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# One-pot Pd-catalyzed hydrostannation/Stille reaction with acid chlorides as the electrophiles

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**Abstract**

A one-pot hydrostannation/Stille coupling sequence amenable to the employment of acid chloride electrophiles has been developed. In this protocol, palladium mediated alkyne hydrostannations using $Me_3SnF$/PMHS as an in situ trimethyltin hydride source are followed by the addition of the acid chloride to afford a variety of α,β-unsaturated ketones in a single pot.


*Keywords:* Hydrostannation; Stille reaction; Polymethylhydrosiloxane; Tin; Acid chloride; Enone synthesis

Pd-catalyzed cross-couplings of organostannanes and various electrophiles are convenient and widely used reactions for σ-bond construction [1]. Despite the well-established power of the Stille reaction, there are negative issues associated with handling the often unstable and/or toxic organostannanes used in these couplings [2]. To obviate direct manipulation of the stannane coupling partners, our group has developed one-pot Pd-catalyzed hydrostannation/Stille coupling sequences [3] that begin with the in situ generation of triorganotin hydrides [4]. The hydrides so formed react in situ with alkynes to form vinylstannanes, which without isolation undergo Stille cross-coupling reactions (Scheme 1). In earlier reports, we showed that vinyl, aryl, and benzyl halides were all acceptable electrophiles for this sequence [3]. Noticeably absent from this group of electrophiles were acid chlorides.

We considered this omission problematic because acid chlorides represent an important class of Stille electrophiles [5]. In Stille's earliest studies, he showed that reactions with these compounds could efficiently produce α,β-unsaturated ketones [5a]. Thus, we sought to expand the scope of the one pot hydrostannation/Stille protocol to include acid chlorides among the viable electrophiles (Scheme 2).

As it were, the prospect of adopting a straightforward extension of our existing methodology with acid chlorides exposed a number of uncertainties. Unlike previously used electrophiles, reactions with acid chlorides face a host of potential problems. For example, under our standard conditions the triorganotin hydrides used in the hydrostannation step are prepared by the reduction of organotin halides with polymethylhydrosiloxane (PMHS) in the presence of fluoride. Thus, we were confronted with the possibility of residual tin hydride or PMHS reducing the acid chloride [6] or the α,β-unsaturated ketone products [7]. In addition, while Stille reactions with acid chlorides have been done in water [5b], we worried about acid chloride hydrolysis. Furthermore, adventitious formation of HCl from the acid chlorides could promote competitive protiodestannylation of the vinyltin intermediates [8]. Lastly, decarbonylation [5a] of the palladium(II) oxidative addition intermediate was also one of our concerns. Nonetheless, provided these problems could be defeated, achieving the synthesis of various α,β-unsaturated ketones from alkynes and acid chlorides in a single pot using an organotin salt as the initial tin source, a single load of catalyst, and unpurified vinyltin intermediates would be attractive.

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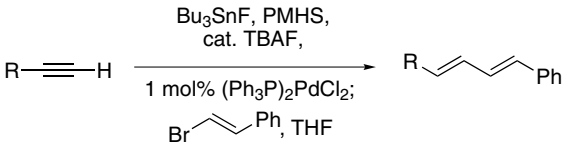
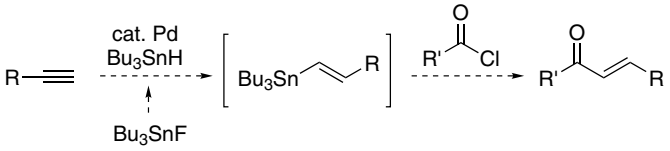



Scheme 1.




Scheme 2.

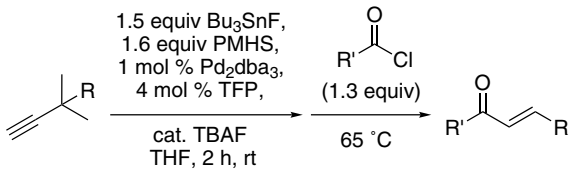
In starting our exploration of this putative one-pot sequence, we opted to use an "anhydrous" variation for the in situ generation of tributyltin hydride [4]. Thus, $Bu_3SnF$, PMHS, and a catalytic amount of TBAF were reacted in the presence of an alkyne and an acid chloride. Not surprisingly, this procedure gave little of the desired α,β-unsaturated ketone as the acid chloride was consumed by the $Bu_3SnF$/PMHS/TBAF combination in advance of the cross-coupling. To avoid this trouble, we simply added the acid chloride (*without any additional Pd-catalyst*) after vinylstannane formation was complete (1 mol% $Pd_2dba_3$, 4 mol% TFP, 1.5 equiv. $Bu_3SnF$, 2.5 equiv. PMHS, cat. TBAF, THF, r.t., ca. 2 h or until complete by GC). Under this two-step one-pot procedure a variety of α,β-unsaturated ketones could be formed (Table 1).

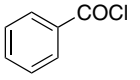
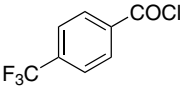
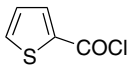
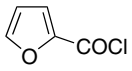
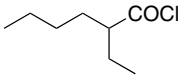
This first generation study only employed alkynes that were tri-substituted at the propargylic position so that our evaluation of the process would not be complicated by the formation of regioisomers. The protocol proved workable with a variety of acid chlorides. Typically cross-couplings were achieved after 6–10 h at 65 °C and the yields could be very high. However, in some cases intrusive amounts of side products were observed. For example, reactions with either 4-trifluoromethylbenzoyl chloride (entry 4) or 2-chlorobenzoyl chloride (Scheme 3) witnessed the formation of the corresponding benzaldehydes and the decarbonylated coupling products [5a]. Moreover, despite our best efforts at reaction optimization some of the product yields remained moderate at best.

We attributed some of these problems to the relatively slow cross-coupling times. In our previously reported tin catalyzed hydrostannation/Stille sequence with other $sp^2$-halides, switching from $Bu_3SnCl$ to the less sterically demanding $Me_3SnCl$ gave faster reaction times and decreased byproduct formation [9]. Looking for a similar outcome for the two-step one-pot acid chloride coupling sequence, the initial tin species was changed from $Bu_3SnF$ to $Me_3SnF$. In doing so, we were gratified to observe a significantly improved process.

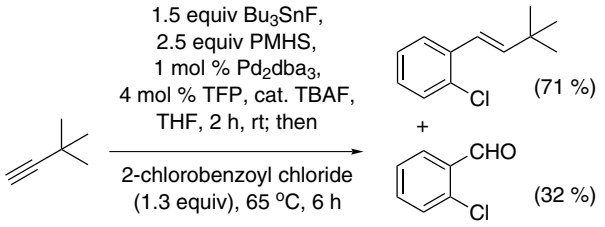
As illustrated in Table 2, using $Me_3SnF$ in place of $Bu_3SnF$ typically decreased cross-coupling times from 6 to 2 h [10]. More importantly; the observed increases in reaction rates were generally met with substantially higher yields and fewer visible side reactions. For example, the previously failed coupling of 2-chlorobenzoyl chloride (entry 3) could now be achieved in an over all yield of 86%. Other entries worthy of further comment include the reaction of 4-bromobenzoyl chloride (entry 6). Despite its two potential coupling sites (acid chloride and aryl bromide) this substrate chemoselectively reacted with the in situ generated vinyl stannane at the acid chloride site to afford the product in near quantitative yield [11]. Furthermore, that product did not suffer from any unwanted dehalogenation of the aryl bromide [12]. Likewise, cinnamoyl chloride afforded the 1,4-diene-3-one in 80% yield without any 1,4-reduction [7] of this activated dienone (entry 12).

Table 1
One-pot hydrostannation/Stille with acid chlorides using $Bu_3SnF$



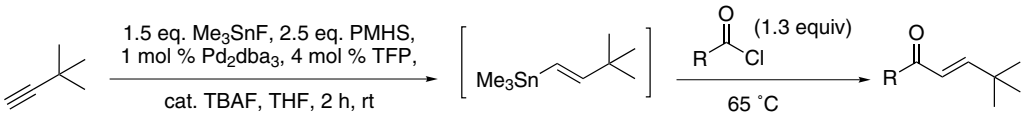

| Entry | R | Acid chloride | Stille rxn time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $CH_3$ |  | 6 | 96 |
| 2 | $CH(CO_2Me)_2$ | | 6 | 84 |
| 3 | $CH_3$ |  | 6 | 56 |
| 4 | $CH(CO_2Me)_2$ | | 2 | 74[b] |
| 5 | $CH_3$ |  | 6 | 57 |
| 6 | $CH_3$ |  | 6 | 63 |
| 7 | $CH_3$ | 1-Naphthoyl acid chloride | 10 | 31 |
| 8 | $CH_3$ |  | 10 | 91 |
| 9 | $CH(CO_2Me)_2$ | | 6 | 58 |

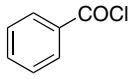
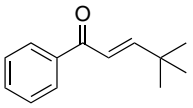
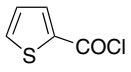
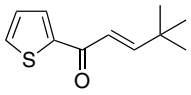
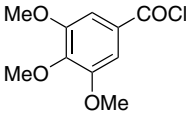
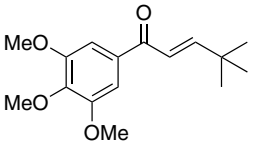
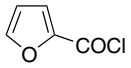
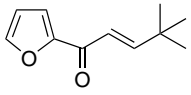
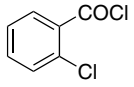
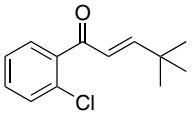
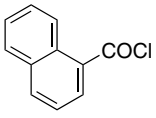
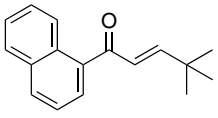
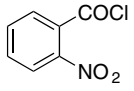
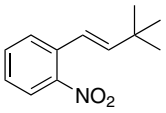
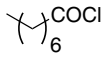
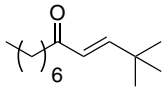
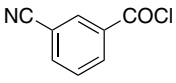
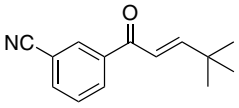
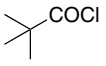
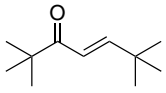
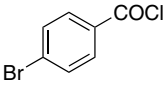
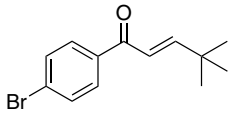
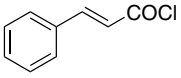
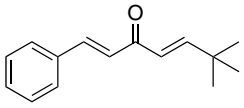
[a] Average isolated yield over two runs.
[b] The decarbonylated product was also observed.




Scheme 3.

Table 2
One-pot hydrostannation/Stille with acid chlorides using $Me_3SnF$ [10]

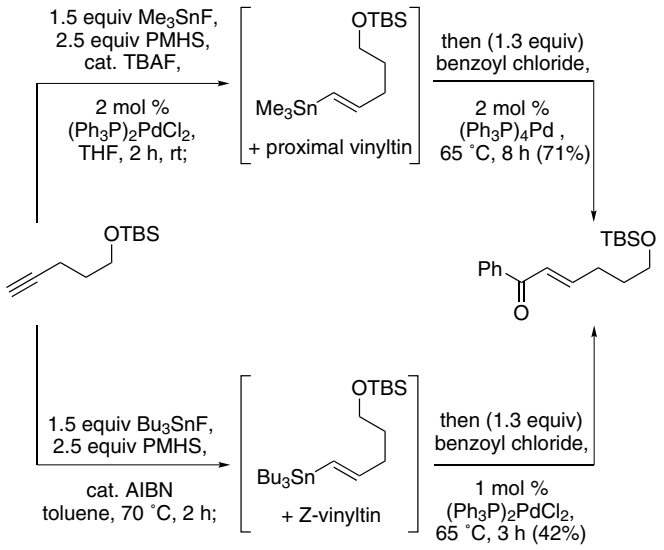



| Entry | Acid chloride | Stille rxn time (h) | Product | Yield[a] (%) | Entry | Acid chloride | Stille rxn time (h) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 2 |  | 94 | 7 |  | 2 |  | 99 |
| 2 |  | 2 |  | 96 | 8 |  | 2 |  | 95 |
| 3 |  | 2 |  | 86 | 9 |  | 2 |  | 92 |
| 4 |  | 2 |  | 72 | 10 |  | 2 |  | 90 |
| 5 |  | 2 |  | 98 | 11 |  | 4 |  | 92 |
| 6 |  | 4 |  | 98 | 12 |  | 4 |  | 80 |

[a] Average isolated yield over two reactions.

Unfortunately, even under these conditions not all substrates were universally accepted. As shown in entry 4, 2-nitrobenzoyl chloride still gave the decarbonylated coupling product, even when the reaction was run under an atmosphere of CO [5a].

Finally, we examined a reaction sequence that started with an alkyne that was not fully substituted at the propargylic position (Scheme 4). As previously mentioned such substrates afford measurable levels of the proximal vinylstannanes under Pd-catalyzed conditions [4,8b,13]. Such vinyltins are known to be sluggish Stille partners [1,14]. This is reflected in the slightly diminished yield (71%) of the cross-coupled product, which arose from the partially selective cross-coupling of the distal vinyltin intermediate with the benzoyl chloride [15]. Furthermore, it must be noted that for this substrate we were also required to add an additional load of the palladium catalyst and extend the Stille reaction time to 8 h to achieve the reported yield. In an attempt to circumvent the distal/proximal regiochemical matter, we first looked at performing the Pd-catalyzed hydrostannation step on the 1-bromoalkyne derivative [3b,8b]. However, for reasons that remain unclear, that substrate did not work well in the hydrostannation/cross-coupling sequence. Another option involved running the hydrostannation step under free radical conditions [4] and then adding the acid chloride along with a Pd-catalysts to carry out the second step. Owing to the volatility [2] of $Me_3SnH$, we chose to run the radical hydrostannation with $Bu_3SnH$. While, this modified procedure was successful at eliminating the proximal isomer (at the cost of some Z-vinylstannane formation), recourse to the tributyltin again gave the α,β-unsaturated ketone in only modest average overall yield (42%). Usefully, the TBS ether survived the fluoride present throughout both successful sequences.




Scheme 4.

In summary, we have expanded the one-pot hydrostannation/Stille coupling method to allow acid chlorides to serve as the electrophilic coupling partner. Problems associated with the use of these reactive building blocks can be avoided by adding the acid chloride to the reaction after the vinylstannane has been produced in situ from $Me_3SnF$/PMHS generated $Me_3SnH$ and a corresponding alkyne. Both aliphatic and electronically varied aromatic acid chlorides can be employed in this one-pot synthesis of α,β-unsaturated ketones.

## Acknowledgments

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.11.041.

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[10] Typical reaction procedure: $Pd_2dba_3$ (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at r.t. for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), $Me_3SnF$ (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.09 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stirr at r.t. for 2 h, at which time the hydrostannation was complete by GC. The acid chloride (1.3 mmol) was then added and the mixture was allowed to stirr at reflux (~65 °C) until the cross-coupling was judged complete by TLC (~2–4 h). At that time, the reaction was diluted with saturated aq. KF (3 mL) and stirred for 0.5 h. The reaction was extracted with $Et_2O$ and $H_2O$ and the aqueous phase was back extracted with $Et_2O$. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the corresponding α,β-unsaturated ketone.

[11] Such chemoselectivity has been previously observed. See: Ref. [5b].

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