Communication

Palladium-Catalyzed #-Arylation of Carboxylic Acids and Secondary Amides via a Traceless Protecting Strategy

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Palladium-Catalyzed α-Arylation of Carboxylic Acids and Secondary Amides via a Traceless Protecting Strategy

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Supporting Information Placeholder

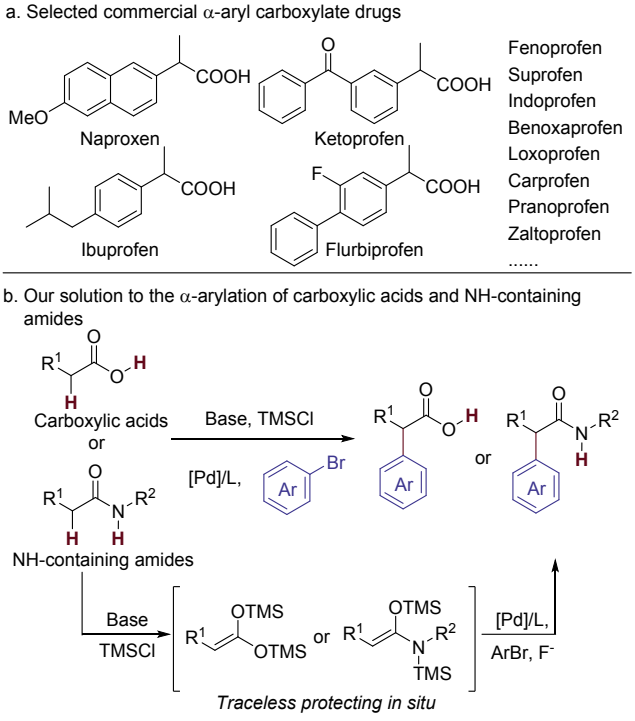
ABSTRACT: A novel traceless protecting strategy is presented for the long-standing challenge of conducting the palladium-catalyzed α-arylation of carboxylic aids and secondary amides with aryl halides. Both of the presented coupling processes occur with a variety of carboxylic acids and amides and with a variety of aryl bromides containing a broad range of functional groups, including base-sensitive functionality like acyl, alkoxycarbonyl, nitro, cyano, and even hydroxyl groups. Five commercial drugs were prepared through this method in one step in 81-96% yield. Gram-scale synthesis of medication Naproxen and Flurbiprofen with low palladium loading further highlights the practical value of this method.

Palladium-catalyzed α-arylation reactions are used for a range of applications.[1] However, the direct α-arylation of free carboxylic acids, one of the simplest carbonyl derivatives and most common derivative in the carboxylic acid oxidation state, has not been reported. Likewise, the α-arylation of common, secondary amides, which contain an acidic N-H bond, has not been reported.[1] Instead, the α-arylation of esters, often serving as masked carboxylic acids, and of tertiary amides containing a narrow range of groups on nitrogen have been reported.[2-3] However, the carboxylic acid, primary amide or secondary amide is often the desired product. Thus, the acid is converted to an ester prior to α-arylation and then converted back to the acid after this catalytic process, and amides must similarly be manipulated to generate α-aryl secondary amides by this catalytic process. For example, the synthesis of the profen drugs by α-arylation involves both installation and removal of the ester groups (Scheme 1a), and the synthesis by classical methods are often even longer.[4]

The absence of direct α-arylation of carboxylic acids and NH-containing amides stems from the strong coordination of carboxylates and amidates to transition metals,[5] the high pKa value of α-CH bonds of carboxylates,[6] and competing C-N coupling of the amidates.[7] Three sets of α-arylations of α-aryl carboxylic acids have been reported, but these reactions have occurred with limited tolerance of functional groups and, most important, were limited to carboxylic acids containing an existing α-aryl group that enhances the acidity of the α-position or acetic acid as both substrate and solvent at a high 130 °C reaction temperature.[8] Likewise, the few prior α-arylations of amides containing an N-H bond were limited to oxindoles for which the pKa value of the α-CH bond is similar to that of the N-H bond.[9]

We considered that the conversion of carboxylic acids and secondary amides to the corresponding disilyl intermediates could lead to reaction of an aryl halide at the alpha position with a palladium catalyst. However, this strategy confronts several challenges. First, the synthesis of the di-TMS protected carboxylic acids or secondary amides must not require purification prior to use in the coupling with aryl halides because purification of the enolate reagent would be an extra step and purification of the labile disilyl ketene acatals could be difficult. Thus, any remaining reagents or byproducts and the solvent used to form the reagent must be tolerated by the coupling reaction. Second, the disilyl reagents contain two nucleophilic centers, one at carbon and one at oxygen or nitrogen, leading to potential interfering C-O or C-N coupling. For such reasons, the intermolecular coupling of aryl halides with an aliphatic carboxylic acid or secondary amide under mild conditions has not been reported.

Scheme 1. Selected Commercial Drugs Containing Free Carboxylic Acids and Our Design



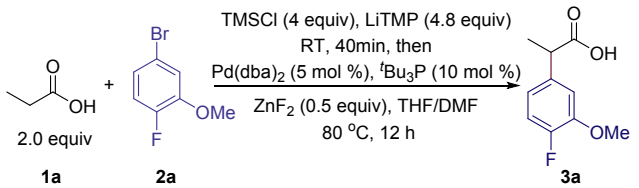
- Novel solution to two long-standing challenges
- Wide tolerance of nitro, cyano, acyl, alkoxycarbonyl, hydroxyl groups
- One-step synthesis of five commercial drugs
- Gram-scale synthesis outside a glovebox with low [Pd] loading

Here, we describe a broadly applicable protocol for the palladium-catalyzed α-arylation of both carboxylic acids and secondary amides via a traceless protecting strategy involving *in situ* installation of silyl groups on the carboxylate or amide under basic conditions and subsequent palladium-catalyzed α-arylation with zinc fluoride as additive (Scheme 1b). The practical value of

this method is shown by a one-pot, gram-scale synthesis of profen drugs with low catalyst loadings, as well as the tolerance of a broad range of functional groups in both aryl and heteroaryl halides.

We began our study to achieve the α-arylation of carboxylic acids by evaluating a series of reagents that could transiently protect the carboxylic acid *in situ* (Table 1). The reaction of propionic acid (2 equiv) with the combination of TMSCl (4 equiv) and LiTMP (4.8 equiv) followed by addition of $Pd(dba)_2$ (5 mol %) and $^tBu_3P$ (10 mol %) as catalyst with ZnF_2 (0.5 equiv) additive[2e] formed the α-arylated product **3a** in 52% yield (entry 1). The same reaction without TMSCl (entry 2), and the same reaction with other silyl groups, such as those from TMSOTf, TBSCl, TESCl and TBDPSCl, gave no detectable **3a** (entry 3). Further changes to the temperatures or types of bases led to lower yields (entry 4-5).

Table 1. Studies on Reaction Development[a]



Entry	Variation from the above conditions	Yield (%)[b]
1	none	52
2	no TMSCl	N.D.
3	TMSOTf, or TBSCl, or TESCl, or TBDPSCl instead of TMSCl	N.D.
4	LDA, or $LiNCy_2$ instead of LiTMP	7-40
5	50, or 65, or 90 °C instead of 80 °C	30-40
6	**1a** (2.5 equiv), TMSCl (6 equiv), LiHMDS (5.3 equiv)	92 (89)[c]

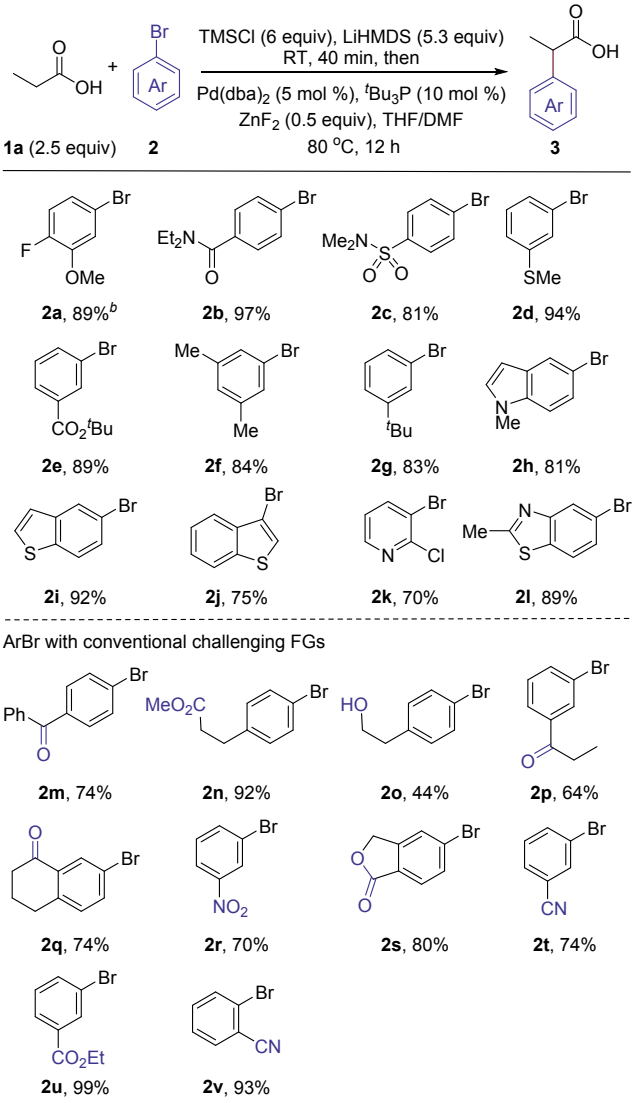
[a]Reactions were conducted on 0.1 mmol scale of **2a**. [b]Determined by crude ^{19}F NMR. [c]Isolated yield in parenthesis. N.D., not detected.

After a series of evaluations of phosphine ligands, sources of palladium, bases, additives and temperature (see SI for a description of these experiments), the α-arylation product **3a** formed in 92% yield by crude ^{19}F NMR spectroscopy and was isolated in 89% yield as the methyl ester with LiHMDS as the base (entry 6). These forming **3a** in the highest yield consisted of the combination of propionic acid **1a** (2.5 equiv), TMSCl (6 equiv), LiHMDS (5.3 equiv), $Pd(dba)_2$ (5 mol %), $^tBu_3P$ (10 mol %) and ZnF_2 (0.5 equiv) in THF/DMF at 80 °C for 12 h.

This palladium-catalyzed α-arylation of carboxylic acids occurred with aryl bromides containing a broad range of functional groups at varying positions (Table 2). Both electron-withdrawing (amide in **2b**, sulfonamide in **2c**, bulky ester in **2e**) and electron-donating substituents (thioether in **2d**, alkyl group in **2g**) were well tolerated, giving arylated product in 83-97% yield. Aryl bromides containing multiple substituents underwent coupling in 84-89% yield (**2a**, **2f**). The coupling of a range of heteroaryl bromides, such as bromo-indole, -benzothiophene, -pyridine and -benzothiazole, with propionic acid also occurred in high yield (**2h-2l**). Reactions with 1 mol% [Pd] instead of the standard 5 mol % occurred; for example, a high 96% yield of product **3a** under this condition was measured by ^{19}F NMR spectroscopy and the same reaction with 1 mol % of the pre-formed catalyst $Pd(^tBu_3P)_2$ gave a comparable 87% yield of **3a**.

During prior studies on the α-arylation of reactants having high p*K*a values, such as esters and amides, in which excess of strong base was used to generate the enolate, the α-arylation was shown to be incompatible with aryl bromides bearing base-sensitive functional groups, such as acyl, cyano, nitro, *etc*.[2a-c, 3a-b] Similar to the reported silyl enolate chemistry of esters,[2a,2e,2g] the current method for the direct α-arylation of carboxylic acids overcomes this limitation; for example, it occurs with aryl bromides containing acyl, alkoxycarbonyl, cyano and nitro groups, giving the coupling product in 70-99% yield (**2m**, **2r**-**2v**). Aryl bromides containing hydrogens alpha to a carbonyl group (ester in **2n**, ketone in **2p** & **2q**) underwent the coupling process with the disilyl-substituted acid **1a** without reaction at the auxiliary α-hydrogen (64-92% yield). Even a free alcohol in the aryl bromide was tolerated; the reaction of alcohols **2o** afforded the product in moderate yield.

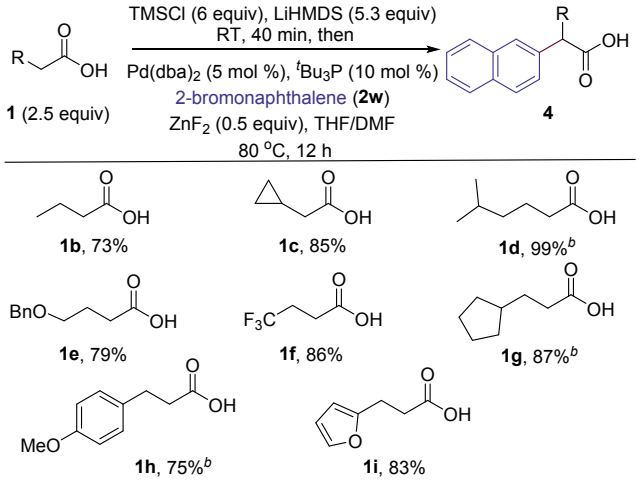
Table 2. Scope of Aryl Bromides that Couple with Propionic Acids[a]



[a]Isolated yields after conversion to corresponding methyl esters for easy purification. [b]96% yield by ^{19}F NMR was observed with only 1 mol % [Pd]; 1 mol % $Pd(^tBu_3P)_2$ gave 87% yield by ^{19}F NMR.

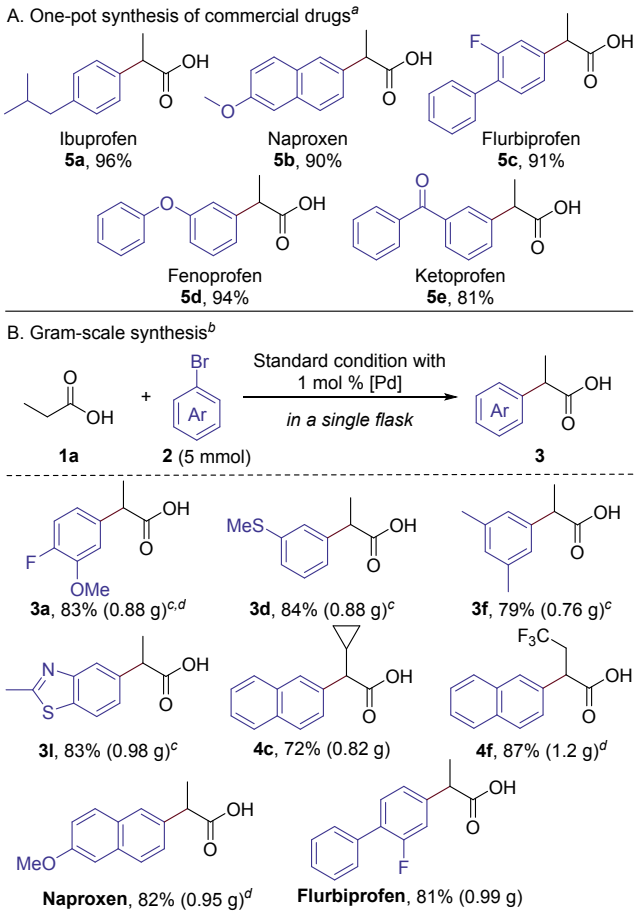
Experiments on the α-arylation of a series of carboxylic acids are summarized in Table 3. Carboxylic acids containing linear alkyl groups (**1b**, **1d**), cycloalkyl groups (**1c**, **1g**), alkoxy (**1e**) and CF_3 groups (**1f**) reacted in 73-99% yield. Carboxylic acids substituted with both aryl (**1h**) and heteroaryl (**1i**) groups on the α-carbon reacted, delivering the α-aryl carboxylic acid products in 75% and 83% yield, respectively. Acids containing two alkyl groups on the alpha carbon did not react.

Table 3. Scope of Carboxylic Acids with 2-Bromonaphthalene as Substrate[a]



[a]Isolated yield of product as carboxylic acid. [b]Isolated yield after conversion to corresponding methyl esters.

Table 4. One-step Synthesis of Commercial Drugs and Gram-scale Tests with Low [Pd] Loading

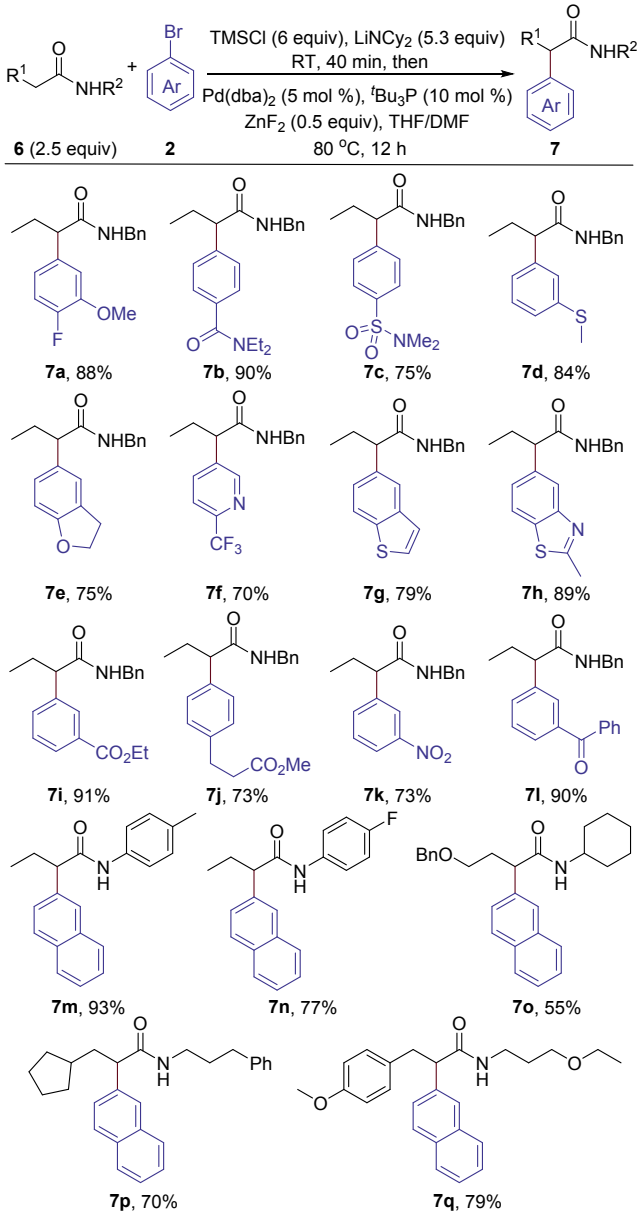


[a]Standard condition as table 1, entry 6. [b]See SI for details. Isolated yield. [c]Isolated yield after conversion to corresponding methyl esters. [d]2 mol % [Pd] was used.

To highlight the synthetic efficiency created by the present method, five commercial anti-inflammatory drugs were prepared in one step in high yield (Table 4A). For example, the well-known, nonsteroidal anti-inflammatory drug (NSAID) Ibuprofen has been prepared commercially in 6 steps (Boot process) or 3 steps (Hoechst process) from *iso*-butylbenzene.[10] The reaction reported here forms the product in 96% yield in a single step by the developed α-arylation of propionic acid with 1-bromo-4-isobutylbenzene. Similarly, Naproxen, Flurbiprofen, Fenoprofen and Ketoprofen, all were synthesized in one step in over 80% yield (**5b**-**5e**).

A series of gram-scale (5 mmol) couplings of aryl bromides with carboxylic acids underscore the convenience and synthetic value of our method (Table 4B). All reactions were conducted in a single flask under nitrogen outside a glovebox with 1-2 mol % [Pd] loading, instead of the 5 mol % used for the assessment of reaction scope. The aryl bromides **2a**, **2d**, **2f**, and **2l** coupled with carboxylic acid **1a** in yields (79-84%) that were comparable to those obtained from reactions on a 0.1 mmol scale. The coupling of 2-naphthylbromide with a series of carboxylic acids also occurred in high yields on gram scale, in this case to give compounds **4c** and **4f** in 72% and 87% yields, respectively. Finally, the synthesis of Naproxen and Flurbiprofen occurred in one-step on gram-scale in over 80% yield.

Table 5. Scope for Pd-catalyzed α-Arylation of Secondary Amides with Different ArBr[a]



[a]Standard condition as table 1, entry 6, except for $LiNCy_2$ used as base instead of LiHMDS. Isolated yield.

The approach to the α-arylation of acids also was applicable to the α-arylation of amides containing NH-bonds with minor modification of the base. The reaction of *N*-benzyl butyramide (**6a**) was chosen as the model substrate. Under the standard conditions described for the reactions of carboxylic acids (*vide supra*), only 14% of α-aryl amide **7a** formed from amide **6a** (See SI for details). Evaluation of the effect of temperatures and base showed that **7a** formed from **6a** in 88% yield with $LiNCy_2$ as the base instead of LiHMDS.

The scope of the α-arylation of secondary amides is illustrated by the examples in Table 5. Both electron-poor (**7b**-**7c**) and electron-rich aryl bromides (**7d**-**7e**) reacted in high yield (75-90%). Heteroaryl bromides, such as a bromo pyridine, benzothiophene and benzothiazole reacted in a good 70%, 79% and 89% yield, respectively (**7f**-**7h**). Like the α-arylation of carboxylic acids, the α-arylation of amides occurred with aryl bromides containing base-sensitive functional groups, such as acyl, alkoxycarbonyl and nitro groups, to give the product in 73-91% yield (**7i**-**7l**).

Studies on the scope of amides showed that a range of secondary amides underwent the α-arylation reaction. Amides derived from alkyl-, alkoxy- or aryl-substituted carboxylic acids and alkyl or aryl amines reacted to give the coupled product in 70-93% yield (**7m**-**7n, 7p**-**7q**). Reaction of an amide containing an α-branched amino group occurred in a moderate 55% yield (**7o**). In this case, the installation of the traceless protection occurred in approximately 84% yield, which is lower than for the less hindered amides, presumably due to the steric properties of the amino group. Like carboxylic acids, amides containing an N-H bonds and two alkyl groups on the alpha carbon did not react.

In summary, we have designed and implemented a strategy for the α-arylation of free carboxylic acids and secondary amides involving a traceless protecting strategy with a broad range of aryl and heteroaryl bromides in up to 99% yield. This coupling tolerates aryl bromides containing base-sensitive groups, such as acyl, alkoxycarbonyl, nitro, cyano and even hydroxyl groups. The value of this coupling was further illustrated by one-step syntheses of the five commercial profen drugs Ibuprofen, Naproxen, Flurbiprofen, Fenoprofen and Ketoprofen in over 80% yield. Gram-scale preparations of a group of arylated carboxylic acids, including Naproxen and Flurbiprofen with 1-2 mol % palladium loading were achieved in one step in 72-87% yield. We hope that this method will be widely used for the direct synthesis of both synthetic intermediates and final products.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental details and procedures, spectra for all unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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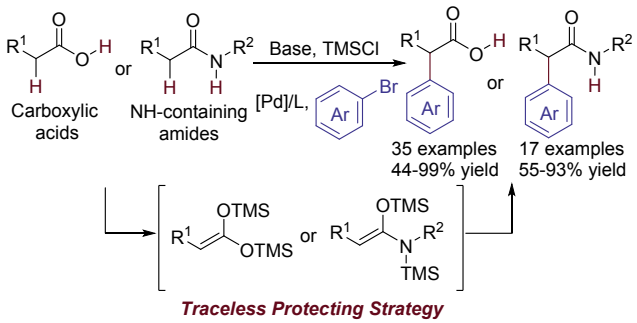

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