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Synthesis of Arylstannanes via Palladium-Catalyzed Decarbonylative Coupling of Aroyl Fluorides

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Abstract: Aryl stannanes are valuable precursors in organic transformations, but their synthetic methods are limited. Here we present a Pd-catalyzed decarbonylative stannylation of acid fluorides in the absence of exogenous base. Various aryl stannanes were efficiently prepared from bench-stable transition metal catalyst and ligand with broad functional group compatibility and substrate scope including natural products and pharmaceuticals. This protocol was also successfully used to a late-stage diversification of an existing uricosuric drug *probenecid*.

Keywords: stannylation; Pd-catalyzed; acyl fluorides; decarbonylation; late-stage diversification

The transformation of carboxylic acids or their derivatives through an efficient and selective activation is an attractive topic.[1] Acyl fluorides, the stable and readily accessible carboxylic acid derivatives, are traditionally used as acylation reagents via nucleophilic substitution or transition-metal (TM) catalyzed cross-coupling reaction.[2] Recently, TM-catalyzed decarbonylative reactions of aroyl fluorides have been successfully realized for a number of transformations, including trifluoromethylation,[3] Suzuki–Miyaura type arylation,[4] reduction,[5] alkylation[6] and direct C–H arylation[7] (Scheme 1a). In addition, a few, although rare, cases of carbon–heteroatom bond formation with acyl fluorides as arylation precursors were also reported, including the Ni-catalyzed borylation[8] and silylation[9] of acyl fluorides.

Arylstannanes are attractive substrates due to their widespread application in the Migita−Kosugi−Stille coupling reaction,[10] which has been commonly used for synthesis of a wide range of target molecules.[11] They are also frequently used in the construction of diverse carbon−heteroatom bonds such as C–F, C–OCF_3, and C–N bonds.[12] Traditional methods to generate arylstannanes involve the reaction of trialkyltin chloride with air-sensitive organometallic reagents. Alternatively, TM-catalyzed stannylation of different electrophiles[13] as well as C–H and C–O bond stannylation have also been developed.[14] In addition, Rueping's group realized nickel-catalyzed decarbonylative stannylation of aryl esters (Scheme 1b).[15] These reported methods usually request a base or fluoride source to activate distannane/silylstanne reagents or to enable the transmetalation. Furthermore, a Lewis acid-mediated stannylation of aryl triazene have been disclosed by Li and Zhang's groups.[16] And the photochemical stannylations have also been reported.[17] Recently, our group reported a convenient C–Sn bond formation by using aryl ammoniums or sulfoniums as substrates in the absence of a TM catalyst.[18] Inspired by these progress and related literature report,[4] we decide to develop a TM-catalyzed decarbonylative stannylation of acid fluorides in the absence of exogenous base using the less active but readily available hexaalkyldistannane as the stannylation reagent (Scheme 1c).

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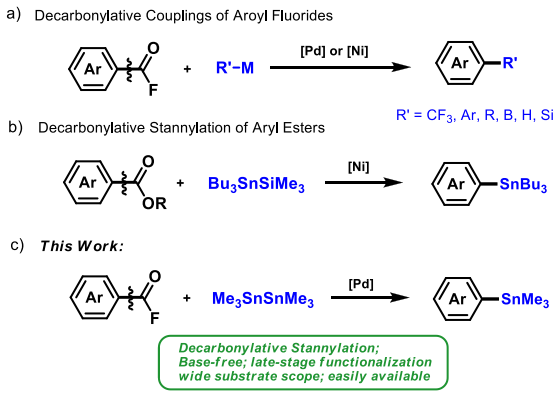
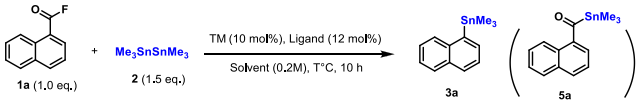


Scheme 1. TM-catalyzed Decarbonylative Coupling of Aroyl Fluoride and Representative Stannylation Reactions.

Initially, we used the reaction of 1-naphthoyl fluoride (**1a**) and hexamethyldistannane (**2**) as the model reaction and optimized the conditions in the absence of a base (Table 1). Several TM catalysts and ligands were first selected for evaluation. However, poor transformations were observed (entries 1–5). We next examined different ligands with $Pd(OAc)_2$ as the catalyst (entries 6–8). To our delight, 1,4-bis(dicyclohexylphosphino)butane (dcypb) displayed a superior result, providing the desired product in 40% yield (entry 8). After evaluation of several Ni or Pd catalysts, $PdCl_2$ was found to provide a good yield (entry 11). Then, we measured the effect of solvents and reaction temperature. The target product **3a** was obtained in 85% yield when *o*-xylene was employed as the solvent at 140 °C (entries 16). In addition, we found that when the reaction was performed with microwave irradiation (entry 18), **3a** was obtained in 84% yield within 1 h. Replacement of $Me_3SnSnMe_3$ with $^nBu_3SnSn^nBu_3$ under identical reaction conditions provided **3a** in a lower yield (entry 19). During the optimization of conditions, we observed the acyltin byproduct **5a** by GC-MS analysis (Table 1). But we could not isolate **5a** effectively because of its low yield and sensitivity to oxygen air.[19]

Table 1. Optimization for Reaction Conditions.[a]



Entry	TM	Ligand	Solvent	T	**3a** yield[b]	**5a** yield[c]
1	$Pd(PPh_3)_4$	–	Dioxane	110	0%	0%
2	$Ni(OAc)_2$	PPh_2Me	Dioxane	110	0%	7%
3	$Pd(dppe)_2$	–	Dioxane	110	trace	25%
4	$Ni(PPh_3)_4$	–	Dioxane	110	25%	35%
5	$[Pd(cinnamyl)Cl]_2$	Xantphos	Dioxane	110	20%	5%
6	$Pd(OAc)_2$	PCy_3	Dioxane	110	trace	40%
7	$Pd(OAc)_2$	IPr	Dioxane	110	0%	15%
8	$Pd(OAc)_2$	dcypb	Dioxane	110	40%	12%
9	$Ni(OAc)_2$	dcypb	Dioxane	110	trace	25%
10	$Pd(acac)_2$	dcypb	Dioxane	110	30%	8%
11	$PdCl_2$	dcypb	Dioxane	110	65%	18%
12	$PdCl_2$	dcypb	THF	110	trace	6%
13	$PdCl_2$	dcypb	DMF	110	15%	30%
14	$PdCl_2$	dcypb	Toluene	110	60%	10%
15	$PdCl_2$	dcypb	Toluene	140	70%	trace
16	$PdCl_2$	dcypb	*o*-Xylene	140	85%	trace
17	$PdCl_2$	dcypb	*o*-Xylene	150	80%	trace
18[d]	$PdCl_2$	dcypb	*o*-Xylene	140	84%	trace
19[e]	$PdCl_2$	dcypb	*o*-Xylene	140	62%	–

[a] Reaction conditions: **1a** (0.2 mmol), $Me_3SnSnMe_3$ (0.3 mmol), TM catalyst (0.02 mmol), Ligand (0.024 mmol), Solvent (1 ml), 10 h. dppe = 1,2-bis(diphenylphosphino) ethane; Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; $[Pd(cinnamyl)Cl]_2$ = Di-chlorobis[(1,2,3 -)-1-phenyl-2-propenyl]dipalladium(II).
[b] Yields were based on ^{1}H-NMR analysis with mesitylene as an internal standard.
[c] Yields were determined by GC analysis with dodecane as an internal standard.
[d] Reaction performed employing microwave reactor at 140 °C in 1 h.
[e] $^nBu_3SnSn^nBu_3$ as the stannylation reagent.

With the optimized condition in hand (entry 16 in table 1), the substrate scope was surveyed (Scheme 2). Acyl fluorides were readily prepared from the corresponding carboxylic acids or acyl chlorides.[3-9] It was found that acyl fluorides with an extended-conjugated system (**1a,c,d**) reacted without difficulty, providing stannylation products in 77–89% isolated yields. Substrates bearing electron-donating groups such as butyl (**1e**), methoxy (**1g**), and sterically congested group (**1f**) gave the corresponding products **3e–g** in 52–83% isolated yields. Electron-deficient acyl fluorides also had excellent reactivity, revealing tolerance of the conditions with a wide range of functional groups, such as cyano (**1h**), acyl (**1i**), and ester (**1j**) groups, generating the corresponding aryl stannanes in 85–93% isolated yields. It was found that heterocyclic substrates such as benzofuran, benzothiophene and indole participated in the reaction smoothly, affording the target products **3k-m** in 52–81% isolated yields. In order to further value the applicability of the method, we investigated stannylation of acyl fluorides **1n–s** derived from biologically active molecules. All the transformations went through smoothly affording corresponding aryl stannanes **3n–s** in moderate to high yields.

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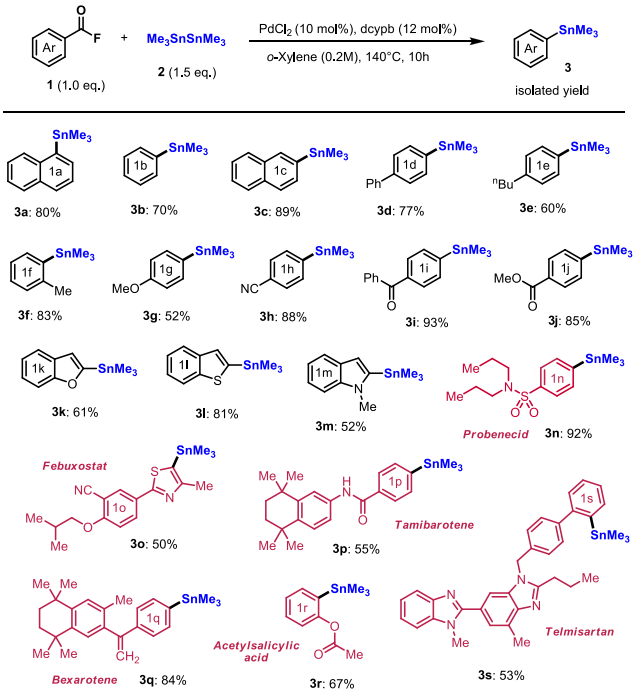
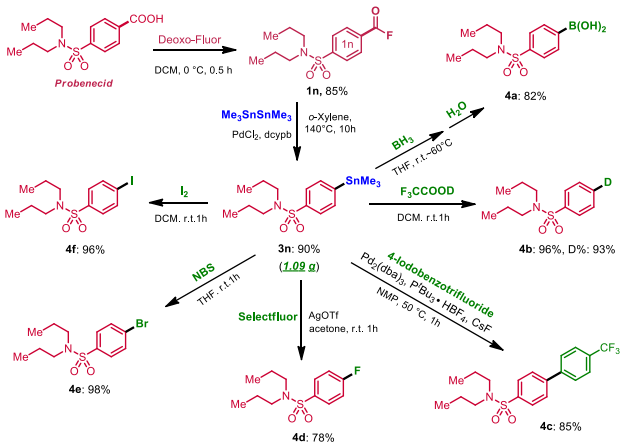


Scheme 2. Substrate Scope. Reaction Conditions: acyl fluoride (0.2 mmol), $Me_3SnSnMe_3$ (0.3 mmol), $PdCl_2$ (0.02 mmol), dcypb (0.024 mmol), *o*-Xylene (1 ml), 140 °C, 10 h. Yields were determined by isolation.

Since arylstannanes are valuable precursors for further functional transformations, late-stage diversification of pharmaceutically useful carboxylic acid derivatives via stannylation−derivatization process was then carried out (Scheme 3). The acyl fluoride **1n** was easily prepared from commercially available *probenecid*, which is primarily used to treat hyperuricemia and gout. The subsequent decarbonylative stannylation went through smoothly under standard condition to give corresponding product **3n** in 90% isolation yield on a gram scale. Boronation of **3n** with borane afforded arylboronic acid **4a** in 82% yield. Stille coupling of **3n** in the presence of Pd(0) catalyst provided biaryl derivative **4c** in 85% yield. In addition, treatment of **3n** with deuterated trifluoroacetic acid, Selectfluor, NBS or iodine provided corresponding deuterated, fluoro, bromo-, or iodo- derivatives **4b, d-f** in high yields. These results sufficiently exemplify the wide applicability of this protocal for late-stage modification of pharmaceutically useful molecules.



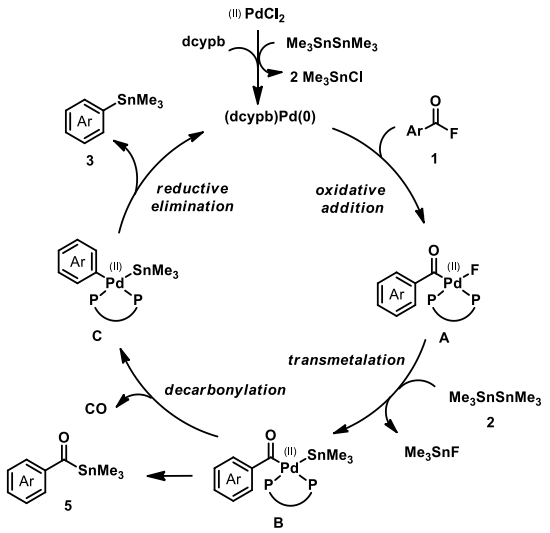
Scheme 3. Late-stage Derivatization of Bioactive Substrates. Yields were determined by isolation.

Finally, a plausible mechanic pathway for current decarbonylative stannylation was proposed. According to the related references,[3,5] the reaction possibly begins with the oxidative addition of the C–F bond of acyl fluorides to the active Pd(0) species, which is formed from reduction of Pd(II) chloride with hexamethyldistannane. The formed ArCO-[Pd(II)]-F intermediate **A** then undergoes decarbonylation followed by transmetalation with $Me_3SnSnMe_3$, or alternatively proceeds through transmetalation prior to CO loss. Schoenebeck[3] and Xie[20] have reported the mechanistic studies on Pd-catalyzed conversion of acyl fluorides by DFT calculations, and found decarbonylation from the intermediate ArCO-[Pd(II)]-F (**A**) is kinetically unfavorable, with high activation free energy barrier. Therefore, we assume that the Pd[II] species **A** is a relatively 'transmetalation-active' intermediate, and transmetalation should occur prior to decarbonylation. Experimentally, we have also detected trimethylacyltin byproduct **5** from the direct reductive elimination of ArCO-[Pd(II)]-$SnMe_3$ (**B**) when reducing the reaction temperature (for details, see Supporting Information). Finally, reductive elimination of the Pd[II] species **C** provides arylstannanes **3**, and regenerates the Pd(0) species to complete a catalytic cycle.

It has to be mentioned that during the completion of this work, Nishihara and co-workers[21] reported the first decarbonylative stannylation of acid fluorides under Ni(II) catalysis in the presence of CsF as the base. In their work, the more active Bu_3Sn-$SiMe_3$ was used as the stannylation reagent, and the hexaalkyldistannane as used in our protocol is inactive.

In conclusion, we have established a convenient approach to prepare arylstannanes via Pd-catalyzed decarbonylative stannylation of acyl fluorides without an exogenous base. The reaction performs efficiently with bench-stable TM catalyst and ligand with broad functional group compatibility and substrate scope. A range of acyl fluorides derived from natural products and pharmaceuticals were successfully stannylated.

The stannylation product was then applied for late-stage diversification of pharmaceutically useful molecules.



Scheme 4. Proposed Mechanism

Experimental Section

General Procedure for Decarbonylative Stannylation of Acid Fluorides

To a 10 mL dried schlenk tube was added acid fluoride (0.2 mmol), $Me_3SnSnMe_3$ (0.3 mmol), $PdCl_2$ (0.02 mmol) and dcypb (0.024 mmol). The schlenk tube was then evacuated and back-filled with argon, that was repeated for several times. Subsequently, dry *o*-Xylene (1.0 ml) was added via syring. The mixture was stirred for 10 h at 140 ^oC, and the reaction solution was extracted with ethyl acetate, The organic phase was washed with brine and dried over Na_2SO_4, then concentrated in vacuum. The residue was purified on column chromatography or preparative HPLC to give the product.

Acknowledgements

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