Domino Reactions

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Electrophilic Activation of Benzaldehydes through *ortho* Palladation: One-Pot Synthesis of 3-Methylene-indan-1-ols through a Domino Allylstannylation/Heck Reaction under Neutral Conditions**

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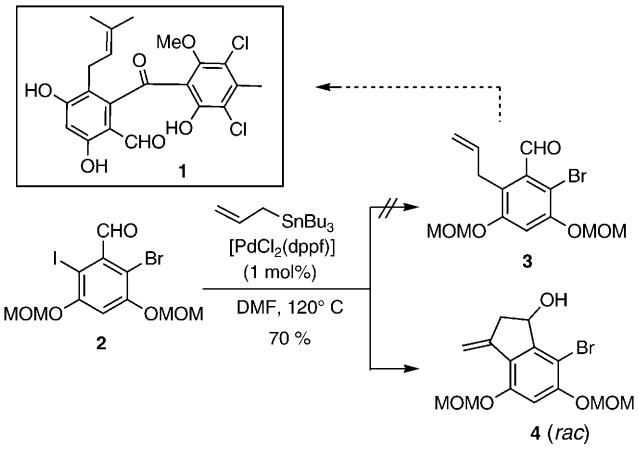
Dedicated to Professor Gerd Meyer on the occasion of his 60th birthday

Palladium-catalyzed transformations are of immense importance in modern organic synthesis, especially for C–C bond formation.[1] Prominent examples are, among many others, the Heck reaction[2] and the Stille cross-coupling,[3] which both enjoy frequent application in the synthesis of complex organic molecules.[4]

In the course of our research aimed at the synthesis of the antibiotic pestalone (**1**),[5] we recently attempted to prepare compound **3** from the iodobromobenzaldehyde **2** by palladium-catalyzed Stille cross-coupling using allyltributylstannane (Scheme 1). However, the NMR data of the sole product did not correspond to those expected for **3**. Instead, the isomeric indanol *rac*-**4** had formed as was unambiguously confirmed by X-ray crystallography (Figure 1).



Scheme 1. Unexpected course of the palladium-catalyzed reaction of **2** with allyltributylstannane to give the indanol derivative *rac*-**4**. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene; MOM = methoxymethyl.

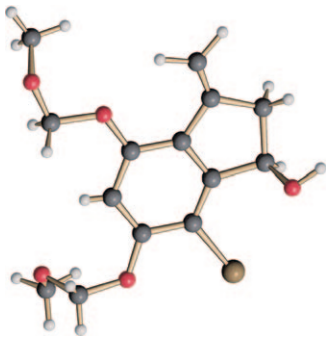
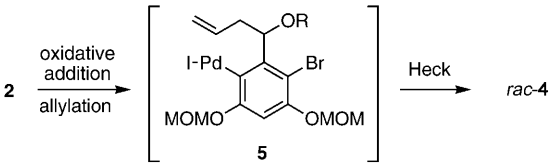


Figure 1. Structure of the indanol *rac*-**4** in the crystalline state.

To explain the unexpected formation of *rac*-**4**, we assumed a domino process[6] (via an intermediate of type **5**) consisting of an allylation of the aldehyde group[7] and a subsequent intramolecular Heck reaction (Scheme 2).[8]



Scheme 2. Suggested formation of *rac*-**4** through Heck cyclization of an allylated intermediate of type **5**.

Because 3-alkyl-1-indanols represent valuable building blocks for organic synthesis[9] we decided to probe the generality of the transformation. We report herein that the method is applicable to a variety of aryl halides and triflates bearing an *ortho*-carbaldehyde functional group. Moreover, we revealed two unique mechanistic aspects of the reaction, that is, the electrophilic activation of benzaldehydes through *ortho* palladation (a new catalytic activation mode) and the use of an alkoxystannane as a base equivalent in Heck-type reactions proceeding under neutral conditions.

In a first set of experiments (Table 1), we reacted several *ortho*-iodo- and *ortho*-bromobenzaldehydes with allyltributylstannane (2 equiv), using DMF as a solvent, in the presence of 1 mol% of [$PdCl_2$(dppf)]. Under these standard conditions (130 °C) most substrates were consumed within a few hours (monitored by TLC analysis). After workup, the tin-contain-

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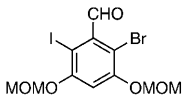
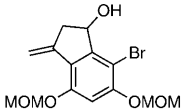
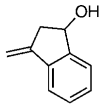
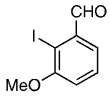
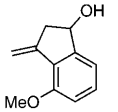
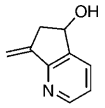
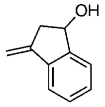
Table 1: Synthesis of 3-methylene-1-indanols from *ortho*-iodo- or *ortho*-bromobenzaldehydes.[a]

Entry	Substrate	T [°C]	t [h]	Product	Yield[b] [%]
1	 **2**	120	4	 **4** (*rac*)	70
2	 **6**	130	6	 **7** (*rac*)	85
3		80	12		87
4		130	24		96[c]
5		130	3		79[d]
6	 **8**	130	4	 **9** (*rac*)	91
7	 **10**	130	2.5	 **11** (*rac*)	56
8		130	3.5		53[d]
9	 **12**	130	23	 **7** (*rac*)	86

[a] Reaction conditions: Substrate (ca. 0.5 mmol), [$PdCl_2$(dppf)] (1 mol%), allyltributylstannane (2 equiv), DMF. [b] Yields of isolated products after flash chromatography. [c] NMP was used as a solvent. [d] Only 1 equiv of allyltributylstannane was used.

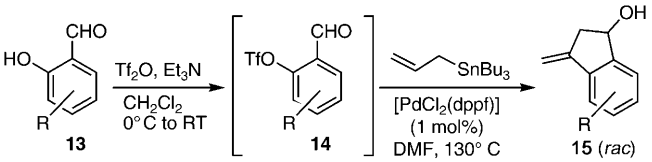
ing impurities were removed by using chromatography on a SiO_2/KF (9:1) column,[10] and the (racemic) products were isolated in good yield.

Some variations of reaction parameters were investigated while using the parent substrate **6**. Lowering the temperature to 80 °C resulted in a significantly slower conversion (Table 1, entry 3). Variation of the solvent confirmed DMF as being particularly suitable, as little to no conversion was observed in solvents such as toluene, water, dichloromethane, or THF. *N*-methylpyrrolidone (NMP) proved to be a suitable alternative to DMF (giving *rac*-**7** in 96% yield); however, much longer reaction times were required with this solvent (Table 1, entry 4). When the amount of allyltributylstannane was reduced to one equivalent, the product was obtained in only a slightly lower yield (Table 1, entries 5 and 8). Interestingly, the electron-poor bromopyridine **10** reacted rapidly under the standard conditions (Table 1, entry 7), whereas the parent *ortho*-bromobenzaldehyde (**12**) required a much longer reaction time than the corresponding iodide **6**, possibly as a result of slower oxidative addition of palladium(0) into the C_{Ar}–Br bond (Table 1, entry 9). Whereas reactions were usually conducted under inert conditions to achieve optimum yields, its notable that good results were obtained using non-degassed solvents.

As an alternative class of substrates, we examined *ortho*-formylaryltriflates of type **14** prepared from readily available salicylic aldehydes **13** with trifluoromethanesulfonic anhydride in dichloromethane in the presence of Et_3N.[11]

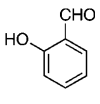
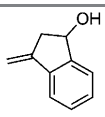
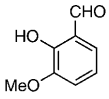
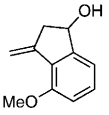
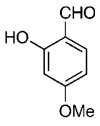
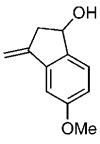
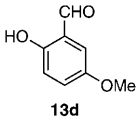
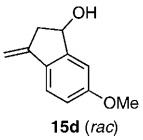
Because of their pronounced air sensitivity, the crude triflates **14**[12] were used directly in the subsequent palladium-catalyzed reaction with allyltributylstannane under the established conditions (Scheme 3). As the results given in Table 2 show, good yields of indanols of the type *rac*-**15** were obtained again. The products were even easier to purify in these cases than the iodide-derived samples.

We next turned our attention to a more detailed understanding of the mechanism. As a result of various experiments, we propose the catalytic cycle shown in Scheme 4. As a first step we assume the oxidative addition of a [L_2Pd^0] species into the C–X bond of the substrate **16** to give an *ortho*-palladated intermediate **17**.[13] We consider this intermediate to exist as a chelated species in which the aldehyde oxygen atom is coordinated to the palladium(II) center.[14] Instead of undergoing transmetalation (cross-coupling pathway) the electrophilic activation of the carbonyl group in **17** by the adjacent Lewis acidic palladium(II) center seems to be sufficiently strong to promote a selective allylstannylation of

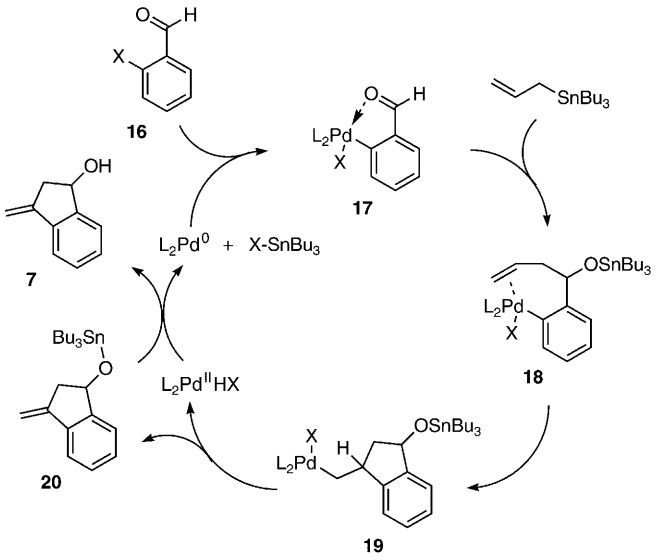


Scheme 3. Synthesis of 3-methylene-1-indanols of type *rac*-**15** from salicylic aldehydes. Tf = trifluoromethanesulfonyl.

Table 2: Synthesis of indanols from *ortho*-formylaryltriflates according to Scheme 3.[a]

Entry	Substrate	t [h][b]	Product	Yield[b] [%]
1	 **13a**	2.5	 **7** (*rac*)	73
2	 **13b**	4.0	 **9** (*rac*)	60
3	 **13c**	3.0	 **15c** (*rac*)	45
4	 **13d**	2.5	 **15d** (*rac*)	66

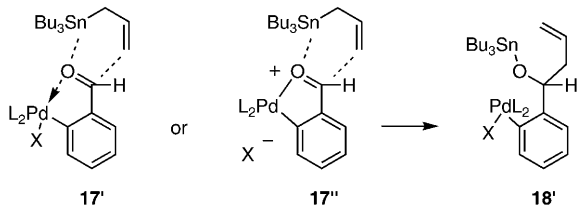
[a] Reaction conditions: Tf_2O (1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, 0 °C to RT, overnight, then triflate of type **14** (ca. 1.0 mmol), [$PdCl_2$(dppf)] (1 mol%), allyltributylstannane (2 equiv), DMF, 130 °C. [b] Reaction time for the palladium-catalyzed step. [c] Yields of isolated products (*rac*-**15**) over both steps.



Scheme 4. Proposed catalytic cycle for the domino allylstannylation/Heck process.

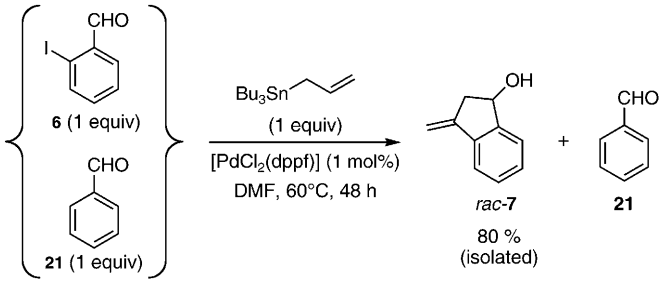
the aldehyde group, probably via a six-membered transition state of type **17′** or **17″** (Scheme 5).[15]

The resulting intermediate **18′** may easily form a palladium(II) chelate complex (**18**) which could undergo a Heck-type process starting with a β insertion (5-*exo-trig* cyclization) to give **19** (Scheme 4). Subsequent β-hydride elimination then gives rise to the alkoxystannane **20** and a [$L_2Pd^{II}HX$] complex. In contrast to normal Heck reactions, no base is required in this transformation, and we therefore assume **20** to act as a base equivalent inducing reductive elimination (of HX) to regenerate the [L_2Pd^0] species and thus to close the catalytic cycle.



Scheme 5. Electrophilic activation of the aldehyde group towards alkoxystannylation by the palladium(II) center at the *ortho* position.

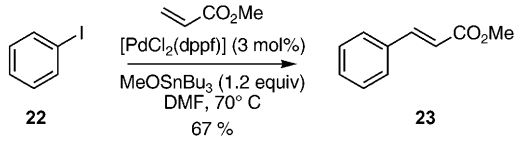
Initially, postulating an intramolecular electrophilic activation of the aldehyde function (intermediate of type **17**) was triggered by the observation that no byproducts (homoallylic alcohols) arising from a primary allylation step were observed.[15] Nevertheless, one could argue that the primary palladium(II)-catalyzed alkoxystannylation of **16** could also occur in an intermolecular fashion[16] and a more rapid, subsequent Heck-type cyclization. To exclude this possibility, a competition experiment was performed as shown in Scheme 6. Thus, when a 1:1 mixture of benzaldehyde (**21**)



Scheme 6. Competition experiment to demonstrate the intramolecular activation of the aldehyde function by *ortho* palladation (compare with Scheme 4).

and *ortho*-iodobenzaldehyde (**6**) was subjected to the standard reaction conditions, the indanol *rac*-**7** was isolated in 80% yield. Monitoring the reaction by means of GLC methods (using dodecane as an internal standard) showed **21** to be not consumed at all whereas *rac*-**7** cleanly emerged as the major product along with some tin-containing byproducts. This result strongly supports the proposed intramolecular mode of aldehyde activation.

In a second control experiment supporting the proposed mechanistic cycle, we probed an alkoxystannane as a base equivalent in a Heck reaction. Indeed, the reaction of iodobenzene (**22**) with methyl acrylate in the presence of [$PdCl_2$(dppf)] (3 mol%) and one equivalent of $MeSnBu_3$ afforded the expected Heck product **23** (Scheme 7). Even if the yield of the isolated product was only 67% (non-optimized conditions), this result clearly confirmed our suspicion that the alkoxystannane serves to regenerate the palladium(0) species in the catalytic cycle.



Scheme 7. Control experiment: A Heck reaction under "neutral conditions" using $MeOSnBu_3$ as a base equivalent.

In conclusion, we have serendipitously discovered a new and synthetically useful plladium-catalyzed domino process allowing an efficient synthetic entry into 3-alkyl- and 3-alkylidene-1-indanols. Moreover, and even more importantly, we were able to identify two mechanistic implications, which open new perspectives for future research: 1) The possibility to perform Heck reactions under virtually neutral conditions by using alkoxystannanes as a base equivalent may broaden the applicability of this reaction type in the context of complex synthesis (in the case of base-sensitive substrates). 2) The Lewis acid activation of a carbonyl group by means of oxidative addition of palladium(0) into an adjacent C–X bond (as part of a catalytic cycle) represents an unexplored concept, which might be exploited in the design and elaboration of novel synthetic methods (domino transfomations) in the future.

Experimental Section

Benzaldehyde **2** (200 mg, 0.46 mmol) and [$PdCl_2$(dppf)] (3.8 mg, 4.6 μmol, 1 mol%) were dissolved in absolute DMF (8 mL) under an argon atmosphere. Allyltributylstannane (0.17 mL, 0.54 mmol) was added to the reaction flask, and the resulting mixture was stirred at 120°C for 4 h. After the reaction mixture had cooled to RT, a saturated aqueous solution of KF (10 mL) was added. After extraction with MTBE (4×10 mL) the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$, and the solvents were then evaporated. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc = 6:1) to give indanol **4** as an orange solid (111 mg, 0.32 mmol, 70%); ^{1}H NMR: (250 MHz, $CDCl_3$): $\delta = 2.72$ (d, $J = 17.5$ Hz, 1H), 3.11 (dd, $J = 17.5$ Hz, 7.5 Hz, 1H), 3.46 (s, 3H), 3.49 (s, 3H), 5.13 (s, 1H), 5.20 (s, 2H), 5.23 (s, 2H), 5.23 (m, 1H), 5.81 (s, 1H), 6.91 ppm (s, 1H); ^{13}C NMR: (75 MHz, $CDCl_3$): $\delta = 41.2$ (t), 56.2 (q), 56.5 (q), 73.5 (d), 94.3 (t), 95.5 (t), 101.9 (s), 103.5 (d), 108.6 (t), 124.7 (s), 144.3 (s), 148.6 (s), 154.1 (s), 154.3 ppm (s); MS: (EI, 70 eV): typical isotope pattern corresponding to a molecule containing one bromine atom, m/z (%) = 346 (11, $[M(C_{14}H_{17}O_5{}^{81}Br)]^+$), 344 (11, $[M(C_{14}H_{17}O_5{}^{79}Br)]^+$), 284 (10), 282 (12); HRMS: calc. for $C_{14}H_{17}O_5{}^{79}Br$: 344.0259, found: 344.026.

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[14] Monitoring the reaction at 65°C in [D_7]DMF by means of in situ ^{1}H NMR analysis (500 MHz) revealed the formation of a second aldehyde species indicated by a singlet at $\delta = 10.50$ ppm in low concentration besides the starting material **6** (10.25 ppm). The assignments were supported by two-dimensional correlation spectra. Species related to **17** have been structurally characterized; see: J. Vicente, J.-A. Abad, E. Martínez-Viviente, B. M. C. Ramírez de Arellano, *Organometallics* **2000**, *19*, 752–760.

[15] Only when *ortho*-bromobenzaldehydes (in contrast to the corresponding iodides and triflates) were used as substrates, were small amounts of byproducts arising from primary allylation of the aldehyde function observed.

[16] a) R. B. Bedford, L. T. Pilarski, *Tetrahedron Lett.* **2008**, *49*, 4216–4219; a Lewis acid type activation in the palladium(II)-catalyzed allylation of aldehydes by allyltributylstannane seems to be much more favorable than alternative pathways via allyl–palladium intermediates; see: b) O. Piechaczyk, T. Cantat, N. Mézailles, P. Le Floch, *J. Org. Chem.* **2007**, *72*, 4228–4237.

