6-Chloro- and 6-Bromo-Substituted Steroids in the Suzuki–Miyaura Cross-Coupling Reaction. A Convenient Route to Potential Aromatase Inhibitors

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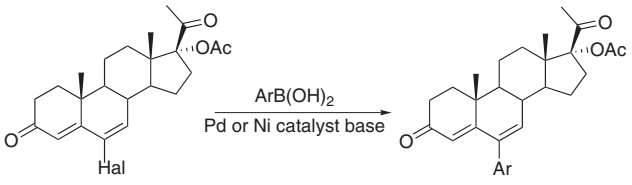
Abstract: Chlorine at an sp^2-carbon in steroids has been shown to be reactive in Suzuki–Miyaura cross-coupling reactions with either Ni or Pd catalysts. The coupling of analogous 6-bromo derivatives has also been demonstrated to be applicable to a wider scope of substrates. The Suzuki–Miyaura arylation of 6-bromo-$\Delta^{3,5}$-steroid enol ethers with subsequent hydrolysis is a useful route to 6-arylated steroids bearing aryl at a saturated carbon.

Key words: cross-coupling, palladium, steroids, Suzuki reaction, nickel

Breast cancer is the most commonly detected form of cancer in women and one of the major causes of cancer-related deaths.[1] Approximately 66% of patients have steroid receptor positive (ER/PR+) tumors. The endocrine therapy has shown significant efficacy in such cases compared with that of cytotoxic chemotherapy, with less toxicity and fewer side effects.[2] The anticancer effect of the endocrine therapy is based on the decrease of stimulating effects of estrogens on the proliferation of cancer cells. The aromatase inhibitors lower the estrogen level in the tumor by blocking the aromatase enzyme, which is responsible for the conversion of androgens (mainly androst-4-ene-3,17-dione) to estrogens. Thus, they can be useful in the treatment of breast cancer along with well-established but rather toxic antiestrogens and progestines.[3] Of particular interest are the steroidal aromatase inhibitors, which are capable of the irreversible inhibition of the aromatase by covalent binding to the enzyme active center.

A variety of potential aromatase inhibitors has been synthesized and evaluated so far.[4] However, little is known about the synthesis of arylated steroid derivatives. The commonly used ring opening of steroid epoxides with Grignard reagents requires the protection of almost all functionalities, both in the organometallic reagent and the steroid.[5] The introduction of palladium-catalyzed cross-coupling reactions in steroid syntheses allowed for the simple and efficient attachment of aryl, vinyl, and alkynyl groups to the steroid core.[6] The coupling of steroid enol triflates and vinyl iodides with organozinc[7] and organoboron[7c,8] compounds is a well-established way of introduction of aryl groups in 3- and 17-position. Although operationally simple, these methods restrict the position of incoming aryl group by the availability of keto derivatives and are not applicable to compounds with more than one carbonyl group.

Earlier we described a simple route to 4-aryl-substituted steroids via the Suzuki–Miyaura coupling of 4-bromosteroids.[9] Though the Suzuki–Miyaura arylation of steroid vinyl bromides affords high yields of arylsteroids, the use of vinyl chlorides would allow for a more practical synthesis. Of particular interest is the arylation of commercially available chlormadinone acetate (**1**) (17-acetoxy-6-chloro-pregna-4,6-diene-3,20-dione), a synthetic progestin used as oral contraceptive. Unfortunately, little is known about the Suzuki–Miyaura coupling of vinyl chlorides. Though the coupling with highly activated substrates such as β-chloroketones takes place relatively readily,[10] unactivated substrates remain a challenging problem.



1 Hal = Cl
2 Hal = Br

3a–f

Scheme 1

The nickel catalysts were actively used for activation of 'inert' aryl chlorides in the Suzuki–Miyaura coupling.[11] Therefore we investigated the nickel-catalyzed coupling of **1** with 4-anisylboronic acid (Scheme 1, where Ar = *p*-methoxyphenyl). The best results were achieved in the $Ni(dppe)Cl_2$-catalyzed reaction in anhydrous dioxane with K_3PO_4 as base (Table 1, entry 2). The use of the bulky and electron-rich Cy_3P as ligand was less effective. The main factor affecting the activity of the catalyst is probably the ligand bite angle, since the electronic factors are roughly equal for the ligands used (Table 1, entries 1, 2, 4, and 5).

The coupling was most efficient in dioxane. The yield of the $Ni(dppe)Cl_2$-catalyzed reaction in toluene was much lower (21%), and high amounts of unidentified byproducts were detected in acetonitrile or DMF. K_2CO_3 can be used instead of K_3PO_4, but no arylated product was detected with other bases (Table 2).

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Table 1 The Effect of the Ni Catalyst on the Arylation of **1**[a]

Entry	Catalyst	Yield[b] (%)
1	$Ni(dppm)Cl_2$	32
2	$Ni(dppe)Cl_2$	60
3	$Ni(Cy_3P)_2Cl_2$	26
4	$Ni(Ph_2PMe)_2Cl_2$	38
5	$Ni(dppb)Cl_2$	31

[a] Conditions: 10 mol% catalyst, 1.5 equiv 4-$MeOC_6H_4B(OH)_2$, 3 equiv K_3PO_4, dioxane, 100 °C, 48 h.
[b] ^1H NMR yield.

Table 2 The Effect of Base on the Ni-Catalyzed Arylation of **1**[a]

Base	Yield[b] (%)	Base	Yield[b] (%)
NaOAc	0	Li_2CO_3	0
KO*t*-Bu	0	K_2CO_3	53
K_3PO_4	60	Cs_2CO_3	0

[a] Conditions: 10 mol% $Ni(dppe)Cl_2$, 3 equiv base, 100 °C, 48 h.
[b] ^1H NMR yield.

Though the nickel catalyst allowed for activation of **1** in the Suzuki–Miyaura coupling, the process was rather slow and the yield was moderate.

The palladium-catalyzed Suzuki–Miyaura cross-coupling often provides excellent results in mixtures of organic solvents with water.[12] However, aqueous solvents are not the best choice for **1**, as it possesses hydrolysis-sensitive acetate groups. Indeed, we have found that the $Pd(PPh_3)_2Cl_2$-catalyzed coupling of **1** with anisylboronic acid in aqueous dioxane afforded arylated product **3a** . However, the yield was low and a substantial amount of deacetylated 17-hydroxyprogesterone derivatives was formed. It is important that no arylated product was detected in the same reaction in anhydrous dioxane.

Recently palladium catalysts with bulky phosphine[13] or phosphite[14] ligands were proposed for activation of vinyl chlorides. The competitive experiments showed that cyclopentenyl chloride is less active in the Suzuki–Miyaura coupling than chlorobenzene.[13]

We showed that unlike $Pd(PPh_3)_2Cl_2$, palladium catalysts with electron-donating and bidentate ligands do catalyze the cross coupling of **1** with 4-anisylboronic acid at 100 °C in dioxane. $Pd(dppb)Cl_2$ and $Pd(dppf)Cl_2$ were found to be the most active catalysts (Table 3).

To improve the catalyst activity, various solvents and bases were screened in $Pd(dppb)Cl_2$-catalyzed reactions at incomplete conversion. While no reaction was detected in acetone or DMF, the coupling with 4-anisylboronic acid was faster in MeCN and especially in toluene than in dioxane (Table 4). The cross-coupling rates were almost equal in dioxane and THF.

Table 3 The Effect of the Pd Catalyst on the Arylation of **1**[a]

Catalyst	Yield[b] (%)	Catalyst	Yield[b] (%)
$Pd(PPh_3)_2Cl_2$	0	$Pd(Cy_3P)_2Cl_2$	69
$Pd(MeCN)_2Cl_2$/dppe	55	$Pd(dppf)Cl_2$	92
$Pd(dppb)Cl_2$	100	PdL_2Cl_2 [c]	65

[a] Conditions: 5 mol% 'Pd', 2 equiv K_2CO_3, dioxane, 100 °C, 24 h.
[b] ^1H NMR yield.
[c] L = 2-$MeOC_6H_4P$(*t*-Bu)*i*-Pr.

Table 4 The Effect of Solvent on the Pd-Catalyzed Arylation of **1**[a]

Solvent	Yield[b] (%)	Solvent	Yield[b] (%)
Me_2CO	0	THF	31
DMF	0	MeCN	43
Dioxane	30	Toluene	76

[a] Conditions: 5 mol% $Pd(dppb)Cl_2$, K_2CO_3, 100 °C, 4 h in a sealed tube.
[b] ^1H NMR yield.

The choice of base greatly affects the yield of the arylated product (Table 5). The use of K_2CO_3 gave the fastest conversion and highest yield, but only traces of product were detected with Na_2CO_3, Cs_2CO_3, or Et_3N.

To determine the scope and limitations of this process, the reaction of **1** with various arylboronic acids was investigated under optimized conditions (Table 6).

The coupling with 4-fluorophenylboronic acid was faster in dioxane than in toluene. Surprisingly, only 11% yield of the arylated steroid was detected in the reaction with 3-tolylboronic acid in dioxane, compared with 91% in toluene. While the reaction with electron-rich arylboronic acids afforded the products in high yields, the coupling with 3-acetylphenylboronic acid led to 43% yield of **3e**, and only traces of product were detected in the reaction with 4-carboxyphenylboronic acid. Besides, less than 10% of the product was formed in the reaction with 2-thienylboronic acid.

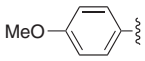
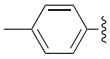
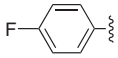
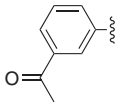
While the coupling of **1** with nucleophilic arylboronic acids gave excellent yields of arylated products, the procedure proved to be unsuitable for the preparation of 6-

Table 5 The Effect of Base on the Pd-Catalyzed Arylation of **1**[a]

Base	Yield,% [b]	Base	Yield[b] (%)
Na_2CO_3	0	Et_3N	1
K_2CO_3	76	NaOAc	8
Cs_2CO_3	1	K_3PO_4	41

[a] Conditions: 5 mol% $Pd(dppb)Cl_2$, toluene, 100 °C, 4 h.
[b] ^1H NMR yield.

Table 6 Yields of Arylation of **1** with Arylboronic Acids[a]

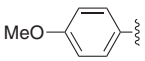
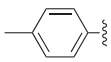
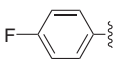
Product	Ar	Solvent	Time (h)	Yield[b] (%)
3a		Toluene	12	(93)
3b		Toluene	13	(100)
3c		Dioxane	24	(97)
3d		Toluene	12	91[c]
3e		Dioxane	24	43
3f		Dioxane or toluene	48	<10

[a] Conditions: 5 mol% $Pd(dppb)Cl_2$, 1.5 equiv $RB(OH)_2$, 3 equiv K_2CO_3, 100 °C.
[b] ^1H NMR yield; isolated yield in parentheses.
[c] Inseparable mixture with 9% of **1**.

arylsteroids containing heterocyclic and electron-withdrawing aryl groups. Therefore, we investigated the utility of more reactive 17-acetoxy-6-bromopregna-4,6-diene-3,20-dione (**2**) in this reaction (Table 7). The coupling proceeds smoothly within five hours (instead of 12–24 hours for **1**) with $Pd(dppf)Cl_2$ as catalyst in absolute acetonitrile and with K_3PO_4 as base.

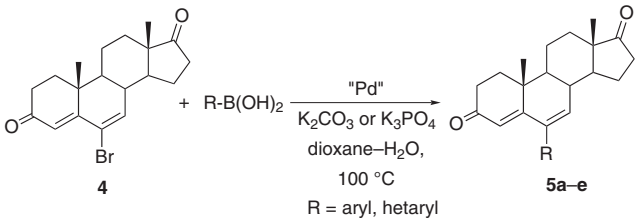
Unlike **1**, the Suzuki coupling of **2** with 2-thienylboronic acid affords a high yield of the arylated product **3f**, though prolonged heating is required to accomplish the reaction.

Table 7 Yields of Arylation of **2** with Arylboronic Acids[a]

Product	Ar	Yield[b] (%)
3a		93
3b		82
3c		93
3f		94[c]

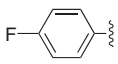
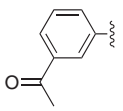
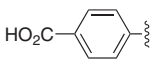
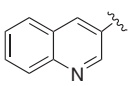
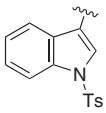
[a] Conditions: 5 mol% $Pd(dppf)Cl_2$, 2 equiv K_3PO_4, MeCN, 100 °C, 5 h.
[b] Isolated yield.
[c] ^1H NMR yield, determined at 24 h.

A substantial acceleration of the Suzuki coupling can be achieved by addition of water. Thus the reaction of 6-bromoandrosta-4,6-diene-3,17-dione **4**, lacking the sensitive acetate group, affords 6-arylated androstadienes **5a–e** within 3–4 hours in aqueous dioxane at 100 °C (Scheme 2, Table 8).



Scheme 2

Table 8 Yields of 6-Aryl-androsta-4,6-diene-3,17-diones **5**[a]

Product	Ar	Catalyst (2 mol%)	Base	Time (h)	Yield[b] (%)
5a		$Pd(PPh_3)_2Cl_2$	2 equiv K_2CO_3	3	93
5b		$Pd(PPh_3)_2Cl_2$	2 equiv K_2CO_3	3	99
5c		$Pd(PPh_3)_2Cl_2$ $Pd(dppf)Cl_2$	3 equiv K_2CO_3	3	90[c] 87
5d		$Pd(dppf)Cl_2$	2 equiv K_3PO_4	3	76
5e		$Pd(dppf)Cl_2$	2 equiv K_3PO_4	4	84

[a] Conditions: dioxane–H_2O (3:1), 100 °C.
[b] Isolated yield.
[c] As inseparable mixture with 4% Ph_3PO.

However, the use of $Pd(PPh_3)_2Cl_2$ as palladium source sometimes led to the contamination of the arylsteroid with triphenylphosphine oxide. We found that coupling in the presence of $Pd(dppf)Cl_2$ can be used in these cases without any significant decrease of yield. These conditions can be applied successfully for the coupling with poorly nucleophilic aryl(hetaryl)boronic acids with good to excellent yields of products **5b–e**.

The catalytic synthesis of 6-arylated steroids **10** with an aryl group attached to the sp^3-hybridized C^6 atom implies the coupling of the allylpalladium complex obtained from readily available 6-halosteroids with an 'aryl carbanion'. Though allylpalladium complexes of steroids are well known[15] they have only been used in stoichiometric reactions with 'soft nucleophiles'. Moreover, the Stille coupling of 6-bromotestosterone acetate with alkynylstannane was shown to afford a complex mixture of unidentified products.[16] We found that the Suzuki coupling of 6-bromo-androst-4-ene-3,17-dione (**6**) with anisylboronic acid yields only androstadiene **7** due to fast dehydrobromination. So we tried to 'mask' the active halide by converting **6** to methyl enol ether **8** (Scheme 3).

The enol ethers **8** should probably be less active substrates for the Suzuki–Miyaura coupling than **2** due to electron-donating properties of the methoxy group. However, almost quantitative yields of arylated products **9** were obtained in $Pd(PPh_3)_2Cl_2$- or $Pd(dppf)Cl_2$-catalyzed reactions with various (hetero)arylboronic acids.

The subsequent 'unmasking' of **9** affords 6-aryl-androst-4-ene-3,17-diones **10a–g**. Thus the hydrolysis of **9a** (obtained with 85% yield by Suzuki coupling) with concentrated HCl in aqueous ethanol affords 72% of **10a**. This procedure can be accomplished without isolation of intermediate **9** by addition of excess of concentrated HCl to the crude reaction mixture after cross-coupling. This method can also be applied for the preparation of 6-aryl pregnane derivative **10h** (Table 9), though the cross coupling should be conducted in anhydrous acetonitrile with K_3PO_4 as base.

The α-configuration of the 6-aryl group was assigned for all products by ^1H NMR. The presence of 10% of the 6-β epimer was detected for 6-thienyl-substituted product **10d**.

In conclusion, we described a versatile and efficient way for the introduction of aryl(hetaryl) groups in 6-position of $\Delta^{4,6}$-steroids via the palladium catalyzed Suzuki–Miyaura coupling of 6-chloro- or 6-bromosteroids. The arylation of 6-bromo-$\Delta^{3,5}$-steroid enol ethers with subsequent hydrolysis is a useful route to 6-arylated steroids bearing aryl at a saturated carbon.

NMR spectroscopy was performed on a Varian VXR400 (400 MHz) spectrometer. Melting points were recorded on an Electrothermal Engineering IA9100 melting point apparatus and are uncorrected. MALDI-TOF spectra were recorded on a Bruker Daltonics Proflex III spectrometer.

Arylation of Chlormadinone Acetate (1); General Procedure

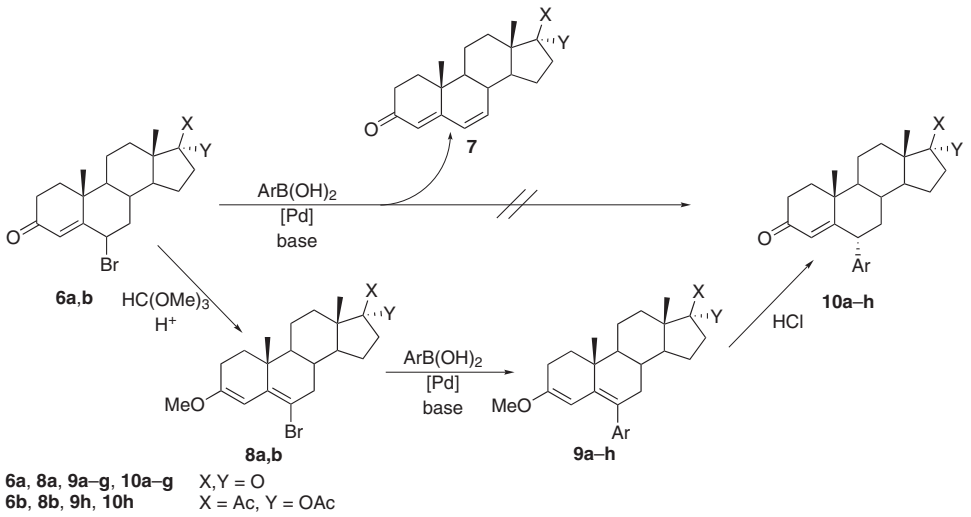
In a vial with a screw cap, **1** (40.5 mg, 0.100 mmol), arylboronic acid (0.18 mmol), K_2CO_3 (41.4 mg, 0.300 mmol), and $Pd(dppb)Cl_2$ (3.0 mg, 5 μmol, 5 mol%) were mixed under Ar atmosphere in toluene (2 mL). The mixture was stirred at 100 °C for 12–24 h, then diluted with $CHCl_3$ (10 mL) and H_2O (10 mL), and the aq layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. The arylated products **3a–d** were isolated by column chromatography on silica gel ($CHCl_3$–Et_2O, 4:1).

17-Acetoxy-6-(4-methoxyphenyl)pregna-4,6-diene-3,20-dione (3a)

White solid, yield: 44.3 mg (93%); mp 132–135 °C.

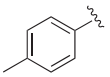
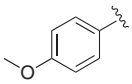
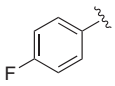
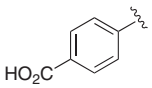
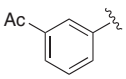
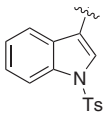
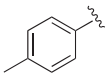
^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (m, 2 H), 6.83 (m, 2 H), 5.97 (d, 1 H, J = 2.2 Hz, H^4), 5.64 (s, 1 H, H^7), 3.79 (s, 3 H), 2.98 (m, 1 H), 2.59 (m, 1 H), 2.39 (m, 2 H), 2.11 (s, 3 H), 2.05 (s, 3 H), 2.09–1.71 (m, 7 H), 1.62 (m, 1 H), 1.45 (m, 3 H) 1.21 (s, 3 H, CH_3), 0.73 (s, 3 H, CH_3).

Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.45; H, 7.63.



Scheme 3

Table 9 Yields of 6α-Aryl-Δ^4-steroids **10**

Product	Ar	X, Y	Catalyst	Base	Time (h)	Yield[a] (%)
10a		O	$Pd(PPh_3)_2Cl_2$	K_2CO_3	3	72
10b		O	$Pd(dppf)Cl_2$	K_2CO_3	3	84
10c		O	$Pd(PPh_3)_2Cl_2$	K_2CO_3	3	90
10d		O	$Pd(dppf)Cl_2$	K_2CO_3	4.5	80
10e		O	$Pd(dppf)Cl_2$	K_2CO_3	3	69
10f		O	$Pd(dppf)Cl_2$	K_2CO_3	3	85
10g		O	$Pd(dppf)Cl_2$	K_3PO_4	4	83
10h		Ac, OAc	$Pd(dppf)Cl_2$	K_3PO_4[b]	5	70

[a] Isolated yield, from **8**.
[b] Reaction in absolute MeCN.

17-Acetoxy-6-(4-methylphenyl)pregna-4,6-diene-3,20-dione (3b)
White solid, yield: 46.1 mg (100%); mp 138–141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (m, 2 H), 7.00 (m, 2 H), 5.99 (d, 1 H, *J* = 2.2 Hz, H^4), 5.62 (s, 1 H, H^7), 2.98 (m, 1 H), 2.58 (m, 1 H), 2.39 (m, 2 H), 2.33 (s, 3 H), 2.11 (s, 3 H), 2.05 (s, 3 H), 2.09–1.71 (m, 7 H), 1.62 (m, 1 H), 1.44 (m, 3 H), 1.21 (s, 3 H, CH_3), 0.73 (s, 3 H, CH_3).

Anal Calcd for $C_{30}H_{36}O_4$: C, 78.23; H, 7.88. Found: C, 78.65; H, 7.86.

17-Acetoxy-6-(4-fluorophenyl)pregna-4,6-diene-3,20-dione (3c)
Reaction in dioxane; white solid, yield: 44.9 mg (97%); mp 132–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (m, 2 H), 6.99 (m, 2 H), 5.98 (d, 1 H, *J* = 2.2 Hz), 5.56 (s, 1 H, H^7), 2.99 (m, 1 H,), 2.59 (m, 1 H), 2.40 (m, 2 H), 2.11 (s, 3 H), 2.06 (s, 3 H), 2.09–1.71 (m, 7 H), 1.63 (m, 1 H), 1.45 (m, 3 H) 1.21 (s, 3 H), 0.74 (s, 3 H).

Anal. Calcd for $C_{29}H_{33}FO_4$: C, 74.98; H, 7.16. Found: C, 74.85; H, 7.24.

17-Acetoxy-6-(3-methylphenyl)pregna-4,6-diene-3,20-dione (3d)
White solid, yield: 41.7 mg (91%); mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 7.19 (m, 1 H), 7.09 (m, 1 H), 6.91 (m, 2 H), 5.99 (d, *J* = 2.2 Hz, 1 H), 5.62 (s, 1 H), 2.98 (m, 1 H), 2.59 (m, 1 H), 2.39 (m, 2 H), 2.32 (s, 3 H), 2.11 (s, 3 H), 2.06 (s, 3 H), 2.09–1.71 (m, 7 H), 1.63 (m, 1 H), 1.44 (m, 3 H), 1.22 (s, 3 H), 0.74 (s, 3 H).

Anal. Calcd for $C_{30}H_{36}O_4$: C, 78.23; H, 7.88. Found: C, 78.36; H, 7.88.

Arylation of 17-Acetoxy-6-bromopregna-4,6-diene-3,20-dione (2); General Procedure
In a vial with a screw cap, **2** (67.4 mg, 0.150 mmol), arylboronic acid (0.195 mmol), K_3PO_4 (95.4 mg, 0.450 mmol), $Pd(dppf)Cl_2$ (5.5 mg, 7.5 μmol, 5 mol%) were mixed under Ar atmosphere in MeCN (2 mL). The mixture was stirred at 100 °C for 5 h, then diluted with $CHCl_3$ (10 mL) and H_2O (10 mL), and the aq layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. The arylated products **3a–c** were isolated by column chromatography on silica gel ($CHCl_3$–Et_2O, 4:1) (Table 7).

6-Bromoandrosta-4,6-diene-3,17-dione (4)
In a two-necked flask, equipped with reflux condenser, NBS (583 mg, 3.28 mmol) was slowly added to a suspension of 6-bromo-3-methoxyandrosta-3,5-diene-17-one (1.20 g, 3.16 mmol) in 96% aq acetone (9.3 mL) at 0 °C under flow of Ar. After stirring at 0 °C for 20 min, LiBr (504 mg, 5.80 mmol), Li_2CO_3 (497 mg, 6.73 mmol), and DMF (4.8 mL) were added and the mixture was stirred at 80 °C for 6 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL), washed with H_2O (6 × 20 mL), and dried with $MgSO_4$. The product was isolated by column chromatography on silica gel (CH_2Cl_2–Et_2O, 20:1).

White solid, yield: 977 mg (85%); mp 155–157 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (d, 1 H, *J* = 2.3 Hz, H^4), 6.31 (s, 1 H, H^7), 2.50 (m, 4 H), 2.16 (m, 2 H), 2.02 (m, 1 H), 1.90 (m, 1 H), 1.73 (m, 3 H), 1.58–1.28 (m, 4 H), 1,17 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3).

Anal. Calcd for $C_{19}H_{23}BrO_2$: C, 62.82; H, 6.38. Found: C, 62.53; H, 6.61.

Arylation of 6-Bromoandrosta-4,6-diene-3,17-dione (4); General Procedure

In a vial with a screw cap, **4** (54.5 mg, 0.150 mmol), arylboronic acid (0.165 mmol), K_2CO_3 (41.4 mg, 0.300 mmol), and $Pd(PPh_3)_2Cl_2$ or $Pd(dppf)Cl_2$ (3 μmol, 2 mol%) were mixed under Ar atmosphere in dioxane (1.5 mL) and H_2O (0.5 mL). The mixture was stirred at 100 °C for 3–4 h, then diluted with $CHCl_3$ (10 mL) and H_2O (10 mL), and the aq layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. The arylated products **5** were isolated by column chromatography on silica gel (CH_2Cl_2–Et_2O, 20:1 or CH_2Cl_2–MeOH, 2:1).

6-(4-Fluorophenyl)androsta-4,6-diene-3,17-dione (5a)

White solid, yield: 53 mg (93%); mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (m, 2 H,), 7.00 (m, 2 H), 6.06 (d, 1 H, *J* = 2.1 Hz, H^4), 5.56 (s, 1 H, H^7), 2.51 (m, 4 H), 2.11 (m, 3 H), 1.92 (m, 1 H), 1.74 (m, 3 H), 1.60–1.33 (m, 4 H), 1.23 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3).

Anal. Calcd for $C_{25}H_{27}FO_2$: C, 79.26; H, 7.13. Found: C, 79.50; H 7.00.

6-(3-Acetylphenyl)androsta-4,6-diene-3,17-dione (5b)

White solid, yield: 60 mg (99%); mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 1 H), 7.72 (m, 1 H), 7.43 (m, 1 H), 7.32 (m, 1 H), 6.10 (d, 1 H, *J* = 2.1 Hz, H^4), 5.48 (s, 1 H, H^7), 2.60 (s, 3 H), 2.52 (m, 4 H), 2.12 (m, 3 H), 1.93 (m, 1 H), 1.76 (m, 3 H), 1.62–1.33 (m, 4 H), 2.16 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3).

Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.27; H, 7.42.

6-(4-Carboxyphenyl)androsta-4,6-diene-3,17-dione (5c)

White solid, yield: 53 mg (87%); mp 255–256 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (m, 2 H), 7.23 (m, 2 H), 6.13 (d, 1 H, *J* = 1.8 Hz, H^4), 5.61 (s, 1 H, H^7), 2.56 (m, 4 H), 2.13 (m, 3 H), 2.93 (m, 1 H), 1.75 (m, 3 H), 1.63–1.33 (m, 4 H), 1.26 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3).

MS (MALDI-TOF): *m*/*z* = 405.50 $[M + H]^+$.

6-(3-Quinolinyl)androsta-4,6-diene-3,17-dione (5d)

White solid, yield: 46.9 mg (76%); mp 223–225 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, 1 H, *J* = 2.1 Hz), 8.10 (d, 1 H, *J* = 8.5 Hz), 7.92 (d, 1 H, *J* = 2.1 Hz), 7.78 (dd, 1 H, *J* = 8.3, 1.0 Hz), 7.72 (m, 1 H), 7.56 (m, 1 H), 6.21 (d, 1 H, *J* = 2.0 Hz, H^4), 5.57 (s, 1 H, H^7), 2.54 (m, 5 H), 2.15 (m, 3 H), 1.96–1.24 (m, 7 H,), 1.30 (s, 3 H, CH_3,), 1.00 (s, 3 H, CH_3).

Anal. Calcd for $C_{28}H_{29}NO_2$: C, 81.72; H, 7.10; N, 3.40. Found: C, 81.43; H, 7.25; N, 3.17.

6-(*N*-Tosylindole-3-yl)androsta-4,6-diene-3,17-dione (5e)

White solid, yield: 70 mg (84%); mp 173–174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (m, 1 H), 7.76 (m, 2 H,), 7.47 (s, 1 H,), 7.25 (m, 3 H), 7.18 (m, 2 H), 6.26 (d, 1 H, *J* = 2.1 Hz, H^4), 5.51 (s, 1 H, H^7), 2.51 (m, 4 H), 2.34 (s, 3 H), 2.12 (m, 3 H), 1.92 (m, 1 H), 1.75 (m, 3 H), 1.61–1.32 (m, 4 H), 1.29 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3).

MS (MALDI-TOF): *m*/*z* = 554.37 $[M + H]^+$.

6-Bromoandrost-4-ene-3,17-dione (6a)

To a suspension of 3-methoxyandrosta-3,5-diene-17-one (10.0 g, 33.3 mmol) and NaOAc (2.7 g, 33 mmol) in 96% aq acetone (350 mL), NBS (7.64 g, 42.9 mmol) was slowly added. After stirring for 30 min at r.t. the solution was concentrated at reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and the organic layer was washed with H_2O (6 × 50 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give a 2:1 mixture of β:α epimers (11.85 g, 97%), which was used without further purification for the preparation of **8a**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (d, 1 H, J = 1.8 Hz, H^4)[a], 5.91 (s, 1 H, H^4)[b], 5.01 (m, 1 H, H^6)[a], 4.89 (m, 1 H, H^6)[b], 2.60–1.07 (m, 17 H), 1.56 (s, 3 H, CH_3)[a], 1.24 (s, 3 H, CH_3)[b], 0.97 (s, 3 H, CH_3)[a], 0.91 (s, 3 H, CH_3)[b]. [a] 6α-bromoandrost-4-ene-3,17-dione. [b] 6β-bromoandrost-4-ene-3,17-dione.

6-Bromo-3-methoxyandrosta-3,5-diene-17-one (8a)

To a mixture of 6-bromoandrost-4-ene-3,17-dione (**6a**) (2.00 g, 5.47 mmol) and sulfosalicylic acid (24 mg, 0.11 mmol), toluene (6 mL) and trimethyl orthoformate (1.31 mL, 12.0 mmol) were added under the flow of Ar. The mixture was stirred at r.t. for 1 h, then Et_3N (0.1 mL) was added. The solution was cooled to 0 °C and 2% NaOH soln (10 mL) was added, while stirring vigorously. The product was extracted with CH_2Cl_2 (20 mL) and dried with Na_2SO_4. The solvents were evaporated and the residue was treated with cold *i*-PrOH, washed with cold Et_2O, and dried in vacuo.

White solid, yield: 1.89 g (91%); mp 174–175 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (d, 1 H, *J* = 1.5 Hz, H^4), 3.64 (s, 3 H, OCH_3), 2.71 (m, 1 H), 2.46 (m, 1 H,), 2.29 (m, 2 H), 2.05 (m, 4 H), 1.82 (m, 2 H), 1.70 (m, 1 H), 1.57 (m, 1 H), 1.34 (m, 4 H), 1.16 (m, 1 H), 1.01 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3).

Anal. Calcd for $C_{20}H_{27}BrO_2$: C, 63.33; H, 7.17. Found: C, 63.40; H, 7.43.

6α-Aryl-Δ^4-steroids; General Procedure

In a vial with a screw cap, **8a** or **8b** (0.15 mmol), arylboronic acid (0.165 mmol), K_2CO_3 or K_3PO_4 (0.3 mmol), $Pd(PPh_3)_2Cl_2$ or $Pd(dppf)Cl_2$ (3.0–7.5 μmol, 2 mol%) were mixed under Ar atmosphere in dioxane (1.5 mL) and H_2O (0.5 mL) or MeCN (2 mL) for 10 h. After stirring at 100 °C for 3–5 h, the mixture was cooled to r.t. and 37% HCl soln (0.25 mL) was added. The reaction was stirred for 2–3 h, then diluted with $CHCl_3$ (10 mL) and H_2O (10 mL), and the aq layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried with Na_2SO_4. The arylated products **10a–h** were isolated by column chromatography on silica gel (CH_2Cl_2–Et_2O, 20:1 or CH_2Cl_2–EtOAc, 2:1).

6α-(4-Methylphenyl)androst-4-ene-3,17-dione (10a)

White solid, yield: 41 mg (72%); mp 105–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (m, 2 H), 6.98 (m, 2 H), 5.18 (d, 1 H, *J* = 1.5 Hz, H^4), 3.55 (m, 1 H, H^6), 2.38 (m, 3 H), 2.32 (s, 3 H), 2.09 (m, 3 H), 1.93 (m, 3 H), 1.76 (m, 2 H), 1.54 (m, 3 H), 1.35 (m, 2 H), 1.33 (s, 3 H, CH_3), 1.15 (m, 1 H), 0.93 (s, 3 H, CH_3).

Anal. Calcd for $C_{26}H_{32}O_2$: C, 82.94; H, 8.57. Found: C, 83.04; H, 8.44.

6α-(4-Methoxyphenyl)androst-4-ene-3,17-dione (10b)

White solid, yield: 49 mg (84%); mp 110–111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (m, 2 H), 6.85 (m, 2 H), 5.18 (d, 1 H, *J* = 1.8 Hz, H^4), 3.79 (s, 3 H), 3.53 (m, 1 H, H^6), 2.40 (m, 3 H), 2.09 (m, 3 H), 1.93 (m, 3 H), 1.76 (m, 2 H), 1.53 (m, 3 H), 1.35 (m, 2 H), 1.14 (m, 1 H), 1.33 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3).

Anal. Calcd for $C_{26}H_{32}O_3$: C, 79.56; H, 8.22. Found: C, 79.20; H, 8.31.

6α-(4-Fluorophenyl)androst-4-ene-3,17-dione (10c)

White solid, yield: 51 mg (90%); mp 114–115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (m, 2 H), 7.01 (m, 2 H), 5.13 (d, 1 H, *J* = 1.5 Hz, H^4), 3.58 (m, 1 H, H^6), 2.40 (m, 3 H), 2.09 (m, 3 H), 1.94 (m, 3 H), 1.77 (m, 2 H), 1.53 (m, 3 H), 1.35 (m, 2 H), 1.33 (s, 3 H, CH_3), 1.15 (m, 1 H), 0.94 (s, 3 H, CH_3).

Anal. Calcd for $C_{25}H_{29}FO_2$: C, 8.84; H, 7.62. Found: C, 78.77; H, 7.42.

6-(2-Thienyl)androst-4-ene-3,17-dione (10d)
White solid, yield: 44 mg (80%); mp 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 1 H), 6.97 (m, 1 H), 6.81 (m, 1 H), 6.02 (s, 1 H, H^4)^2, 5.37 (d, 1 H, *J* = 1.8 Hz, H^4)^1, 3.98 (m, 1 H, H^6)^2, 3.92 (m, 1 H, H^6)^1, 2.37 (m, 4 H), 2.10 (m, 2 H), 1.93 (m, 3 H), 1.76 (m, 2 H), 1.53 (m, 3 H), 1.34 (m, 2 H), 1.32 (s, 3 H, CH_3)^1, 1.16 (m, 1 H), 0.93 (s, 3 H, CH_3)^1. ^{1} 6α-(2-thienyl)androst-4-ene-3,17-dione. ^{2} 6β-(2-thienyl)androst-4-ene-3,17-dione.

Anal. Calcd for $C_{23}H_{28}O_2S$: C, 74.96; H, 7.66. Found: C, 74.70; H, 7.45.

6α-(4-Carboxyphenyl)androst-4-ene-3,17-dione (10e)
White solid, yield: 42 mg (69%); mp 202–203 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (m, 2 H), 7.22 (m, 2 H), 5.16 (d, 1 H, *J* = 1.5 Hz, H^4), 3.67 (m, 1 H, H^6), 2.44 (m, 3 H), 2.13 (m, 3 H), 1.93 (m, 3 H), 1.79 (m, 2 H), 1.57 (m, 3 H), 1.39 (m, 2 H), 1.36 (s, 3 H, CH_3), 1.19 (m, 1 H), 0.95 (s, 3 H, CH_3).

MS (MALDI-TOF): *m*/*z* = 407.45 $[M + H]^+$.

6α-(3-Acetylphenyl)androst-4-ene-3,17-dione (10f)
White solid, yield; 52 mg (85%); mp 117–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (m, 1 H), 7.73 (m, 1 H), 7.43 (m, 1 H), 7.33 (m, 1 H), 5.07 (d, 1 H, *J* = 1.5 Hz, H^4), 3.67 (m, 1 H, H^6), 2.59 (s, 3 H), 2.41 (m, 3 H), 2.10 (m, 3 H), 1.93 (m, 3 H), 1.78 (m, 2 H), 1.58 (m, 3 H), 1.37 (m, 2 H), 1.36 (s, 3 H, CH_3), 1.18 (m, 1 H), 0.94 (s, 3 H, CH_3).

Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 79.97; H, 7.96.

6α-(*N*-Tosylindol-3-yl)androst-4-ene-3,17-dione (10g)
White solid, yield: 69 mg (83%); mp 184–185 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (m, 1 H), 7.73 (m, 2 H), 7.39 (s, 1 H), 7.23 (m, 4 H), 7.15 (m, 1 H), 5.12 (d, 1 H, *J* = 1.2 Hz, H^4), 3.81 (m, 1 H, H^6), 2.38 (m, 3 H), 2.33 (s, 3 H), 2.12 (m, 3 H), 1.94 (m, 3 H), 1.77 (m, 2 H), 1.56 (m, 3 H), 1.38 (s, 3 H, CH_3), 1.35 (m, 2 H), 1.17 (m, 1 H), 0.94 (s, 3 H, CH_3).

MS (MALDI-TOF): *m*/*z* = 556.28 $[M + H]^+$.

17-Acetoxy-6α-(4-methylphenyl)pregn-4-ene-3,20-dione (10h)
White solid, yield: 50.0 mg (70%); mp 137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (m, 2 H), 6.97 (m, 2 H), 5.17 (d, 1 H, *J* = 1.6 Hz, H^4), 3.52 (s, 1 H, H^6), 2.92 (m, 1 H), 2.36 (m, 2 H), 2.31 (s, 3 H), 2.11 (s, 3 H), 2.06 (m, 3 H), 2.04 (s, 3 H), 1.82–1.16 (m, 11 H), 1.31 (s, 3 H, CH_3), 0.69 (s, 3 H, CH_3).

Anal. Calcd for $C_{30}H_{38}O_4$: C, 77.89; H, 8.28. Found: C, 77.65; H, 8.47.

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