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Pd-mediated cross-coupling of C-17 lithiated androst-16-en-3-ol – An access to functionalized arylated steroid derivatives

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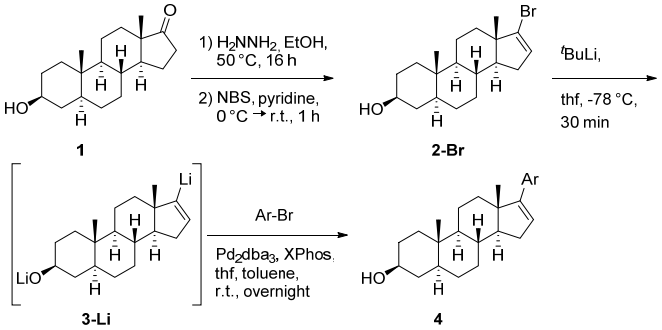
Herein, we report on a Pd-mediated cross-coupling of vinyllithium steroids and aryl bromides to introduce various substituted aryls at C-17 of steroidal frameworks based on the structure of *epi*-androsterone. Compared to other C–C cross-couplings, this method turned out to be an easy and competitive access to biologically interesting C-17 modified steroids.

Palladium-catalysed cross-coupling reactions for C–C bond formation play a key role in all fields of organic synthesis.[1-5] Among these, Suzuki-Miyaura with organoboron as organometallic nucleophile[6-9] and Stille (organotin reagent)[10-15] are mainly used as they tolerate a huge range of substituents. However, the high toxicity of organostannanes is often undesirable in particular with regard to pharmaceutical and medical applications. To over-come this disadvantage many coupling reactions based on different „metal nucleophiles“ such as magnesium (Kumada)[16, 17], zinc (Negishi)[18] and even silicon (Hiyama-Denmark)[19, 20] were already examined. Although organolithium reagents are inexpensive and either commercially available or easily accessible *via* halogen-metal exchange or direct metallation, the application of organolithium compounds as cross-coupling reagents is not well established until now. Early studies on Pd-mediated C–C bond formation with organolithium reagents as nucleophile by Murahashi demonstrated the limitations of this method resulting from the high reactivity and poor selectivity of organolithium reagents in general.[21-23] To overcome these difficulties, Feringa *et al.*[24, 25] recently reported on a novel protocol under mild conditions avoiding the lithium halogen exchange as well as the competing homocoupling. Using Pd_2dba_3 and different phosphine ligands like XPhos or P^tBu_3 as catalytic system enables the alkylation and arylation of different aryl halides as well as the arylation of different alkenylhalides by employing the corresponding organolithium reagents.[24, 25] This new methodology attracted interest in our research to find a novel method for introducing various substituents at C-17 of a steroidal precursor within a few steps since many natural products based on a steroidal framework carry different residues at C-17. Applying this method should submit access to biologically active and important steroid analogues without using any toxic reagents. Herein, we present a fast and convenient method for introducing different substituted aryls at C-17 of a steroid framework *via* a direct cross-coupling of the easily accessible and *in-situ* prepared vinyllithium steroid **3**.



Scheme 1: Synthesis of the lithiated steroid **3** and Palladium-catalysed cross-coupling of **3** with aryl bromides.

The lithiated vinyl steroid **3** is easy accessible within 2 steps (Schema 1) from commercially available *epi*-androsterone (**1**). Therefore *epi*-androsterone (**1**) was converted to the corresponding vinyl bromide **2-Br** using first hydrazine to build the hydrazone and then NBS and pyridine yielding the vinyl bromide **2-Br** in good yields of 76%. Best results for lithiation of vinyl bromide **2-Br** were achieved when using 3.1 equivalents of *tert*-butyllithium in dry thf.

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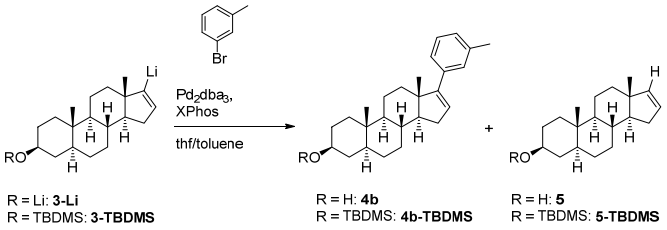
Table 1: Optimization of the reaction conditions.

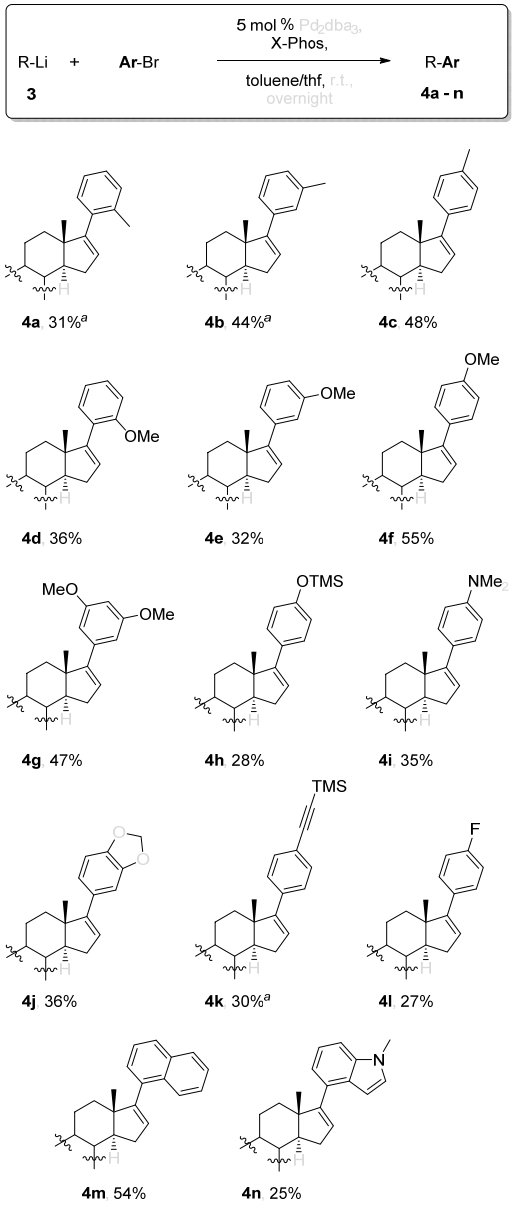


Entry	Starting material	Conditions[a)]	Ratio **4** : **5**	Yield of **4** [%]
1	**3**	syringe pump (1 h) 3 h at r.t.	-	traces
2	**3**	syringe pump (1 h) overnight at r.t.	1.0 : 3.0	10
3	**3**	syringe pump (1 h) overnight at 60 °C	1.0 : 0.56	10
4	**3**	cannulation (30 min) overnight at r.t.	1.0 : 0.43	44
5	**3-PG**	cannulation (30 min) overnight at r.t.	1.0 : 0.28	33

a) Lithiated steroid **3**/**3-PG** (1.0 eq.) in dry thf was added to a solution of 3-bromotoluene (1.3 eq.), Pd_2dba_3 (5 mol%) and XPhos (20 mol%) in dry toluene and maintained at the appropriate temperature for the stated amount of time.

For our initial model reaction (Table 1) we selected 3-bromotoluene in a mixture of toluene and thf as solvent system and Pd_2dba_3/XPhos as catalytic system based on the work of Feringa *et al*.[24, 25] We started our investigations with the usage of a syringe pump to ensure a slow addition of the highly reactive organolithium reagent (entries 1 – 3) varying the reaction time and temperature afterwards. By increasing the reaction time from 3 h to overnight, we were able to obtain at least 10% instead of traces of the desired product **4b** which was isolated as a mixture with the defunctionalized steroid **5**. By increasing the reaction temperature to 60 °C the ratio of the coupled product **4b** and the defunctionalized steroid **5** could be drastically improved (entry 3). However, best yields were achieved if the freshly prepared lithium steroid was directly cannulated as thf solution at -78 °C (entry 4) which is reasonable due to the lower stability of **3** compared to the substrates of the Feringa group. Anyway, even with equimolar amounts of the catalyst system, yields could not be further improved indicating that the moderate yields are not a result of an interrupted catalytic cycle. To exclude that these rather moderate yields are due to effects caused by the deprotonated hydroxyl group of the steroid, the OH was protected with a TBDMS group and again subjected to the developed protocol giving the product **4b-PG** in a better ratio, but unfortunately with no further enhancement of the yield (entry 5). Along with the described catalytic system, different palladium sources like $Pd(PPh_3)_4$ as well as alternative phosphine ligands like P^tBu_3 were tested but without further improvements. With the optimal conditions in hand, the scope of the reaction was examined (Table 2) including different substituted aryl bromides bearing electron-donating and electron-withdrawing groups as well as annulated systems. Regarding the electron-donating methyl (hyper-conjugation) and methoxy (+M-effect) group, moderate yields were achieved in the case of *ortho*- and *meta*-substituted bromotoluenes whereas *para*-substitution gave the arylated product in good yield of 48% (*para*-methyl) and 55% (*para*-methoxy).

Table 2: Scope of substrates.



[a] This steroid could not be isolated purely (traces of the defunctionalized steroid **5** could not be completely removed *via* column chromatography). Yields were estimated *via* integration of the signals of the ^1H NMR spectrum.

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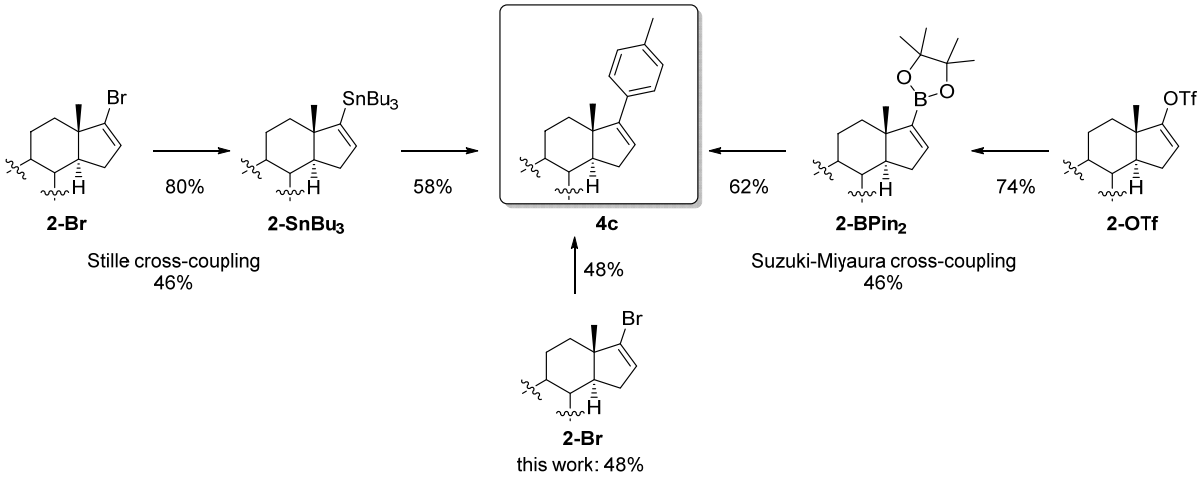

Scheme 2: Comparison of the presented method with Stille and Suzuki cross-coupling protocols.

It is worth mentioning that the usage of very polar substituted bromides like 1-bromo-3,5-dimethoxybenzene facilitates the column chromatography extremely since the separation from the deprotected steroid **5** is, in particular for unpolar aryls, challenging and in some cases not completely possible even after multiple column chromatography. Also, TMS-protected bromophenol and dimethyl protected bromoaniline could be introduced at C-17 of the steroid in moderate yields. Furthermore, TMS-protected alkynes and also acetals were tolerated giving the arylated steroids **4k** and **4j** in 30% and 36% yield, respectively. In accordance with the results of Feringa *et al.*[24, 25] nitriles, nitro- and keto groups were not compatible with the organolithium reagent, mainly due to the formation of 1,2-addition side products. Furthermore, it could be proven that an electron-poor aryl bromide like 1-bromo-4-fluorobenzene can be introduced successfully to the steroid pattern even if the yield is not as good as those for electron-rich aryl bromides. The arylated systems could be extended to naphthylbromides which was linked to the steroid in a yield of 54%. Motivated by this result also a heterocyclic example for an annulated system like methyl protected 4-bromoindole was examined giving the arylated steroid in 25% yield. In order to evaluate the power of this novel method Stille and Suzuki-Miyaura cross-couplings were performed for comparison starting from the vinylbromide **2** and the analogous vinyltriflate **2-OTf** (Scheme 2) whereas *para*-bromotoluene served as model bromide. It is noteworthy that other arylbromides bearing electron withdrawing (e.g. *para*-fluorine) and electron donating substituents (e.g. *para*-methoxy) yield similar results. For the Stille cross-coupling vinyl stannyl derivative **2a-SnBu$_3$** as nucleophile had to be synthesized *via* lithiation with ^{t}BuLi followed by the reaction with tributyltin chloride giving **2a-SnBu$_3$** in good yields of 80%. Using $Pd(PPh_3)_4$ as catalyst and LiCl and CuCl as additives the arylated product **4c** was obtained in moderate yield of 58%. For the Suzuki-Miyaura cross-coupling, we installed a pinacolatoboron moiety at C-17 of the steroid starting from the vinyl triflate **2-OTf** (see ESI for further information). Applying an optimized protocol for Suzuki cross-coupling with $Pd(PPh_3)_4$ as catalyst and Na_2CO_3 as base the arylated product was isolated in 62% yield. When comparing the yield of the cross-couplings themselves as well as their overall yield over two steps with the herein presented method it becomes obvious that this method is competitive with other well established methods. On top of it, considering aspects of toxicity, waste disposal and effort the shown coupling is even superior to Stille and Suzuki reaction.

Conclusions

In summary, we presented a Pd-mediated cross-coupling of vinyllithium steroids based on the core structure of *epi*-androsterone with different substituted aryl bromides using the well-known catalytic system Pd_2dba_3/XPhos in toluene and thf as solvent system in order to create new derivatives based on highly biologically active steroids. Comparing this method to established methods like Stille or Suzuki cross-coupling reactions illustrates its competitiveness and advantages with respect to toxicity, the amount of waste and overall yields.

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Notes and references

Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data, 1H and 13C NMR spectra. See DOI: 10.1039/c000000x/

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