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PAPER

Stannylated allyl carbonates as versatile building blocks for the diversity oriented synthesis of allylic amines and amides†

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

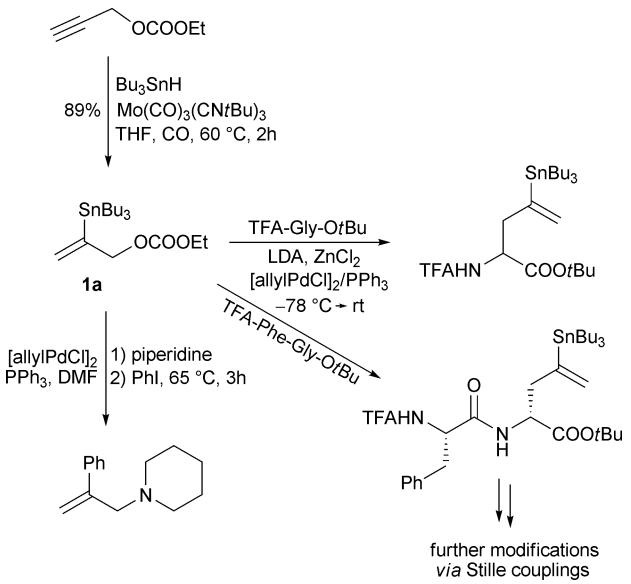
Introduction

In pharmaceutical chemistry as well as in chemical biology the generation of libraries of small molecules is a powerful tool to find new lead structures for the development of new drug candidates.[1] In particular diversity oriented synthesis (DOS), introduced by Schreiber *et al.*,[2] is a concept that provides a high degree of substitutional, stereochemical and scaffold diversity.[3]

A key point for a successful application of this protocol is the proper choice of suitable building blocks, allowing a wide range of different modifications and the generation of molecular complexity. Stannylated allylic carbonates, such as **1a**, are absolutely predestined for this purpose, because they combine the structural features of two very important cross coupling reactions, the allylic alkylation[4] and the Stille coupling.[5] The stannylated carbonates can easily be obtained by a molybdenum-catalyzed hydrostannation of the corresponding propargyl carbonate in a highly regioselective fashion (Scheme 1).[6] The best results were obtained under an atmosphere of CO, which suppressed side reactions such as protodestannylations nearly completely.[7] With these stannanes in hand we could show that highly reactive nucleophiles, such as chelated enolates of α-amino esters, undergo a very clean allylic alkylation, giving rise to stannylated amino acid derivatives.[8] This protocol can also be applied to the modification of peptides by using peptide enolates.[9] In this case, the stereochemical outcome of the reaction can be controlled by the stereogenic centers in the peptide chain. The stannylated amino acids and peptides obtained can subsequently be subjected to Stille couplings, which proceed under neutral conditions, allowing side chain modification without epimerization of the stereogenic centers.[10]

These examples clearly indicate that with reactive nucleophiles it is possible to selectively address the allylcarbonate subunit, without affecting the vinylstannane functionality. This is not a trivial issue, because vinylstannanes can also react as electrophiles in allylic alkylations, which might result in an oligo- or polymerization of the allylic substrate **1**. With less reactive nucleophiles such as malonates, in general no stannylated allylation products are obtained, because elimination of the substrate **1** towards the corresponding allene is a faster process.[11]

To increase the synthetic potential of the stannylated allyl substrates **1**, we investigated a wide range of other nucleophiles including several types of amines. Amines are more nucleophilic compared to *C*-nucleophiles such as malonates, allowing allylations under milder conditions without decomposition. In principle, under optimized conditions the allylic amination and the subsequent Stille coupling can be carried out in an one-pot protocol.[12] Herein we describe the details as well as scope and limitations of this interesting allylic amination process.



Scheme 1 Stannylated allyl carbonates (**1a**) as versatile building blocks.

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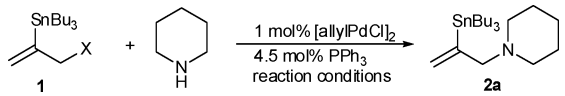
Table 1 Investigation of the reaction conditions and the leaving groups



Entry	Subs.	X	Reaction conditions	Yield (%)[a]
1	**1b**	OCOOMe	THF, 0 °C, 5 h	74
2	**1b**	OCOOMe	THF, 20 °C, 1 h	0
3	**1b**	OCOOMe	DMF, 20 °C, 1 h	70
4	**1b**	OCOOMe	DMF, 0 °C, 2 h	79
5	**1b**	OCOOMe	DMF, −20 °C, 7 h	80
6	**1a**	OCOOEt	DMF, 0 °C, 2 h	81
7	**1c**	OCOO*t*Bu	DMF, 0 °C, 2 h	56
8	**1d**	OAc	DMF, 0 °C, 2 h	88 (impure)
9	**1e**	OTHP	DMF, 0 °C, 2 h	71

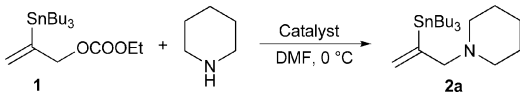
[a] 1.1 equiv of piperidine were used.

Results and discussion

To avoid side reactions such as double allylations we started our investigations with piperidine as the nucleophile (1.1 equiv). THF was used as the solvent and [allylPdCl]$_2$/PPh$_3$ as the catalyst, as these were the conditions which gave the best results in previous work with the amino acid enolates.[8] While a good conversion and yield was obtained at 0 °C from the methyl carbonate **1b** (Table 1, entry 1), absolutely no allylation product was obtained at room temperature (entry 2). Under these conditions, elimination towards the allene, as also observed previously with malonates, is much faster than the allylic substitution. Obviously THF is a good solvent for allylic alkylations at low temperatures, but not at room temperature. Therefore, we investigated several other solvents. By far the best results were obtained in DMF, which provided a clean allylation product at room temperature (entry 3). At 0 °C the reaction was significantly faster than in THF (entry 4), and even at −20 °C a high yield of allylated piperidine was obtained, although the reaction is much slower at this temperature (entry 5). Therefore, we carried out our further investigations concerning the influence of the leaving group at 0 °C. The results with the ethylcarbonate **1a** (entry 6) were comparable to those obtained with the methyl derivative **1b**, while with the sterically more demanding *t*-butylcarbonate **1c** a significant drop in the yield was observed (entry 7). So far the best yield was obtained with the acetate **1d**, but in this case the allylation product was contaminated with a not identified side product, which could not be removed by flash chromatography. Interestingly, even the THP ether **1e** gave a satisfying yield, although THP is not a typical leaving group for allylic alkylations (entry 9).

Of course, one might also expect to see an influence of the catalyst system on the outcome of the reaction. This forced us to investigate the influence of different ligands under the optimized reaction conditions (Table 2). No difference was observed by switching from PPh$_3$ to the bidentate ligand dppf, while with electron-rich phosphine PBu$_3$ a significant drop of the reactivity was observed (entry 2). By far the best yield was obtained with commercial Pd(PPh$_3$)$_4$ (entry 3). This catalyst is relatively sensitive and should be stored under argon at low temperature (−20 °C). Otherwise the yields vary (5–10%) depending on the quality of the catalyst. Therefore, it is a good alternative to generate the active catalyst *in situ* from Pd(OAc)$_2$ and PPh$_3$ (entry 4).

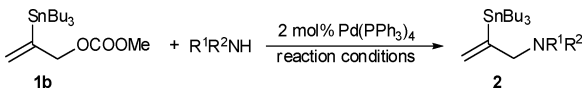
Table 2 Optimization of the catalyst for allylic aminations



Entry	Catalyst	Yield (%)[a]
1	1 mol% [allylPdCl]$_2$, 4.5 mol% dppf	79
2	1 mol% [allylPdCl]$_2$, 4.5 mol% PBu$_3$	n.d.[b]
3	2 mol% Pd(PPh$_3$)$_4$	94
4	2 mol% Pd(OAc)$_2$, 4.5 mol% PPh$_3$	94

[a] 1.1 equiv of piperidine were used. [b] Slow reaction and incomplete conversion.

Table 3 Allylation of a wide range of amines



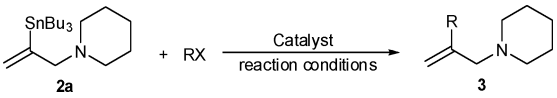
Entry	R^1R^2NH	Reaction conditions	Product	Yield (%)
1	morpholine	DMF, 0 °C, 2 h	**2b**	87
2	pyrrolidine	DMF, 0 °C, 2 h	**2c**	86
3	Et_2NH	DMF, 0 °C, 2 h	**2d**	90
4	$(allyl)_2NH$	DMF, 0 °C to rt, 16 h	**2e**	84
5	Bn_2NH	DMF, 0 °C to rt, 16 h	**2f**	53
6	$(cHex)_2NH$	DMF, 0 °C to rt, 16 h	**2g**	17
7	Ph_2NH	DMF, 0 °C to rt, 16 h	—	0
8	$PhNH_2$	DMF, 0 °C to rt, 16 h	**2h**	25
9	*p*-$MeOC_6H_4NH_2$	DMF, 0 °C to rt, 16 h	**2i**	58
10	$BnNH_2$	DMF, 0 °C to rt, 16 h	**2k**	51[a]
11	$cHexNH_2$	DMF, 0 °C to rt, 16 h	**2l**	65[b]
12	$PhCH(CH_3)NH_2$	DMF, 0 °C to rt, 16 h	**2m**	84

[a] In addition 34% of the diallylated product **2k′** was obtained. [b] In addition 19% of the diallylated product **2l′** was obtained.

Under these optimized reaction conditions we next examined the allylation of a wide range of amines to evaluate the scope and limitations of this reaction (Table 3). Sterically unhindered secondary amines such as morpholine, pyrrolidine, diethylamine, diallylamine showed a reactivity comparable to piperidine and gave a comparable yields (entries 1 to 4). With increasing steric demand of the nucleophile the yield dropped significantly, becoming as low as 17% in case of the dicyclohexyl derivative **2g** (entry 6). No reaction at all was observed with diphenylamine (entry 7), but here probably also the electronic effect of the two phenyl groups has to be considered, in addition to the steric aspects. For example, with the sterically unhindered but not very nucleophilic aniline also a low yield was obtained (entry 8). Increasing the nucleophilic character of this amine by introduction of an electron donating group, such as in anisidine, resulted in acceptable yield of the allylation product **2i** (entry 9). As expected, primary alkylamines (entries 10 and 11) gave better yields, but in these cases also significant amounts of diallylated products were formed, which could be separated by flash chromatography. By far the best results with primary amines were obtained with 1-phenylethylamine (entry 12) which provided the monoallylated product **2m** exclusively in high yield.

With these stannylated allylamines in hand we next tried to optimize the reaction conditions for the subsequent Stille coupling (Table 4). As standard substrate we used the allylated piperidine

Table 4 Optimization of the Stille coupling

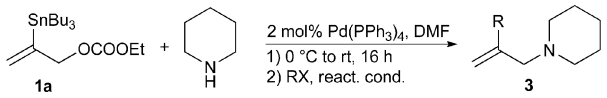


2a 3

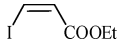
Entry	RX[a]	Cat.[b]	Reaction conditions	Product	Yield (%)
1	allylBr	**A**	THF, 60 °C, 2 d	**3a**	97
2	PhI	**A**	THF, 60 °C, 3 d	**3b**	99
3	PhBr	**A**	THF, 60 °C, 3 d	**3b**	98
4	BnBr	**A**	THF, 60 °C, 3 d	**3c**	37
5	allylBr	**A**	THF, MW, 300 W, 100 °C, 1 h	**3a**	97
6	allylBr	**A**	DMF, MW, 300 W, 100 °C, 1 h	**3a**	0
7	allylBr	**B**	THF, MW, 300 W, 100 °C, 1 h	**3a**	0

[a] 2 equiv of the electrophile RX were used. [b] Catalysts used: **A**: 2 mol% $[allylPdCl]_2$, 4 mol% PPh_3; **B**: 2 mol% $Pd(PPh_3)_4$.

Table 5 One-pot allylic amination–Stille couplings



1a 3

Entry	RX[a]	Reaction conditions	Product	Yield (%)
1		rt, 3 h	**3d**	96[b]
2	PhI	1) 65 °C, 3 h; 2) 90 °C, 1 h	**3b**	82
3	*p*-$NO_2C_6H_4Br$	1) 65 °C, 3 h; 2) 90 °C, 1 h	**3e**	80
4	*p*-BrC_6H_4CHO	90 °C, 16 h	**3f**	70

[a] 2 equiv of the electrophile RX were used. [b] *E*/*Z* ratio 9/91.

derivative **2a** and we investigated the coupling with allylbromide under various reaction conditions with the aim to find conditions which allow the combination of the two Pd-catalyzed processes to a simple one-pot protocol.

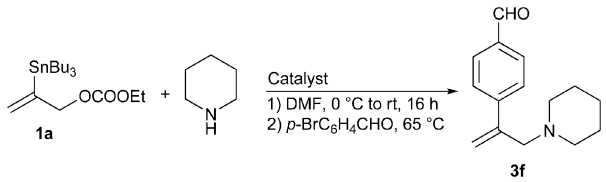
An excellent yield of the coupling product **3a** was obtained in THF, using $[allylPdCl]_2$ and PPh_3 (ratio Pd : PPh_3 1 : 1) as catalyst, reaction conditions which have been optimized previously for the modification of stannylated amino acids and peptides.[8,9] After 2 d at 60 °C an almost quantitative yield of coupling product **3a** was obtained (Table 4, entry 1). In principle, comparable results were obtained with aryl halides (entries 2 and 3), although these substrates were slightly less reactive. In contrast, with benzylbromide the yield of Stille product dropped significantly (entry 4), probably because of side reactions such as *N*-benzylation. The relatively long reaction time under the standard conditions for the Stille coupling could be dramatically reduced by using microwave (MW) irradiation. Under these conditions an almost quantitative yield was obtained after 1 h of irradiation. It is worth mentioning, that no coupling product could be obtained in DMF or if $Pd(PPh_3)_4$ was used as a catalyst (entries 6 and 7), conditions which had been found to be the best for the allylic aminations.

Based on these encouraging results we next focused on the development of an one-pot process for the allylic amination and the subsequent Stille coupling. This is not a trivial issue, because the reaction conditions are different for both reactions, although Pd is used as the catalyst in each of these processes. While a phosphine/Pd-ratio of >2 : 1 is perfect for allylic alkylations, the best results in the Stille coupling are generally obtained with an 1 : 1 ratio. Therefore, we tried to find conditions which were a good compromise for both reactions. To make sure that the first step—the allylic amination—proceeds without problems, we first used the optimized conditions for this reaction (Table 5). Piperidine was reacted with stannylated allylcarbonate **1a** at 0 °C and the reaction mixture was warmed to room temperature overnight. As a reactive electrophile (*Z*)-iodoacrylate was added in excess (2 equiv.) and the reaction mixture was stirred at room temperature. After 3 h a complete conversion was observed and the coupling product **3d** was obtained in excellent yield (entry 1). Interestingly, around 10% of the isomerized (*E*)-coupling product was obtained. Under the same conditions no reaction was observed with iodobenzene (entry 2). After heating to 65 °C for 3 h product formation was observed, but the reaction was not complete, but after increasing the temperature to 90 °C the reaction was complete after 1 h and the coupling product **3b** was isolated in high yield (entry 2). A similar reactivity and yield were observed for *p*-nitrobromobenzene (entry 3), while with *p*-bromobenzaldehyde the reaction mixture had to be warmed to 90 °C for 16 h to get a complete consumption of the starting material (entry 4). But under these conditions the catalyst was not stable and precipitation of $Pd_{(s)}$ was observed.

Therefore, we decided to use this reaction to optimize our catalyst system for the one-pot process (Table 6). A comparable yield was obtained if the reaction mixture was warmed to 65 °C for 48 h, although already after 1 h $Pd_{(s)}$ started to precipitate (entry 1). To reduce the Pd : P ratio into a range which should be more suitable for Stille couplings, we added $[allylPdCl]_2$ together with the elctrophile after the allylic amination step. And indeed, if the two Pd-catalysts were used in equimolar amounts (Pd/P 1 : 2), the yield could be increased to 82% (entry 2), but also here a slow precipitation of $Pd_{(s)}$ was observed. A further reduction of the Pd/P-ratio definitely was counterproductive (entry 3). $Pd_{(s)}$ was formed immediately, no complete conversion was observed, and the yield dropped dramatically. Because $[allylPdCl]_2$ in general is also a good catalyst for allylic alkylations, we decided to use this Pd source solely and to vary the Pd/P-ratio simply by adding different amounts of PPh_3. Interestingly, the catalytic species generated by this protocol seems to be more reactive and at the same time more stable, giving better yields in a shorter time. Although a slow precipitation of $Pd_{(s)}$ was observed at a Pd/P-ratio of 1 : 2, the reaction was complete after 7 h (entry 4). Increasing the amount of phosphine resulted in the formation of a stable catalyst and at a 1 : 4 ratio nearly a quantitative yield of the coupling product **3f** was obtained (entry 5).

Under these optimized conditions we investigated a wide range of further one-pot reactions, using different electrophiles and amines (Table 7). For example, the yield of the reaction with piperidine and PhI could be increased to 96% (entry 1), and a comparable result was obtained with the corresponding triflate (entry 2). Aryl bromides are less reactive, requiring higher reaction temperatures (entries 3–7). For example, with *p*-methoxybromobenzene a slow reaction was observed at 65 °C, while the reaction was complete after 6 h at 100 °C (entry 5). Replacing the methoxy group by an electron-withdrawing nitro group allowed the reduction of the temperature (entry 6) and the coupling of aryl chlorides (entry 8). β-Bromostryrene showed a reactivity comparable to the aryl iodides and triflates (entry 9). Replacing piperidine by other

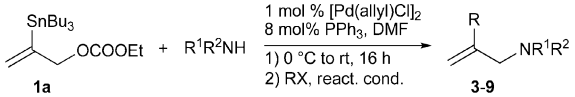
Table 6 Optimization of the catalyst system for one-pot reactions



Entry	Catalyst	Ratio Pd : P	*t* (h)	Yield (%)	Comment
1	2 mol% $Pd(PPh_3)_4$	1 : 4	48	70[a]	$Pd_{(s)}$ after 1 h
2	1) 2 mol% $Pd(PPh_3)_4$ 2) 1 mol% $[allylPdCl]_2$	1 : 2	48	82[a]	$Pd_{(s)}$ after 1 h
3	1) 2 mol% $Pd(PPh_3)_4$ 2) 3 mol% $[allylPdCl]_2$	1 : 1	48	39[a]	$Pd_{(s)}$ immediately, no compl. conv.
4	1 mol% $[allylPdCl]_2$, 4 mol% PPh_3	1 : 2	7	86[a]	$Pd_{(s)}$ formed slowly, compl. conversion.
5	1 mol% $[allylPdCl]_2$, 8 mol% PPh_3	1 : 4	16	95[b]	compl. conversion.

[a] 2 equiv of electrophile were used. [b] 1.2 equiv of electrophile were used.

Table 7 Optimized one-pot allylic amination–Stille couplings



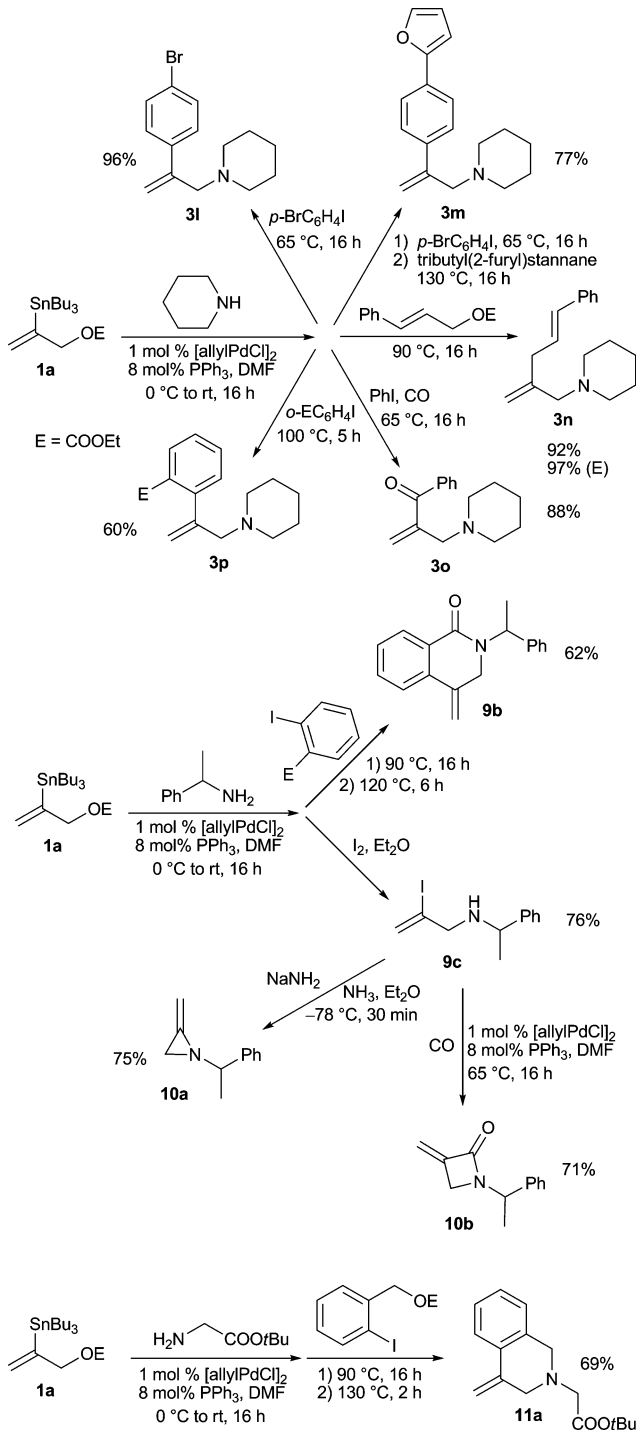
Entry	R^1R^2NH	RX	React. cond.	Product	Yield (%)
1	piperidine	PhI	65 °C, 16 h	**3b**	96
2	piperidine	PhOTf	65 °C, 16 h	**3b**	94
3	piperidine	PhBr	100 °C, 6 h	**3b**	64
4	piperidine	2-bromo-naphthalin	90 °C, 16 h	**3g**	62
5	piperidine	5-bromo-pyrimidine	90 °C, 16 h	**3h**	97
6	piperidine	*p*-$MeOC_6H_4Br$	100 °C, 6 h	**3i**	69
7	piperidine	*p*-$NO_2C_6H_4Br$	65 °C, 16 h	**3e**	80
8	piperidine	*p*-$NO_2C_6H_4Cl$	90 °C, 16 h	**3e**	67
9	piperidine	β-bromostyrene	65 °C, 16 h	**3k**	95
10	morpholine	PhI	65 °C, 16 h	**4a**	96
11	pyrrolidine	PhI	65 °C, 16 h	**5a**	91
12	Et_2NH	PhI	65 °C, 16 h	**6a**	74
13	$(allyl)_2NH$	PhI	65 °C, 16 h	**7a**	66
14	*t*$BuNH_2$	PhI	65 °C, 16 h	**8a**	89
15		PhI	65 °C, 16 h	**9a**	73

secondary and sterically hindered primary amines provided the coupling products **4–9** in comparable yields (entries 10–15).

The difference in reactivity between aryl iodides and aryl bromides could be used to selectively react *p*-bromoiodobenzene at lower temperature at the iodo position without touching the bromo substituent (Scheme 2). The corresponding product **3l** was obtained in excellent yield. This intermediate could then be further modified in a second Stille coupling at higher temperature with tributyl(2-furyl)stannane. This reaction sequence yielded product **3m** in a four component one pot procedure in very good yield.

Interestingly, no coupling products were obtained with acyl halides such as benzoyl chloride, probably because of an acylation of the amine functionality. But this problem could easily be solved by combining the Stille coupling with a CO-insertion, giving rise to α,β-unsaturated ketone **3o**. Reactions with alkyl and allyl halides, such as allyl or cinnamyl bromide, also failed (alkylation of the tertiary amine) but the stannylated amine intermediate could successfully be coupled *via* allylic alkylation. For example, cinnamyl carbonate provided diene **3n** in excellent yield and very high regioselectivity (> 97% of the linear product). Probably for steric reasons, the reaction with *o*-iodobenzoate was rather sluggish. No reaction was observed at 65 °C, but at 100 °C a complete conversion was obtained after 5 h, providing **3p** in acceptable yield.

o-Iodobenzoate is an interesting candidate for the synthesis of more complex products because of its two electrophilic centres. For example, if primary amines are used in the allylic alkylation step, the Stille coupling product can undergo a subsequent cyclization providing lactam **9b** with an exocyclic methylene group. With the similar electrophile ethyl 2-iodobenzyl carbonate the isoquinoline derivative **11a** was obtained after allylic alkylation, Stille coupling and benzylic amination. Interestingly in both reactions, no isomerization of the exocyclic methylene double bond to the endo position was observed, even under the relatively harsh reaction conditions.



Scheme 2 Allylic aminations and following reactions.

The stannylated allylamine intermediate can also be subjected to a tin-halogen exchange, giving rise *e.g.* to iodinated allylamines such as **9c**, compounds which are interesting synthetic intermediates as well. Treatment of **9c** with strong base resulted in an intramolecular S_N-reaction towards methylene aziridine **10a**,[13] while a Pd-catalyzed carbonylation gave direct access to methylene-substitued β-lactams (**10b**).[14]

Conclusion

In conclusion, we have shown, that stannylated allyl carbonates are versatile synthetic building blocks for the synthesis of stannylated allylamines, which can be further modified *via* Stille couplings. Under optimized conditions both reactions can be carried out in an one-pot protocol, giving rise to a wide range of substituted and functionalized allylamines, including aziridines and lactams.

Experimental

General remarks

All reactions were carried out in oven-dried glassware (70 °C) under an atmosphere of nitrogen. Dried solvents were distilled before use: THF was distilled from $LiAlH_4$, dry DMF was purchased from Sigma-Aldrich. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexanes were generally used as eluents. Analytical TLC was performed on precoated silica gel plates (Macherey–Nagel, Polygram® SIL G/UV254). Visualization was accomplished with UV-light, $KMnO_4$ solution or Iodine. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-400 [400 MHz (^1H) and 100 MHz (^{13}C)] spectrometer in $CDCl_3$. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ was used as the internal standard. Mass spectra were recorded with a Finnigan MAT 95 spectrometer using the CI or EI technique. Elemental analyses were performed at the Saarland University. Microwave reactions were carried out in a CEM Discover microwave oven.

General procedure for allylic aminations

In a Schlenk flask $Pd(PPh_3)_4$ (6 mg, 5.0 μmol, 2 mol%) was dissolved in dry DMF (2 mL) and stirred for 15 min at room temperature under nitrogen. After addition of the amine (0.275–0.5 mmol), the solution was cooled to 0 °C and ethyl 2-(tributylstannyl)allyl carbonate **1a** (105 mg, 0.25 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h or was allowed to warm up to room temperature within 16 h. After evaporation of the solvent *in vacuo* and flash chromatography (hexanes/ethyl acetate/triethylamine = 99 : 0 : 1–97 : 2 : 1) the pure product was obtained.

1-(2-(Tributylstannyl)allyl)piperidine (2a). Following the general procedure for allylic aminations **2a** was obtained from piperidine (24 mg, 0.275 mmol) and 2-(tributylstannyl)allyl carbonate **1a** (105 mg, 0.25 mmol) in 2 h at 0 °C. After evaporation of the solvent *in vacuo* and flash chromatography (hexanes/ethyl acetate/triethylamine = 99 : 0 : 1–97 : 2 : 1) the desired product could be isolated in 94% yield (98 mg, 0.236 mmol) as a colorless oil. ^1H NMR: δ 5.76 (m, J_{Sn} = 138.6 Hz, 1H), 5.17 (m, J_{Sn} = 62.8 Hz, 1H), 2.98 (m, J_{Sn} = 47.1 Hz, 2H), 2.27 (m, 4H), 1.59–1.44 (m, 10H), 1.40 (m, 2H), 1.36–1.27 (m, 6H), 0.97–0.80 (m, 15H). ^{13}C NMR: δ 155.8, 124.9, 69.8, 54.7, 29.2 (J_{Sn} = 19.4 Hz), 27.5 (J_{Sn} = 57.3 Hz), 26.1, 24.5, 13.7, 9.6 (J_{Sn} = 328.8 Hz). ^{119}Sn NMR: δ –50.1. MS (CI) *m/z* 415 (5, M^+), 359 (100), 125 (9), 84 (18). HRMS (CI) *m/z* calcd for $C_{20}H_{41}NSn$ $[M]^+$: 415.2261. Found: 415.2273. Anal. calcd for $C_{20}H_{41}NSn$ (414.24): C 57.99; H 9.98; N 3.38. Found: C 57.89; H 10.04; N 3.27.

General procedure for Stille couplings of stannylated amines

Method 1: Thermal conditions. In a Schlenk flask $[allylPdCl]_2$ (2.0 mg, 5 μmol, 2 mol%) and PPh_3 (2.6 mg, 10 μmol, 4 mol%) were dissolved in dry THF (1 mL) and stirred for 15 min at room temperature under nitrogen. In a second Schlenk flask 2-(tributylstannyl)allyl piperidine 2a (105 mg, 0.25 mmol) and the electrophile (0.5 mmol) were dissolved in dry THF (1 mL) and heated to 60 °C. Then the catalyst solution was added and the reaction mixture was stirred at the indicated temperature until TLC showed complete consumption of the stannylated amine (2 to 3 d). After completion of the reaction, water (5 mL) and a small amount of KF were added and the resulting mixture was stirred overnight. Then ethyl acetate was added and the organic layer was separated. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography.

Method 2: Microwave conditions. In a microwave reaction vessel $[allylPdCl]_2$ (2.0 mg, 5 μmol, 2 mol%) and PPh_3 (2.6 mg, 10 μmol, 4 mol%) were dissolved in dry THF (2 mL) and stirred for 15 min at room temperature under nitrogen. After addition of 2-(tributylstannyl)allyl piperidine **2a** (105 mg, 0.25 mmol) and the electrophile (0.5 mmol) the reaction mixture was heated in a microwave oven for 1 h to 100 °C (300 W). After completion of the reaction, water (5 mL) and a small amount of KF were added and the resulting mixture was stirred overnight. Then ethyl acetate was added and the organic layer was separated. The aqueous phase was extracted three times with ethyl acetate and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography.

1-(2-Methylenepent-4-enyl)piperidine (3a). Following the general procedure for Stille couplings of stannylated amines under Microwave conditions, 3a was obtained from 2-(tributylstannyl)allyl piperidine 2a (105 mg, 0.25 mmol) and allyl bromide (61 mg, 0.5 mmol, 2 equiv). After work-up and flash chromatography (hexanes/ethyl acetate = 95 : 5–8 : 2) the product could be isolated in 97% yield (40 mg, 0.243 mmol) as a colorless oil. ^{1}H NMR: δ 5.85 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.09–5.01 (m, 2H), 4.93 (m, 1H), 4.85 (m, 1H), 2.83 (s, 2H), 2.81 (d, J = 7.0 Hz, 2H), 2.37–2.25 (m, 4H), 1.58–1.52 (m, 4H), 1.44–1.40 (m, 2H). ^{13}C NMR: δ 145.7, 136.5, 115.9, 112.3, 64.7, 54.6, 38.7, 26.1 24.5. MS (CI) m/z 165 (40, M^+), 98 (100), 84 (40). HRMS (CI) m/z calcd for $C_{11}H_{19}N$ $[M]^+$: 165.1517. Found: 165.1528.

General procedure for one-pot allylic aminations/Stille couplings

$Pd(PPh_3)_4$ (6 mg, 5.0 μmol, 2 mol%) or $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) were dissolved in dry DMF (2 mL) in a Schlenk flask under nitrogen and stirred for 15 min at room temperature after which a yellow solution was obtained. After addition of the amine (0.25 mmol) the solution was cooled to 0 °C before ethyl 2-(tributylstannyl) allyl carbonate **1a** (109 mg, 0.26 mmol) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature overnight. Subsequently, 1.2 to 2.0 equiv of the electrophile were added and the mixture was stirred at the indicated temperature (room temperature to 120 °C) until TLC showed complete consumption of the intermediate stannylated amine (0.5 to 24 h). After the solution was cooled to room temperature, it was diluted with diethyl ether and extracted three times with 1 N HCl. The combined aqueous layers were neutralised with sat. $NaHCO_3$ solution and then extracted twice with diethyl ether. The combined organic layers were dried with anhydrous Na_2SO_4, and after evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography.

1-(2-Phenylallyl)piperidine (3b). Following the general procedure for one-pot allylic aminations/Stille couplings **3b** was obtained from piperidine (21.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)allyl carbonate **1a** (109 mg, 0.26 mmol) and phenyliodide (102 mg, 0.5 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. For the Stille coupling the reaction mixture was heated up to 65 °C for 16 h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 96% yield (48 mg, 0.240 mmol) as a colorless oil. ^{1}H NMR: δ 7.54–7.51 (m, 2H), 7.34–7.29 (m, 2H), 7.27–7.24 (m, 1H), 5.45 (s, 1H), 5.24 (s, 1H), 3.29 (s, 2H), 2.41 (m, 4H), 1.58–1.52 (m, 4H), 1.44–1.38 (m, 2H). ^{13}C NMR: δ 144.6, 140.8, 128.1, 127.3, 126.3, 114.8, 63.7, 54.6, 26.0, 24.5. MS (CI) m/z 201 (20, M^+), 115 (4), 98 (100). HRMS (CI) m/z calcd for $C_{14}H_{19}N$ $[M]^+$: 201.1517. Found: 201.1482.

1-(2-(4-Bromophenyl)allyl)piperidine (3l). Following the general procedure for one-pot allylic aminations/Stille couplings **3l** was obtained from piperidine (21.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)allyl carbonate **1a** (109 mg, 0.26 mmol) and *p*-bromophenyliodide (74 mg, 0.26 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. For the Stille coupling the reaction mixture was heated up to 65 °C for 16 h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 96% yield (67 mg, 0.240 mmol) as a colorless oil. ^{1}H NMR: δ 7.42 (m, 4H), 5.44 (m, 1H), 5.23 (m, 1H), 3.24 (s, 2H), 2.37 (m, 4H), 1.53 (m, 4H), 1.42 (m, 2H). ^{13}C NMR: δ 143.6, 139.5, 131.1, 128.1, 121.3, 115.5, 63.7, 54.5, 26.0, 24.4. MS (CI) m/z 280 (31, M^+), 202 (10), 116 (1), 98 (100). HRMS (CI) m/z calcd for $C_{14}H_{18}NBr$ $[M]^+$: 279.0623. Found: 279.0581.

1-(2-Phenylallyl)piperidine (3m). Following the general procedure for one-pot allylic aminations/Stille couplings **3m** was obtained from piperidine (21.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)allyl carbonate **1a** (109 mg, 0.26 mmol) *p*-bromophenyliodide (74 mg, 0.26 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. For the first Stille coupling the reaction mixture was heated up to 65 °C for 16 h. Then tributyl(2-furyl)stannane (179 mg, 0.50 mmol) and LiCl (32 mg, 0.75 mmol) were added and the mixture was heated up to 130 °C for 16 h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 77% yield (53 mg, 0.192 mmol) as a colorless oil. ^{1}H NMR: δ 7.62 (m, 2H), 7.56 (m, 2H), 7.47 (m, 1H), 6.65 (m, 1H), 6.47 (m, 1H), 5.49 (s, 1H), 5.24 (s, 1H), 3.30 (s, 2H), 2.41 (m, 4H), 1.54 (m, 4H), 1.42 (m, 2H). ^{13}C NMR: δ 154.0, 144.0, 142.0, 139.6, 128.1, 126.6, 123.5, 114.9, 111.7, 104.9, 63.7, 54.6, 26.0, 24.5. MS (CI) m/z 268 (27, M^+ + 1), 184 (58), 149 (56),

98 (100). HRMS (CI) *m/z* calcd for $C_{18}H_{21}NO$ $[M]^+$: 267.1623. Found: 267.1601.

(*E*)-1-(2-Methylene-5-phenylpent-4-enyl)piperidine (3n). Following the general procedure for one-pot allylic aminations/Stille couplings **3n** was obtained from piperidine (21.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)allyl carbonate **1a** (109 mg, 0.26 mmol) and cinnamyl ethyl carbonate (103 mg, 0.50 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. For the Stille coupling the reaction mixture was heated up to 90 °C for 16h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 92% yield (55 mg, 0.230 mmol) as a colorless oil with 97% (*E*)-double bond geometry. ^{1}H NMR: δ 7.36 (m, 2H), 7.29 (m, 2H), 7.20 (m, 1H), 6.44 (d, J = 15.8 Hz, 1H), 6.26 (dt, J = 15.8, 7.1 Hz, 1H), 4.97 (m, 1H), 4.92 (m, 1H), 2.98 (m, 2H), 2.89 (s, 2H), 2.33 (m, 4H), 1.58 (m, 4H), 1.43 (m, 2H); (*Z*)-isomer (selected signals): δ 6.55 (d, J = 11.5 Hz, 1H), 5.76 (dt, J = 11.6, 7.8 Hz, 1H), 3.06 (d, J = 7.7 Hz, 2H). ^{13}C NMR: δ 145.8; 137.7, 131.2, 128.4, 126.8, 126.0, 117.7, 112.6, 64.7, 54.6; 37.8, 26.0, 24.5. MS (CI) *m/z* 241 (100, M^+), 136 (52), 98 (62). HRMS (CI) *m/z* calcd for $C_{17}H_{23}N$ $[M]^+$: 241.1830. Found: 241.1831.

1-Phenyl-2-(piperidin-1-ylmethyl)prop-2-en-1-one (3o). Following a modified procedure for one-pot allylic aminations/Stille couplings **3o** was obtained from piperidine (21.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)allyl carbonate **1a** (109 mg, 0.26 mmol), CO and phenyliodide (102 mg, 0.50 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. After completion of the allylic amination, the atmosphere above the reaction mixture was changed to a CO atmosphere, and the reaction mixture was stirred for 15 min before the phenyliodide was added. The mixture was then heated to 65 °C for 16 h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 88% (50 mg, 0.220 mmol) yield as a colorless oil. ^{1}H NMR: δ 7.79 (m, 2H), 7.54 (m, 1H), 7.44 (m, 2H), 6.02 (m, 1H), 5.73 (m, 1H), 3.38 (s, 2H), 2.46 (m, 4H), 1.57 (m, 4H), 1.42 (m, 2H). ^{13}C NMR: δ 192.7, 144.9, 137.5, 132.2, 131.7, 129.5, 128.2, 54.5, 25.9, 24.2. MS (CI) *m/z* 230 (34, M^+ + 1), 212 (42), 98 (100). HRMS (CI) *m/z* calcd for $C_{15}H_{19}NO$ $[M]^+$: 229.1467. Found: 229.1448.

4-Methylene-2-(1-phenylethyl)-3,4-dihydroisoquinolin-1(2H)-one (9b). Following the general procedure for one-pot allylic aminations/Stille couplings **9b** was obtained from phenylethylamine (30.3 mg, 0.25 mmol), ethyl 2-(tributylstannyl)-allyl carbonate **1a** (109 mg, 0.26 mmol) and ethyl 2-iodobenzoate (138 mg, 0.50 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 μmol, 1 mol%) and PPh_3 (5.2 mg, 20 μmol, 8 mol%) as catalyst. For the Stille coupling the reaction mixture was heated up to 90 °C for 16 h and then to 120 °C for 6 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether and washed with 1 N HCl, sat. $NaHCO_3$ solution and conc. KF solution. The organic layer was dried with anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo* and flash chromatography (hexanes/ethyl acetate = 90 : 10) the desired product could be isolated in 62% yield (41 mg, 0.155 mmol) as a colorless oil. ^{1}H NMR: δ 8.22 (m, 1H), 7.53–7.43 (m, 3H), 7.39–7.33 (m, 4H), 7.28 (m, 1H), 6.29 (q, J = 7.1 Hz, 1H), 5.49 (m, 1H), 5.06 (m, 1H), 4.02 (ddd, J = 14.2, 1.6, 1.6 Hz, 1H), 3.71 (ddd, J = 14.2, 1.3, 1.3 Hz, 1H), 1.62 (d, J = 7.1 Hz, 3H). ^{13}C NMR: δ 163.3, 140.2, 137.1, 135.7, 131.9, 128.8, 128.8, 128.5, 128.2, 127.4, 127.3, 123.0, 112.0, 50.3, 46.6, 15.7. MS (CI) *m/z* 274 (98, M^+ + 1), 218 (100), 172 (48), 130 (15), 115 (10). HRMS (CI) *m/z* calcd for $C_{16}H_{19}N$ $[M]^+$: 273.1365. Found: 273.1336.

2-Iodo-N-(1-phenylethyl)prop-2-en-1-amine (9c). In a Schlenk flask $Pd(PPh_3)_4$ (32 mg, 28.0 μmol, 5 mol%) and 1-phenylethylamine (667 mg, 5.5 mmol) were dissolved in dry DMF (10 mL) under nitrogen. The solution was cooled to 0 °C and ethyl 2-(tributylstannyl)allyl carbonate **1a** (2.10 g, 5.0 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature within 16 h and was diluted with diethyl ether (10 mL). I_2 (1.52 g, 6.0 mmol) was slowly added and the mixture was stirred for 30 min at room temperature. The solution was diluted with diethyl ether and washed with a mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ solution. The organic layer was extracted three times with 1 N HCl. The combined aqueous layers were neutralised with sat. $NaHCO_3$ solution and then extracted twice with diethyl ether. The combined organic layers were dried with anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo* and flash chromatography (hexanes/ethyl acetate = 90 : 10) the desired product could be isolated in 76% yield (1.06 g, 3.69 mmol) as a yellow oil. ^{1}H NMR: δ 7.37–7.30 (m, 4H), 7.25 (m, 1H), 6.13 (m, 1H), 5.85 (m, 1H), 3.78 (q, J = 6.6 Hz, 1H), 3.31 (m, 1H), 3.13 (m, 1H), 1.85 (bs, 1H), 1.37 (d, J = 6.6 Hz, 3H). ^{13}C NMR: δ 144.8, 128.4, 127.1, 126.9, 126.2, 113.7, 58.5, 55.3, 24.2. MS (CI) *m/z* 288 (16, M^+ + 1), 272 (100), 210 ((3), 144 (8), 105 (25), 77 (5). HRMS (CI) *m/z* calcd for $C_{11}H_{14}IN$ $[M]^+$: 287.0171. Found: 287.0170. Anal. calcd for $C_{11}H_{14}IN$ (287.14): C 46.01; H 4.91; N 4.88. Found: C 46.07; H 4.71; N 5.37.

2-Methylene-1-(1-phenylethyl)aziridine (10a). Under nitrogen $NaNH_2$ (146 mg, 3.75 mmol) was added to a Schlenk flask. The flask was cooled to −78 °C and NH_3 (1 mL) was condensed. **9c** (72 mg, 0.25 mmol) was added and the resulting suspension was stirred for 30 min at −78 °C. Dry THF (2 mL) was added dropwise and the solution was stirred for 30 min at −78 °C after which TLC showed completion of the reaction. Diethyl ether (5 mL) and water (5 mL) were slowly added and the mixture was allowed to warm up to room temperature. The ether layer was separated and the aqueous phase was extracted three times with diethyl ether. The combined organic layers were washed with 1 M NaOH solution and then dried over Na_2SO_4. After evaporation of the solvent *in vacuo* and flash chromatography (pentane/ether 95 : 5) the desired product could be isolated in 75% yield (30 mg, 0.188 mmol) as a colorless oil. ^{1}H NMR: δ 7.31–7.24 (m, 4H), 7.19 (m, 1H), 4.58–4.56 (m, 2H), 2.85 (q, J = 6.6 Hz, 1H), 2.03 (s, 1H), 1.93 (s, 1H), 1.44 (d, J = 6.6 Hz, 3H). ^{13}C NMR: δ 143.9, 137.1, 128.4, 127.2, 126.7, 83.1, 68.5, 29.9, 23.5. MS (CI) *m/z* 160 (100, M^+ + 1), 105 (8), 56 (1). HRMS (CI) *m/z* calcd for $C_{11}H_{13}N$ $[M]^+$: 159.1048. Found: 159.1040.

3-Methylene-1-(1-phenylethyl)azetidin-2-one (10b). In a Schlenk flask $[allylPdCl]_2$ (2.0 mg, 5 μmol, 2 mol%) and PPh_3 (2.6 mg, 10 μmol, 4 mol%) were dissolved in dry DMF (2 mL) and stirred for 10 min at room temperature under nitrogen. The nitrogen atmosphere was removed and the Schlenk flask was connected *via* a syringe to a balloon filled with CO. The catalyst solution was stirred for 10 min under CO. Triethylamine (51 mg,

0.5 mmol) and **9c** (72 mg, 0.25 mmol) were then added and the resulting mixture was stirred for 16 h at 65 °C, during which the color of the solution turned from yellow to red. After the reaction mixture was cooled to room temperature, it was diluted with diethyl ether and washed with 1 N HCl and sat. $NaHCO_3$ solution. The organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. After flash chromatography (hexanes/ethyl acetate = 1 : 1) the desired product could be isolated in 71% yield (33 mg, 0.178 mmol) as a colorless oil. ^{1}H NMR: δ 7.38–7.26 (m, 5H), 5.70 (m, 1H), 5.13 (m, 1H), 5.04 (q, J = 7.0 Hz, 1H), 3.71 (dt, J = 7.5, 1.4 Hz, 1H), 3.52 (dt, J = 7.5, 1.4 Hz, 1H), 1.64 (d, J = 7.0 Hz, 3H). ^{13}C NMR: δ 163.0, 144.5, 140.3, 128.8, 127.7, 126.7, 109.3, 51.6, 45.9, 18.5. MS (CI) m/z 188 (13, M^+ + 1), 172 (100), 132 (15), 105 (35), 91 (8), 69 (13). HRMS (CI) m/z calcd for $C_{12}H_{13}NO$ $[M]^+$: 187.0997. Found: 187.1014. Anal. calcd for $C_{12}H_{13}NO$ (187.24): C 76.98; H 7.00; N 7.48. Found: C 76.49; H 7.01; N 7.43.

***tert*-Butyl 2-(4-methylene-3,4-dihydroisoquinolin-2(1H)-yl)acetate (11a).** Following the general procedure for one-pot allylic aminations/Stille couplings **11a** was obtained from H_2N-Gly-O*t*Bu (33 mg, 0.25 mmol), ethyl 2-(tributylstannyl)-allyl carbonate **1a** (109 mg, 0.26 mmol) and ethyl 2-iodobenzyl carbonate (92 mg, 0.30 mmol) with $[allylPdCl]_2$ (0.9 mg, 2.5 µmol, 1 mol%) and PPh_3 (5.2 mg, 20 µmol, 8 mol%) as catalyst. For the Stille coupling the reaction mixture was heated up to 90 °C for 16 h and then to 130 °C for 2 h. After work-up and flash chromatography (hexanes/ethyl acetate = 9 : 1–1 : 1) the product could be isolated in 69% (45 mg, 0.173 mmol) yield as a colorless oil. ^{1}H NMR: δ 7.66 (m, 1H), 7.22–7.05 (m, 2H), 7.06 (m, 1H), 5.62 (s, 1H), 5.02 (s, 1H), 3.95 (s, 2H), 3.31 (s, 2H), 1.48 (s, 9H). ^{13}C NMR: δ 169.6, 138.5, 134.0, 132.0, 127.9, 126.9, 126.6, 123.4, 108.3, 81.2, 57.7, 57.6, 55.7, 28.2. MS (CI) m/z 259 (41, M^+ + 1), 232 (50), 204 (30), 158 (50), 144 (100), 115 (13), 57 (82). HRMS (CI) m/z calcd for $C_{11}H_{12}N$ [M-*t*Bu-CO_2]$^+$: 158.0970. Found: 158.0931.

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