of C–H activation. Gratifyingly, no changes were necessary to apply this protocol to more oxidatively-sensitive α-primary benzylamines, and the corresponding *o*-biaryls could be prepared without concomitant oxidation of the benzylamine (**2l** and **2m**). Even α-secondary benzylamines, which could be expected to undergo β-hydride elimination to generate imines during the reaction,[41] gave the unoxidized amine products in excellent yields (**2n** – **2p**).

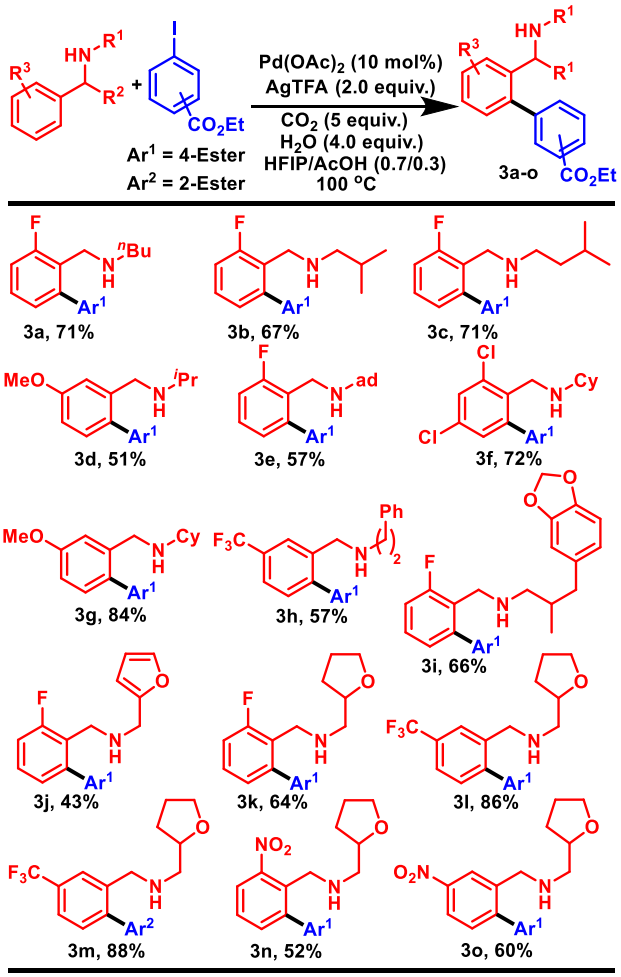


Table 3. Secondary Benzylamine Scope of the γ-C(sp^2)–H Arylation with Aryl Halides.

Based on our previous success applying carbon dioxide to the functionalization of secondary amines, we considered that it might help prevent oxidation[67] problems that had limited the substrate scope of Daugulis' original report.[41] The optimized conditions were found to indeed promote the C–H arylation of secondary benzylamines while preventing deleterious oxidation pathways. Substrates bearing linear (**Table 3**, **3a**) and branched (**3b** – **3d**) chains added to the benzylamine were able to participate in the reaction. Amines bearing various carbocycles (**3e** – **3g**) were also viable under the standard reaction conditions. Aryl groups could be added to the benzylamine via either a β (**3h**) or γ (**3i**) linkage without degraded regioselectivity for arylation of the γ-C(sp^2)–H bond. We were delighted to find that unsaturated (**3j**) as well as saturated (**3k** – **3o**) heterocycles appended to the benzylamine could also survive the reaction conditions, although it is worth noting that appending an *N*-methylpyrrole moiety to the benzylamine failed to give product under these conditions, presumably due to its increased nucleophilicity.

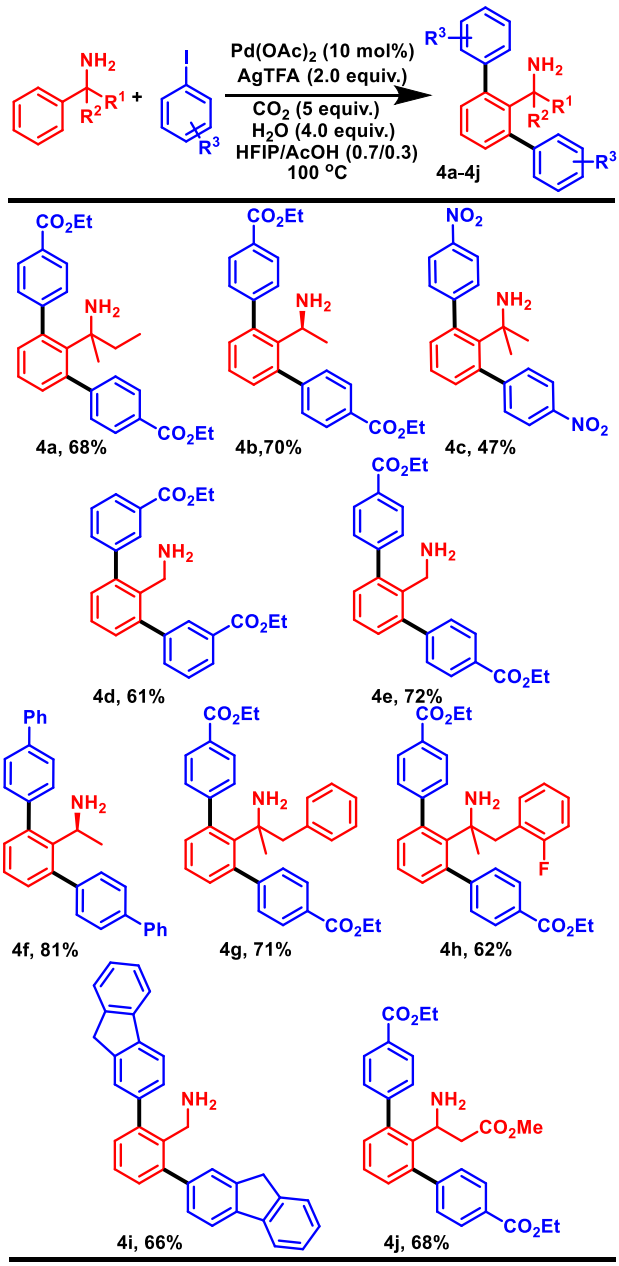


Table 4. Scope of the Di-γ-C(sp^2)–H Arylation of Sterically-Accessible Benzylamines.

A common issue in the intermolecular *o*-C(sp^2)–H activation literature is the challenge of achieving selective monofunctionalization *without* blocking the 2-position or sterically protecting the 2-position by pre-installation of a group at the 3-position.[68] Unsurprisingly, we found that in the absence of a substituent at the 2 or 3-position, diarylation products were afforded with great selectivity when excess aryl halide was used

(**Table 4**), although dropping the ratio to less than five equivalents of halide led to a mixture of *mono* and *di*-arylation products. The rationale for this is that although the reactive C–H bond is not forced towards the catalyst during the initial reaction, after arylation the aromatic ring will adopt a conformation where the second *o*-C–H bond becomes more accessible, leading to faster C–H activation of the monosubstituted benzylamines compared to the unsubstituted starting material. The *m*-terphenyl products could be achieved with α-tertiary benzylamines without (**4a**) or with (**4b** and **4c**) a substituent at the 4'-position of the benzylamine. Notably a chiral amine survived the reaction with no loss of chirality (**4b**). α-Primary benzylamines are also viable substrates in the reaction (**4d** and **4e**).

By using 4-phenyl iodobenzene as the electrophile, it is even possible to rapidly access a highly conjugated *m*-pentaphenyl with an amine moiety (**4f**). Substrates containing both benzylic and homobenzylic positions also still gave complete selective for diarylation of solely the benzylic ring (**4g** and **4h**). Given the ability to potentially synthesize highly conjugated substrates, we next targeted a bis-fluorene (**4i**), although this was not particularly emissive. Finally, use of a β-phenylalanine ester also led to the diarylation products in good yield with no observable α-arylation (**4j**) of either the amine or ester group.

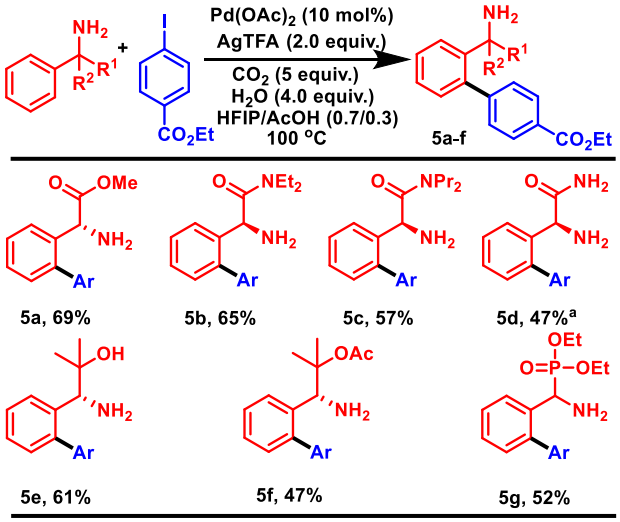
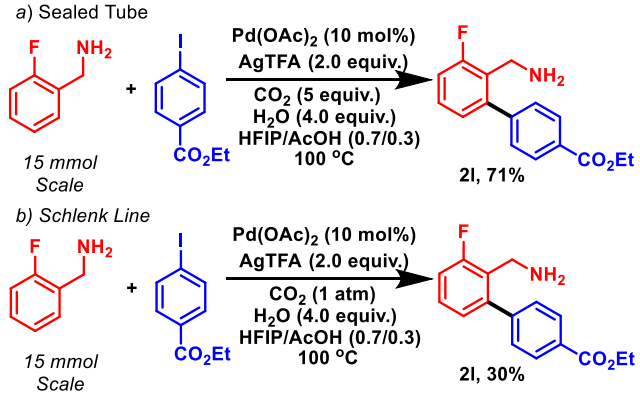


Table 5. Scope of the Selective Mono-γ-C(sp^2)–H Arylation of Sterically-Accessible Benzylamines. [a] HFIP used as solvent.

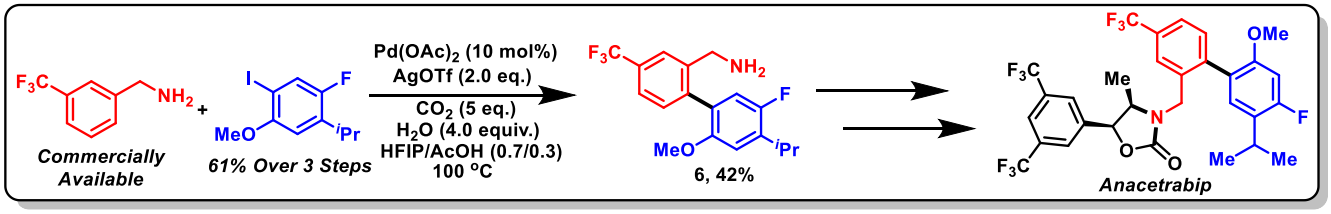
While exploring the diarylation of benzylamines, we discovered an interesting outlier: subjecting methyl phenylglycine to the reaction conditions led to selective monoarylation (**Table 5**, **5a**), *even without utilizing the blocking method*. We assumed there might be a chelation effect from the pendant ester that leads to the unusual selectivity. Gratifyingly, despite the addition of a third group to lower the pKa of the α-proton, we still saw retention of configuration of the chiral amine.[31] Encouraged by this result, we explored a number of other substrates with chelating groups: replacing the ester with an amide (**5b** – **5d**) still led to monoarylation when only three equivalents of aryl halide were utilized. Notably, the free amide required a slight modification to the conditions (**5d**). While the presence of a β-carbonyl was clearly effective, we wondered if other groups might facilitate this monoarylation, and found that placing an alcohol β to the amine could also prevent diarylation (**5e**). Protection of the alcohol as an ester was also effective in the selective monoarylation (**5f**). To our surprise, even an α-phosphonate ester could be used to achieve selective monoarylation (**5g**). The effect was also observed with a tertiary β-thiol as well as an α-nitrile, although the products of these reactions could not be successfully purified. Interestingly, the α-nitrile gave rise to the *ortho*-aryl aminoacid due to hydrolysis of the nitrile.

After gaining a better understanding of the substrate scope, our next goal was to demonstrate the utility of the reaction to a known synthetic target, and so we applied this C–H arylation approach to a key step in the synthesis of Anacetrapib, a CETP inhibitor that until recently was being investigated by Merck (**Scheme 1**).[69] The requisite aryl halide can be synthesized in three steps, and although *ortho*-substituted aryl halides are generally poor substrates for C–H arylation reactions, by using AgOTf as the additive, the *o*-biaryl can be achieved in 42%. The use of Ag additives with relatively poorly coordinating counterions for C–H arylation with *o*-substituted iodoarenes appears to be a relatively reliable approach for using these more sterically-hindered aryl halide substrates.[31, 70] The amine can then be treated with the corresponding epoxide and cyclized to give Anacetrapib using a known procedure.[71]

To demonstrate the synthetic utility for this chemistry, we also wanted to show that the reactions could be performed on larger scale (**Scheme 2**). Performing the reaction at 100 times the scale (from 0.15 mmol to 15 mmol) gave a similar yield (**Scheme 2a**). We wondered if higher than 1 atmosphere of CO_2 pressure was still needed at this scale, and so we performed the reaction under standard Schlenk conditions with 1 atmosphere of CO_2. Under these conditions the yield was less than half (**Scheme 2b**), showing that the pressure of CO_2 is critical for the optimal functioning of this chemistry.



Scheme 2. Scale-up Experiments.



Scheme 1. Total Synthesis of *rac*-Anacetrapib via γ-C(sp^2)–H Arylation of a Benzylamine Precursor.

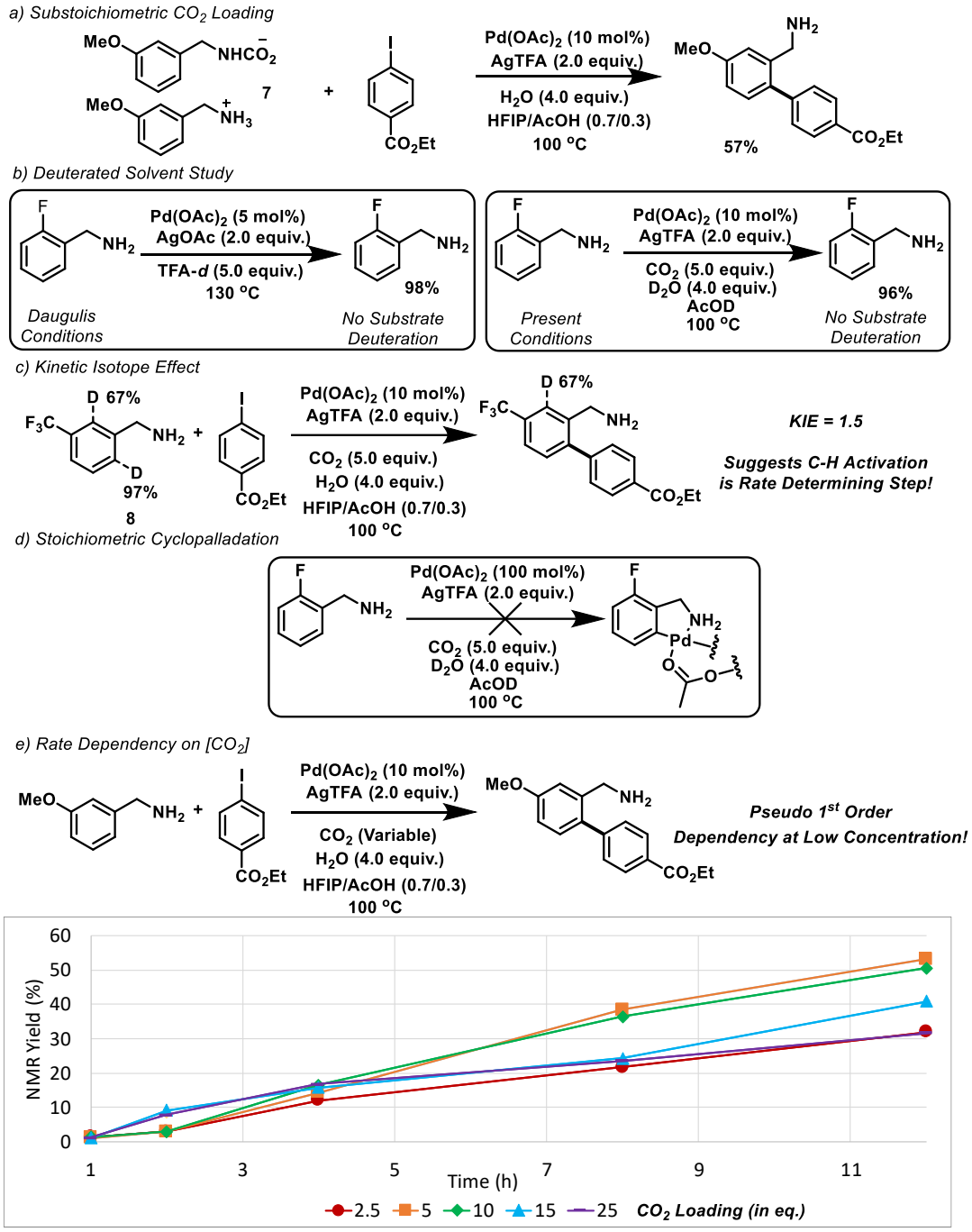


Figure 2. Experimental Mechanistic Studies on the CO_2-Mediated C–H Arylation of Benzylamines.

Having demonstrated the synthetic utility of our approach, our final goal was to try to better understand the mechanism of this C–H arylation. Control reactions indicated a vital role for CO_2 during the reaction, yet cyclopalladated intermediates of primary and secondary benzylamines have been made before under relatively mild conditions without the need for an additional directing group.[72] This left us to consider whether or not CO_2 was acting as a directing group, or serving in a separate capacity. One possibility would be that dimeric species that might be present that CO_2 disrupts, although these are expected to be destabilized under acidic conditions, and so we didn't consider this to be a likely cause.[70, 73]

To probe the mechanism experimentally, our first question was whether or not substoichiometric carbon dioxide was sufficient to catalyze the reaction (**Figure 2a**). The ammonium carbamate salt **7** was prepared, which would introduce only a half equivalent of carbon dioxide into the reaction. This gave 57% yield in the arylation reaction (in the absence of additional CO_2), suggesting that catalytic loading of CO_2 was satisfactory for the reaction to proceed (although considering the results in **Scheme 2b**, there is some importance to the CO_2 pressure, regardless of the stoichiometry). We next probed whether the C–H activation step was reversible. Using both Daugulis' condi-

tions as well as our own in the presence of fully deuterated solvents, no deuteration was observed (**Figure 2b**). To further explore this, the rate of reaction was compared between the proteo and deutero substrates under our conditions, and was found to exhibit a kinetic isotope effect of ~1.5, providing additional evidence that the rate-determining step is the initial breaking of the C–H bond (**Figure 2c**).

Considering that C–H activation is rate determining, but also that we anticipated C–H metalation should actually be facile, we wondered if C–H palladation was likely to occur readily in the absence of CO_2. When we attempted the cyclometallation with stoichiometric $Pd(OAc)_2$ in neat acetic acid, however, negligible C–H activation was observed (**Figure 2d**), suggesting that at least under the reaction conditions, the barrier to C–H activation is higher under our conditions than it is in solvents such as chloroform. This suggests that CO_2 may indeed be serving as a directing group under the catalytic conditions. We rationalized that if CO_2 was serving as a directing group that the overall rate of arylation should also exhibit 1st order rate dependency on the concentration of CO_2. For this reason we explored the rate of reaction at varied loadings of CO_2 (**Figure 2e**). At low concentrations of CO_2 (2.5 and 5 mol. equivalents), pseudo 1st order rate dependency was observed, with the yield at 12 h of reaction time being almost doubled when the amount of CO_2 was doubled. This supports our initial hypothesis that CO_2 is involved in the rate determining C–H activation step. Notably, as the amount of CO_2 was increased beyond 5 mol. equivalents, the reaction yield began to decrease. Although we considered this may due to activation of the amine by CO_2 and subsequent decomposition to the Pd-π-allyl, analysis of the reaction mixture did not show any obvious decomposition products from such a pathway, suggesting a more complex roll for CO_2 than only serving as a directing group.

In summary, we have demonstrated how carbon dioxide can be used to achieve *ortho*-arylation of benzylamine substrates under milder conditions than the free amine alone[41] or from using an aldehyde-based transient directing group approach.[31] This allows a broad substrate scope of primary benzylamines, while simultaneously allowing oxidatively-sensitive secondary benzylamines to participate in the reaction. By appending chelating groups β to the amine, we have even shown how unblocked benzylamine substrates can be selectively monoarylated due to a putative chelate effect. Further efforts are underway in our lab to better understand the role of CO_2 in these reactions, as well as to expand the list of functional groups that can be installed utilizing this approach to C–H activation.

ASSOCIATED CONTENT

Supporting Information. Details related to synthesis of starting materials, reaction optimization, and products, as well as characterization for all new compounds including ^{1}H and ^{13}C NMR as well as mass spectrometric data, can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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