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# Palladium-Catalyzed Stille-Type Coupling of *N*-Acyl Iminium Ions with Distannanes: A Multicomponent Synthesis of α-Amidostannanes

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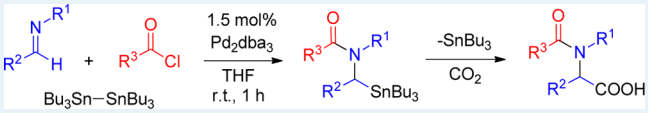
Supporting Information

**ABSTRACT:** The palladium-catalyzed three-component coupling of imines, acid chlorides, and hexabutyldistannane is described. This results in the synthesis of various α-amidostannanes in good yields, without the use of strong nucleophilic organometallic reagents. The reaction is believed to proceed via a Stille-type cross coupling of an *in situ*-generated *N*-acyl iminium salt with $Bu_3SnSnBu_3$ and reaches completion within 1 h at ambient temperature using simple, unligated $Pd_2dba_3$ as a catalyst. Combining the formation of α-amidostannanes with lithiation and carboxylation allows the overall synthesis of amino acid derivatives in two steps from imines, acid chlorides, and $CO_2$.

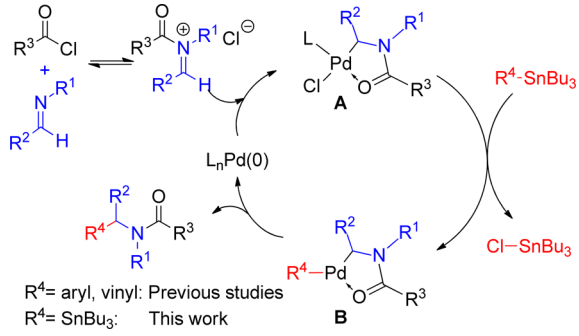



**KEYWORDS:** *palladium catalysis, organostannanes, iminium ions, cross coupling, amino acids*

Transition metal-catalyzed multicomponent coupling reactions have attracted interest in the design of new synthetic methods.[1] A useful feature of these transformations is the ability of the metal catalyst both to activate simple and unreactive building blocks toward reaction and at the same time to control how several of these are assembled. These can provide routes for coupling multiple basic units directly to products, where a single metal catalyst mediates several bond-forming operations in a single reaction. A wide range of metal-catalyzed multicomponent coupling reactions have been developed.[2] One variant that we have been actively developing involves the use of iminium ions in palladium-catalyzed cross coupling reactions. While imines are typically not viable electrophiles in cross coupling reactions, we demonstrated several years ago that acid chlorides can induce imines both to undergo facile oxidative addition and to be coupled with transmetalation with organostannanes to generate α-substituted amides.[3] This reaction presumably proceeds via the initial *in situ* generation of *N*-acyl iminium salts, which undergo oxidative addition to palladium (Scheme 1). We and others have demonstrated that this general platform can provide mild routes for the creation of a range of substituted amides from three or more available units.[4,5]

In considering this reactivity, we noted that addition of palladium to the *N*-acyl iminium salts converts this typically strongly electrophilic substrate into a more covalent, palladated intermediate **A**. α-Metalated amines and amides are useful building blocks in synthesis, as they provide access to umpolung reactivity relative to the typically electrophilic reactivity at carbon imines.[6] Important examples are α-aminostannanes, which can serve as precursors to amino-substituted carbon nucleophiles (Scheme 2).[7] Subsequent reaction with electrophiles can provide a flexible platform for synthesizing a diverse range of α-substituted amines, amino alcohols, or amino acids. The synthesis of aminostannanes typically requires the addition of nucleophilic $Bu_3Sn^-$ to imines or aminosulfones.[8] These tin reagents are highly reactive compounds that must first be generated or, as demonstrated by Sato, generated *in situ* via the use of $TMSSnBu_3$ and stoichiometric fluoride.[9]

**Scheme 1. Multicomponent Synthesis of Substituted Amides**




As an alternative, it is well established that distannanes can participate in palladium-catalyzed cross coupling reactions with aryl and vinyl halides to generate organotin reagents.[10] Considering the similarity between classic Stille couplings and that shown in Scheme 1, we became interested in the potential of acid chlorides to induce imines to participate in palladium-catalyzed coupling with distannanes, as a mild approach to generating α-amidostannanes. The results of these studies are reported below. This has provided a convenient route for the

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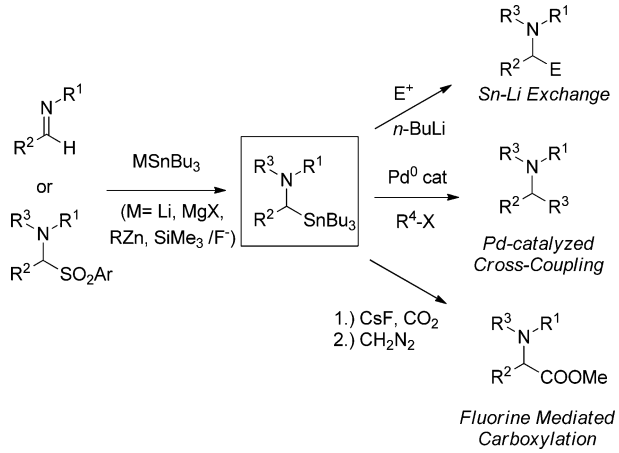
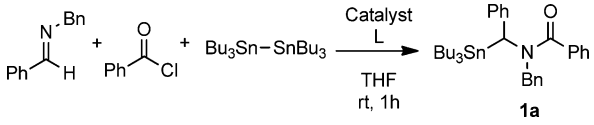
**Scheme 2. Synthesis and Utility of α-Aminostannanes**




preparation of metalated amides from three simple and/or commercially available reagents (imines, acid chlorides, and $Bu_3SnSnBu_3$) that can be readily diversified and does so without the need to employ presynthesized or strongly nucleophilic substrates.

Table 1 details our attempts to generate α-amidostannane **1a** from imine, acid chloride, and $Bu_3SnSnBu_3$. Phosphine-coordinated palladium catalysts such as $Pd(PPh_3)_4$ or $Pd_2dba_3/PR_3$ do not mediate the formation of **1a** (entries 1–5). Instead, $^1H$ nuclear magnetic resonance (NMR) analysis shows the bisstannane and the *in situ*-formed *N*-acyl iminium salt essentially unreacted. Copper catalysts, which we have found to behave like palladium in the coupling of *N*-acyl iminium salts with organostannanes, are also ineffective (entry 6).[4c]

**Table 1. Catalyst Development for Multicomponent Coupling**[a]




| entry | catalyst | ligand | yield (%) |
|---|---|---|---|
| 1 | – | – | – |
| 2 | 10% $Pd(PPh_3)_4$ | – | – |
| 3 | 5% $Pd_2dba_3{\cdot}CHCl_3$ | 15% $P(tBu)_3$ | – |
| 4 | 5% $Pd_2dba_3{\cdot}CHCl_3$ | 15% $PPh_3$ | – |
| 5 | 5% $Pd_2dba_3{\cdot}CHCl_3$ | 15% $PCy_3$ | – |
| 6 | 10% CuCl | – | – |
| 7 | 5% $Pd_2dba_3{\cdot}CHCl_3$ | – | 40 |
| 8[b] | 5% $Pd_2dba_3{\cdot}CHCl_3$ | – | 70 |
| 9[b] | 1.5% $Pd_2dba_3{\cdot}CHCl_3$ | – | 73 |
| 10[b,c] | 1.5% $Pd_2dba_3{\cdot}CHCl_3$ | | 33 |
| 11[b,d] | 1.5% $Pd_2dba_3{\cdot}CHCl_3$ | | 38 |

[a]General: imine (0.1 mmol), acid chloride (0.1 mmol), $(SnBu_3)_2$ (0.1 mmol), Pd, and L as indicated, 2 mL of THF, 1 h. Yield by $^1H$ NMR relative to a benzyl benzoate standard. [b]Use of 0.15 mmol of acid chloride and $(SnBu_3)_2$. [c]With $(SnMe_3)_2$ to yield $SnMe_3$-substituted product. [d]With $Me_3SiSnBu_3$ and a 16 h reaction time.

We postulated that the lack of coupling in these systems is due to the presence of phosphine. In contrast to typical palladium-catalyzed cross coupling reactions with aryl halides, the oxidative addition of *N*-acyl iminium salts to palladium creates an intermediate, **A**, in which there is presumably only one coordination site available. The association of a strongly coordinating phosphine to this site could inhibit transmetalation of **A** with the stannane.[11,12] Consistent with this, the use of simple 5% $Pd_2dba_3CHCl_3$ without an added ligand leads to the rapid formation of amidostannane **1a** in a moderate 40% yield (entry 7). Slightly increasing the amount of acid chloride employed (1.5 equiv) allows the synthesis of **1a** in good overall yield (entry 8). Despite employing no activating ligands, the reaction is rapid and occurs at ambient temperature and within 1 h. The catalyst loading can be decreased to 1.5 mol % without any loss of yield (entry 9). Other organometallic reagents can also be employed in this reaction, such as $(SnMe_3)_2$ or $Bu_3SnSiMe_3$ (entry 10 or 11, respectively), albeit with lower yields. In the case of $Bu_3SnSiMe_3$, a mixture of stannyl and silylated products is formed.[13]

As shown in Table 2, this reaction can be readily diversified. A variety of *N*-substituted imines are compatible with this coupling, including those with common protecting groups, such *N*-benzyl, *N*-allyl, and *N*-2,4-dimethoxybenzyl units (entries 1, 2, and 8, respectively). Both electron-donating and -withdrawing units can be employed on the imine carbon (entries 9–14). However, C-aliphatic imines are not amenable to the reaction, and imines derived from α,β-unsaturated aldehydes lead to mixtures of products. In addition to benzoyl chloride, functionalized aryl and even furanyl and thiophenyl acid chlorides can be employed (entries 4–7). Chloroformates, on the other hand, were not reactive under these conditions. The reaction is also compatible with substrates that can undergo other palladium-catalyzed transformations. For example, imines containing both terminal olefinic (entries 2 and 4) and aryl bromide (entry 10) functionalities react selectively with the distannane to form **1**. These units can be problematic in palladium catalysis because of their potential to participate in Heck or cross coupling reactions. The selectivity in this case is presumably driven by the rapid oxidative addition of the *in situ*-generated *N*-acyl iminium salt, and the subsequent rapid transmetalation with the distannane, and leaves these functional groups available as synthetic handles for other metal-catalyzed transformations. The reaction is also easily scalable and can be performed on a 1 mmol scale without an appreciable loss of yield (entry 1).

As an illustration of the potential utility of this reaction, it is established that α-aminostannanes can undergo facile Sn–Li exchange for subsequent reaction with electrophiles.[7,8] This reactivity can also be applied to the amidostannanes **1**. The addition of *n*-butyllitium to **1** leads to the *in situ* generation of the lithiated amide, which can be trapped with $CO_2$ to form the carboxylated **2** in good synthetic yields (Scheme 3). Overall, this provides a route for the preparation of a variety of trisubstituted α-amido acid derivatives in two synthetic steps from imines, acid chlorides, and $CO_2$.[9a]

In conclusion, we have reported a mild, palladium-catalyzed method for generating α-amidostannanes from imines, acid chlorides, and $(SnBu_3)_2$. This reaction proceeds at ambient temperature, shows good functional group compatibility, and is easily diversified. Studies directed toward the application of this approach to other metalated products are currently underway.


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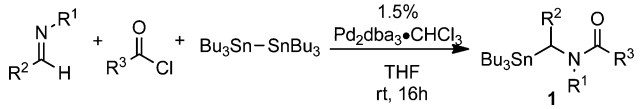
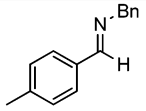
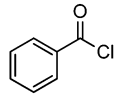
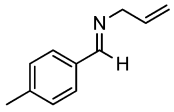
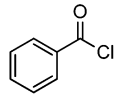
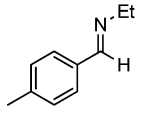
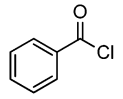
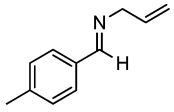
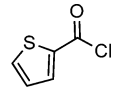
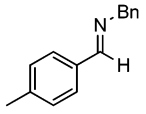
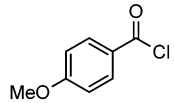
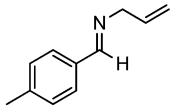
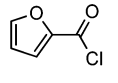
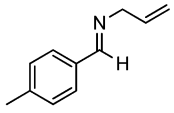
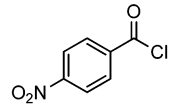
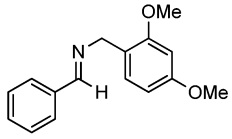
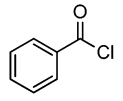
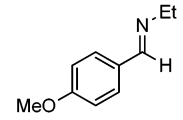
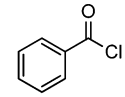
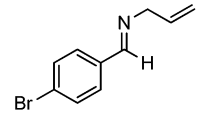
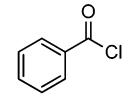
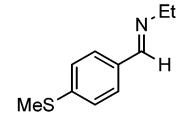
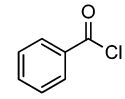
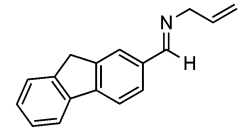
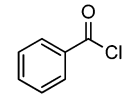
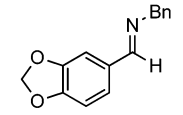
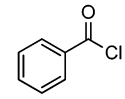
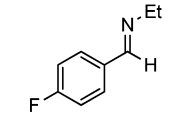
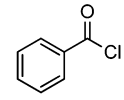
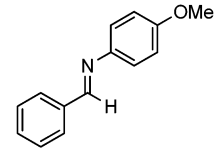
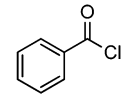
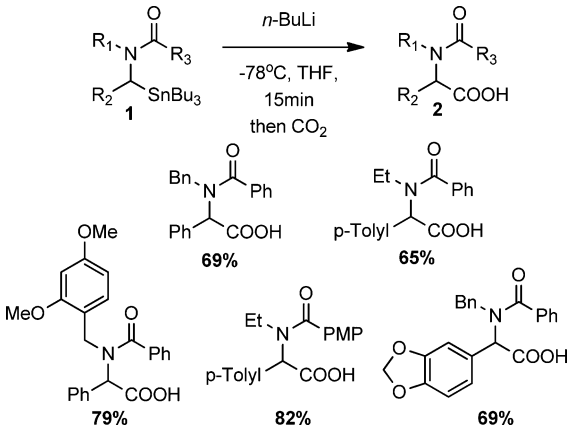
**Table 2. Substrate Scope in α-Amidostannane Synthesis[d]**




| Entry | Imine | Acid Chloride | Yield |
|---|---|---|---|
| 1 |  |  | 74%<br>73%[a] |
| 2 |  |  | 76% |
| 3 |  |  | 67% |
| 4 |  |  | 65% |
| 5 |  |  | 54% |
| 6 |  |  | 67% |
| 7 |  |  | 64% |
| 8 |  |  | 47% |
| 9[b] |  |  | 60% |
| 10[c] |  |  | 46% |
| 11[b] |  |  | 64% |
| 12[c] |  |  | 77% |
| 13[c] |  |  | 75% |
| 14[c] |  |  | 59% |
| 15[c] |  |  | 64% |

[a]On a 1 mmol scale. [b]With 5 mol % Pd. [c]Acid chloride (0.35 mmol), $(SnBu_3)_2$ (0.35 mmol), and 5 mol % Pd. [d]General: imine (0.2 mmol), acid chloride (0.3 mmol), $(SnBu_3)_2$ (0.3 mmol), and 1.5% $Pd_2dba_3{\cdot}CHCl_3$ in 3 mL of THF for 16 h. Isolated yields.

**Scheme 3. Synthesis of α-Amido Acid Derivatives**




## ■ ASSOCIATED CONTENT

### Supporting Information

Details of experimental procedures and $^1H$ and $^{13}C$ NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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