

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 $\text{Me}_3\text{SnF/PMHS}$ 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.

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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.

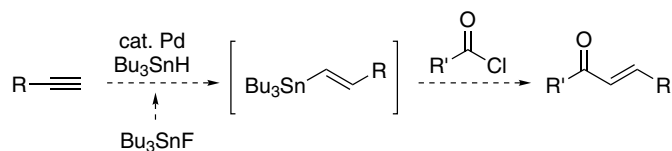
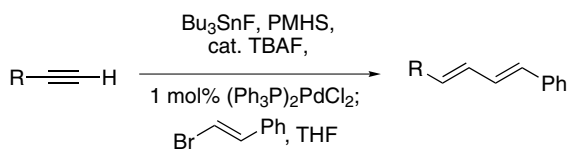
We considered this omission problematic because acid chlorides represent an important class of Stille electrophiles [5]. In Stille's earliest studies, he showed that reactions with these compounds could efficiently produce α,β -unsaturated ketones [5a]. Thus, we sought to expand the scope of the

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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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.

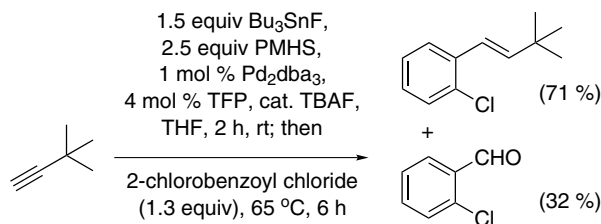
We attributed some of these problems to the relatively slow cross-coupling times. In our previously reported tin catalyzed hydrostannation/Stille sequence with other sp^2 -halides, switching from Bu_3SnCl to the less sterically demanding Me_3SnCl gave faster reaction times and decreased byproduct formation [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

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 ₂ Me) ₂		6	84
3	CH ₃		6	56
4	CH(CO ₂ Me) 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 ₂ Me) ₂		6	58

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

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).

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