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A Straightforward Protocol for One-Pot Allylic Aminations/Stille Couplings

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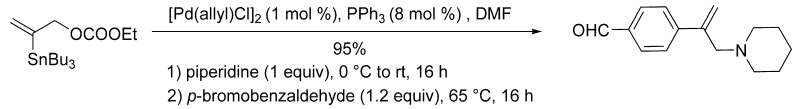
ABSTRACT



Stannylated allylic carbonates are suitable substrates for Pd-catalyzed allylic aminations. In DMF and with [Pd(allyl)Cl]$_2$ as catalyst, the stannylated allyl amines formed can be directly coupled with electrophiles according to the Stille protocol, giving rise to highly functionalized building blocks in excellent yields.

A key topic in chemical biology and pharmaceutical chemistry is the design and synthesis of compound libraries, with the focus on small molecules. Such molecules are suitable candidates to investigate the biological function of proteins and can be used as lead structures for the development of drug candidates.[1] The diversity-oriented synthesis (DOS) concept, introduced by Schreiber et al.,[2] is an excellent tool to generate libraries with high substitutional, stereochemical, and/or scaffold diversity.[3] In principle, one can differentiate three different phases. In the first step, building blocks with orthogonal sets of functionality, suitable for subsequent couplings, are created. In the next step, intermolecular coupling reactions generate molecular complexity, and subsequent cyclizations in the final step allow for the synthesis of complex three-dimensional frameworks and topological structures.[4] For example, Meldal et al. used this approach for the synthesis of complex peptidic structures.[5]

Our group is also involved in the synthesis of unusual amino acids and peptides,[6] and we developed a straightforward approach to peptide libraries based on Stille couplings.[7] The Stille reaction[8] is especially suited for this purpose, because no epimerization is observed in reactions of stannylated amino acids because of the neutral reaction condi-

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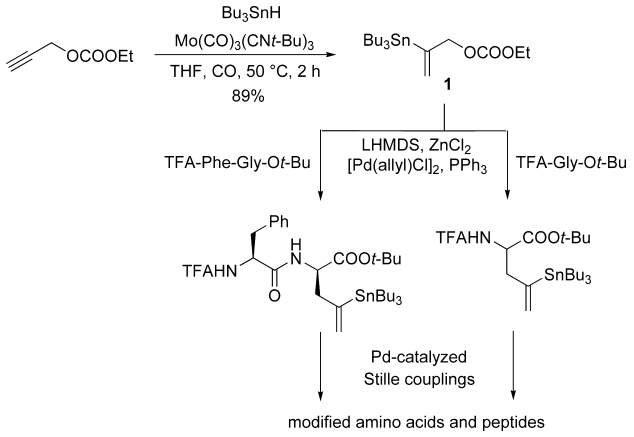
tions.[9] The stannylated amino acids are accessible via chelate-Claisen rearrangement of stannylated allylic esters or via Pd-catalyzed allylic alkylation.[10] The required stannylated allylic esters can be obtained by a Mo-catalyzed regioselective hydrostannation of the corresponding propargylic substrates (Scheme 1).[11]

Scheme 1. Synthesis of Stannylated Amino Acids and Peptides



This Mo-catalyzed hydrostannation can be applied to a wide range of (electron-demanding) alkynes,[12] giving rise to orthogonal functionalized substrates such as stannylated allylic sulfones[13] or phosphonates,[14] which can be subjected to a subsequent Stille coupling/olefination protocol. With respect to DOS the stannylated esters and carbonates (**1**) are especially interesting substrates, because they can be further modified at the allylic positions via nucleophilic substitution and at the central position via cross-coupling with electrophiles. Both reactions can be catalyzed by Pd, and in principle, it should be possible to combine both couplings to a one-pot protocol. However, this is not a trivial issue, because the reaction conditions for these two processes are generally different. In addition, vinylstannanes can undergo Pd-catalyzed cross-couplings with allylic substrates,[15] and therefore oligo- and polymerizations of the stannylated allyl compound have to be avoided. Therefore, one has to find reaction conditions where one of the two functionalities reacts selectively. Very recently, Fillion et al. reported a sequential Rh(I)-catalyzed 1,4-addition of stannylated allyl carbonates toward alkylidene Meldrum's acids, followed by Pd-catalyzed intramolecular allylations.[16]

Our previous work with the chelated enolates of amino acids and peptides indicated that the stannylated allylic acetates and carbonates react with good nucleophiles already at low temperatures (<−20 °C), while the Stille couplings generally occur at temperatures around 50 °C. Unfortunately, the strong basic reaction conditions for the enolate allylation were not compatible with the cross-coupling conditions. Therefore, we focused our investigations on other reactive nucleophiles allowing a selective reaction of the allyl fragment without affecting the vinylstannane moiety. Malonates, the "standard nucleophiles" in allylic alkylations, are unsuitable candidates, reacting in a temperature range where decomposition of the stannylated substrate is competitive with the nucleophilic substitution. Detailed investigations showed that the decomposition in the presence of Pd^0 toward the corresponding allenes is a fast process as determined by in situ NMR.[17]

Therefore, we next switched to the more reactive amines (Table 1) that are suitable candidates for the synthesis of alkaloids. To avoid double allylation, we started our investigations with piperidine as nucleophile. Interestingly, no allylation product was obtained in THF at room temperature, although a complete consumption of allyl carbonate **1** was observed (entry 1). Obviously the decomposition is also faster under these conditions, but at 0 °C a good yield of coupling product was obtained (entry 2). Obviously THF is not the solvent of choice for these allylations, because in the more polar DMF no decomposition was observed even at room temperature (entry 3). The yield could be slightly increased if the reaction was run at 0 °C (entry 4). A further improvement was observed after switching from $[Pd(allyl)Cl]_2$ to $Pd(PPh_3)_4$ as catalyst (entry 5). Under these optimized conditions we investigated the allylation of several other, also primary, amines. While dialkylation was observed with sterically unhindered amines, this side reaction is no issue in allylations of sterically hindered, branched amines such as phenylethylamine (entry 6) or amino acid esters (entry 7). Even with alaninate **2c** and glycinate **2d**, an excellent yield was obtained, especially if 2 equiv of the nucleophile was used (entries 7, 8).

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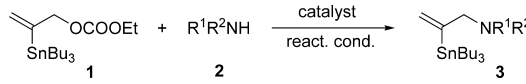
Table 1. Allylic Aminations of Stannylated Allyl Carbonates

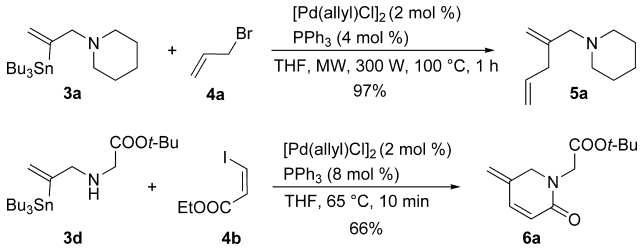


entry	R^1R^2NH	reaction conditions	catalyst[a]	product	yield (%)
1	piperidine (**2a**)[b]	THF, rt, 1 h	**A**	**3a**	0
2	piperidine (**2a**)[b]	THF, 0 °C, 5 h	**A**	**3a**	74
3	piperidine (**2a**)[b]	DMF, rt, 1 h	**A**	**3a**	70
4	piperidine (**2a**)[b]	DMF, 0 °C, 1.5 h	**A**	**3a**	79
5	piperidine (**2a**)[b]	DMF, 0 °C, 2 h	**B**	**3a**	94
6	1-phenylethylamine (**2b**)[b]	DMF, 0 °C, 16 h	**B**	**3b**	84
7	Ala-O*t*-Bu (**2c**)[c]	DMF, 0 °C, 16 h	**B**	**3c**	94
8	Gly-O*t*-Bu (**2d**)[c]	DMF, 0 °C, 16 h	**B**	**3d**	87

[a] Catalysts: **A**, 1 mol % $[Pd(allyl)Cl]_2$, 4.5 mol % PPh_3; **B**, 2 mol % $Pd(PPh_3)_4$. [b] 1.2 equiv amine used. [c] 2 equiv amine used.

With these stannylated allyl amines in hand we tried to optimize the reaction conditions for the subsequent Stille coupling (Scheme 2). Interestingly, no reaction was observed

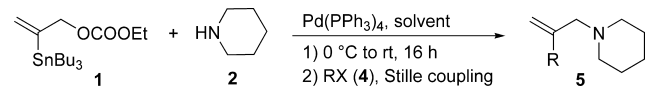
Scheme 2. Stille Couplings of Stannylated Amines

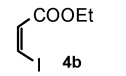
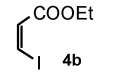
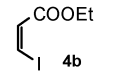
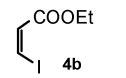
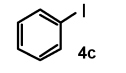
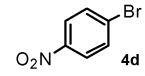
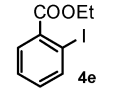
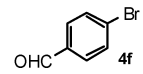


in DMF or by using $Pd(PPh_3)_4$ (the best conditions in the allylic amination), but excellent yields were obtained with $[Pd(allyl)Cl]_2/PPh_3$ in THF, either by conventional heating or under microwave (MW) irradiation. In the case of the stannylated glycine derivative **3d**, the Stille coupling with iodoacrylate gave direct access to lactame **6a**.

On the basis of these encouraging results, we focused next on the one-pot protocol of allylic aminations/Stille couplings (Table 2). In our first attempts we used piperidine as nucleophile and (*Z*)-iodoacrylate as electrophile, because both reagents in general give clean and good coupling results. Indeed, with this electrophile excellent yields were obtained in absolute acetonitrile (entry 1) and DMF (entry 2) as well. For the allylic amination the reaction mixture was warmed from 0 °C to room temp.erature, and for the Stille coupling the mixture was heated to 65 °C after the addition of the electrophile. Under these conditions a partial isomerization of the double bond was observed, which was slightly worse in acetonitrile. To suppress this undesired process, we carried out the reaction also at room temperature (entry 3). Although the reaction was a little slower, under these conditions a complete conversion was observed after 3 h, and the isomerization could be reduced to a minimum. Obviously the higher temperature is responsible for the (*E*/*Z*)-interconversion. The (*E*)-product could be obtained nearly exclusively if the reaction was carried out in "wet" DMF (entry 4). In this solvent, the allylic amination was significantly faster, but the Stille coupling slowed down. After 4 h at 65 °C only incomplete conversion was observed, and the reaction mixture was heated to 90 °C after further 2 equiv of the electrophile had been added. Under these conditions the

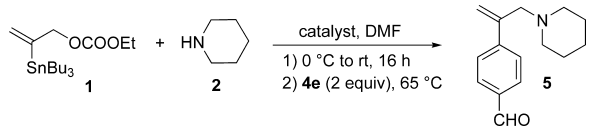
Table 2. One-Pot Allylic Alkylation/Stille Coupling



entry	solvent	RX[a]	Stille coupling	**5**	yield (%)	ratio *E*/*Z*
1	$MeCN_{abs.}$	 **4b**	65 °C, 30 min	**5b**	91	34/64
2	$DMF_{abs.}$	 **4b**	65 °C, 30 min	**5b**	91	18/82
3	$DMF_{abs.}$	 **4b**	rt, 3 h	**5b**	96	9/91
4	DMF_{wet}	 **4b**	1) 65 °C, 4 h; 90 °C, 1 h 2) + 1 equiv RX, 90 °C, 0.5 h	**5b**	91	94/6
5	$DMF_{abs.}$	 **4c**	65 °C, 3 h; 90 °C, 1 h	**5c**	82	--
6	$DMF_{abs.}$	 **4d**	65 °C, 3 h; 90 °C, 1 h	**5d**	80	--
7	$DMF_{abs.}$	 **4e**	65 °C, 3 h; 90 °C, 1 h	**5e**	34	--
8	$DMF_{abs.}$	 **4f**	90 °C, 16 h	**5f**	70	--

[a] Amount of reagents used: **2** (1.2 equiv), **4b** (1.05 equiv), **4c** (2 equiv), **4d** (2 equiv), **4e** (2 equiv), **4f** (1.2 equiv).

Table 3. Optimization of the Catalyst



entry	catalyst	ratio Pd:P	yield (%)	time (h)	observation
1	$Pd(PPh_3)_4$ (2 mol %)	1:4	70	48	$Pd_{(s)}$ after 1 h
2	(1) $Pd(PPh_3)_4$ (2 mol %); (2) $[Pd(allyl)Cl]_2$ (1 mol %)	1:2	82	48	$Pd_{(s)}$ after 1 h
3	(1) $Pd(PPh_3)_4$ (2 mol %); (2) Pd/C (10%, 1 mol %)		88	20	complete conversion
4	(1) $Pd(PPh_3)_4$ (2 mol %); (2) $[Pd(allyl)Cl]_2$ (3 mol %)	1:1	39	48	$Pd_{(s)}$ immediately, incomplete conversion
5	$[Pd(allyl)Cl]_2$ (1 mol %), PPh_3 (2 mol %)	1:1	61	16	$Pd_{(s)}$ immediately
6	$[Pd(allyl)Cl]_2$ (1 mol %), PPh_3 (4 mol %)	1:2	86	7	$Pd_{(s)}$ formed slowly, complete conversion
7	$[Pd(allyl)Cl]_2$ (1 mol %), PPh_3 (6 mol %)	1:3	88	16	no $Pd_{(s)}$, complete conversion
8	$[Pd(allyl)Cl]_2$ (1 mol %), PPh_3 (8 mol %)	1:4	92	16	no $Pd_{(s)}$, complete conversion
9	$[Pd(allyl)Cl]_2$ (1 mol %), PPh_3 (8 mol %)	1:4	95	16	complete conversion, only 1.2 equiv of **3e**

isomerization obviously is faster than the Stille coupling. Now, both coupling products can be obtained from the same starting materials by simple changing of the reaction conditions.

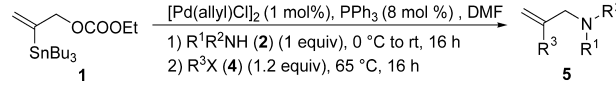
To prove the generality of this new one-pot process, we investigated the Stille coupling of several other electrophiles. High yields were also obtained with iodobenzene and *p*-nitrobromobenzene (entries 5 and 6), but substituents in the *O*-positions seem to be detrimental (entry 7). In this case precipitation of $Pd_{(s)}$ was observed, which was also the reason for the lower yield obtained with *p*-bromobenzaldehyde (entry 8).

Because this observation was made also with several other less reactive electrophiles, we next focused on an optimization of our catalyst system to avoid this undesired side reaction (Table 3). *p*-Bromobenzaldehyde (**3e**) was the investigated substrate, and 2 equiv of this electrophile was used to ensure complete conversion. As before, piperidine was used in a slight excess (1.2 equiv). Under the standard conditions, formation of $Pd_{(s)}$ was observed after 1 h, and prolonging the reaction time did not result in a better yield (entry 1). The yield could be increased by adding allylpalladiumchloride (entry 2) or Pd/C (entry 3) during the Stille coupling step. Interestingly, if $[allylPdCl]_2$ was added in such a ratio that the overall Pd/PPh_3 ratio was 1:1, a direct precipitation of $Pd_{(s)}$ was observed, resulting in a minimal conversion.

Because $[allylPdCl]_2$ is also a good catalyst for allylic alkylations, we tried to use this catalyst solely for both steps and varied the amount of phosphine added (entries 5−9). At a Pd/Pd ratio of 1:1, again $Pd_{(s)}$ was formed immediately (entry 5). Increasing the amount of PPh_3 resulted in a stabilization of the catalyst, resulting in excellent overall yields. In the presence of 4 equiv of PPh_3, complete conversion was observed even in the presence of only 1.2 equiv of the electrophile (entry 9).

Under these optimized conditions, we investiaged a range of further one-pot reactions (Table 4). Besides aryliodides also the corresponding triflates (entry 1) and vinylbromides (entry 2) can be used, and both primary and secondary amines give good to excellent results.

Table 4. One-Pot Allylation/Stille Coupling under Optimized Conditions



entry	R^1R^2NH	R^3X	product	yield (%)
1	piperidine (**2a**)	PhOTf (**4g**)	**5c**	94
2	piperidine (**2a**)	(*E*)-*β*-Br-styrene (**4h**)	**5g**	84
3	1-phenylethylamine (**2b**)	PhI (**4c**)	**5h**	73
4	*t*-$BuNH_2$ (**2e**)	PhI (**4c**)	**5i**	89
5	Ile-O*t*-Bu (**2f**)	PhI (**4c**)	**5k**	72

In conclusion, we could show that stannylated allylic carbonates are excellent C3 building blocks for the diversity-oriented syntheses of functionalized amines. By careful optimization of the reaction conditions, an allylic amination and a subsequent Stille coupling can be performed as a one-pot reaction. Synthetic applications of this straightforward protocol are currently under investigation.

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Supporting Information Available: Experimental procedures and well as analytical and spectroscopic data of coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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