

Palladium-Catalyzed Decarboxylative Coupling of Potassium Nitrophenyl Acetates with Aryl Halides

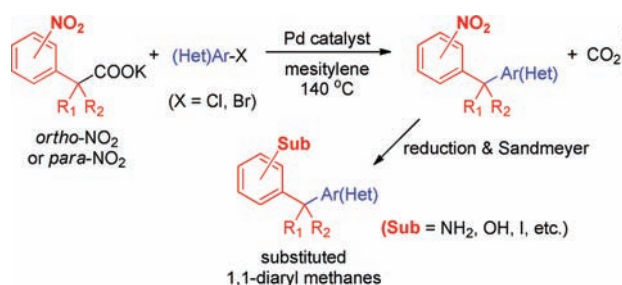
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ABSTRACT



A palladium-catalyzed decarboxylative cross-coupling of potassium 2- and 4-nitrophenyl acetates with aryl chlorides and bromides has been developed. Because the nitro group can be readily converted to many other functional groups, the new reaction provides a useful method for the preparation of diverse 1,1-diaryl methanes and their derivatives.

Transition-metal-catalyzed decarboxylative cross-coupling has emerged recently as a useful method for C–C bond formation.¹ By using carboxylic acids as alternative reagents over organometal compounds, this type of

transformation avoids highly basic reaction conditions and produces nontoxic CO₂ instead of stoichiometric metal waste. Pioneering studies by Myers,² Forgione,³ and Goossen⁴ focused on the intermolecular decarboxylative coupling reactions of aromatic, alkenyl, and alkynyl acids,⁵ whereas Tunge,⁶ Trost,⁷ Stoltz,⁸ and others⁹ studied

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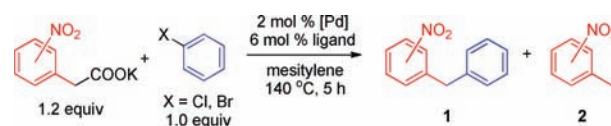
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intramolecular decarboxylative allylation and benzylation reactions. Despite these achievements, relatively less has been examined on the intermolecular decarboxylative coupling of aliphatic carboxylic acids.¹⁰

In our previous studies we described Pd-catalyzed decarboxylative couplings of the alkali salts of 2-(2-azaaryl)-acetates¹¹ and cyanoacetates¹² with aryl halides. These reactions not only provide conceptually alternative methods for the preparation of functionalized azaarenes and α -aryl nitriles but also are practically favored in terms of both reagent accessibility and reaction scope. Here we report a new example of this family of reactions, namely, the decarboxylative cross-coupling of potassium 2- and 4-nitrophenyl acetates. Due to the versatile conversion of the nitro group to many other functional groups,¹³ the new reaction provides a useful method for the preparation of diverse 1,1-diaryl methanes and their derivatives.^{14,15} Note that Waetzig and Tunge previously described the Pd-catalyzed decarboxylative allylation of nitrophenyl acetates.^{6c}

Our work started with the decarboxylative coupling of potassium 2-nitrophenyl acetate with chlorobenzene (Table 1). When [PdCl(allyl)]₂ and P(Ad)₂ⁿBu were used as the catalyst and ligand, the desired transformation took place readily to give a good yield (83%) of the coupling product **1** (entry 1), whereas decarboxylative protonation

Table 1. Pd-Catalyzed Decarboxylative Coupling of Potassium Nitrophenyl Acetates with Phenyl Halides^a



entry	X	position	[Pd]	ligand	GC yield (%)	
					1	2
1	Cl	2-NO ₂	[PdCl(allyl)] ₂	P(Ad) ₂ ⁿ Bu	83	18
2	Cl	2-NO ₂	[PdCl(allyl)] ₂	P(^t Bu) ₃	<5	61
3	Cl	2-NO ₂	[PdCl(allyl)] ₂	<i>t</i> -BuX-Phos	<5	74
4	Cl	2-NO ₂	[PdCl(allyl)] ₂	S-Phos	85	16
5	Cl	2-NO ₂	[PdCl(allyl)] ₂	Dave-Phos	83	17
6	Cl	2-NO ₂	[PdCl(allyl)] ₂	DCyPF	51	43
7	Cl	2-NO ₂	[PdCl(allyl)] ₂	Brett-Phos	56	36
8	Cl	2-NO₂	[PdCl(allyl)]₂	X-Phos	91	16
9	Cl	2-NO ₂	Pd ₂ (dba) ₃	X-Phos	87	21
10 ^b	Cl	2-NO ₂	Pd(OAc) ₂	X-Phos	7	73
11	Cl	4-NO ₂	[PdCl(allyl)] ₂	X-Phos	89	16
12	Cl	3-NO ₂	[PdCl(allyl)] ₂	X-Phos	n.r.	<5
13	Br	2-NO ₂	[PdCl(allyl)] ₂	X-Phos	85	18
14	Br	4-NO ₂	[PdCl(allyl)] ₂	X-Phos	87	19

^a All the reactions were carried out at a 0.25 mmol scale in 0.5 mL of mesitylene. GC yields are measured as an average of two runs, using benzophenone as internal standard. ^b 4% mol [Pd].

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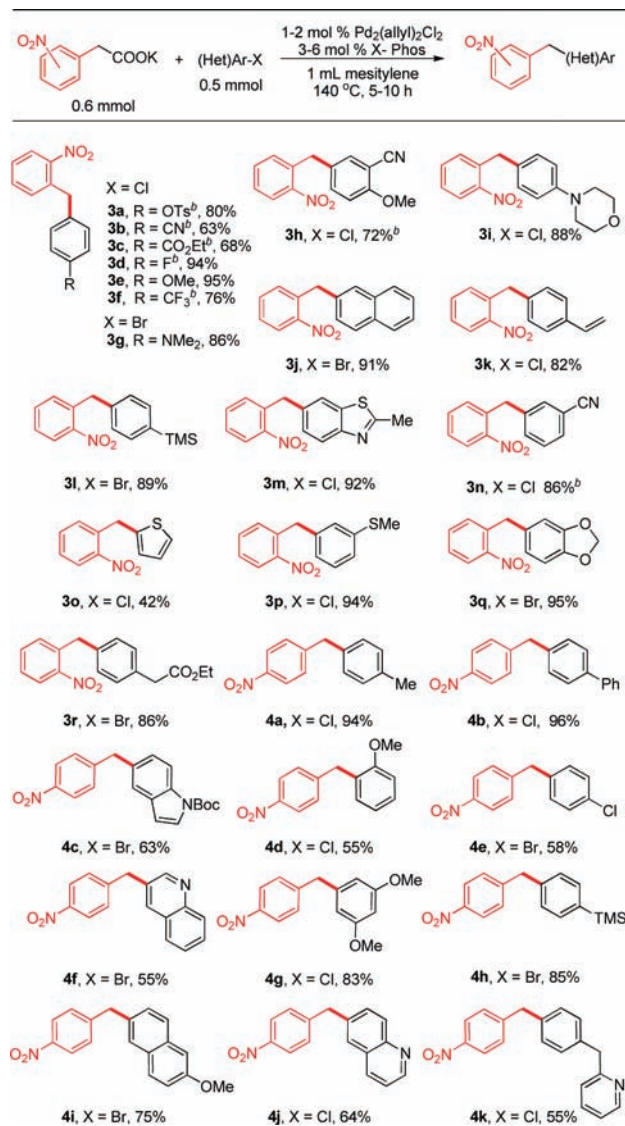
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also occurred to produce byproduct **2**. To improve the yield of decarboxylative coupling we tested a number of different phosphine ligands. It is interesting to find that P(^tBu)₃ and *t*-BuX-Phos completely inhibited the coupling process (entries 2–3), while S-Phos, Dave-Phos, DCyPF, and Brett-Phos promoted the coupling to various extents (entries 4–7). The optimal ligand turned out to be X-Phos, and the corresponding yield was 91% (entry 8). Note that X-Phos can also be used with Pd₂(dba)₃ as the catalyst in the decarboxylative coupling reaction (entry 9), but when Pd(OAc)₂ was used the major reaction turned again to decarboxylative protonation (entry 10). Extension of the optimized reaction conditions to potassium 4-nitrophenyl acetate was successful, and the yield was 89% (entry 11). However, potassium 3-nitrophenyl acetate was completely unreactive in the present transformation (entry 12). Furthermore, bromobenzene can be used in the decarboxylative coupling with the potassium salts of both 2- and 4-nitrophenyl acetates (entries 13–14). Note that radical trap experiments were performed and the results indicated no involvement of radical intermediates (Supporting Information).

To explore the substrate scope, we examined a variety of aryl halides in the decarboxylative coupling (Table 2). Both electron-rich and -poor aryl chlorides as well as bromides can be successfully converted across a wide range of functional groups including ether (**3e**, **4g**, **4i**), ester (**3c**, **3r**), tosyl (**3a**), fluoro (**3d**), trifluoromethyl (**3f**), thioether (**3p**), silyl

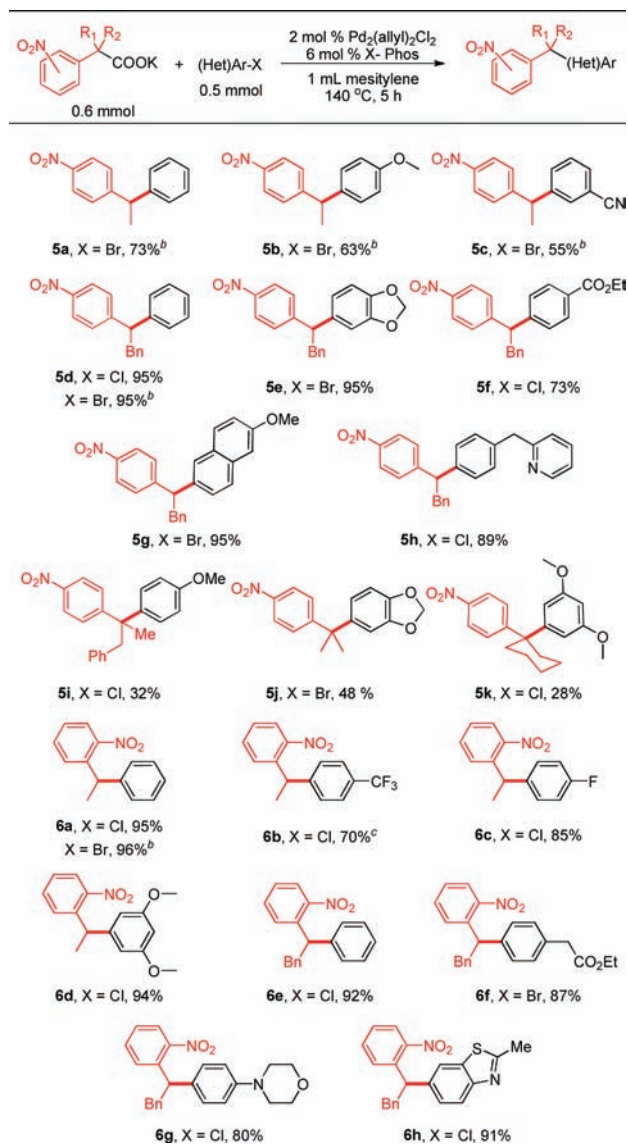
Table 2. Aryl Halide Scope^a

^a All the reactions were carried out at a 0.50 mmol scale in 1.0 mL of mesitylene. The yield (average of two runs) of the isolated product was calculated based on the quantity of the aryl halide. More details can be found in the Supporting Information. ^b S-Phos was used as a ligand.

(**3l**, **4h**), nitrile (**3b**, **3h**, **3n**), olefin (**3k**), acetal (**3q**), and amine (**3g**, **3i**). The isolated yields range from modest to excellent (55–96%). Note that, for some electron-poor aryl halides, S-Phos has to be used to replace X-Phos to improve the reaction yields. Substitution at the *ortho*-position (**4d**) can be tolerated. Halogenated heterocycles such as benzothiazole (**3m**), thiophene (**3o**), indole (**4c**), pyridine (**4k**), and quinoline (**4f**, **4j**) are also good substrates. Finally, the aryl-Br bond can be selectively cross-coupled in the presence of the aryl-Cl bond (**4e**).

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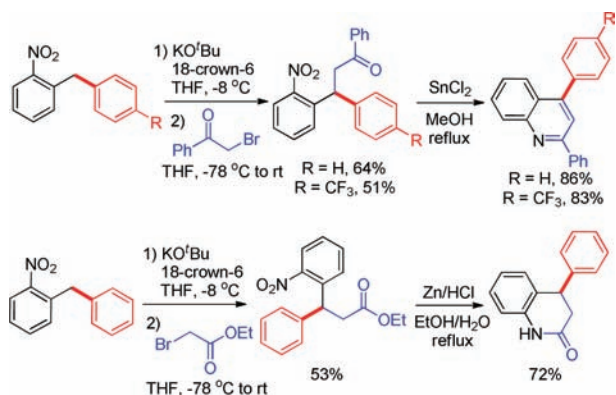
In the above reactions the carboxylate reagents are easily generated from commercially available 2- and 4-nitrophenyl acetic acids. According to the previous studies,¹⁶ the potassium salts of α -alkylated 2- and 4-nitrophenyl acetates can also be readily prepared through the simple alkylation reactions of 2- and 4-nitrophenyl acetate esters (Supporting Information). Gratifyingly, we found that these substituted potassium carboxylates can also react with various aryl halides through decarboxylative cross-coupling (Table 3). These reactions again tolerate diverse functional groups including ether, ester, fluoro, trifluoromethyl, nitrile, acetal, and amine and heterocycles such as pyridine and benzothiazole. It is significant to notice

Table 3. Coupling of α -Alkylated Substrates^a

^a All the reactions were carried out at a 0.50 mmol scale in 1.0 mL of mesitylene. The yield (average of two runs) of the isolated product was calculated based on the quantity of the aryl halide. More details can be found in the Supporting Information. ^b Xant-Phos was used as a ligand. ^c S-Phos was used as a ligand.

that α -dialkylated substrates (**5i**, **5j**, **5k**) can undergo the decarboxylative coupling to generate quaternary carbon centers. The reactions of these particular substrates suggest that decarboxylation takes place prior to cross-coupling.

Scheme 1. New Synthesis of 4-Aryl Quinolines and Dihydroquinolinones



By using the above decarboxylative coupling reactions we can now synthesize a variety of nitro-substituted 1,1-diaryl methanes. The synthetic utility of this method may be substantially increased when the NO_2 substituent is converted to other groups.¹³ Scheme 1 shows a new synthesis of 4-aryl quinolines and dihydroquinolinones starting from the products of the decarboxylative coupling reactions. The reduction of NO_2 to NH_2 by either SnCl_2 or Zn/HCl constitutes the critical step of the synthesis. In the previous catalytic allylation of nitrophenyl acetates, Tunge et al. also showed that decarboxylative coupling can be followed by reductive cyclization to afford dihydroquinolones or quinolines.^{6e}

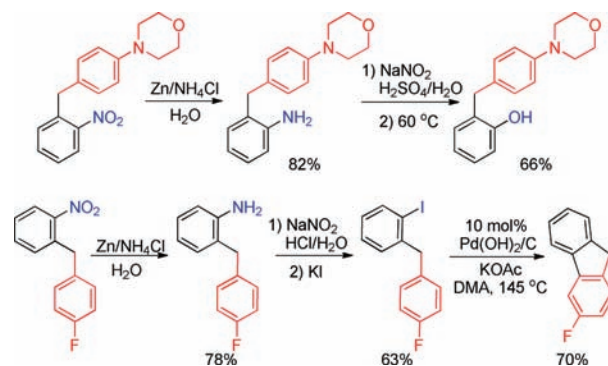
Importantly, NH_2 can be further converted to many other groups through the Sandmeyer reaction. Therefore,

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(18) We also tested the potassium salts of 4-cyanophenyl acetate, 4-trifluoromethylphenyl acetate, and pentafluorophenyl acetate. These substrates do not provide the cross-coupling products.

the above decarboxylative coupling reactions can be used to prepare a variety of 1,1-diaryl methanes. Scheme 2 shows that a 2-benzylated phenol can be synthesized by using the decarboxylative cross-coupling. Furthermore, by converting NH_2 to I we synthesized a substituted fluorene.¹⁷

Scheme 2. Further Transformations by Using Sandmeyer Reaction



In summary, we report a practical protocol for the palladium-catalyzed decarboxylative cross-coupling of potassium 2- and 4-nitrophenyl acetates with aryl chlorides and bromides. This reaction adds a new example to the repertoire of catalytic decarboxylative cross-coupling of activated aliphatic carboxylic acids.¹⁸ Because the nitro group can be readily converted to many other functional groups, the new reaction provides a useful method for the preparation of diverse 1,1-diaryl methanes and their derivatives.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.