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Authors: Matthew James Gaunt, William Whitehurst, John Henry Blackwell, and Gary Hermann

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Carboxylate-assisted oxidative addition to aminoalkyl-Pd(II) complexes enables catalyzed C(sp^3)–H arylation of alkylamines via distinct Pd(II)/Pd(IV) pathway

William G. Whitehurst, J. Henry Blackwell, Gary N. Hermann and Matthew J. Gaunt*

Dedication ((optional))

Abstract: We report the discovery of an approach to functionalize secondary alkylamines using 2-halobenzoic acids as aryl transfer reagents. These reagents promote an unusually mild carboxylate-assisted oxidative addition to alkylamine-derived palladacycles. In the presence of Ag(I) salts, a decarboxylative C(sp^3)–C(sp^2) bond reductive elimination leads to γ-aryl secondary alkylamines and renders the carboxylate motif a traceless directing group. Stoichiometric mechanistic studies were effectively translated to a Pd-catalyzed γ-C(sp^3)–H arylation process for secondary alkylamines.

The transformation of unactivated C(sp^3)–H bonds into C–aryl bonds using transition metal catalysts has been the focus of intense academic research over the past decade.[1] Within this field, Pd-catalyzed C(sp^3)–H arylation of alkylamines has stimulated significant interest as the products of such a transformation display structural features that are highly represented in pharmaceutical agents.[2,3] As a general premise, amine-directed C–H activation leads to the formation of a palladacycle intermediate, from which arylation can be promoted through a variety of pathways. Yu and co-workers have established that sulfonamide and thioamide derivatives of alkylamines undergo C–H arylation with arylboronic acids and esters.[4] Similarly aryl iodides have been commonly employed reagents for C(sp^3)–H arylation of auxiliary-derived amine derivatives, wherein the selective nature of the oxidative addition to electron-rich Pd(II)-centres in the corresponding palladacycles affords broad substrate scope and functional group compatibility.[5] An important aspect to the reactivity of aryl iodides is the necessary complexation of the iodide or π-system to the metal in advance of the carbon–iodine bond cleavage.[6] Consequently, the ligand environment in the key palladacyclic intermediate must allow for the displacement of a neutral ligand to promote the oxidative functionalization. In consideration of this requirement, a number of subtly distinct strategies have been developed for Pd-catalyzed C(sp^3)–H arylation in alkylamine derivatives and can be defined by the coordinating nature of the directing group. Firstly, Daugulis, Chen and Carretero[5a-c] have reported amide- and sulfonamide-linked pyridyl auxiliaries which enable C–H activation to palladacycles comprising a bidentate

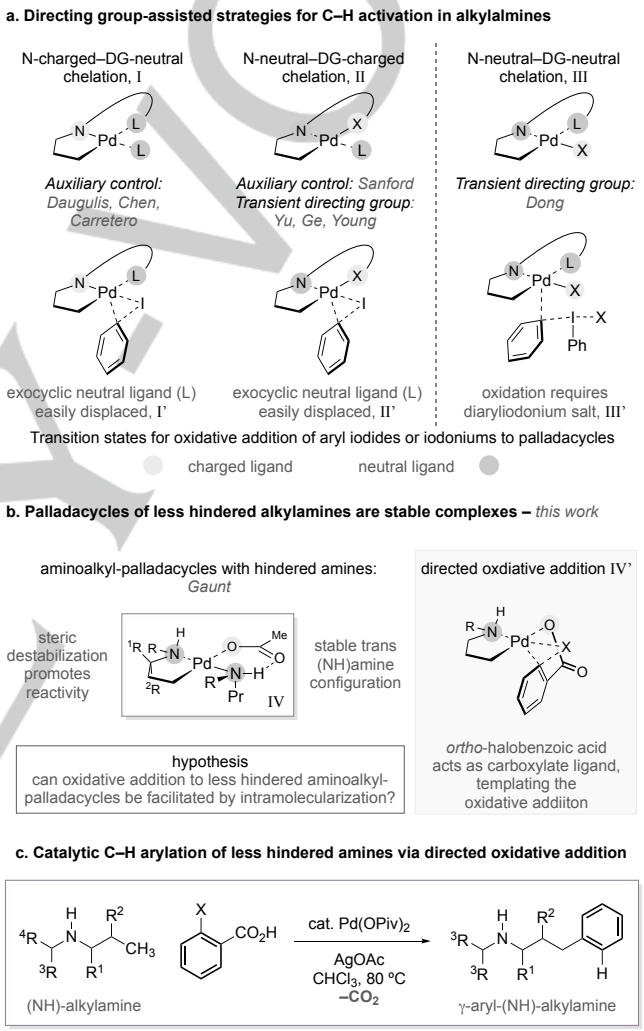

Figure 1. Towards a carboxylate-assisted C–H arylation of alkylamines.

directing motif with anionic and neutral coordinating groups. The remaining site exo to the palladacycle motif is occupied by a neutral ligand that can be displaced by an aryl iodide, leading to arylation (Figure 1a, I, I'). Secondly, Sanford[5g] equipped a hindered, neutral tertiary amine derivative with an additional anionic amide to promote the formation of a palladacycle (Figure 1a, II, II'). In a related class of C–H activation reactions, Yu, Ge and Young[5j-m] have reported a series of transient directing groups that lead to conceptually similar intermediates (vide supra). In these cases, a neutral amino-derivative forms a palladacycle in

[*] W. G. Whitehurst, J. H. Blackwell, G. N. Hermann, M. J. Gaunt
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
E-mail: mjg32@cam.ac.uk

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conjunction with a charged ligand, with the remaining site once again occupied by a displaceable neutral ligand. Finally, Dong[7] reported a variant of the transient directing group concept by employing an imine with a tethered neutral ligand, resulting in a palladacycle with an anionic ligand occupying the remaining site (Figure 1a, III, III'). In this distinct scenario, the use of reactive diaryliodonium salts is required to enable oxidation of the palladacycle, because there is no readily displaced neutral ligand available.[8]

Over the last five years, our laboratory has been engaged in a research program geared towards the use of free(NH) alkylamines in Pd(II)-catalyzed β and γ C(sp^3)–H activation reactions.[2] The success of these strategies has been dependent on either (a) the use of hindered alkylamine substrates, which destabilize rapidly formed bis-amine Pd(II) complexes and lead to a higher concentration of the mono-amine Pd(II) species empirically required for C–H activation;[9] or (b) the presence of reagents (such as CO) that strongly impact on the mechanism of the process.[10] While we have frequently observed stoichiometric C–H activation with a range of alkylamines, we recognized that the structure of a putative monocyclic aminoalkyl-palladacycle formed in a catalytic reaction with a secondary alkylamine would likely be reflected by a complex wherein a second molecule of alkylamine acts as a neutral ligand alongside a charged carboxylate ligand (Figure 1b, IV). The structural integrity of a complex of this nature would be reinforced by the favourable thermodynamic scenario of having opposingly dispersed (NH)amine ligands, which replicates the profoundly stable ligand arrangement that is observed for trans bis-amine Pd(II) complexes.[10a,11] This effect is particularly pertinent to a potential C–H arylation with aryl iodides, whose weak complexing ability may not be sufficient to displace a tightly ligated-(NH)amine. Analogous to the situation of Dong, the absence of a readily displaced neutral ligand precludes the straightforward reaction of the palladacycle with aryl iodides. However, strongly oxidizing iodine(III) reagents are typically incompatible with less hindered free(NH) alkylamines due to the presence of α-hydrogens in facilitating decomposition pathways.[9a,c] Therefore, a conceptually distinct approach from both our previous works and the approaches of others (vide supra) would be required to enable free(NH) amine-directed C(sp^3)–H arylation. To address the lack of reactivity of these aminoalkyl-palladacycles towards oxidative addition, we speculated that installing a carboxylate group at the ortho position to the carbon–iodine bond in the aryl iodide would displace an anionic group on the aminoalkyl-palladacycle and promote a proximity-driven oxidative addition that could lead to C(sp^3)–H arylation (Figure 1b, IV').

Here, we report the successful realization of these ideals, culminating in the development of a Pd(II)-catalyzed C(sp^3)–H arylation of less hindered alkylamines. Key to the success of this strategy is the deployment of an ortho-carboxylate-substituted aryl halide as coupling partner, which facilitates a templated oxidative addition to the stable aminoalkyl-palladacycle. Furthermore, the reaction proceeds via a distinct pathway involving a spontaneous decarboxylation and palladium migration step, which renders the overall process traceless with respect to the activating carboxylate motif.

At the outset of these studies, we focused on investigating the reactivity of a representative 5-membered mononuclear γ-

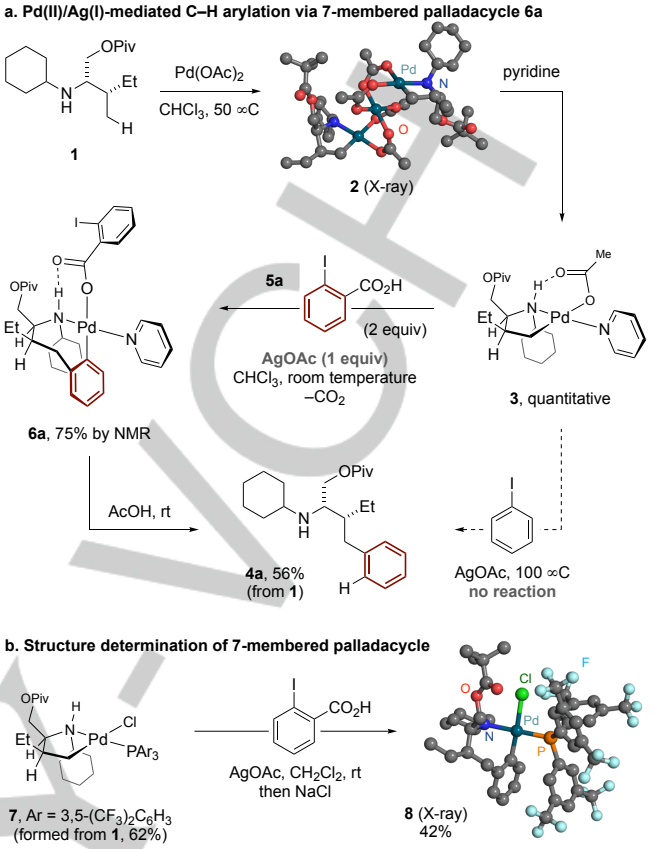

Figure 2. Stoichiometric studies from mononuclear palladacycles **3** and **7**.

aminoalkyl-palladacycle **3**, formed from the reaction of secondary alkylamine **1** and $Pd(OAc)_2$, followed by treatment of the initially formed polynuclear species **2** with pyridine (Figure 2a). This complex served as a characterizable model for the putative catalytic species that would have a second molecule of the alkylamine in place of the pyridine. Treatment of palladacycle **3** under conditions commonly used in C–H arylation reactions, namely phenyl iodide and AgOAc (as additive) at 100 ˚C in DCE, AcOH or as a neat reaction, gave no conversion to the corresponding γ-aryl alkylamine **4a**. As highlighted in Figure 1b, a possible reason for the lack of reactivity of **3** is the stability imparted by the trans orientation of nitrogen ligands on Pd(II), meaning the iodoarene cannot displace the ligated pyridine. To disrupt this apparently stable complex, we tested the reactivity of an aryl iodide containing an ortho carboxylic acid, which we reasoned would displace the acetate ligand and locate the aryl iodide in proximity to the Pd(II) center (Figure 1b, IV'), facilitating the oxidative addition to give the putative γ-aminoalkyl Pd(IV) complex required for C–C bond reductive elimination. When palladacycle **3** was treated with 2 equivalents of 2-iodobenzoic acid **5a** in the presence of one equivalent of AgOAc at room temperature, we observed complete conversion to a 7-membered palladacycle (**6a**, 75% yield by NMR).[12] Formally, the overall transformation from **3** to **6a** corresponds to a 1,2-insertion of an aryl group into the Pd–C bond of the 5-membered palladacycle, wherein C(sp^3)–C(sp^2) bond formation and an unusually facile

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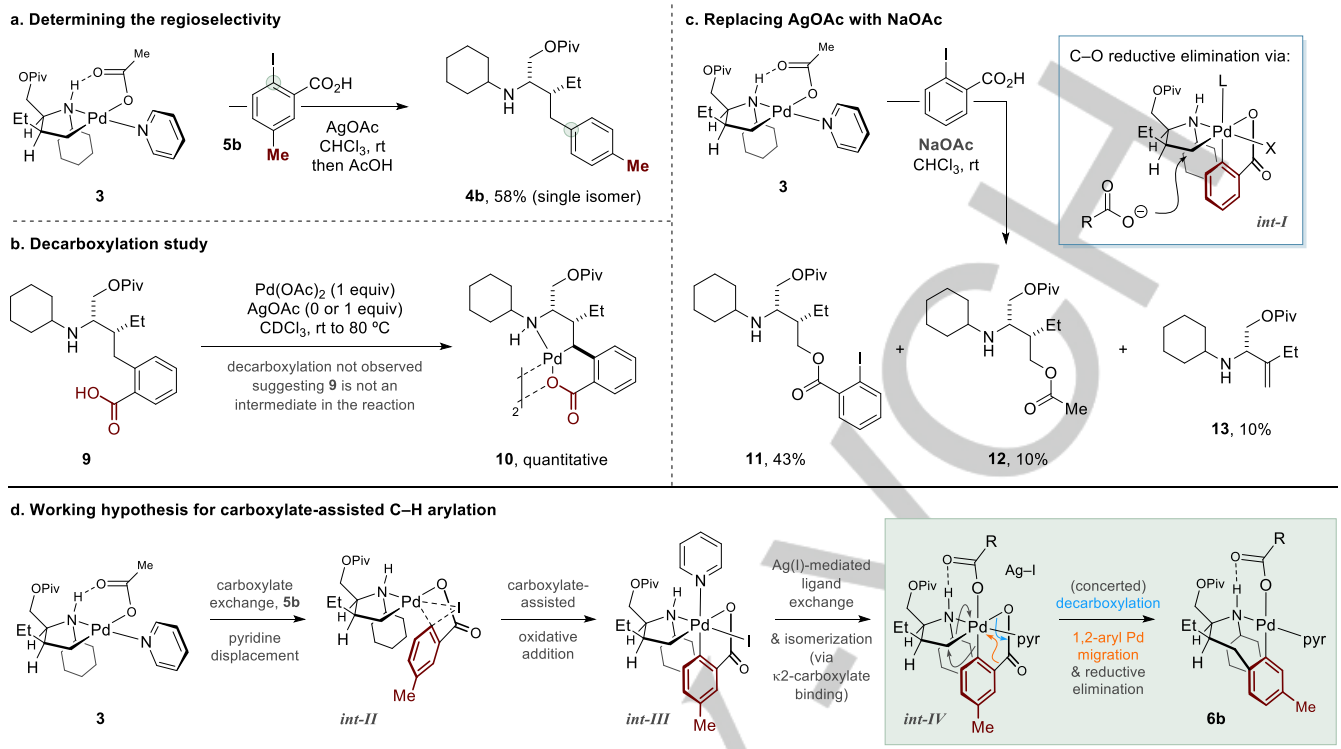

Figure 3. Control experiments and proposed mechanism for carboxylate-assisted C–H arylation.

decarboxylation event have taken place. Palladacycle **6a** was isolable and could be characterized by ^{1}H and ^{13}C NMR spectroscopy; although **6a** was not a crystalline compound, the structure of a related phosphine-ligated 7-membered palladacycle **8** could be confirmed through X-ray diffraction of a single crystal (Figure 2b). Consequently, treatment of palladacycle **6a** with AcOH gave γ-aryl alkylamine **4a** (56% yield from **1**), completing the overall C–H arylation process.

Intrigued by the formation of the 7-memebred palladacycle, we conducted a series of control experiments to shed light on the mechanistic steps underpinning the decarboxylative arylation process. Firstly, subjecting **3** to 2-bromobenzoic acid instead of 2-iodobenzoic acid simply resulted in a ligand exchange of acetate for 2-bromobenzoate at room temperature, with the 5-membered (NH)amine palladacycle remaining intact.[13] Stirring the reaction at 80 °C restored reactivity analogous to that of the aryl iodide, which is consistent with a Pd(II)–Pd(IV) mechanism based on the diminished reactivity of the aryl bromide relative to the iodide.[14] Secondly, using 5-methyl-2-iodobenzoic acid **5b** as coupling partner, the arylated product was formed as a single regioisomer (**4b**) in which the newly formed C–C bond is derived from the C–I bond in the reagent (Figure 3a). The exclusive regioselectivity observed cannot be accounted for by a mechanism invoking aryne intermediates, as this would generate regioisomeric product mixtures.[15] Further evidence opposing aryne formation was provided by trapping experiments employing arynophile additives in the stoichiometric arylation procedure, which did not lead to the formation of cycloaddition by-products.[16] Thirdly, we investigated the point at which decarboxylation occurs along the reaction pathway. Intuitively, one might assume that C–C bond reductive elimination from a putative Pd(IV) species would initially install an aryl-2-carboxylic acid group at the γ position, giving an amino acid intermediate that may then undergo a known Pd(II)- or Ag(I)-mediated decarboxylation process to form the γ-arylated amine.[17] To test this hypothesis, amino acid **9** was synthesized and subjected to stoichiometric quantities of $Pd(OAc)_2$ and AgOAc (Figure 3b). Although minimal conversion occurred at room temperature, stirring the reaction at 80 °C led to the formation of a new palladacyclic species (**10**) resulting from a methylene C–H activation. Crucially, given that the product of decarboxylation (**4a**) was not observed, the hypothesis invoking amino acid **9** as an intermediate was not supported. Rather, it became apparent that decarboxylation must occur prior to C–C bond reductive elimination and therefore from a high valent Pd(IV) species, which could explain the facile nature of this process compared to reported decarboxylation procedures that typically require high temperatures (>100 °C).[17] Lastly, replacing AgOAc with NaOAc led to a significant change in the distribution of products (Figure 3c); C–O coupled products **11** (43%) and **12** (10%) as well as elimination product **13** (10%) were obtained. According to literature precedence, C–O reductive elimination is expected to proceed via external attack of an *O*-centred nucleophile at the Pd(IV)-bound carbon (**int-I**),[18] thus accounting for the presence of the ortho-iodide moiety in major product **11**. Notably, arylated product **4a** was not observed in the reaction with NaOAc, and therefore in the current system Ag(I) was found to be an essential additive for C–C bond reductive elimination.

Based on these preliminary mechanistic studies, we propose a pathway that first involves carboxylate-directed oxidative addition (via **int-II**) to form the bis-palladacyclic γ-

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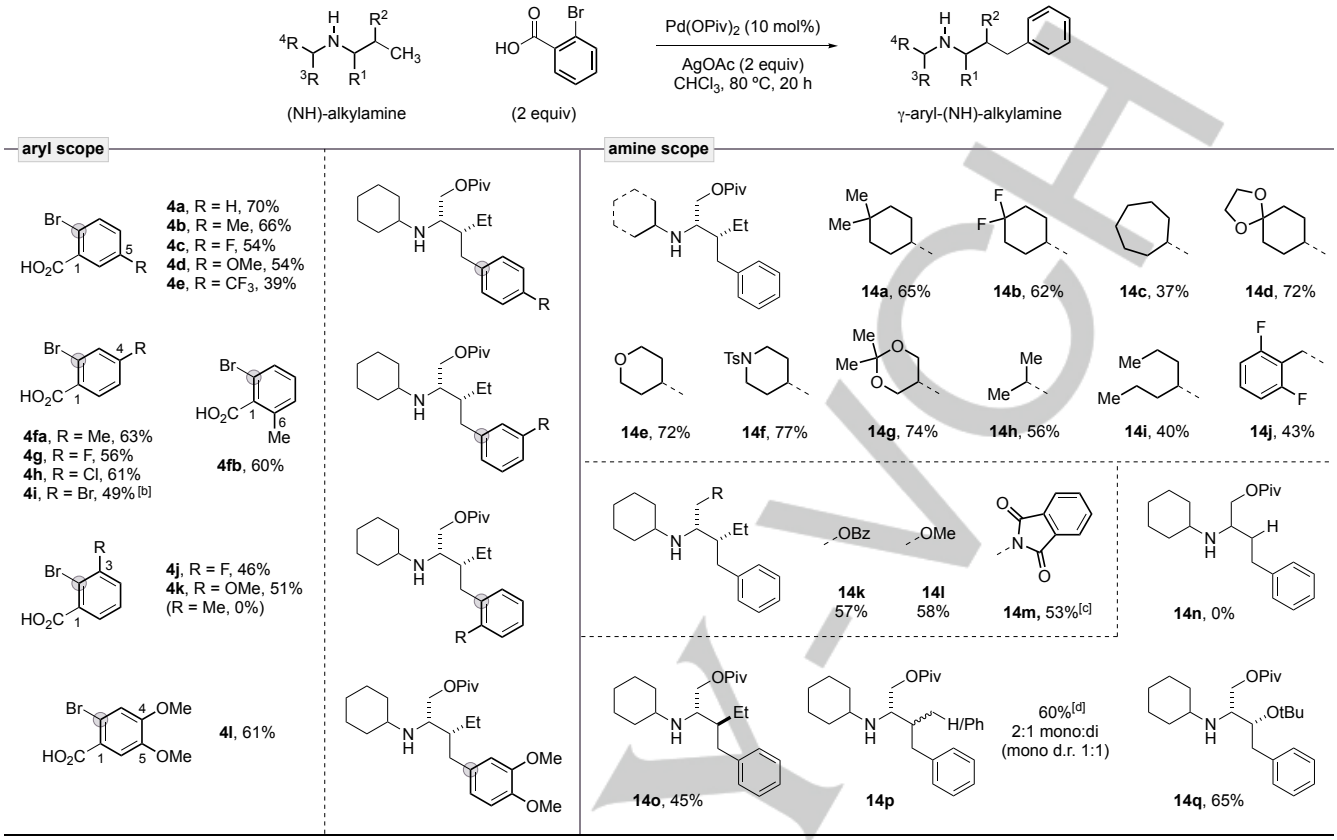
Table 1. Scope of the Pd-catalyzed C(sp^3)–H arylation of alkylamines.[a]



[a] Reactions carried out on 0.1 mmol scale. [b] 2.5 equiv Ar–Br and 2.5 equiv AgOAc were used. [c] Reaction temperature was 70 ˚C. [d] Yield and d.r. determined by ^{1}H NMR analysis of the crude reaction mixture.

aminoalkyl-Pd(IV) species **int-III** (Figure 3d). Presumably, Ag(I)-mediated iodide-to-carboxylate ligand exchange generates the corresponding Pd(IV)-carboxylate complex, which through pyridine-displacing κ2-carboxylate binding, can trigger a series of geometric isomerizations to form hydrogen bond-stabilized Pd(IV) intermediate **int-IV**. C(sp^3)–C(sp^2) bond reductive elimination from **int-IV** does not occur, most likely due to the geometric constraints of the bis-palladacycle. However, based on the observed regioselectivity and the absence of aryne intermediates, we believe a decarboxylation triggers a concerted 1,2-arylpalladium migration and reductive elimination, forging (i) the C(sp^3)–C(sp^2) bond between the alkylamine and aryl group and (ii) the ortho C(sp^2)–Pd bond, giving the 7-memebered palladacycle (**6b**). To the best of our knowledge, 1,2-arylpalladium migrations have been rarely observed outside the context of norbornene-assisted Catellani processes,[19] despite the analogy with commonly encountered 1,2-palladium migrations on indole or of alkenyl-Pd(II) species.[20]

Next, we tested the decarboxylative C–H arylation under catalytic conditions. Gratifyingly, using 10 mol% $Pd(OAc)_2$ in the presence of amine **1**, 2-iodobenzoic acid **5a** and AgOAc in $CHCl_3$ at 80 °C gave arylated product **4a** in 51% yield by NMR. C–O coupling was observed as a minor side reaction (**11**, 8%). Significantly, the use of 2-bromobenzoic acid gave an increased yield of **4a**, whereas 2-chloro- and 2-(OTf)benzoic acid resulted in zero product formation.[21] Optimal conditions required the treatment of amine **1** with 10 mol% $Pd(OPiv)_2$, 2 equivalents of 2-bromobenzoic acid and 2 equivalents of AgOAc in $CHCl_3$ at 80 ˚C for 20 h, affording **4a** in 74% yield by NMR (70% isolated yield, Table 1).

With the optimal conditions for C–H arylation identified, the scope of aryl reagents was investigated (Table 1). Electron-donating and -withdrawing substituents at the 4- and 5-positions of the 2-bromobenzoic acid were well tolerated, affording meta- and para-substituted arylated products in moderate to good yields (**4b–i**). Interestingly, 2-bromo-6-methylbenzoic acid was an effective reagent, demonstrating that increased steric bulk ortho to the carboxylic acid is tolerated. The meta-methyl product was formed in similar yield (60%, **4fb**) to the reaction using 2-bromo-4-methylbenzoic acid (63%, **4fa**), which gives the same product after decarboxylation. Conversely, the reaction was sensitive to steric effects at the position ortho to the C–Br bond. While ortho-fluoride and -methoxy derivatives could be obtained in moderate yields (**4j**, **4k**), 2-bromo-3-methylbenzoic acid gave no reactivity. Finally, 2-bromo-4,5-dimethoxybenzoic acid gave access to more highly substituted derivative **4l**.

The scope of amine substrates was also investigated (Table 1). A range of functional groups was tolerated in the non-activating substituent of the substrates (**14a–j**), including alkyl, fluoroalkyl, ketal, ether and sulfonamide groups. Cyclic as well as

acyclic sidechains could be incorporated. Generally, *n*-alkyl substituents were not tolerated, though an *N*-benzyl derivative gave a moderate yield of the arylated product (**14j**, 43%). Various substituents could be tolerated along the activating chain, including benzoate, methyl ether and phthalimide groups (**14k**–**m**). A substrate without β-branching gave no conversion to the corresponding arylated product (**14n**), whereas a substrate derived from the non-natural diastereomer of isoleucine gave an average yield in the reaction (**14o**, 45%). A valinol derivative was also suitable and gave **14p** as a mixture of diastereomers and mono-/di-arylated products (60% by NMR, 2:1 mono:di, mono d.r. = 1:1). Finally, we were pleased to find that a derivative of threoninol gave the γ-aryl amino alcohol product in good yield (**14q**, 65%).

In summary, we have described a new method for C(sp^3)–H arylation of free(NH) secondary amines mediated by Pd(II)/Ag(I) using 2-halobenzoic acid reagents. Stoichiometric studies from the Pd(II) metallacycle demonstrated a remarkably mild, room temperature decarboxylative arylation is possible when using 2-iodobenzoic acid in the presence of AgOAc. Mechanistic studies suggest that the decarboxylation occurs from a high valent Pd(IV) centre and that a 1,2-arylpalladium migration ultimately leads to the required reductive elimination event. The conditions were found to effectively translate to a catalytic system, providing access to a variety of γ-arylated amine derivatives.

Acknowledgements

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Keywords: C–H activation • palladium • palladacycle • alkylamine • decarboxylation

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[13] See the Supplementary Information for details of the control experiment of **3** with 2-bromobenzoic acid.

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[21] See the Supplementary Information for full details of the optimization of the Pd-catalyzed C(sp^3)–H arylation reaction.

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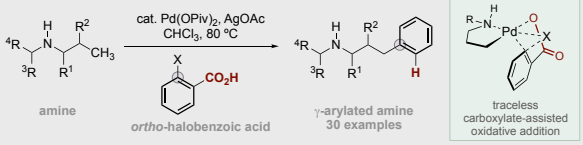

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