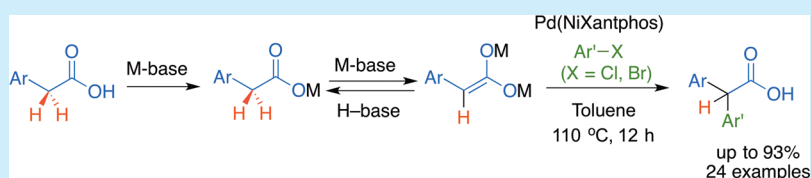


Palladium-Catalyzed α -Arylation of Aryl Acetic Acid Derivatives via Dienolate Intermediates with Aryl Chlorides and Bromides

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S Supporting Information



ABSTRACT: To date, examples of α -arylation of carboxylic acids remain scarce. Using a deprotonative cross-coupling process (DCCP), a method for palladium-catalyzed γ -arylation of aryl acetic acids with aryl halides has been developed. This protocol is applicable to a wide range of aryl bromides and chlorides. A procedure for the palladium-catalyzed α -arylation of styryl acetic acids is also described.

Transition-metal-catalyzed α -arylation of enolates and their derivatives is of great importance due to the diversity of compounds that can be accessed.¹ In 1997 pioneering studies on palladium-catalyzed α -arylation of ketones with aryl bromides was independently reported by the Miura,² Buchwald,³ and Hartwig⁴ groups. Since these seminal works, intensive studies on α -arylation of carbonyl compounds have been reported.^{5,6} To date, however, examples of α -arylation of simple carboxylic acids remain scarce.^{7–9}

In 2007, Daugulis and co-workers studied the palladium-catalyzed *ortho* arylation of benzoic acids. They reported a byproduct derived from the α -arylation of acetic acid with 3,5-dimethyl iodobenzene (Scheme 1A).⁷ The scope and mechanism of this reaction were recently investigated by Han and Zhao.⁸ In

both cases, the reaction required use of excess acetic acid (3.5 to >50 equiv) and supra-stoichiometric silver acetate and gave poor to moderate yields (18–68%).

In 2000, Wolfe and co-workers reported the reaction of phenyl acetic acid dienolate with aryl bromides and iodides in liquid ammonia under near-UV irradiation to afford *alpha* and *para* arylation products via a proposed $S_{RN}1$ process (Scheme 1B).¹⁰ The inconvenient reaction conditions ($NH_3(l)$, $h\nu$) preclude large-scale applications of this chemistry.

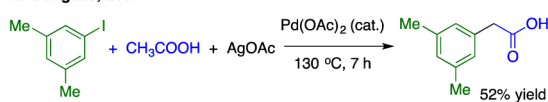
During the preparation of this manuscript, Mori and co-workers described α -arylation of carboxylic acids in a two-step process (Scheme 1C). The substrates are first irreversibly deprotonated using $EtMgCl$ to generate dienolates followed by palladium-catalyzed α -arylation with aryl bromides and iodides.⁹

Our approach to the α -arylation of carboxylic acids differs from that of Mori and co-workers. We envisioned reversible deprotonation of the substrate in the presence of the catalyst, allowing the use of less reactive bases. Under these conditions, the carboxylate would be in equilibrium with the dienolate, as shown in Scheme 1D. To develop this approach, a few issues must be considered. Prior studies on the generation of dienolates by double deprotonation of carboxylic acids^{11–14} indicate strong bases (e.g., $nBuLi$, LDA, Grignard reagents) are needed to achieve the second deprotonation.

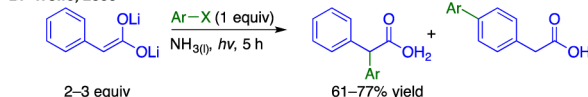
Other challenges include control of chemoselectivity, undesired reactivity of the aryl acetic acid starting materials, and decomposition/further reactions of the diaryl acetic acid product. As noted above, aryl acetic acid derivatives are known to undergo palladium-catalyzed *ortho* arylation via a C–H activation pathway.^{15,16} In this process the carboxylate moiety serves as a directing group to facilitate the C–H bond cleavage.

Scheme 1. Previous Examples of α -Arylation of Carboxylic Acid Derivatives

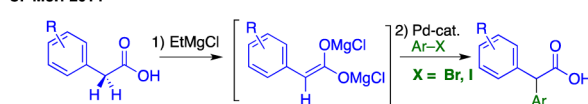
A. Daugulis, 2007



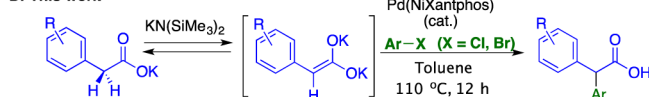
B. Wolfe, 2000



C. Mori 2014



D. This work



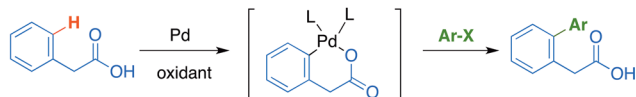
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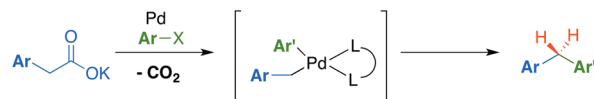
For example, Yu and co-workers demonstrated that *ortho*-C–H activation of phenyl acetic acid derivatives by palladium could be followed by cross-coupling (Scheme 2A). Furthermore, aryl

Scheme 2. Selectivity in Arylation of Aryl Acetic Acid Derivatives

A. Yu 2008–2013



B. Liu 2010

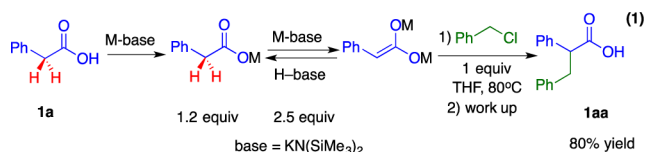


Ar = 2-pyridyl, 2-nitrophenyl, 4-nitrophenyl

acetates have been reported to be unstable in the presence of palladium catalysts and undergo decarboxylative cross-coupling.^{17–23} This reaction pathway is exemplified by the report of Liu and co-workers, who demonstrated diarylmethanes can be formed using 2-pyridyl or nitroaryl acetates with aryl halides via palladium-catalyzed decarboxylative coupling (Scheme 2B).^{22,23} These studies indicate a potential side reaction involving intermediates such as those in Scheme 1D that may compete with the desired α -arylation of dienolates.

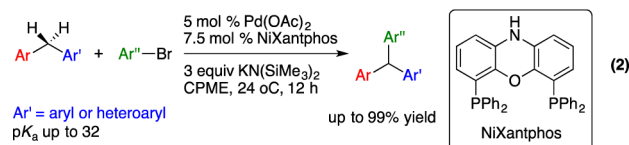
Despite these issues, our experience with deprotonative cross-coupling processes (DCCP) of weakly acidic substrates ($pK_a > 25$) positioned us to pursue the α -arylation of acids.^{24–31} An important feature of the DCCP is an *in situ* reversible metalation of the substrate via C–H deprotonation under catalytic cross-coupling conditions. Herein, we describe a general protocol for the palladium-catalyzed α -arylation of carboxylic acids with aryl chlorides and bromides involving reversible deprotonation of the carboxylate.

The first step in our reaction development focused on deprotonation of phenyl acetic acid to form the dienolate intermediate. To evaluate bases to deprotonate the carboxylate substrate, we employed a benzylation reaction with benzyl chloride to trap the dienolate (eq 1).



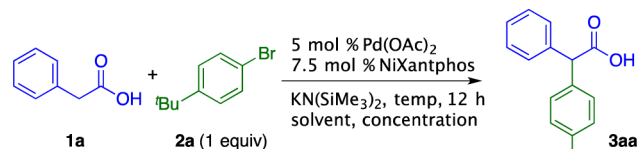
We chose to use $\text{KN}(\text{SiMe}_3)_2$ as the base, because it exhibits good compatibility with catalysts, reagents, and products in deprotonative cross-coupling processes.²⁸ Employing $\text{KN}(\text{SiMe}_3)_2$ at 80 °C (eq 1), the benzylation product **1aa** was isolated in 80% yield, indicating formation of the dienolate under these conditions. With this result in hand, we chose the $\text{NiXantphos}/\text{Pd}(\text{OAc})_2$ -based catalyst due to its ability to arylate weakly acidic substrates, such as diphenylmethanes ($pK_a = 32.3$,³² eq 2).²⁸

We examined the α -arylation of phenyl acetic acid **1a** (1.2 equiv) with 1-bromo-4-*tert*-butylbenzene **2a** (limiting reagent) in the presence of $\text{KN}(\text{SiMe}_3)_2$ (2.5 equiv) and catalytic $\text{Pd}(\text{OAc})_2$ (5 mol %) and NiXantphos (7.5 mol %). These studies were initiated with a solvent screen. The reaction in



cyclopentyl methyl ether (CPME), an excellent solvent for DCCPs, failed to afford an arylation product (Scheme 3, entry 1).

Scheme 3. Optimization of Phenyl Acetic Acid α -Arylation^a

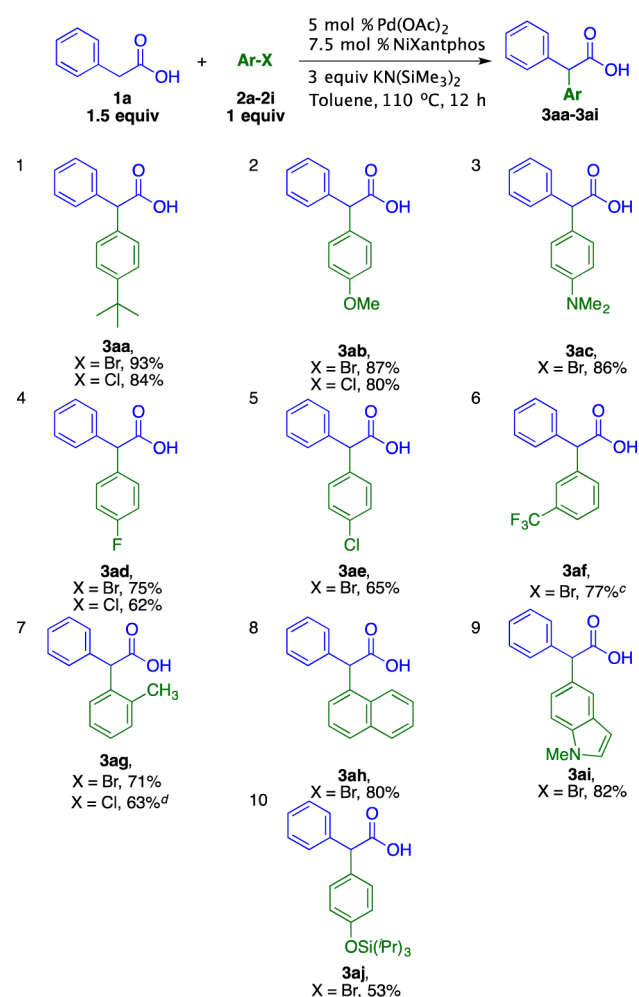


entry	(1a:base)	temp (°C)	solvent	concn	yield ^b (%)
1	1.2 : 2.5	110	CPME	0.1	0
2	1.2 : 2.5	110	dioxane	0.1	56
3	1.2 : 2.5	80	THF	0.1	75
4	1.2 : 2.5	80	2-MeTHF	0.1	20
5	1.2 : 2.5	80	DME	0.1	80
6	1.2 : 2.5	110	toluene	0.1	80
7	1.5 : 3.0	110	toluene	0.1	83
8	1.5 : 3.0	110	toluene	0.05	>95 (93)
9 ^c	1.5 : 3.0	80	toluene	0.05	65
10 ^{c,d}	1.5 : 3.0	110	toluene	0.05	88 (85)

^aReaction conducted on a 0.1 mmol scale. ^bYield determined by ¹H NMR spectroscopy of the crude reaction mixture. ^cIsolated yield after chromatographic purification. ^d2.5 mol % $\text{Pd}(\text{OAc})_2/3.75$ mol % NiXantphos .

Dioxane initially appeared promising, with a 56% yield (entry 2). Attempts to increase the yield, however, were unsuccessful. THF, 2-methyl-THF, and DME (entries 3–5) were examined at 80 °C, with DME giving up to 80% yield. Likewise, toluene at 110 °C afforded the product in 80% yield (entry 6). Both THF and DME resulted in generation of 5–10% of an inseparable byproduct that was not observed in toluene, making toluene a better choice for further optimization. In the reaction in toluene (entry 6), some decomposition of phenyl acetic acid was observed, presumably resulting in lower yields. To address this issue, the equivalents of aryl acetic acid and base were increased to 1.5 and 3, respectively, resulting in an 83% yield (entry 7). Reducing the reaction concentration to 0.05 M resulted in a >95% yield by ¹H NMR of the crude product (entry 8). Lowering the temperature (entry 9) or catalyst loading (entry 10) resulted in lower yields.

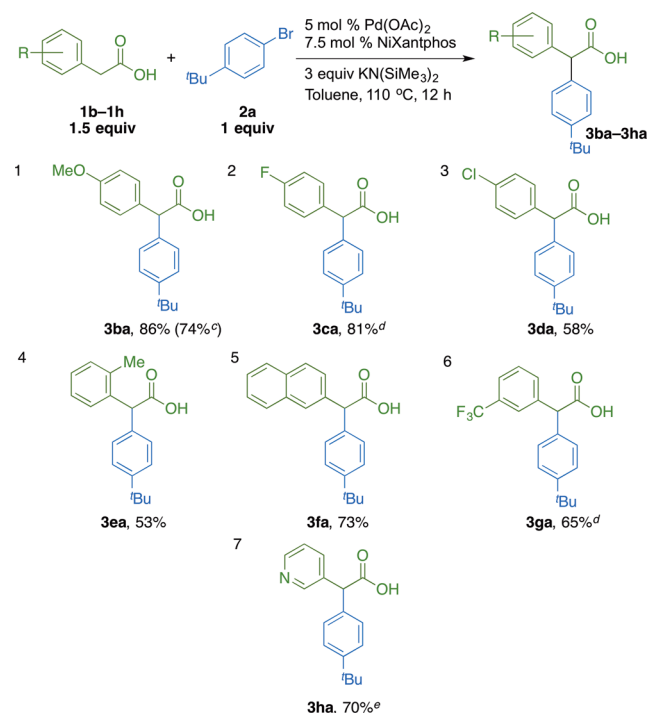
With the optimized conditions of Scheme 3 (entry 8), the scope of aryl halides in the α -arylation of phenyl acetic acid was examined (Scheme 4). 1-Bromo- and 1-chloro-4-*tert*-butylbenzene gave **3aa** in 93% and 84% yield, respectively (entry 1). Substrates with electron-donating groups, such as 4-bromo- and 4-chloroanisole, exhibited good reactivity, generating 87% and 80% yields of the arylation products (entry 2). 4-Bromo-*N,N*-dimethylaniline furnished **3ac** in 86% yield. Aryl bromides and chlorides with electron-withdrawing groups, such as 4-F, 4-Cl, and 3-CF₃, were all tolerated. 1-Bromo- and 1-chloro-4-fluorobenzene furnished diaryl acetic acid in 75% and 62% yield, respectively, while 1-bromo-4-chlorobenzene underwent coupling to give **3ae** in 65% yield. In the latter case, no byproducts derived from oxidative addition of the C–Cl bond were observed. Aryl bromide bearing a 3-CF₃ substituent

Scheme 4. Scope of Aryl Halides in the α -Arylation of Phenyl Acetic Acid^{a,b}

^aReaction conducted on a 0.1 mmol scale at 0.05 M. ^bIsolated yield after chromatographic purification. ^c2 equiv of 1a and 4 equiv of KN(SiMe₃)₂. ^d10 mol % Pd(OAc)₂/15 mol % NiXantphos.

furnished the product in 77% yield. Sterically hindered 2-bromotoluene and 1-bromonaphthalene gave 3ag and 3ah in 71% and 80% yields, respectively. In the case of 1-bromo-3-(trifluoromethyl)benzene, both the aryl acetic acid and base equivalents were increased to 2 and 4, respectively. For the more challenging 2-chlorotoluene, 10% Pd(OAc)₂ was required to render 3ag in 63% isolated yield. Heterocyclic *N*-methyl-5-bromoindole exhibited good reactivity with phenyl acetic acid to form 3ai in 82% yield. The TIPS silyl ether derived from 4-bromophenol was subjected to the reaction conditions and afforded 3aj in 53% yield (Scheme 4, entry 10). Unfortunately, aryl bromides containing ketone, ester, or amide groups failed to give desired products.

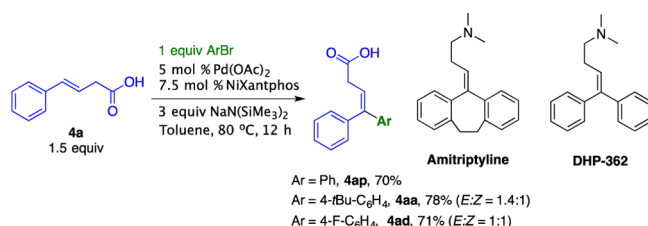
The scope of α -arylation with substituted aryl acetic acids was examined with 1-bromo-4-*tert*-butylbenzene 2a (Scheme 5). Electron-neutral 2-naphthyl acetic acid afforded the coupling product in 73% yield. Electron-donating 4-methoxy phenyl acetic acid underwent coupling in 86% yield. Aryl acetic acids with withdrawing 4-F, 4-Cl, and 3-CF₃ groups furnished coupling products in 81%, 58%, and 65% yield, respectively. Sterically hindered 2-tolyl acetic acid proved to be a challenging substrate with a 53% yield obtained despite repeated attempts to optimize

Scheme 5. Scope of α -Arylation with Aryl Acetic Acids^{a,b}

^aReaction conducted on a 0.1 mmol scale at 0.05 M. ^bIsolated yield after chromatographic purification. ^cReaction conducted on a 5 mmol scale at 0.05 M; 1.1 g of product was obtained. ^d2 equiv of acid and 4 equiv of KN(SiMe₃)₂. ^e2 equiv of acid and 6 equiv of NaO^{*t*}Bu.

the reaction. We next examined 3-pyridyl acetic acid in the α -arylation. With our standard reaction conditions, only decomposition of the acid was observed. We then screened bases KN(SiMe₃)₂, NaN(SiMe₃)₂, LiN(SiMe₃)₂, KO^{*t*}Bu, NaO^{*t*}Bu, and LiO^{*t*}Bu and identified NaO^{*t*}Bu as a better option, generating a 70% isolated yield in the coupling (entry 7). In order to demonstrate the scalability of the protocol, a gram-scale reaction was performed with 4-methoxy phenyl acetic acid (1b) and 4-*tert*-butyl bromobenzene (2a). The arylation product 3ba (1.1 g) was isolated in 74% (Scheme 5, entry 1).

After demonstrating the scope of aryl halides and aryl acetic acids, we turned our attention to styryl acetic acids (Scheme 6).

Scheme 6. Arylation of *trans*-Styryl Acetic Acid 4a

trans-Styryl acetic acid 4a is an interesting substrate, because it has two sites that can potentially undergo arylation. After screening different bases with this substrate, we observed that, with NaN(SiMe₃)₂, only one regioisomeric arylation product was obtained. It appears that the initially formed product undergoes isomerization of the double bond to form the more conjugated product 4ap in 70% isolated yield. This product could also be envisioned to arise from a Heck reaction. We are unaware,

however, of literature precedence involving *trans*-styryl acetic acids undergoing Heck-type reactions.

It is noteworthy that the structure of **4ap** is related to Amitriptyline, a medication that has been used in the treatment of migraines,^{33,34} diabetic neuropathy,³⁵ postherpetic neuralgia,³⁶ and chronic lower back pain.^{35,37} In addition, Brown and co-workers reported an analog of Amitriptyline, diphenylamine DHP-362, which exhibits higher potency as a sodium channel blocker.³⁸ The synthesis of DHP-362 is only two steps away from **4ap**. We next examined the arylation of *trans*-styryl acetic acid **4a** with different aryl bromides. Both 4-*tert*-Bu and 4-F groups underwent reaction with excellent regioselectivity and afforded *E/Z*-mixtures in 71–78% yields.³⁹

In summary, we have developed a general method for palladium-catalyzed α -arylation of aryl acetic acids with aryl bromides and chlorides. The reaction also affords product with *trans*-styryl acetic acid, which provides intermediates in route to biologically active compounds. We anticipate that this protocol will be an important complement to the existing arsenal of palladium-catalyzed α -arylation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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