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Stille and Suzuki Cross-Coupling Reactions as Versatile Tools for Modifications at C-17 of Steroidal Skeletons – A Comprehensive Study

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Abstract: Herein, we report on a comparative Stille and Suzuki cross-coupling study of steroidal vinyl (pseudo)halides with different boronic acids and tributyltin organyls. Furthermore, we have investigated the "inverse" case of those cross-coupling reactions, i.e., the reaction of a steroidal vinylpinacolatoborane or a tributyltin steroid with various bromides. The development of both methods allows the introduction of different residues at C-17 of steroid skeletons providing access to a broad variety of steroid analogues which are of high interest for biological screenings or natural product synthesis.

Keywords: stannylation; steroids; Stille coupling; Suzuki coupling

Introduction

Palladium-mediated cross-coupling reactions have revolutionized all fields of organic synthesis since their discovery in the mid-1970s. They are known to offer mild reaction conditions and a great tolerance towards functional groups, thus representing a versatile tool not only in organic synthesis, but also in natural product synthesis.[1] Among the manifold scopes of application, all types of cross-coupling reactions like the Heck,[2] Suzuki–Miyaura,[3] Stille,[4] Sonogashira–Hagihara,[5] Negishi,[6] and Kumada[7] versions were also applied to modify or construct steroidal frameworks.[8] For example, various group were inserted at every biologically or synthetically important position of the steroid skeleton like C-3,[9] C-17,[9a–c,10] or at the side chain.[11] Also, the formation of the basic steroidal skeleton was achieved *via* cyclization reactions based on cross-coupling reactions.[12] Regarding the total synthesis of prominent steroids, especially Stille and Suzuki couplings represent an efficient method to introduce several heterocyclic moieties at the C-17 position of a steroidal backbone.[13] This residue is of particular importance since it characterizes different classes of steroids like bufenolides and cardenolides (Figure 1).

Although there is an increasing interest in introducing various functional groups to specific positions of the steroid backbone, like C-17, to alter biological properties, no fundamental studies have been report-

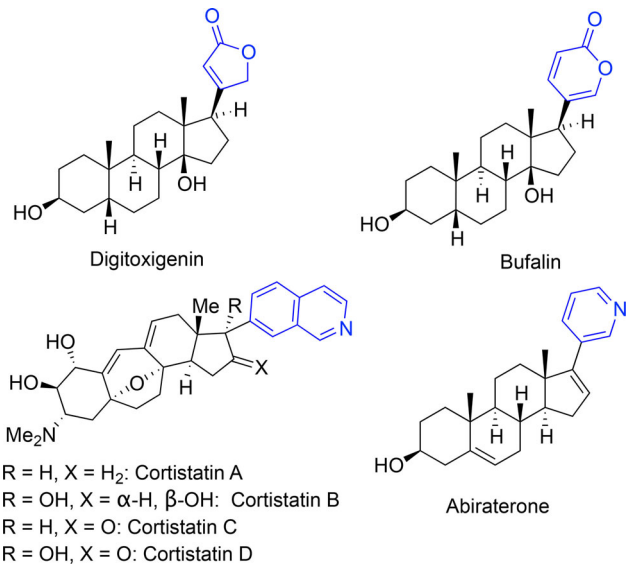


Figure 1. Important steroids with C-17 heterocyclic substituents.

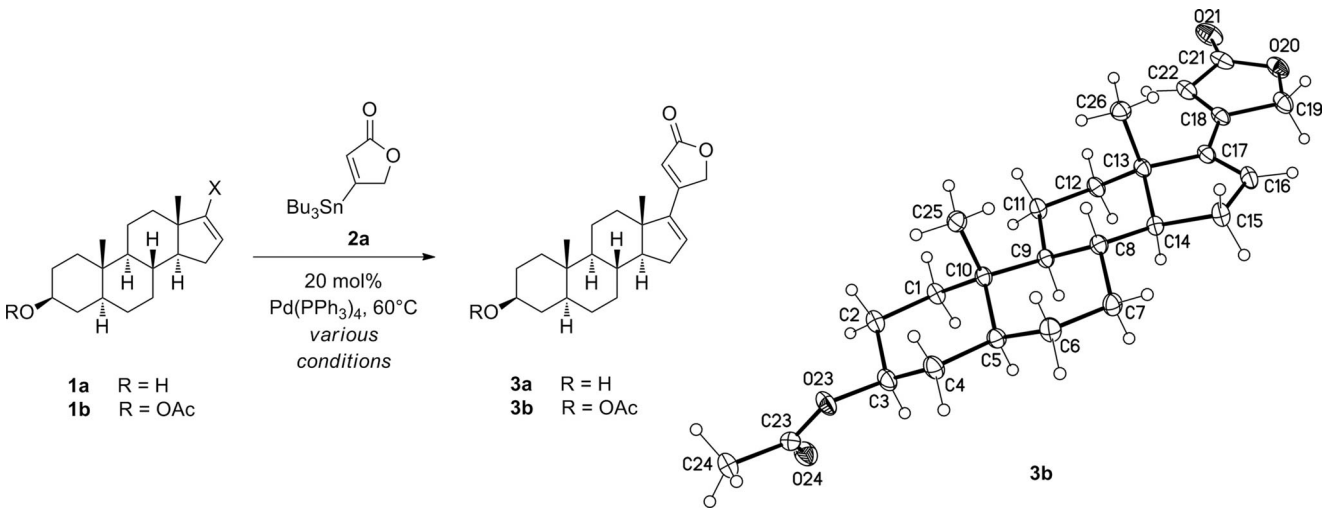
ed so far. In order to demonstrate the applicability and differences between the two most applied coupling reactions, we want to report on Suzuki and Stille cross-coupling reactions of steroidal vinyl (pseudo)halides with different boronic acids/tributyltin compounds as well as cross-couplings of steroidal pinacol boronates/organotin substrates with selected halides to introduce the desired moieties at C-17.

Results and Discussion

Since vinyl (pseudo)halides are easily accessible and well-known precursors for coupling reactions in organic and also steroidal chemistry, we addressed these substrates first with the most diversely used Stille coupling reaction. For this purpose, *epi*-androsterone was converted to the corresponding vinyl bromide/iodide **1a-Br**/**1a-I** (see the Supporting Information for synthesis of **1a-Br** and its crystal structure) using first hydrazine to build the hydrazone and then NBS and pyridine as base or iodine and trimethylamine, respectively, according to known protocols.[14] The vinyl triflate **1b-OTf** was accessible by protection of the OH group of *epi*-androsterone as an acetate followed by the treatment with KHMDS and $PhN(Tf)_2$ at −78 °C.[10d] Then we tested several sets of general reaction conditions for the Stille coupling of 4-tributyltinvinylfuran-2(3*H*)-one **2a** and vinyl bromide **1a-Br**, vinyl iodide **1a-I** and vinyl triflate **1b-OTf** constructing the cardenolide **3a/3b** (Table 1) with 20 mol% $Pd(PPh_3)_4$ as catalyst. The obtained crystal structure of cardenolide **3b** confirms the molecular structure and illustrates the topology of this molecule.

Comparing the tested solvents THF, DMSO and DMF, best yields were achieved in all cases with DMF or DMSO (Table 1, all entries) which explains why DMSO is often used as solvent in several examples in the literature.[13a,b] Regarding **1a-Br** as starting material, yields could be drastically improved by ap-

Table 1. .Table 1Conditions for Stille cross-coupling reactions; molecular structure of **3b** (displacement parameters are drawn at 50% probability level).



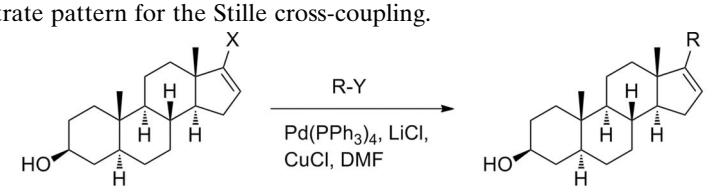
Entry	1-X	Time	Additives	Solvent	Product	Isolated yield [%]
1	**1a-Br**	16 h	LiCl, CuCl	THF	**3a**	traces
2	**1a-Br**	48 h	LiCl, CuCl	THF	**3a**	traces
3	**1a-Br**	16 h	LiCl, CuCl	DMSO	**3a**	11
4	**1a-Br**	16 h	CuTc, $[Ph_2PO_2][NBu_4]$	DMSO	**3a**	43
5	**1a-Br**	48 h	LiCl, CuCl	DMSO	**3a**	57
6	**1a-Br**	16 h	LiCl, CuCl	DMF	**3a**	16
7	**1a-Br**	48 h	LiCl, CuCl	DMF	**3a**	60
8	**Ia-I**	16 h	LiCl, CuCl	THF	**3a**	22
9	**Ia-I**	16 h	LiCl, CuCl	DMSO	**3a**	64
10	**Ia-I**	16 h	CuTc, $[Ph_2PO_2][NBu_4]$	DMSO	**3a**	45
11	**1a-I**	16 h	LiCl, CuCl	DMF	**3a**	48
12	**1a-I**	16 h	–	DMF	**3a**	traces
13	**1b-OTf**	16 h	LiCl, CuCl	THF	**3b**	43
14	**1b-OTf**	16 h	LiCl, CuCl	DMSO	**3b**	49
15	**1b-OTf**	16 h	LiCl, CuCl	DMF	**3b**	55

plying longer reactions times of 2 days (Table 1, entries 3 and 6). When the conditions reported by Fürstner and co-workers,[15] optimized for other substrates, were applied, the reaction seemed to proceed more rapidly and after 16 h the cardenolide **3a** was isolated in 43% yield (Table 1, entry 4). Nevertheless, the reaction times were prolonged to 2 days and the product was obtained in good yields of up to 60% (Table 1, entries 5 and 7). Alternatively, the more reactive but less stable vinyl iodide **1a-I** was used (Table 1, entries 8–12). Starting from **1a-I** even better yields of up to 64% were obtained in shorter reaction times with DMSO as solvent (Table 1, entry 9).

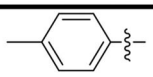
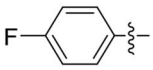
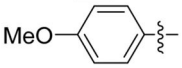
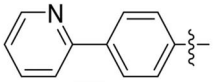
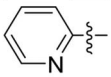
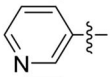
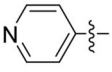
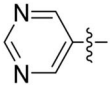
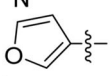
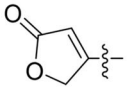
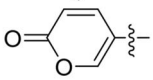
Applying Fürstner's conditions[15] to the system could not lead to further improvements (Table 1, entry 10). When omitting the additives LiCl and CuCl the cardenolide **3a** could be isolated only in traces, which demonstrates their accelerating and important function (Table 1, entry 12). Using **1b-OTf** as substrate provides good yields of from 43–55% within 16 h (Table 1, entries 13–15).

Afterwards, the substrate scope was explored by introducing different residues at C-17 (Table 2) including naturally occurring ones like differently connected pyridines or pyran-2-one as well as artificial ones like the phenyl derivatives. Therefore different tin organyls have been synthesized which were then subjected to the developed protocol of the Stille reaction in DMF using **Ia-I** as starting material and 20 mol% $Pd(PPh_3)_4$ as palladium source. We were able to show that different substituted phenyl derivatives containing both electron-withdrawing (Table 2, entry 3) and

Table 2. Selected substrate pattern for the Stille cross-coupling.



1a **3a–14a**

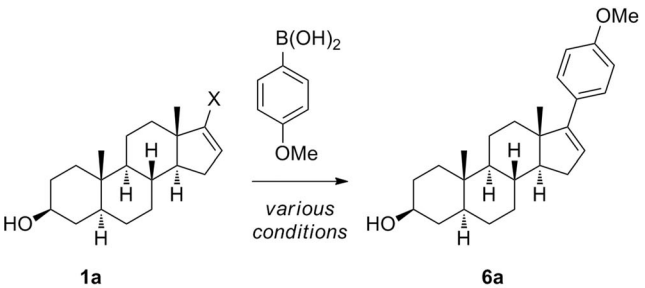
Entry	1-X	R	Y	Temp./Time	Product	Isolated yield [%]
1	**Ia-I**		$SnBu_3$	60 °C, 16 h	**4a**	58
2	**1a-$SnBu_3$**		Br	60 °C, 16 h	**4a**	71
3	**Ia-I**		$SnBu_3$	60 °C, 2 d	**5a**	68
4	**1a-$SnBu_3$**		Br		**5a**	68
5	**Ia-I**		$SnBu_3$	60 °C, 16 h	**6a**	59
6	**1a-$SnBu_3$**		Br	60 °C, 16 h	**6a**	29
7	**Ia-I**		$SnBu_3$	60 °C, 16 h	**7a**	64
8	**1a-$SnBu_3$**		Br	60 °C, 16 h	**7a**	26
9	**1a-I**		$SnBu_3$	60 °C, 16 h	**8a**	70
10	**1a-$SnBu_3$**		Br	80 °C, 16 h	**8a**	29
11	**1a-I**		$SnBu_3$	60 °C, 3 d	**9a**	60
12	**1a-$SnBu_3$**		Br	80 °C, 3 d	**9a**	33
13	**1a-Br**		$SnBu_3$	60° C, 2 d	**10a**	68
14	**1a-$SnBu_3$**		Br	80 °C, 3 d	**10a**	0
15	**1a-I**		$SnBu_3$	60 °C, 2 d	**11a**	82
16	**1a-$SnBu_3$**		Br	60 °C, 2 d	**11a**	0
17	**1a-I**		$SnBu_3$	60 °C, 16 h	**12a**	53
18	**1a-I**		$SnBu_3$	60 °C, 16 h	**3a**	48
19	**1a-$SnBu_3$**		Br	60 °C, 16 h	**3a**	79
20	**1a-Br**		$SnBu_3$	80 °C, 3 d	**13a**	28
21	**1a-$SnBu_3$**		Br	80 °C, 3 d	**13a**	48
22	**1a-I**		$SnBu_3$	60 °C, 3 d	**14a**	46

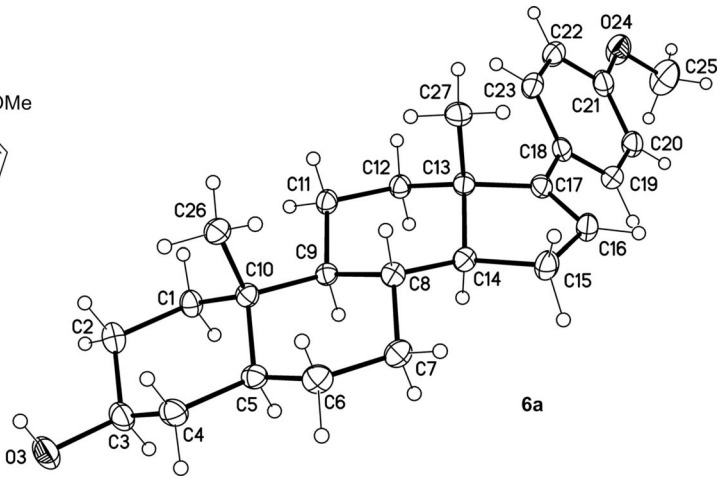
electron-donating groups (Table 2, entries 1, 5 and 7) could be easily introduced at C-17 in mostly good yields. Since the naturally occurring pyridine residues are important targets of medicinal chemistry, we synthesized their tin derivatives and subjected them to our developed conditions. Fortunately, the corresponding products were obtained in good yields of about 60–73% (Table 2, entries 9, 11 and 13) and the obtained crystal structure of **9a** could confirm the molecular structure (see the Supporting information). Moreover, we attempted to introduce other aromatic and non-aromatic heterocycles at C-17 of the steroid skeleton to confirm the versatile applicability of this method. For the stannylated 5-pyrimidine derivative as reagent we were able to isolate the desired product **10a** in a very good yield of 82% (Table 2, entry 15). Furthermore oxygen-containing heterocycles were successfully installed at C-17 *via* Stille coupling resulting in moderate yields (Table 2, entries 17, 18 and 20) which proves our method to be powerful for building up cardenolides or bufenolides (Figure 1) and being competitive with previously reported approaches in natural product synthesis.

Even more challenging non-aromatic stannanes using the commercially available tributylvinyltin as an example were connected in 46% yield (Table 2, entry 21), which gives in principle after hydrogenation access to steroids carrying an aliphatic side chain like cholesterol. In addition, we wanted to figure out the effect of the inversion of the halogen and tributylstannyl functional groups. For this reason, we synthesized the vinyl stannyl derivative **1a-SnBu$_3$** in good yields of 80% by lithiation of vinyl bromide **1a-Br** with *t*-BuLi followed by the reaction with tributyltin chloride. Although we did observe that aryl or heteroaryl groups could be successfully introduced to C-17 by coupling with the proper bromides the yields were not always sufficient for synthetic applications (Table 2, entries 4, 6, 8, 10 and 12). Surprisingly, the reactions with 4-bromotoluene and 4-bromofuran-2(3*H*)-one gave the corresponding coupling products in good yields of 71% and 79% (Table 2, entries 2 and 19). In previously reported approaches for the synthesis of bufadienolides the metallic center was installed at the pyrone moiety and then coupled to the steroid in good yields *via* Suzuki or Stille cross-coupling.[13a,b,16] Since we observed in the case of the furanone moiety that better yields were isolated if the metallic center is installed at the steroid (entries 18 and 19) we wanted to find out whether bufadienolides could be constructed in the same manner. "Inverse" Stille coupling affords the desired product **13a** in moderate yield of about 48%.

Since Suzuki couplings possess some general advantages over Stille reactions, like the non-toxic and commercially available boronic acids as reagent, Suzuki reactions were also part of our systematic investigations on the C-17 modification. Therefore, several established catalytic systems were screened in order to find the best reaction conditions for the steroidal

Table 3. Tested conditions for the Suzuki–Miyaura cross-coupling; molecular structure of **6a** (displacement parameters are drawn at 50% probability level).





Entry	1-X	Temp./Time	Catalyst/Ligands	Base	Solvent system	Isolated yield [%]
1	**1a-I**	reflux, overnight	$PdCl_2(dppf)_2$	Cs_2CO_3	THF	30
2	**1a-I**	reflux, overnight	Pd_2dba_3, SPhos	*t*-BuOK	THF	traces
3	**1a-I**	reflux, overnight	Pd_2dba_3, XPhos	*t*-BuOK	THF	28
4	**1a-I**	reflux, overnight	$Pd(PPh_3)_4$	2 M Na_2CO_3	DME/H_2O	traces
5	**1a-I**	reflux, overnight	$Pd(PPh_3)_4$	2 M Na_2CO_3	benzene/MeOH/H_2O	52
6	**1a-I**	reflux, overnight	$Pd(PPh_3)_4$	2 M Na_2CO_3	toluene/MeOH/H_2O	22

backbone **1a** (Table 3) with 4-methoxyphenylboronic acid as model using different palladium sources as well as bases and solvent systems. However, best results were achieved using again $Pd(PPh_3)_4$ as palladium source, Na_2CO_3 as base and a biphasic solvent system containing benzene, methanol and water (Table 3, entry 5). $PdCl_2(dppf)_2$ and Cs_2CO_3 or Pd_2dba_3 and *t*-BuOK in THF gave only moderate yields of 30 and 28% (Table 3, entries 1 and 3). The reaction system seems to be relatively sensitive to its conditions since very small changes in conditions decreased the yield of the product **6a** drastically to only traces (Table 3, compare entries 2 and 3 or 4 and 5). Unfortunately, benzene could not be replaced by toluene as a less toxic alternative without significant decreases in the yield (Table 3, entry 6). A crystal structure of the product **6a** could be obtained illustrating the molecular structure of the steroid. With the best conditions in hand, we investigated the substrate scope for Suzuki couplings and the most important results are listed in Table 4.

We were able to obtain the phenyl-substituted steroid framework **15a** in the good yield of 65% (Table 4, entry 1). However, methyl-substituted phenyls serving as an example for slightly donating groups (hyper-conjugation) could be introduced as well in moderate to good yields with the order *ortho* < *para* < *meta* (Table 4, entries 2, 4, and 5). Apart from pyridylboronic acids (not shown here), different substituted aryls were introduced successfully at C-17 in mostly good yields (Table 4). Phenyl groups containing electron-withdrawing substituents were incorporated to the steroidal skeleton in moderate yields of about 40% (Table 4, entries 8 and 11) demonstrating that the quantity of the groups has no effect on the isolated yield. By increasing the reaction time and simultaneous usage of the more stable vinyl bromide **1a-Br** significantly better yields could be obtained as shown for the coupling with the fluorinated phenylboronic acid (Table 4, entry 9, see the Supporting Information for the crystal structure). Heterocyclic aryl structures were subjected to our investigations as well and gave successfully the corresponding products with the exception of the already mentioned nitrogen heterocycles like pyridine or pyrimidine (Table 4, entries 19, 22 and 23). Fortunately, a successful reaction with good yields has been observed in the case of the 5-indolylboronic acid and the isomeric, synthesized 7-indolylpinacolborane (Table 4, entries 15 and 16). Commercially available 8- and even 3-quinolineboronic acid were successfully coupled to C-17 (Table 4, entries 17 and 18) mimicking the natural occurring Cortistatin[17] bearing an isoquinoline moiety. It is noteworthy that this is the only example for a boronic acid that is directly connected to a nitrogen heterocycle which could be successfully attached to the C-17 of the steroid pattern. A furyl moiety (Table 4, entry 23) as well as two thienyls (Table 4, entries 25 and 26) were introduced in good yields at C-17 demonstrating that Suzuki couplings also work well for other heteroaromatics. In addition, we explored whether non-aromatic sp^2 boronic acids reacted similarly, as this would represent a non-toxic alternative for the conventionally applied Stille cross-coupling. Fortunately, we are able to build up a non-aromatic sp^2–sp^2 C–C bond using differently substituted double bonds. As previously discussed, excellent yields were obtained in these cases starting from the vinyl bromide **1a-Br** with longer reaction times (Table 4, entries 12–14).

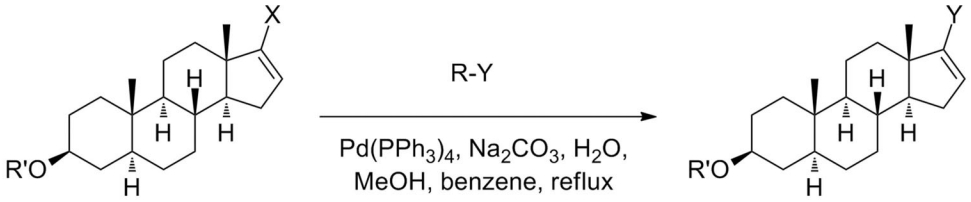
Since pyrimidine and pyridines could not be introduced to the skeleton using the Suzuki reaction, we decided to incorporate the boron functionality into the steroid skeleton. This approach might be advantageous to introduce even more residues at C-17, because not every boronic acid is commercially available. For this reason, we installed a pinacolatoboron moiety at C-17 (see the Supporting Information for further information) and tested the potential of this "inverse" Suzuki reaction. In the case of the phenyl bromides no dependency on the electronic character of their *para*-substituents was observed (Table 4, entries 3, 7 and 10). Then, we investigated whether bromopyridine and bromopyrimidine react with the vinylpinacolatoborane **1b-BPin**. This time, the corresponding pyridyl-substituted products **8b**, **9b** and **10b** were obtained in moderate to good yields following the expected order *ortho* < *para* < *meta* regarding their deactivation (Table 4, entries 19–21). With the less expensive 3-chloropyridine as substrate no product was isolated, limiting the presented method to bromides. Also, the pyrimidine derivative **11b** could be synthesized in 43% yield (Table 4, entry 22) and a crystal structure confirming the molecular structure could be obtained (see the Supporting Information).

Even the challenging 5-bromo-2*H*-pyran-2-one was successfully coupled to the steroid (Table 4, entry 24), but the product **3b** was not obtained in good yield limiting the applications of the method to aromatic sp^2 centers.

Conclusions

Herein, we have reported on two C–C cross-coupling reactions for the introduction of several different residues at C-17 of a steroidal skeleton, a widespread core structure of natural products and medicinally important compounds. During our investigations, the elaborated Stille and Suzuki cross-coupling reactions turned out to be complementary to each other, enabling us to introduce any desired moiety carrying an sp^2 center using either one of the two methods.

Table 4. Substrate scope for the Suzuki-coupling reaction.



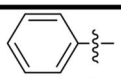
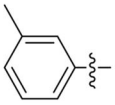
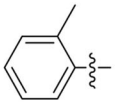
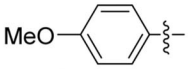
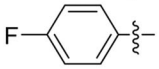
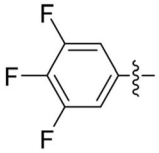
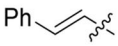
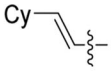
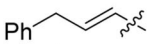
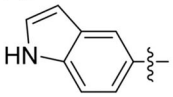
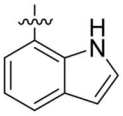
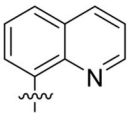
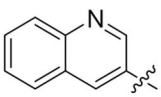
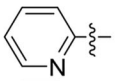
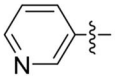
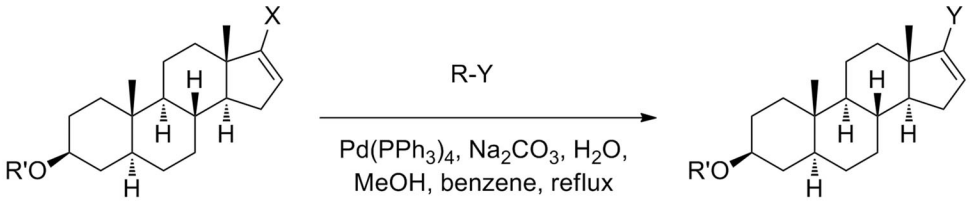
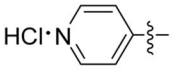
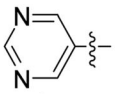
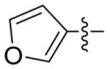
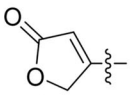
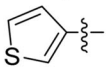
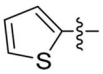
	1-X	R	Y	R'	Time	Product	Isolated yield [%]
1	**1a-I**		$B(OH)_2$	H	1 d	**15a**	65
2	**1a-I**		$B(OH)_2$	H	1 d	**4a**	75
3	**1b-BPin**		Br	OAc	4 d	**4b**	62[a]
4	**1a-I**		$B(OH)_2$	H	1 d	**16a**	82
5	**1a-I**		$B(OH)_2$	H	1 d	**17a**	31[a]
6	**1a-I**		$B(OH)_2$	H	1 d	**6a**	52
7	**1a- BPin**		Br	OAc	4 d	**6b**	54
8	**1a-I**		$B(OH)_2$	H	1 d	**5a**	38
9	**1a-Br**		$B(OH)_2$	H	2 d	**5a**	63
10	**1b-BPin**		Br	OAc	4 d	**5b**	51
11	**1a-I**		$B(OH)_2$	H	1 d	**18a**	35
12	**Ia-Br**		$B(OH)_2$	H	5 d	**19a**	81
13	**1a-Br**		$B(OH)_2$	H	5 d	**20a**	93
14	**Ia-Br**		$B(OH)_2$	H	5 d	**21a**	87
15	**Ia-I**		$B(OH)_2$	H	1 d	**22a**	51
16	**Ia-Br**		BPin	OAc	2 d	**23a**	86
17	**Ia-I**		$B(OH)_2$	H	2 d	**24a**	41
18	**Ia-I**		$B(OH)_2$	H	1 d	**25a**	30
19	**1b-BPin**		Br	OAc	4 d	**8b**	22
20	**1b-BPin**		Br	OAc	1 d	**9b**	80

Table 4. (Continued)



	1-X	R	Y	R'	Time	Product	Isolated yield [%]
21	**1b-BPin**		Br	OAc	2 d	**10b**	53
22	**1b-BPin**		Br	OAc	2 d	**11b**	43
23	**Ia-Br**		$B(OH)_2$	H	1 d	**12a**	80
24	**1b-BPin**		Br	OAc	5 d	**3b**	14
25	**Ia-I**		$B(OH)_2$	H	1 d	**26a**	77
26	**Ia-I**		$B(OH)_2$	H	1 d	**27a**	67

[a] Product could not be isolated purely after column chromatography (defunctionalized product (Y = H) has been observed). Yields were estimated *via* ^{1}H NMR spectroscopy.

Experimental Section

General Procedure for the Stille Coupling Reactions

A Schlenk tube was charged with the vinyl halide **1a-I**, **1a-Br**, **1b-OTf** (1.00 equiv.) or the vinyl stannane **1a-SnBu$_3$** (1.00 equiv.), the stannane (1.50–3.00 equiv.) or the bromide (1.10 equiv.), LiCl (10.0 equiv.) and CuCl (10.0 equiv.). Dry DMF was added under an argon atmosphere and the reaction mixture was degassed using three freeze-pump-thaw cycles. Then $Pd(PPh_3)_4$ (20 mol%) was added and the reaction mixture was stirred at 60 °C. After cooling to room temperature, an aqueous solution of KF (3 M, 4.00 equiv.) was added to the reaction mixture and stirred for 30 min, followed by filtration over Celite®. Aqueous saturated NH_4Cl solution was added and the mixture was extracted twice with dichloromethane. The organic layers were washed with brine and then dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica.

General Procedure for the Suzuki Coupling Reactions

A Schlenk tube was charged with the vinyl halide **1a-I**, **1a-Br** (1.00 equiv.) or the vinyl pinacolatoborane **1b-BPin$_2$** (1.00 equiv.) and the boronic acid (1.10 equiv) or the bromide (1.10 equiv.). Benzene, MeOH and 2 M Na_2CO_3 solution in water were added and the mixture was degassed using three freeze-pump-thaw cycles. Then $Pd(PPh_3)_4$ (10 mol%) was added and the reaction mixture was stirred under reflux. After cooling to room temperature, H_2O was added to the mixture which was then extracted three times with dichloromethane. The organic layers were washed with brine, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica.

Crystal Structure Determinations

The single-crystal X-ray diffraction studies of **1a-Br**, **3b**, **5a**, **6a**, **9a** and **11b** were carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Kα radiation ($\lambda = 1.54178$ Å. Direct methods (SHELXS-97)[18] or dual space methods (SHELXT for **5a**)[19] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2).[20] Hydrogen atoms were localized by difference electron density determination and refined using a riding model [H(O) free, except **1a-Br**]. Semi-empirical absorption corrections were applied. For **3b** and **11b** extinction corrections were applied. The absolute configuration was determined by refinement of Parsons' x-parameter[21] and using Bayesian statistics on Bijvoet differences (Hooft's y-parameter).[22] For **5a** the absolute configuration could not been established because of

anomalous dispersion effects in diffraction measurements on the crystal. The enantiomer has been assigned by reference to an unchanging chiral center in the synthetic procedure (see cif-files for details). Due to the bad quality of the data of **1a-Br** they were not deposited with The Cambridge Crystallographic Data Centre. However, the constitution and absolute configuration was determined reliably (see 2a-Br.cif and 2a-Br checkcif.pdf for more information).

3b: colourless crystals, $C_{25}H_{34}O_4$, $M_r = 398.52$, crystal size $0.30 \times 0.16 \times 0.06$ mm, monoclinic, space group $P2_1$ (No. 4), $a = 11.0356(5)$ Å, $b = 7.0949(3)$ Å, $c = 13.2814(6)$ Å, $\beta = 91.549(1)°$, $V = 1039.51(8)$ Å^3, $Z = 2$, $\rho = 1.273$ Mg/m^{-3}, μ(Cu-K$_\alpha$) $= 0.671$ mm^{-1}, $F(000) = 432$, $2\theta_{max} = 144.2°$, 13696 reflections, of which 4059 were independent ($R_{int} = 0.021$), 264 parameters, 1 restraint, $R_1 = 0.028$ (for 4011 $I > 2\sigma(I)$), $wR_2 = 0.076$ (all data), $S = 1.07$, largest diff. peak/hole $= 0.253/-0.120$ e Å^{-3}, x $= -0.06(4)$, y $= -0.05(4)$.

6a: colourless crystals, $C_{26}H_{36}O_2$, $M_r = 380.55$, crystal size $0.20 \times 0.12 \times 0.06$ mm, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 5.7932(3)$ Å, $b = 12.4890(7)$ Å, $c = 29.5589(17)$ Å, $V = 2138.6(2)$ Å^3, $Z = 4$, $\rho = 1.182$ Mg/m^{-3}, μ(Cu-K$_\alpha$) $= 0.555$ mm^{-1}, $F(000) = 832$, $2\theta_{max} = 144.0°$, 20419 reflections, of which 4195 were independent ($R_{int} = 0.019$), 257 parameters, 1 restraint, $R_1 = 0.032$ (for 4138 $I > 2\sigma(I)$), $wR_2 = 0.085$ (all data), $S = 1.02$, largest diff. peak/hole $= 0.234/-0.172$ e Å^{-3}, x $= -0.09(4)$, y $= -0.08(4)$.

CCDC 1511909 (**3b**), CCDC 1511910 (**5a**), CCDC 1511911 (**6a**), CCDC 1521243 (**9a**) and CCDC 1511912 (**11b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Due to the bad quality of the data of **1a-Br** the data were not deposited with The Cambridge Crystallographic Data Centre.

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