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Expanding the limit of Pd-catalyzed decarboxylative benzylations†

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The Pd-catalyzed decarboxylative cross-coupling of electron-deficient aryl acetates with aryl bromides is reported. The method widens the scope of benzylic partners that can undergo efficient reactivity from highly activated nitrophenylacetates established previously, to a diverse series of substrates bearing modestly stabilizing groups, allowing direct access to functionalized diarylmethanes. Mechanistic studies support the role of dienolates as key intermediates in the coupling process.

The abundance and stability of carboxylic acids make decarboxylative cross-coupling reactions valuable complements to traditional coupling manifolds.[1] The inherent kinetic stability of most carboxylates requires that activation strategies be considered when using these substrates in metal-catalyzed C–C bond forming processes.[1e,2] The extrusion of CO_2 from acids to generate reactive intermediates can be induced by single electron oxidation.[3] The use of single-electron oxidants, photoredox methods, or chemical activation of acids with groups that induce homolysis have each been demonstrated to enable efficient cross-coupling type reactions of carboxylates.[4,5]

The decarboxylative generation of reactive intermediates in cross-coupling catalysts can, in select cases, be induced by the input of thermal energy. While attractive from the standpoint of simplicity and economy, the scope of carboxylic acids that can engage in such processes at reasonable temperatures (<180 °C) remains limited.[1d,e,2,6] The thermal activation of aryl acetates has been established by Liu[7] and Zhu,[8] who developed Pd-catalyzed decarboxylative benzylation reactions of aryl and vinyl electrophiles. While these methods allow for the formation of sp^2–sp^3 C–C bonds from carboxylic acids without chemical activation or oxidation, reactivity is limited to highly stabilized nitrophenylacetate substrates, restricting broader applications in synthesis.[9,10] We recently reported that under Cu-catalyzed conditions, nitrophenylacetates undergo decarboxylation and subsequent oxidative trapping with Cu-aryl species;[11] however, less activated aryl acetates were again not suitable reaction partners. Thus, a more general, metal-catalyzed decarboxylative benzylation process would be of considerable value for generating functionalized diarylmethane derivatives.[12] Herein, we report that a diversity of modestly electron-deficient aryl acetates can undergo Pd-catalyzed decarboxylative benzylation reactions with aryl bromides under appropriate conditions. Sulfonyl, sulfonamide, nitrile, ester, amide, ketone, and trifluoromethyl groups are suitable activating moieties to enable cross-coupling reactivity of aryl acetates with a diverse range of (hetero)aryl bromides. Mechanistic studies support a mechanism in which a strong base is generated by an initial decarboxylation event enabling the formation of dienolate nucleophiles that undergo arylation and subsequent decarboxylation (Fig. 1).

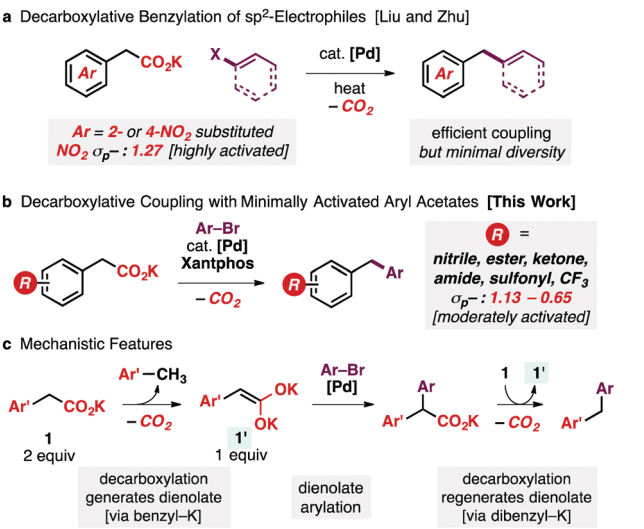

Fig. 1 Overview of Pd-catalyzed decarboxylative cross-coupling of aryl acetates and sp^2-electrophiles. *para*-π-electron accepting capacity of R-group indicated by σ_{p-} values.

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With the hypothesis that, in polar solvents and in the presence of suitable Pd-catalysts, decarboxylative arylation of moderately activated aryl acetates could occur, a variety of experimental parameters were examined (Fig. 2a). We selected the 4-carboxyaryl acetate **1a** for our optimization campaign due to its moderate anion stabilizing ability (NO_2 σ_{p^-} = 1.27, CO_2Et σ_{p^-} = 0.75).[13] Ultimately, it was found that in DMF at 110 °C, [Pd(cinnamyl)Cl]$_2$/Xantphos mixtures catalyzed the cross-coupling with 4-(trifluoromethyl)bromobenzene to give 87% yield of the diarylmethane product. The use of less polar solvents or lower reaction temperatures provided minimal product. If the free acid was used in combination with KO*t*-Bu instead of the K-carboxylate, significant protodecarboxylation was observed with 34% product formation. Ni-based catalysts were ineffective, while an aryl chloride substrate gave moderate yield (66%). Use of Xantphos-type ligands was essential, other chelating bisphosphines (BINAP, DPPF) or monophosphines provided very low yields (see the ESI† for additional optimization data). Within the Xantphos family, a series of derivatives performed similarity in the test reaction, including diethylamino(DEA)-Xantphos, *N*-Xantphos, and a 3,5-bis-CF_3-ligand variant, more significant ligand effects were observed with other substrates (see the ESI† for kinetic plots and data on ligand aryl group exchange).

Having established that a weakly activated ester-substituted aryl acetate undergoes efficient Pd-catalyzed arylation, the scope of the benzylic partner was explored (Fig. 2b). Functional groups at the 4-position that provide increased stabilization of an anionic intermediate compared to an ester group, such as SO_2Me (σ_{p^-} = 1.13), CN (σ_{p^-} = 1.00), or acetyl (σ_{p^-} = 0.84) could be arylated in good yields between 90 and 110 °C (**2b–2d**, 79–72% yield). Less stabilizing amide (**2e**) and trifluoromethyl (**2f**) groups (σ_{p^-} = 0.70 and 0.65 respectively) still provided synthetically useful yields (60–66%) at increased temperatures (125–135 °C). In these cases, the DEA-Xantphos ligand variant dramatically outperformed Xantphos.

Arylacetates with electron-withdrawing groups at the 2- or 3-position also undergo productive decarboxylative coupling, including 3,5-bis-CF_3, 3-NO_2, 2-CN and 2-CF_3 functionalized substrates (**2g–2j**). Aryl acetates containing sulfonamides (**2k**) as well as nitrophenylacetates substituted with electron-donating groups (**2l**) can also be employed in the reaction with good yields. Given that previous examples of Pd-catalyzed decarboxylative functionalizations of aryl acetates are limited to nitroaryl[7] or pyridine carboxylates,[14] these results demonstrate the potential for broad classes of aryl acetates to be useful coupling partners under suitable conditions.

A variety of functionalized aryl bromides could undergo decarboxylative benzylation using the optimized conditions (Fig. 3). With cyano, ester, or sulfonyl substituted aryl acetate partners, both electron-rich and electron-poor aryl bromides were coupled in moderate to excellent yields, including those with halogen, cyano, ester, methoxy, and boronic ester groups. Pyridine (**3j**) and pyrimidine (**3h**, **3i**) heterocycles could be benzylated in good yields, including complex examples (**3m**). The less activated 4-(trifluoromethyl)phenylacetate could be arylated with electron-poor aryl bromides, including heterocyclic examples,

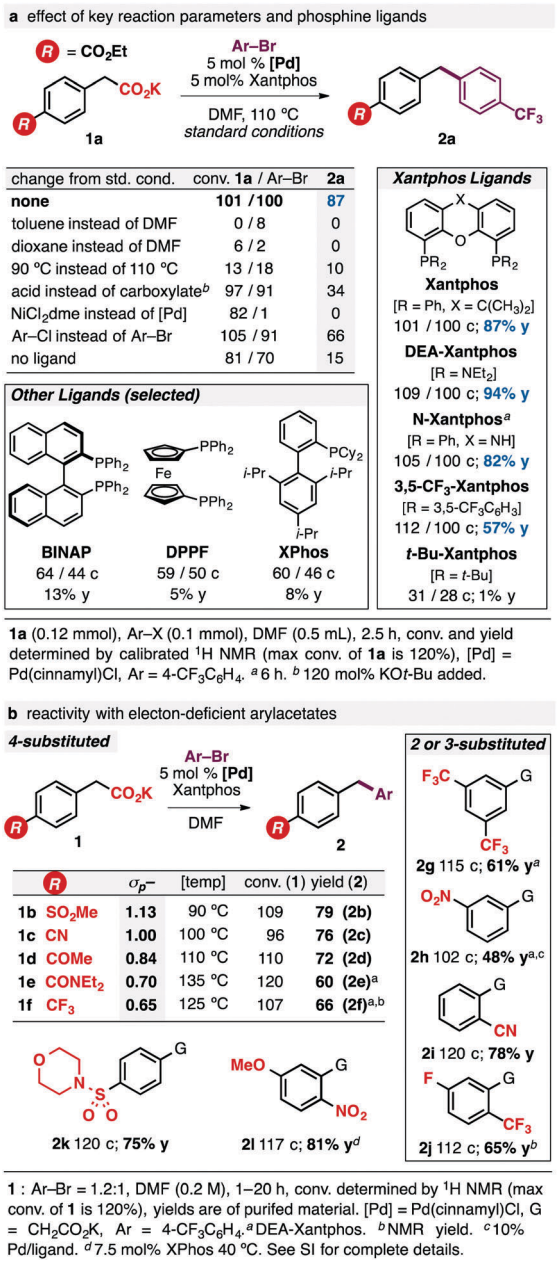
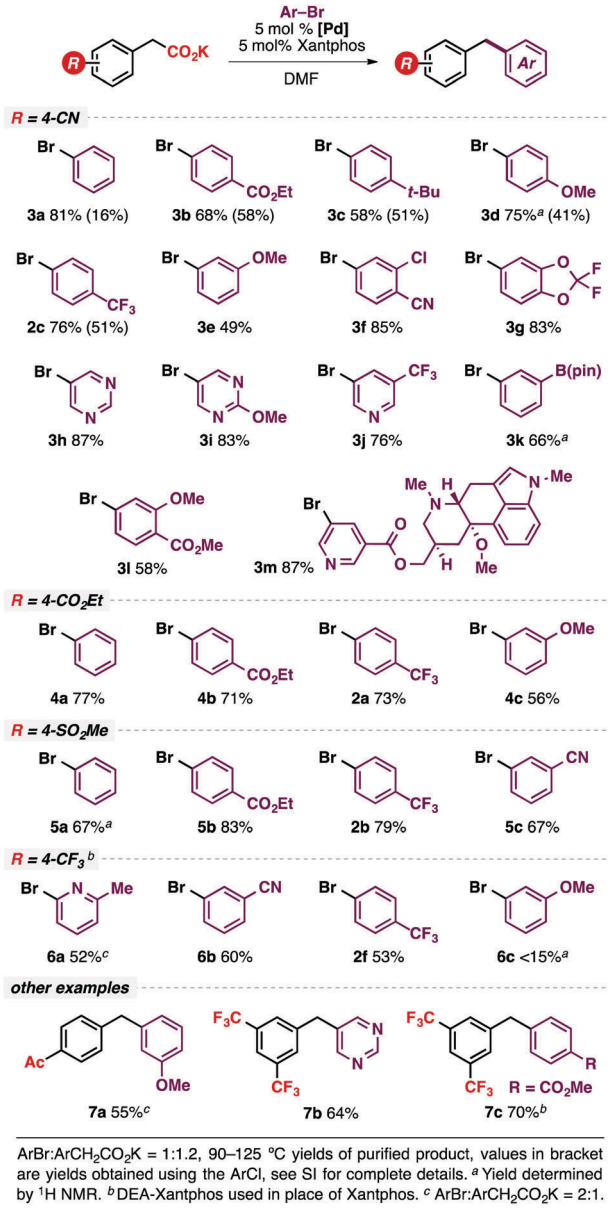


Fig. 2 (a) Key reaction parameters in the development of th Pd-catalyzed decarboxylative benzylation of aryl bromides; (b) scope of electron-deficient arylacetates.

however electron-rich aryl bromides represented a limit to reactivity in this case (**6c**).

The use of carboxylic acids as (pro)nucleophiles in metal-catalyzed cross-coupling reactions leads to the question of which species is the active nucleophile in the bond-forming process and at which stage decarboxylation occurs. For the process developed above, two general mechanistic pathways exist (Fig. 4). One involves the generation of a benzylic nucleophile *via* decarboxylation of aryl acetate (path A). Palladium may be involved in this step, but ultimately a Pd(aryl)(benzyl) species is formed which can undergo product-forming reductive elimination. An alternative mechanism involves the generation



ArBr:ArCH$_2$CO$_2$K = 1:1.2, 90–125 °C yields of purified product, values in bracket are yields obtained using the ArCl, see SI for complete details. [a] Yield determined by ^{1}H NMR. [b] DEA-Xantphos used in place of Xantphos. [c] ArBr:ArCH$_2$CO$_2$K = 2:1.

Fig. 3 Scope of the Pd-catalyzed decarboxylative cross-coupling of aryl acetates with aryl bromides and chlorides.

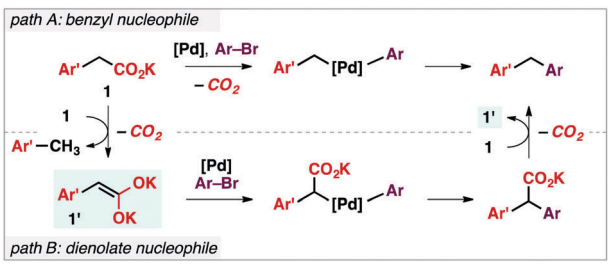


Fig. 4 Potential mechanistic pathways for the Pd-catalyzed decarboxylative benzylation of aryl halides.

of a dienolate species (path B). Here, aryl acetate decarboxylation generates a basic benzyl potassium which can deprotonate another aryl acetate partner. After Pd-catalyzed arylation, the corresponding diaryl carboxylate could undergo decarboxylation and abstract a proton from another equivalent of aryl acetate. As both Pd-catalyzed cross-coupling of benzylic nucleophiles[15] and dienolates[16] have been reported, we investigated the process to gain insight into the fundamental steps involved in the decarboxylative benzylation reaction.

Subjecting aryl acetate to standard reaction conditions without catalyst or aryl bromide leads to substrate decarboxylation. The decarboxylation stops at ~50% toluene (**Tol**) formation, suggesting against the accumulation of benzyl anion and instead the generation of a dienolate (**1′**) in solution which would be resistant to spontaneous extrusion of CO_2 (Fig. 5a). The initial rate of decarboxylation is similar to that of product formation under standard conditions, a small amount of non-productive aryl acetate decarboxylation is observed under catalytic conditions (Fig. 5b). A crossover experiment in which a 1 : 1 ratio of aryl acetate and D_2-aryl acetate lead to rapid H/D exchange at the methylene position (Fig. 5c). This observation was mirrored in catalytic reactions, where the diarylmethane product was generated with approximately the statistic mixture of H_2/HD/D_2 labelled products. The formation of crossover products makes the direct arylation of a benzyl nucleophile unlikely. Finally, for aryl acetate that has been allowed to decarboxylate in the absence of catalyst and aryl bromide (reaching ~50% toluene formation), D_2O quenching does not form D-labelled toluene derivative, but instead generates methylene D-labelled aryl acetic acid. Under the same conditions, introduction of catalyst and aryl bromide leads to diarylmethane product formation without

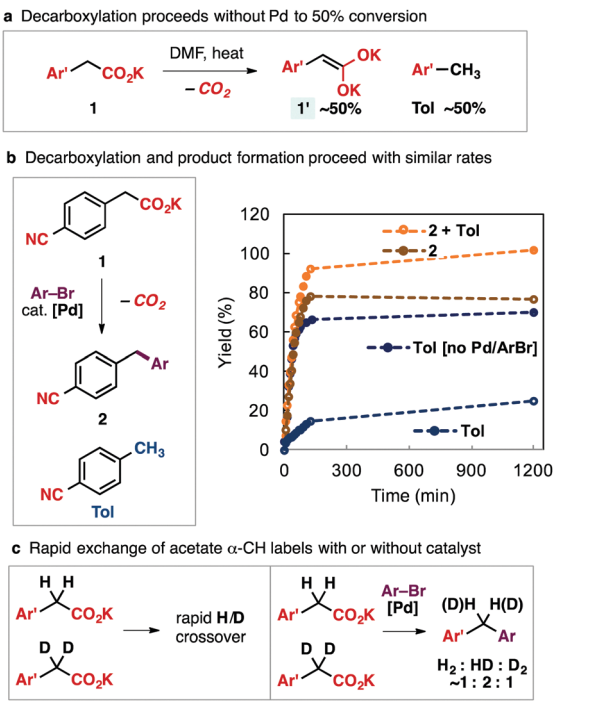


Fig. 5 Mechanistic experiments suggest aryl acetate decarboxylation generates a dienolate nucleophile which undergoes arylation in the presence of Pd of aryl electrophile.

change in the amount of toluene derivative. Collectively these experiments support a pathway in which an initial decarboxylation event generates a base which can lead to the formation of a dienolate nucleophile.

In summary, the scope of Pd-catalyzed decarboxylative benzylations of aryl electrophiles has been enhanced significantly to include a wide range of aryl acetate partners. Given that decarboxylation occurs from otherwise stable precursors by mild heating, this simple protocol should be of value for preparing functionalized diarylmethanes. Mechanistic experiments point towards the formation of a dienolate species being the active nucleophile, which should guide the development of related decarboxylative cross-couplings using poorly-activated acids.

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Conflicts of interest

There are no conflicts to declare.

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