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Mechanistic Studies on the SCS-Pincer Palladium(II)-Catalyzed Tandem Stannylation/Electrophilic Allylic Substitution of Allyl Chlorides with Hexamethylditin and Benzaldehydes**

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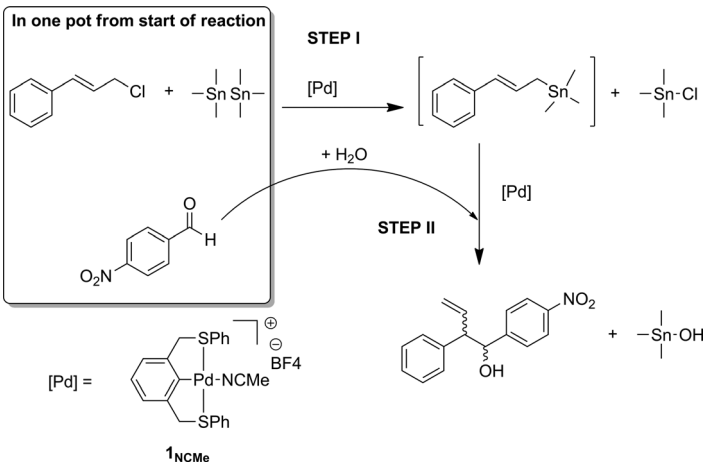
Abstract: This paper describes a mechanistic study of the SCS-pincer Pd^{II}-catalyzed auto-tandem reaction consisting of the stannylation of cinnamyl chloride with hexamethylditin, followed by an electrophilic allylic substitution of the primary tandem-reaction product with 4-nitrobenzaldehyde to yield homoallylic alcohols as the secondary tandem products. As it turned out, the anticipated stannylation product, cinnamyl trimethylstannane, is not a substrate for the second part of the tandem reaction. These studies have provided insight in the catalytic behavior of SCS-pincer Pd^{II} complexes in the auto-tandem reaction and on the formation and possible involvement of Pd^0 species during prolonged reaction times. This has led to optimized reaction conditions in which the overall tandem reaction proceeds through SCS-pincer Pd^{II}-mediated catalysis, that is, true auto-tandem catalysis. Accordingly, this study has provided the appropriate reaction conditions that allow the pincer catalysts to be recycled and reused.

Keywords: homogeneous catalysis · palladium · pincers · reaction mechanisms · substitution reactions

Introduction

ECE-pincer palladium complexes have proven to be versatile catalysts that show unique catalytic properties due to 1) the strong Pd–C σ bond that provides a stable ligand–metal manifold for catalysis and 2) the limitation of available coordination sites due to the tridentate nature of the ECE-pincer ligand. These properties modify the catalytic applications of palladium significantly.[1–6] Palladium pincer complexes serve as excellent catalysts for, among others, the stannylation of allylic chlorides, propargylic chlorides, allylic alcohols, phosphonates and epoxides by using hexaalkylditin, as was published recently by Szabó and co-workers.[7,8] The same group also reported that palladium pincer complexes can act as catalysts for the electrophilic allylic substitution of allylstannanes with imines, sulfonimines, and aldehydes.[9,10] Since some of the products of the stannylation reactions (e.g., allyl trialkylstannanes) can act as a starting material for the electrophilic addition, studies have been performed to combine these two reactions in a one-pot procedure by using two different orthogonal ECE-pincer palladium complexes[7] or in an auto-tandem system by using a single SCS-pincer palladium complex catalyzing both reactions (SCS = $[2,6\text{-}(CH_2SPh)_2C_6H_3]^-$; see Scheme 1).[11]



Scheme 1. Auto-tandem catalytic formation of 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol catalyzed by the SCS-pincer Pd complex $\mathbf{1}_{MeCN}$.

A mechanism consisting of two catalytic cycles was proposed for this auto-tandem reaction (see Scheme 2). This mechanism is a combination of the mechanisms of the two separate reactions.[7,9] First the SCS-pincer Pd^{II} complex $\mathbf{1}_{MeCN}$ reacts with hexamethylditin to give the SCS-pincer Pd^{II}-$SnMe_3$ complex $\mathbf{1}_{SnMe_3}$ (see Scheme 2, A). In the initial

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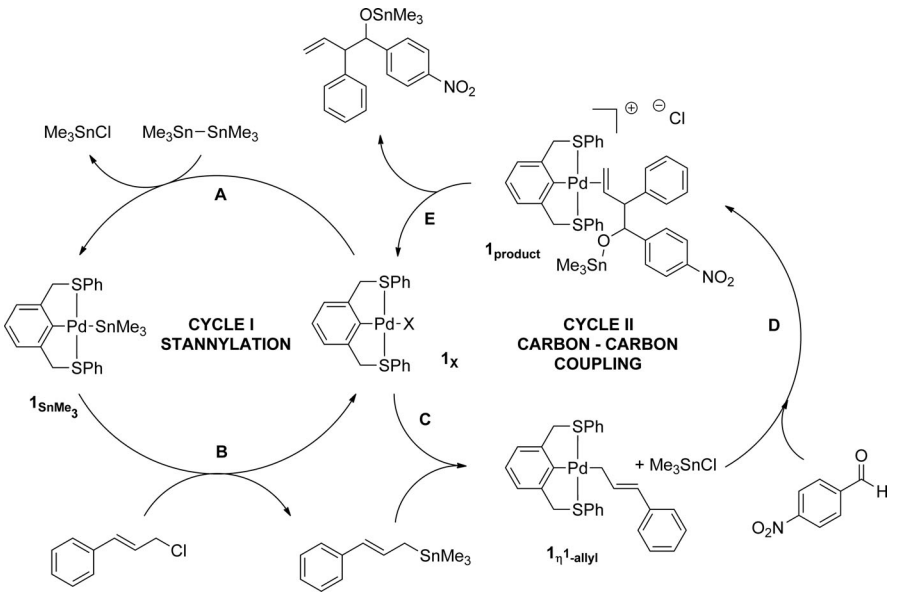
[**] SCS = $[2,6\text{-}(CH_2SPh)_2C_6H_3]^-$



Scheme 2. Proposed mechanism for the SCS-pincer Pd-catalyzed tandem stannylation/electrophilic allylic substitution reaction between allyl chlorides, hexamethylditin and benzaldehydes (X = Cl, MeCN).[11]

report [Pd(SCS)(MeCN)]BF_4 ($\mathbf{1_{MeCN}}$) was used as the catalyst, whereas recently we have reported on the use of [Pd(SCS)Cl] ($\mathbf{1_{Cl}}$) as catalyst.[12] Complex $\mathbf{1_{SnMe_3}}$ undergoes nucleophilic substitution with allyl chloride yielding allyltrimethylstannane and recovering the SCS-pincer Pd complex $\mathbf{1_X}$ (Scheme 2, step B). In the second cycle, the regained catalyst $\mathbf{1_X}$ undergoes a second transmetalation reaction in which it reacts with the formed allyl stannane leading to the formation of the reactive η^1-allylpalladium complex (Scheme 2, C). This complex then acts as a nucleophile towards 4-nitrobenzaldehyde (Scheme 2, D). As the highest nucleophilicity resides on the γ-carbon atom of the allyl fragment of $\mathbf{1_{\eta^1\text{-allyl}}}$, this reaction leads to the formation of a mixture of *syn*- and *anti* homo-allylic alcohol products. After product dissociation, complex $\mathbf{1_X}$ is regenerated in the last step (Scheme 2, E).

Recent investigations on the recycling of dendritic SCS-pincer Pd-catalysts have raised questions concerning this Pd^{II}-only mechanism. In these investigations the catalytic behavior of dendritic SCS-pincer palladium complexes in the tandem reaction was studied both in homogeneous solution and in a membrane dialysis bag.[12] In particular, in the compartmentalized dialysis bag experiments considerable palladium leaching was observed by inductively coupled plasma mass spectrometry (ICP-MS) and ^1H NMR analysis. It was found that after four consecutive runs approximately 30–40% of the pincer moieties of the dendritic catalyst did no longer contain a palladium center, indicating that Pd-leaching had occurred through release of palladium from the SCS-pincer ligands. These individual palladium centers will agglomerate to palladium nanoparticles, and penetration of the palladium nanoparticle through the dialysis bag may or may not occur, depending on its size. ICP-MS analysis of the outer membrane solutions showed a cumulative leaching of 27.5% Pd after four runs, similar to the observed amount of free ligands as analyzed by NMR spectroscopy. This palladium leaching indicates two important drawbacks in the compartmentalized auto-tandem catalysis setup. Firstly, leaching decreases the recycling efficiency of the dendritic catalyst, because the amount of catalytic centers in the dendritic catalyst decreases with each reuse. Secondly, if leaching takes place, it is unclear whether the Pd^0 species plays a role as catalyst and thus contributes to the product formation. In case these species are catalytically active, this might have implications for several reaction parameters, including the overall activity and product selectivity, as was described by Jones et al. in their review on active species in palladium-catalyzed Heck and Suzuki–Miyaura reactions.[13] They demonstrated, for example, that all the catalytic activity in the Heck coupling of *n*-butyl acrylate with iodobenzene catalyzed by soluble polymer-supported SCS-pincer Pd complexes was caused by the leached Pd^0 species and that the starting SCS-pincer Pd^{II} complexes were inactive.[14]

Here, we report a more detailed study of the auto-tandem reaction to obtain an insight in the catalytic behavior of SCS-pincer Pd^{II} complexes and on the formation and possible involvement of Pd^0 species in catalysis. The aim of this study was to find optimized reaction conditions in which the formation of potentially active Pd^0 species can be avoided, to create a catalytic system in which SCS-pincer Pd^{II} complexes are the only catalytically active species. Under such optimized conditions, the use of dendritic SCS-pincer palladium complexes in a compartmentalized setup would allow for their consecutive catalytic application without catalyst decomposition and, accordingly, under constant operation conditions. In our present studies, we have used monomeric SCS-pincer Pd–Cl complexes in a series of kinetic experiments in combination with DFT calculations. These results have led to a more detailed mechanistic insight, which led to the development of improved conditions for running the tandem reaction of cinnamyl chloride with hexamethylditin and 4-nitrobenzaldehyde by using dendritic SCS-pincer Pd^{II} complexes in a compartmentalized reaction setup.

Results and Discussion

Kinetic reaction profile: An ideal tandem reaction consisting of two subsequent reactions deals with two rate con-

stants: k_1 for reaction A+B→C, and k_2 for the subsequent reaction C+D→E (see Scheme 3). In this simplified model it is assumed that all reagents are orthogonal, that is, they do not react with each other in the absence of a catalyst. For the stannylation/electrophilic substitution tandem reaction, this model can be used by assigning cinnamyl chloride as A, hexamethylditin as B, primary product cinnamyl trimethylstannane as C, 4-nitrobenzaldehyde as D and secondary product trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane (or its aqueous workup reaction product 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol) as E.

$$A + B \xrightarrow{k_1} C$$
$$C + D \xrightarrow{k_2} E$$

Scheme 3. Simplified model for a tandem reaction with reagents A, B, and D and two subsequent reactions with rate constants k_1 and k_2.

The kinetic profile of this tandem reaction will vary with the values of the rate constants k_1 and k_2. With the input of the experimental data that was collected for the SCS-pincer palladium-catalyzed tandem reaction earlier by our group,[12] we estimated $k_1 = 8\times10^{-3}\,\mathrm{mol\,s^{-1}}$ and $k_2 = 4\times10^{-4}\,\mathrm{mol\,s^{-1}}$. By using these estimated values, a theoretical kinetic profile for this tandem reaction (see Figure 1) was calculated by using:[15]

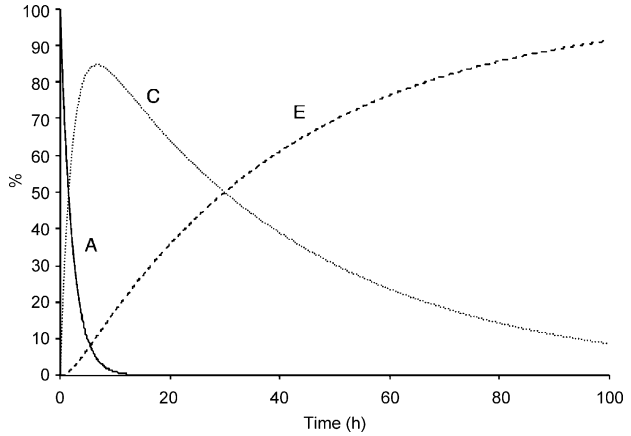


Figure 1. Theoretical kinetic profile for the tandem reaction with $k_1 = 8\times10^{-3}\,\mathrm{mol\,s^{-1}}$ and $k_2 = 4\times10^{-4}\,\mathrm{mol\,s^{-1}}$. A: cinnamyl chloride; C: cinnamyl trimethylstannane; E: trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane.

$$[A] = [A]_0{*}\exp(-k_1{*}t),$$

$$[B] = [A]_0{*}[k_1/(k_2-k_1)]{*}[\exp(-k_1{*}t)-\exp(-k_2{*}t)]$$

$$[C] = [A]_0{*}[1 + ([k_1{*}\exp(-k_2{*}t)-k_2{*}\exp(-k_1{*}t)]/[k_2-k_1])]$$

The experimental kinetic profile of the tandem reaction catalyzed by SCS-pincer Pd complex $\mathbf{1_{Cl}}$ reveals several differences between the theoretical and experimental kinetic profile for this reaction (see Figure 2). Similar reaction profiles were also observed for other monomeric SCS-pincer Pd complexes as well as for dendritic SCS-pincer Pd complexes,[12] thereby showing the single-site nature of each catalytic center in these dendritic complexes. For this reason, the present studies were carried out with monomeric SCS-pincer Pd complex $\mathbf{1_{Cl}}$.

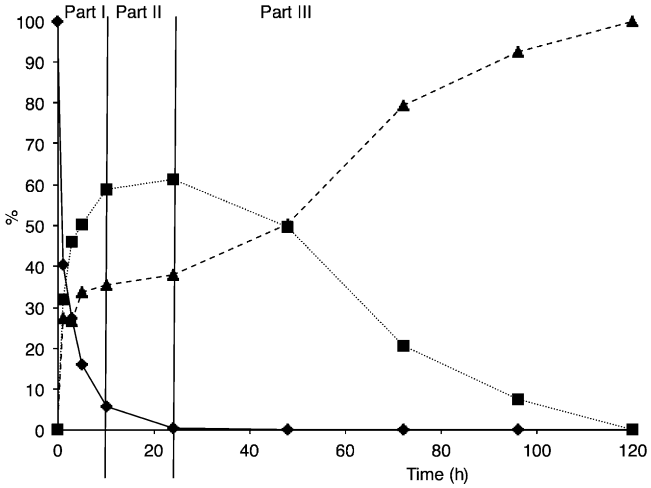


Figure 2. Experimental kinetic profile for the SCS-pincer Pd-catalyzed tandem reaction. Conditions: cinnamyl chloride (0.80 mmol), hexamethylditin (0.80 mmol), 4-nitrobenzaldehyde (0.80 mmol) and Pd catalyst $\mathbf{1_{Cl}}$ (2 mol%) in THF (6 mL; ambient temperature, N_2 atmosphere). ◆: cinnamyl chloride; ■: cinnamyl trimethylstannane; ▲: trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane.

The experimental kinetic profile shows that in the first 5 h of the reaction cinnamyl chloride is consumed relatively fast (84% conversion) and both the primary product cinnamyl trimethylstannane and the secondary product 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol are formed in 50 and 34% yields, respectively (see Part I in Figure 2). The formation of 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol did not show the sinusoidal kinetic curve as predicted for the formation of a secondary product in a tandem reaction (see Figure 1). Instead, the instant formation of both the primary and secondary tandem products was observed; each of them already being formed in substantial amounts after as early as 15 min (typically around 20–30% yields). In the second part of the reaction (Part II in Figure 2), the reaction progression suddenly stops, resulting in a period with minor changes in the concentration of the starting material, or the primary and secondary products. After 24 h, in the third and last part of the reaction (Part III in Figure 2), the reaction catalysis starts again leading to a slow but complete conversion of the primary product, cinnamyl trimethylstannane, to secondary product 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol in 5 days.

In conclusion, the observed reaction profile shows two distinct sections. One section (Part I, Figure 2) that leads to close to complete consumption of starting material and rapid formation of both primary and approximately 35% of the secondary product trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane. The second section involves a combination of parts II and III (Figure 2), in which consumption of the primary product to form the secondary product goes

through a significant lag phase and ultimately leads to almost quantitative formation of trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane. These observations strongly suggest that instead of a single catalytic species, the involvement of at least two catalytically active species seems to be required to describe the experimental kinetic profile of the tandem reaction.

To investigate these findings in more detail, a series of kinetic experiments were performed. Firstly, the two individual reactions that form the tandem reaction were investigated independently to gain more insight in the behavior of catalyst $\mathbf{1_{Cl}}$ in the separate reaction steps. Secondly, control experiments were carried out in which the reactivity of the substrates with respect to each other and/or the catalyst was investigated. The results of these experiments have allowed us to propose a new mechanism that explains the full experimental kinetic reaction profile as shown in Figure 2. This mechanism is corroborated by additional DFT calculations.

First reaction step (stannylation):The conversion of cinnamyl chloride in the first step of the tandem reaction, that is, the stannylation with hexamethylditin, was investigated by using THF and CH_2Cl_2 as solvents and in the absence and presence of 4-nitrobenzaldehyde. In these experiments the loading of catalyst $\mathbf{1_{Cl}}$ was fixed at 2 mol%. The results of these experiments are depicted in Table 1. This reaction exhibits a small solvent effect: reactions carried out in THF tend to be slightly faster than those in CH_2Cl_2. Furthermore, the stannylation of cinnamyl chloride in the absence of the benzaldehyde electrophile was remarkably faster than in the case in which the electrophile was present. For the separate reaction, a complete conversion was found in both solvents after 10 h, whereas after this time in the tandem setup, approximately 20% cinnamyl chloride remained present. The stannylations in the tandem reaction were completed only after a reaction time of 16 h.

Table 1. Conversion of cinnamyl chloride in the SCS-pincer Pd-catalyzed stannylation with hexamethylditin in the absence or presence of 4-nitrobenzaldehyde in THF or CH_2Cl_2.[a]

4-Nitrobenzaldehyde	Solvent	Conversion of cinnamyl chloride [%]		
		1 h	5 h	24 h
absent	CH_2Cl_2	48	100	100
absent	THF	72	100	100
present	CH_2Cl_2	46	80	100
present	THF	53	84	100

[a] Conditions: cinnamyl chloride (0.80 mmol), hexamethylditin (0.80 mmol), $\mathbf{1_{Cl}}$ (2 mol%) and, if present, 4-nitrobenzaldehyde (0.80 mmol) in solvent (6 mL; ambient temperature, N_2 atmosphere).

An NMR experiment was performed to obtain insight into the order of the catalyst in the stannylation reaction. A solution containing equimolar amounts of cinnamyl chloride and hexamethylditin (0.67 mmol) in CD_2Cl_2 was placed in a series of NMR tubes, and solutions of a given concentration of SCS-pincer Pd complex $\mathbf{1_{Cl}}$ were added to reach a constant volume of 0.5 mL. The reaction progression was monitored at regular intervals (see Figure 3). We found that the kinetic order of the catalyst is 1.7 for this reaction (determined at 10% substrate conversion; see the inset in Figure 3). Even at a catalyst loading of 0.0625 mol%, the reaction progressed at a significant rate. The product was not observed in a blank experiment without the pincer palladium complex.

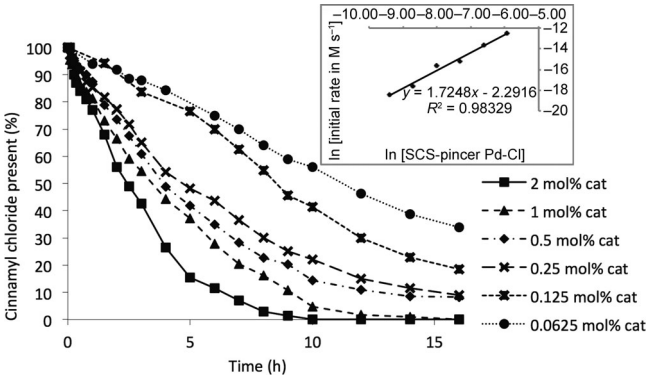


Figure 3. The stannylation of cinnamyl chloride over time using different amounts of catalyst $\mathbf{1_{Cl}}$. Inset: ln ($[\mathbf{1_{Cl}}]$) versus time at 10% cinnamyl chloride conversion.

Poisoning experiments with mercury and polyvinylpyridine (PVPy) were performed to probe the involvement of Pd^0 species in this reaction. Mercury (Hg^0) is known to intercept Pd^0 by amalgamation of palladium colloids or by adsorption of Pd^0 particles to the mercury surface.[15,16] PVPy binds free, unbound Pd atoms to the many pyridine ligands that are present in the polymer.[17,18] Upon addition of either of these poisons, no change in reactivity was observed. These observations rule out the involvement of Pd^0 in cycle I (Scheme 2).

A closer examination of the separate stannylation reaction in the presence of $\mathbf{1_{Cl}}$ by using ^1H NMR spectroscopic analysis showed that small but significant amounts of 1-phenyl-2-propenyl trimethylstannane, the branched isomer of cinnamyl trimethylstannane, were formed in this reaction. Interestingly, the maximum amount of this species reached about 10% after 3 h, whereupon its concentration decreased again (see Figure 4). Identification of 1-phenyl-2-propenyl trimethylstannane is based on the comparison with reported NMR data of the isolated compound.[19] The ^1H NMR spectrum recorded after 3 h of reaction time clearly shows typical signals for cinnamyl chloride, cinnamyl trimethylstannane, as well as 1-phenyl-2-propenyl trimethylstannane (see Figure 5).

Second reaction step (electrophilic allylic substitution): In a separate experiment, the isolated primary tandem product cinnamyl trimethylstannane was treated with 4-nitrobenzaldehyde and the palladium pincer catalyst $\mathbf{1_{Cl}}$ in CH_2Cl_2 or THF to determine the kinetics of cycle II (Scheme 2) of the tandem in an independent manner. In the literature this reaction has mainly been performed with PCP-pincer Pd com-

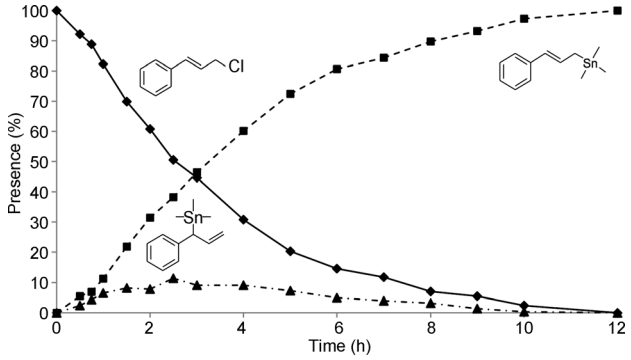


Figure 4. The reaction profile of the stannylation of cinnamyl chloride including the presence of 1-phenyl-2-propenyl trimethylstannane.

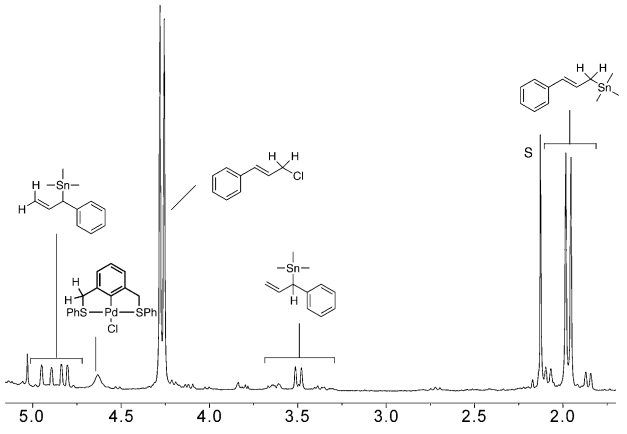


Figure 5. ^{1}H spectrum of a stannylation reaction of cinnamyl chloride with hexamethylditin in the presence of $\mathbf{1_{Cl}}$ at 50% substrate conversion (S = solvent peak).

plexes.[9,20] In collaboration with the group of Szabó, we have reported that this particular reaction also works with cationic SCS- and PCS-pincer Pd complexes as the second reaction of the same tandem reaction that is investigated here.[11] Surprisingly, when this second reaction step was investigated with the neutral SCS-pincer Pd complex $\mathbf{1_{Cl}}$, there was no product formation at all after 16 h. The only reaction observed was the partial decomposition of cinnamyl trimethylstannane by Sn–C bond cleavage towards allylbenzene. Even when this experiment was performed at reflux temperatures, homoallylic alcohol product formation was still not observed after 16 h.

In another experiment, the effect of adding additional trimethyltin chloride to the reaction mixture was investigated. Trimethyltin chloride is present in the tandem reaction mixture as a byproduct of the first reaction step (see Scheme 1). Because the electrophilic substitution reaction was successful in the tandem reaction and not in the separate reaction, the presence of trimethyltin chloride in the reaction mixture might play a role. This appeared not to be the case, since also after addition of trimethyltin chloride no reaction between cinnamyl trimethylstannane and 4-nitrobenzaldehyde was observed after 16 h in the presence of catalytic amounts of $\mathbf{1_{Cl}}$. Finally, a stoichiometric amount of catalyst $\mathbf{1_{Cl}}$ was used, but even under these conditions no carbon–carbon coupling occurred.

Under these conditions (i.e., by using SCS-pincer Pd complex $\mathbf{1_{Cl}}$ in the presence or absence of trimethyltin chloride) the reaction mixtures became darker after one day, probably caused by slow decomposition of the pincer complex and formation of palladium colloids in the solution. After a long period of inactivity, eventually product formation was observed in all of these dark reaction mixtures. When this same reaction was performed by using the same loading of $Pd(dba)_2$ or $Pd(PPh_3)_4$ as catalyst, the reaction proceeded within 1 h showing a full conversion towards secondary product 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol in a *anti*/*syn* product ratio of 1.5:1.

The reactivity of 1-phenyl-2-propenyl trimethylstannane, the branched isomer of cinnamyl trimethylstannane, was investigated in a similar way. To a solution of independently synthesized 1-phenyl-2-propenyl trimethylstannane[19,21] stoichiometric amounts of 4-nitrobenzaldehyde and catalytic amounts (2 mol%) of SCS-pincer Pd complex $\mathbf{1_{Cl}}$ were added and the reaction was followed by NMR spectroscopic analysis. Immediate formation of the allylation product 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol was observed. After 3 h the reaction was complete and did not only yield the secondary tandem product but also cinnamyl trimethylstannane. The ratio between the tandem *anti* product, the tandem *syn* product, and cinnamyl trimethylstannane was 3.5:1:1.

Next, 1-phenyl-2-propenyl trimethylstannane was treated with SCS-pincer Pd-catalyst $\mathbf{1_{Cl}}$ only (i.e., no aldehyde was added) to determine whether the isomerization of 1-phenyl-2-propenyl trimethylstannane to cinnamyl trimethylstannane is catalyzed by the SCS-pincer Pd complex. After 16 h, large amounts of cinnamyl trimethylstannane were formed, whereas there was no 1-phenyl-2-propenyl trimethylstannane left. Because of the unstable character of both isomers, decomposition products (amongst others allylbenzene) were also formed. Indeed, when 1-phenyl-2-propenyl trimethylstannane was stirred in CH_2Cl_2 without additives for 16 h, mainly decomposition products were detected. In addition, small amounts of cinnamyl trimethylstannane were observed, whereas no starting material was recovered. This result is remarkably different from the experiment in which the SCS-pincer Pd-complex $\mathbf{1_{Cl}}$ was present. Apparently, $\mathbf{1_{Cl}}$ catalyzes the isomerization from 1-phenyl-2-propenyl trimethylstannane to its linear isomer cinnamyl trimethylstannane.

Control experiments: To get more insight in the reactivity and orthogonality of the used reagents in the tandem reaction, several experiments were performed in which the added equivalents of substrates and the presence or absence of the catalyst were varied. The outcome of these tests is summarized in Table 2. Entries 1–3 show that Pd pincer complex $\mathbf{1_{Cl}}$ is required for the stannylation reaction: no blank reaction was observed. In the absence of $\mathbf{1_{Cl}}$, also no

Table 2. Control experiments on the reactivity and the orthogonality of the different reagents in the tandem reaction.[a]

Entry	Substrate [equiv]			Cat [%]	Products
	CC	HMDT	4NBA		
1	1	1	1	2	product 2[b]
2	1	1	0	–	–
3	1	1	1	–	–
4	0	1	1	–	–
5	1	1	0	2	product 1
6	1	0	1	2	–
7	0	1	1	2	–[c]
8	1	1	10	2	product 2[c]
9	1	10	1	2	product 1
10	1	10	10	2	product 1
11	10	10	1	2	product 2[d]
12	5	5	1	2	product 2[d]
13	3	3	1	2	product 2[d]
14	1.5	1.5	1	2	product 2[e]

[a] CC = cinnamyl chloride; HMDT = hexamethylditin; 4NBA = 4-nitrobenzaldehyde, product 1 = cinnamyl trimethylstannane, product 2 = trimethyl(1-(4-nitrophenyl)-2-phenylbut-3-enyloxy)stannane. All experiments were performed at 25 °C and followed in time by ^{1}H NMR analysis. [b] The reaction profile of this entry was similar to the one described in Figure 2. [c] Decomposition of 4-nitrobenzaldehyde was observed. [d] Due to the excess of CC and HMDT, also 9 (entry 11), 4 (entry 12) or 2 (entry 13) equivalents of product 1 were formed, respectively. Complete substrate conversion towards tandem product was observed in the first 5 h. [e] Reaction profile of this entry shows 70% product formation in the first 5 h, a plateau at 70% of product formation and finally a gradual completion of the reaction after 120 h.

reaction occurred between hexamethylditin and 4-nitrobenzaldehyde within 16 h (Table 2, entry 4). The presence of hexamethylditin is also essential for the formation of the secondary product: no direct palladium-catalyzed coupling occurred between cinnamyl chloride and 4-nitrobenzaldehyde (Table 2, entry 6). Addition of the Pd-pincer complex $\mathbf{1_{Cl}}$ to a mixture of hexamethylditin and 4-nitrobenzaldehyde led to decomposition of 4-nitrobenzaldehyde (Table 2, entry 7). When this experiment was repeated with another electrophile, that is, 4-cyanobenzaldehyde, no decomposition was found implying the involvement of the nitro-group in the degradation. The use of 4-cyanobenzaldehyde as the substrate in the palladium-catalyzed tandem reaction led to very similar reaction kinetics as described here for 4-nitrobenzaldehyde and the formation of the respective secondary tandem product 1-(4-cyanophenyl)-2-phenyl-3-buten-1-ol.

The use of a large excess of 4-nitrobenzaldehyde with respect to cinnamyl chloride and hexamethylditin led to the complete formation of secondary tandem product, but hardly speeded up the reaction (Table 2, entry 8). Again, a temporary state of reaction inactivity was observed, whereupon product formation proceeded gradually to completion after two days. When hexamethylditin was added in large excess, the stannylation was speeded up enormously (full reaction within 15 min), but the reaction did not proceed beyond the primary product cinnamyl trimethylstannane (Table 2, entry 9), even when a similar excess of 4-nitrobenzaldehyde was used (entry 10). Interestingly, no formation of the secondary tandem product was observed in these cases.

In the presence of an excess of both cinnamyl chloride and hexamethylditin the tandem reaction went to completion in just a few hours (Table 2, entries 11–14). Figure 6

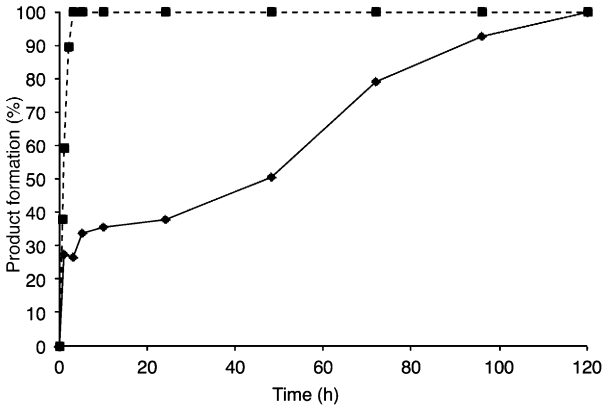
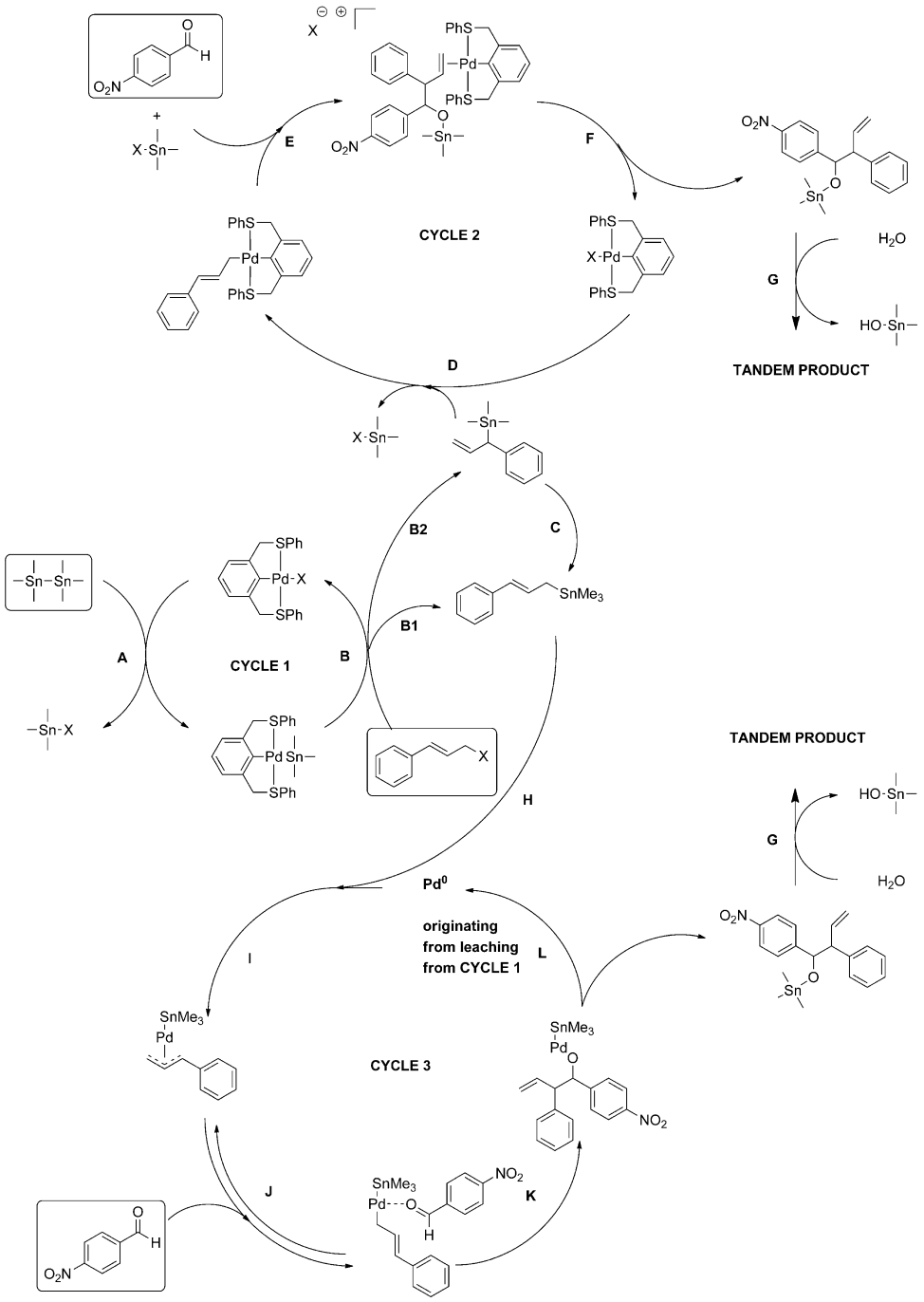


Figure 6. Secondary tandem product formation using 4-nitrobenzaldehyde and one (◆) or three equivalents (■) of cinnamyl chloride and hexamethylditin, respectively.

shows the reaction profile when 3 equivalents of cinnamyl chloride and hexamethylditin were used (Table 2, entry 13). A threefold excess of these substrates with respect to 4-nitrobenzaldehyde therefore resulted in a remarkable 60-fold increase in the reaction rate (120 h vs. 2 h to reach completion) and an entirely different reaction profile. In fact, the observed reaction profile lacks a lag phase and looks much like the theoretical kinetic profile shown in Figure 1. Only upon lowering the amounts of cinnamyl chloride and hexamethylditin to 1.5 equiv with respect to 4-nitrobenzaldehyde was a reaction plateau again observed. In this case, product formation stopped after 5 h at 70% of secondary tandem product (compare 40% secondary tandem product formation at equimolar substrate ratio, Figure 2) and was complete after 120 h.

Discussion

Our investigation of the tandem reaction consisting of the SCS-pincer palladium-catalyzed stannylation of cinnamyl chloride by hexamethylditin and subsequent electrophilic substitution by 4-nitrobenzaldehyde to form homo-allylic alcohols shows that the mechanism of this catalytic auto-tandem reaction is more complex than was anticipated so far. Based on our experiments, we propose an alternative mechanism for the tandem reaction catalyzed by SCS-pincer Pd complex $\mathbf{1_{Cl}}$ that explains the unusual reaction kinetic profile of the reaction, including the high initial 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol formation and the sudden halt of the formation of this secondary tandem product (see Scheme 4). These observations could not be explained with the catalytic cycle described by Gagliardo et al. for cationic SCS-pincer Pd complexes $\mathbf{1_{MeCN}}$.[11]



Scheme 4. Proposed reaction mechanism for the tandem reaction between cinnamyl chloride, hexamethylditin, and 4-nitrobenzaldehyde by using SCS-pincer palladium complexes.

ments in which only the stannylation reaction was investigated showed that a small amount of the branched S_N2' substitution product is formed. This S_N2' product disappears again before the stannylation reaction goes to completion. It either isomerizes in situ to the more stable conjugated cinnamyl trimethylstannane (step C) or enters the second catalytic cycle. The S_N2 product cinnamyl trimethylstannane appeared unreactive and, therefore, does not enter the second catalytic cycle toward the benzaldehyde electrophile in separate reactions. We believe that the formation of 1-phenyl-2-propenyl trimethylstannane is the key to the unusual reaction profile that was observed for the tandem reaction.

As soon as the first reaction step is complete, that is, all the cinnamyl chloride and hexamethylditin have reacted, no 1-phenyl-2-propenyl trimethylstannane is present, because it has either reacted onward to the secondary tandem product or it has been converted to the more stable cinnamyl trimethylstannane. At this point, cycle 2 (Scheme 4) of the tandem reaction cannot take place, since the remaining cinnamyl trimethylstannane has proven to be unreactive in this reaction. This explains the sudden drop in activity at the end of Part I of the reaction profile (Figure 2). Furthermore, this explains why higher amounts of cinnamyl chloride and hexamethylditin relative to 4-nitrobenzaldehyde lead to a reaction plateau at a higher percentage of secondary product (see Table 2, entry 14), or to a completed tandem reaction with a normal kinetic profile (entries 11–13).

Cycle 1: In the mechanism shown in Scheme 4, SCS-Pd complex $\mathbf{1_{Cl}}$ is transmetalated in the first catalytic cycle by hexamethylditin leading to a palladium-tin species (step A), which can undergo substitution with allyl chlorides like cinnamyl chloride (step B). This reaction can either take place through an S_N2-type substitution leading to the linear product cinnamyl trimethylstannane (step B1), or through an S_N2'-type substitution leading to the branched product 1-phenyl-2-propenyl trimethylstannane (step B2). Experi-

An order of 1.7 in palladium was found for this stannylation reaction (see Figure 3), which suggests a certain degree of positive cooperativity of SCS-pincer Pd fragments in the rate-limiting step of the reaction. Therefore, catalysts showing a high local concentration of catalytic centers, for example, dendritic catalysts, might show a higher reaction rate

than their monomeric analogues. Indeed, earlier investigations by us showed that the dendritic SCS-pincer Pd-complexes are more active catalysts for the stannylation of cinnamyl chloride.[12] Here, the monomeric catalyst showed 63% conversion of cinnamyl chloride after 1 h reaction, whereas the G_0 and the G_1 dendritic catalysts are significantly more active showing 71 and 85% conversion, respectively.

In conclusion, only when the first reaction step in the tandem is progressing, that is, when distinct amounts of 1-phenyl-2-propenyl trimethylstannane are present, can the second tandem step take place, since this species is required to feed the second reaction step. As soon as the starting materials cinnamyl chloride and hexamethylditin become depleted, no further formation of 1-phenyl-2-propenyl trimethylstannane occurs that leads to a status quo in the kinetic reaction profile.

Cycle 2: Whereas in our previous investigation we assumed that the second catalytic cycle starts with the formation of a Pd-η^1-allyl intermediate upon reaction of linear cinnamyl trimethylstannane with the (recovered) SCS-pincer Pd complex $\mathbf{1_{Cl}}$,[11] we now propose that this catalytic cycle starts with a transmetalation between branched product 1-phenyl-2-propenyl trimethylstannane and the SCS-pincer Pd-halide complex. This leads to the formation of the η^1-allyl palladium species $\mathbf{1_{\eta^1\text{-allyl}}}$ (Scheme 4, D). The attack of this species on the carbonyl group of the benzaldehyde subsequently takes place through the nucleophilic γ-carbon, creating a tertiary homo-allylic alcohol that is coordinated to the Pd center in a η^2-allyl fashion through the allyl moiety (Scheme 4, E). In this step, the two prochiral reaction partners react to form a mixture of secondary reaction products favoring the *anti* products (*RS, SR*) above the *syn* products (*RR, SS*). The *anti* products are formed in excess due to the more advantageous spatial distribution of the substituents, which reduces steric hindrance in the transition state in step E (Scheme 4). In the absence of available protons, the product is initially stabilized by the earlier released trimethyltin cation. Finally, the formed product is liberated from Pd (Scheme 4, step F), whereupon protonation in the workup leads to the secondary tandem product 1-(4-nitrophenyl)-2-phenyl-3-buten-1-ol (Scheme 4, step G).

Cycle 3: In the third cycle all further reactivity is proposed to be mediated by the in situ formation of Pd^0 species and not by SCS-Pd^{II} complexes. The latter complexes only act as precursors for the formation of Pd nanoparticles. Although ECE-Pd complexes are known to be stable as long as the temperature is not raised to too high values in the presence of strong bases,[22,23] a dramatic color change of the tandem reaction mixtures was observed after one day at room temperature and visible Pd-black formation occurred at room temperature after approximately two days.

We propose that Pd^0 formation is caused by an auto-decomposition of the SCS-pincer palladium-tin species $\mathbf{1_{SnMe_3}}$ in the first catalytic cycle. This species mainly reacts with cinnamyl chloride forming the primary reaction products cinnamyl trimethylstannane and 1-phenyl-2-propenyl trimethylstannane (step B in catalytic cycle 1, Scheme 4), but a small portion is proposed to be reduced to release a free Pd^0 atom (step H). The Pd^0 atoms that are formed in this way provide a starting point for a Pd^0/Pd^{II}-based third catalytic cycle.

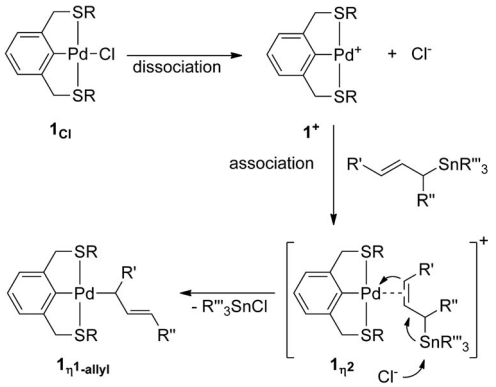
In this cycle, the Pd^0 center is proposed to undergo oxidative addition with cinnamyl trimethylstannane forming a palladium(II) η^3-allyl intermediate similar to Pd^0-catalyzed allylic substitution reactions of allyl halides[24] and Stille couplings.[25,26] It is widely accepted that this palladium(II) η^3-allyl intermediate has an electrophilic nature and reacts with nucleophiles.[27] Nevertheless it is well-known that η^3-allyl groups show exchange between (eventual) *syn* and *anti* substituents and that the intermediate of this process is a η^1-allyl metal complex.[28] Recently, Nakamura and Yamamoto found that bis-η^3-allylpalladium complexes can behave as nucleophiles and are able to react with electrophiles, like aldehydes.[29–31] Szabó and co-workers have performed extensive mechanistic studies on such palladium-catalyzed electrophilic allylation reactions that start from bis-η^3-allylpalladium complexes.[32–35] In these cases, the catalytic reaction proceeds because the aldehyde is able to coordinate to this bis-η^3-allylpalladium complex forming a η^3-allyl-η^1-allylpalladium intermediate. Subsequent nucleophilic attack of the η^1-allyl group on the carbon–oxygen double bond of the aldehyde produces a η^3-allyl-homoallyloxypalladium species. In this mechanism, one of the allyl ligands is a spectator ligand and therefore does not actively take part in the catalytic cycle. Its role is important in blocking one half of the coordination sphere and fine-tuning the activity of this reaction.[33]

In our case, the nucleophilic reactivity might be explained by a similar mechanism that takes place on the surface of a Pd nanoparticle, a situation in which also one half of the coordination sphere is blocked. A surface Pd^0 center might undergo oxidative addition with cinnamyl trimethylstannane forming a palladium(II) η^3-allyl intermediate (Scheme 4, step I), whereupon coordination of 4-nitrobenzaldehyde to this intermediate generates a nucleophilic η^1-allylpalladium intermediate (Scheme 4, step J). This interaction likely is part of an equilibrium in which the palladium(II) η^3-allyl intermediate is favored. The η^1-allylpalladium intermediate can escape from the equilibrium by attacking the carbonyl center of the aldehyde, leading to an alkoxypalladium species (Scheme 4, step K). Through reductive elimination, the catalytic cycle closes (Scheme 4, step L) and the released product leads, after protonation in the workup of this reaction, to the secondary tandem product (Scheme 4, step G). The *anti/syn* product ratio of this secondary product that has been formed through this Pd^0/Pd^{II} mechanism was found to be lower (1.5:1) than the product that has been exclusively formed through a Pd^{II}-only mechanism (3.5–4.0:1).

DFT calculations: In the previous part, we demonstrated that the SCS-pincer palladium complex $\mathbf{1_{Cl}}$ does not catalyze

the electrophilic allylic substitution of cinnamyl trimethylstannane with 4-nitrobenzaldehyde, whereas it successfully performs this reaction in the case of the isomeric substrate 1-phenyl-2-propenyl trimethylstannane. The most likely explanation for this behavior is that complex $\mathbf{1_{Cl}}$ is able to react with the branched 1-phenyl-2-propenyl trimethylstannane to form the (transient) key reactive η^1-allylpalladium intermediate, whereas this transformation cannot be achieved in the case of the cinnamyl trimethylstannane substrate.

A plausible, dissociative pathway for the reaction of complex $\mathbf{1_{Cl}}$ with an allylstannane moiety leading to a η^1-allylpalladium complex $\mathbf{1_{\eta^1\text{-allyl}}}$ is described in Scheme 5. It involves



Scheme 5. Proposed dissociative pathway for the formation of a η^1-allylpalladium complex from an allylstannane moiety and complex $\mathbf{1_{Cl}}$.

1) dissociation of the chloride ligand from $\mathbf{1_{Cl}}$, 2) coordination of the double bond of the allylstannane substrate to the vacant site of the palladium center, and 3) S_N2-type substitution of the chloride anion on the tin center, liberating the corresponding chlorostannane and forming $\mathbf{1_{\eta^1\text{-allyl}}}$.

The viability of such a reaction pathway was tested by using DFT calculations on a model system in which all methyl and phenyl groups of the pincer complex and the stannane substrates were replaced by hydrogen atoms (R = R′ = R″ = R‴ = H). Preliminary results from these calculations indicate that the reaction is unlikely to proceed as it is strongly endothermic ($\Delta G^0 = +12.6$ kcal mol^{-1}), but that the required transition state appears fairly accessible at room temperature ($\Delta G^{\dagger} = 20.6$ kcal mol^{-1}, see Figure 7).

In the real system, the position of the phenyl substituent of the allylstannane moiety appeared to have a crucial influence on the reactivity. This can be qualitatively rationalized by using Scheme 5. For the cinnamyl trimethylstannane substrate (R′ = Ph and R″ = H), the starting material is stabilized by conjugation of the allyl double bond with the phenyl ring, whereas the final product presents a hindered branched η^1-allyl fragment without conjugation between the double bond and the phenyl substituent. On the contrary, for the 1-phenyl-2-propenyl trimethylstannane substrate (R′ = H, R″ = Ph), the starting material is branched and not stabilized by conjugation, whereas the product exhibits a

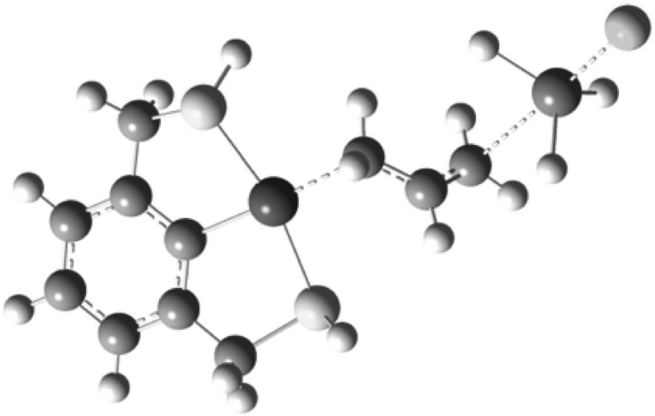


Figure 7. Transition state of the formation of an η^1-allylpalladium complex by nucleophilic attack of a chloride anion on the tin atom of an allylstannane coordinated to a palladium-pincer cation through an S_N2-type mechanism.

non-bulky linear η^1-allyl fragment, which is further stabilized by conjugation of the double bond with the phenyl group.

This qualitative reasoning is reflected in the overall reaction energy as computed by using DFT for both isomers. In the case of the cinnamyl trimethylstannane substrate, the transformation depicted in Scheme 5 is strongly endothermic ($\Delta G^0 = 16.4$ kcal mol^{-1}) and therefore would be difficult to achieve using the current reaction conditions. For 1-phenyl-2-propenyl trimethylstannane, however, the overall reaction is almost athermic ($\Delta G^0 = 2.6$ kcal mol^{-1}) and should consequently be able to proceed smoothly. Therefore, we conclude that our DFT results are in agreement with the hypothesis and our experimental results that 1-phenyl-2-propenyl trimethylstannane is able to react with SCS-pincer Pd-catalyst $\mathbf{1_{Cl}}$ to form a Pd-allyl intermediate, whereas cinnamyl trimethylstannane is unreactive towards this complex.

Conclusion

The SCS-pincer Pd-catalyzed auto-tandem reaction consisting of the stannylation of cinnamyl chloride followed by the electrophilic allylic substitution with 4-nitrobenzaldehyde to form 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol was studied. It was found that when palladium pincer complex $\mathbf{1_{Cl}}$ is used as the catalyst both cinnamyl trimethylstannane and its branched isomer 1-phenyl-2-propenyl trimethylstannane are formed in the first reaction step. The branched isomer turned out to be the active substrate in the second pincer-catalyzed reaction step, the electrophilic substitution with 4-nitrobenzaldehyde towards the secondary tandem product. These findings were corroborated by DFT calculations.

The consequence of this behavior is that as soon as the first catalytic cycle has finished because all substrates for the stannylation reaction have reacted, no branched product 1-phenyl-2-propenyl trimethylstannane is present in the reaction mixture. Since the linear isomer cinnamyl trimethyl-

stannane is not reacting through the Pd^{II}-catalyzed second catalytic cycle, but through another mechanism (catalytic cycle 3, Scheme 4), this second cycle is no longer fed, and as a consequence the electrophilic substitution with 4-nitrobenzaldehyde can no longer take place. This means that the total reaction progress stops and a plateau in the kinetic reaction profile is observed.

Addition of more equivalents of cinnamyl chloride and hexamethylditin with respect to 4-nitrobenzaldehyde leads to higher amounts of branched isomer 1-phenyl-2-propenyl trimethylstannane. Formation of the secondary tandem product 1-(4-nitrophenyl)-2-phenylbut-3-en-1-ol goes to completion using three, or more equivalents of cinnamyl chloride and hexamethylditin, because under these conditions the second catalytic cycle is continuously fed. The reaction rate enormously improves from one week, using one equivalent of cinnamyl chloride and hexamethylditin, to only 2 h by using three equivalents of these substrates, thereby showing normal reaction kinetics for a tandem reaction. Consequently, the tandem reaction takes place rapidly through a Pd^{II}-only mechanism. Under these conditions, a mechanism that makes use of the cinnamyl trimethylstannane product that is also formed in cycle I and of Pd^0 particles leached from the palladium pincer (cycle III) does not take part in this tandem reaction, which improves reaction rate, product selectivity and prevents Pd-leaching from the SCS-pincer Pd complexes.

For further catalytic application of this reaction, it is advised to use an excess of cinnamyl chloride and hexamethylditin relative to 4-nitrobenzaldehyde to guarantee a Pd^{II}-only mechanism. In this way, this auto-tandem reaction was successfully performed in a compartmentalized way by using a dendritic SCS-pincer Pd^{II}-catalyst for four runs in a high catalytic rate (89, 96, 96, and 92% for the respective runs) showing no palladium leaching for the first two runs.[12]

Experimental Section

General: All reactions were carried out using standard Schlenk techniques under an inert dinitrogen atmosphere unless stated otherwise. All solvents were carefully dried and distilled prior to use. All standard reagents were purchased commercially and used without further purification. ^1H (300 MHz), ^{13}C (100 MHz) and ^{29}Si (60 MHz) NMR spectra were recorded on a Varian 400 MHz spectrometer at 25°C, chemical shifts (δ) are given in ppm referenced to residual solvent resonances. ICP-MS analyses were carried out by Kolbe Mikroanalytisches Laboratorium (Mülheim a.d. Ruhr, Germany). GC analysis was carried out using a Perkin–Elmer Clarus 500 GC equipped with an Alltech Econo-Cap EC-5 column.

Synthesis of cinnamyl trimethylstannane: Cinnamyl chloride (8.0 mmol, 1.2 g, 1.1 mL), hexamethylditin (8.0 mmol, 2.8 g, 1.7 mL) and SCS-pincer Pd complex $\mathbf{1_{Cl}}$ (1 mol%, 37 mg) were combined in CH_2Cl_2 (30 mL). After a few hours, quantitative conversion towards cinnamyl trimethylstannane was observed. The solution was separated from the catalyst by using flash chromatography on neutral alumina using *n*-hexane as eluent. The fractions that contained product were collected and PVPy (100 equiv) was added. After stirring for 1 h, the colorless solution was filtered and concentrated under vacuum leading to pure cinnamyl trimethylstannane in 46% yield. Analytical data were in accordance with the data published by Fong et al.[36]

Synthesis of 1-phenyl-2-propenyl trimethylstannane: A solution of cinnamyl trimethylstannane (approximately 0.1 M) in $CDCl_3$ was placed into a NMR tube. Irradiation of this tube with a high pressure mercury UV lamp for 2 h at a distance of 2 cm to the lamp in a cooled water bath (to compensate for the heat caused by the lamp), leads to complete conversion of cinnamyl trimethylstannane to 1-phenyl-2-propenyl trimethylstannane. This NMR tube was directly used for further investigations. Analytical data were in accordance with the data published by Takuwa.[19]

General protocol for the tandem reaction: SCS-pincer palladium complex (2 mol%, 0.016 mmol, 7.4 mg), was added to a solution of cinnamyl chloride (0.80 mmol, 122.1 mg, 113 μL), hexamethylditin (0.80 mmol, 275 mg, 174 μL), 4-nitrobenzaldehyde (0.80 mmol, 126.9 mg), and hexamethylbenzene (internal standard, 0.088 mmol, 14.4 mg) in dry THF (6 mL). The reaction was stirred at room temperature in a nitrogen environment. Aliquots of 50 μL for NMR/GC analysis were regularly taken with an airtight syringe.

Protocol for the first reaction step of the tandem reaction (stannylation): The general protocol for the tandem reaction was followed, but no 4-nitrobenzaldehyde was added. The reaction was performed in dry THF (6 mL) or dry CH_2Cl_2 (6 mL) and analyzed by NMR spectroscopy and GC.

Variation on the concentration of catalyst in the first reaction step of the tandem reaction (stannylation): A solution of cinnamyl chloride (67 μmol, 10.2 mg, 9.4 μL), hexamethylditin (67 μmol, 21.8 mg, 13.8 μL) and hexamethylbenzene (internal standard, 7.4 μmol, 1.2 mg) in of CD_2Cl_2 (0.5 mL) was added into a NMR tube. Subsequently a solution of SCS-pincer palladium complex $\mathbf{1_{Cl}}$ in CD_2Cl_2 (0.1 mL) was introduced to the NMR tube. A series of solutions were made containing 2, 1, 0.5, 0.25, 0.125, or 0.0625% of catalyst $\mathbf{1_{Cl}}$. The experiments were performed inside a Varian 300 MHz spectrometer at 25°C.

Poisoning experiments for the first reaction step of the tandem reaction (electrophilic allylic substitution): The general protocol for the stannylation was followed. Polyvinylpyridine (2% cross linked, 100 equiv, 80 mmol, 8.4 g) or mercury (2 drops) were added to the reaction mixture. Analyses were performed by NMR spectroscopy and GC analysis.

Protocol for the second reaction step of the tandem(electrophilic allylic substitution): SCS-pincer palladium complex $\mathbf{1_{Cl}}$ (2 mol%, 0.016 mmol, 7.4 mg), was added to a solution of cinnamyl trimethylstannane (0.80 mmol, 225 mg), 4-nitrobenzaldehyde (0.80 mmol, 126.9 mg) and hexamethylbenzene (internal standard, 0.088 mmol, 14.4 mg) in dry THF (6 mL). The reaction was stirred at room temperature in a nitrogen environment. Aliquots of 50 μL for NMR/GC analysis were regularly taken with an airtight syringe.

Catalysis using 1-phenyl-2-propenyl trimethylstannane: A solution of 1-phenyl-2-propenyl trimethylstannane (0.25 mmol, 70 mg) in $CDCl_3$ (0.5 mL) was prepared, and 4-nitrobenzaldehyde (0.25 mmol, 38 mg) and SCS-pincer palladium complex ($\mathbf{1_{Cl}}$, ≈5%, few mg) were added to this solution. Limitations in the accuracy of the analytical balances used meant that the catalyst loading could not exactly be determined. The experiments were performed inside a Varian 300 MHz spectrometer at 25°C.

DFT calculations: All calculations were run in gas phase at the DFT level on the software G03W by using the B3LYP functional and the basis set H/C/S/Cl 6–31G*, Pd/Sn LANL2DZ.[37] All geometries were optimized using the regular convergence criteria (keywords opt for intermediates and opt=qst3 for transition states). Intermediates were characterized by the absence of imaginary vibrations in a frequency calculation. Transition states were characterized by the presence of a single imaginary vibration in a frequency calculation. The following simplifications were applied: 1) the phenyl groups of the pincer moieties were replaced by H atoms and 2) the trimethyltin group was replaced by a stannyl group (SnH_3).

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