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An Efficient Approach to Azolyl-Substituted Steroids through Copper-Catalyzed Ullmann C–N Coupling

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Ullmann-type C–N coupling of vinyliodides and nitrogen heterocycles has been shown to be a straightforward and highly efficient approach to azolyl-substituted steroids. The amination reaction proved sensitive to steric effects exerted by the substituents in both iodide and heterocycle. The influence of reaction conditions (catalyst, base, solvent, and temperature) on conversion of the iodosteroid and the selectivity was investigated. The catalytic system comprising 10 mol-% CuI and 20 mol-% dipivaloylmethane with K_2CO_3 in dimethyl sulfoxide at 100 °C delivered the best result. The elaborated protocol has permitted iodosteroids with various substituted indoles, imidazoles, carbazole, indazole, and secamides to be coupled, affording the corresponding azolyl-substituted steroids in good to excellent yields.

Introduction

Steroids occupy a unique position among other natural compounds due to their high biological activity and involvement into the most important processes in living organisms. Structural similarity of the main steroidal hormones and, at the same time, significant dependence of their pharmacological properties upon the nature and position of substituents mean that steroids are ideal precursors for the synthesis of new drugs.[1] For instance, the introduction of heterocyclic moieties into the C-17 position was observed to lead to 17α-hydroxylase inhibitors, which could be applied in anticancer therapy.[2] Therefore, the development of new efficient protocols for steroid functionalization is an important synthetic problem.

Modern methods based on reactions catalyzed by transition-metal complexes provide a wide range of opportunities for the synthesis of steroid derivatives bearing diverse functionality.[3] Previously, Pd-catalyzed cross-coupling reactions have been applied to the synthesis of potential aromatase inhibitors in our group,[4] and a few reports on the use of some Cu-catalyzed protocols in steroid chemistry have also been published.[5] Nevertheless, the application of Cu-catalyzed cross-coupling methodology to modification of steroids and steroid-like compounds remains practically unexplored. Taking into account the rapid development of new protocols in so-called "modified Ullmann chemistry",[6] Cu-catalyzed reactions may become promising tools for steroid derivatization. The amination of aryl and vinyl halides with amines, amides and nitrogen heterocycles attracts a special interest. In these areas Cu-catalyzed methods are often superior to their Pd-catalyzed counterparts.[7]

The methods of bond formation between C(sp^2) atoms of the steroidal framework and N atoms of aromatic heterocycles are of practical interest in the synthesis of biologically active compounds. So far, the only commonly used method to obtain such azolyl-substituted steroids[2a,2b] was Michael addition of azole salts to the corresponding β-chloroenals followed by chloride anion elimination (Scheme 1). An additional step of catalytic decarbonylation is necessary for the removal of the auxiliary formyl group. However, the addition-elimination process is not selective in some cases,[8] and the decarbonylation reaction requires expensive rhodium complexes. In the present work we wanted to develop an alternative approach based on direct vinylation of NH-heterocycles that does not require the introduction and subsequent removal of the activating formyl group.

Results and Discussion

Synthesis of Iodosteroids

Steroidal vinyliodides needed for the modified Ullmann coupling were synthesized according to the standard procedures[9] through the oxidation of hydrazones obtained from the corresponding ketosteroids by iodine.[10]

Thus, enol ether **1** was transformed into 17-hydrazone **2**, which was then treated with iodine, yielding, after subsequent removal of the enol ether protecting group, 17-iodosteroid **3** in good yield (Scheme 2).

A similar procedure was applied to the preparation of testosterone (**4**) and cholest-4-en-3-one (**5**) derivatives **8** and

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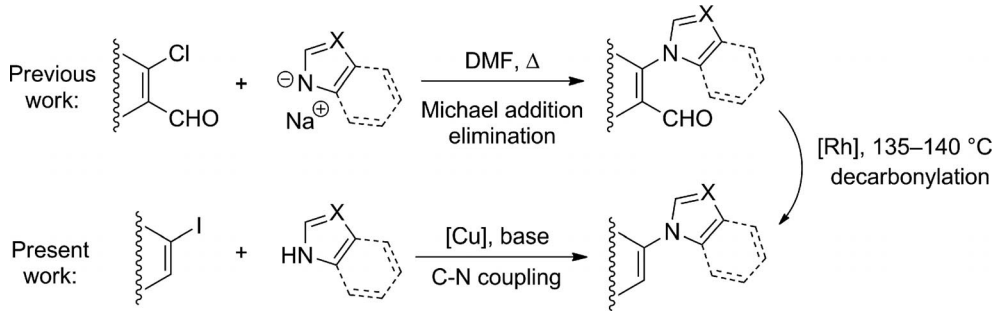
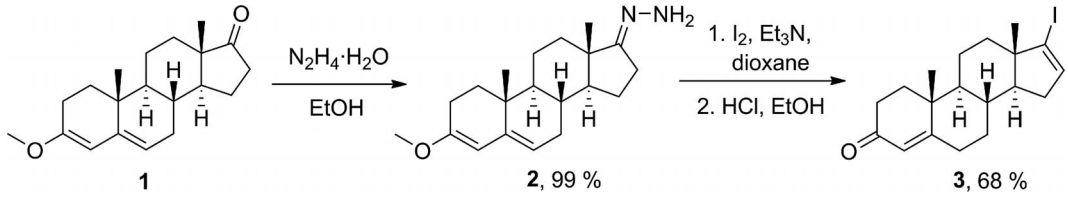
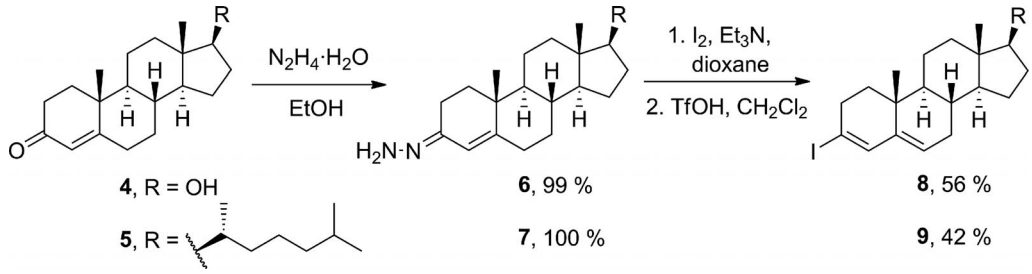


Scheme 1. Synthetic approaches to azolylsteroids.



Scheme 2. Synthesis of 17-iodosteroid **3**.



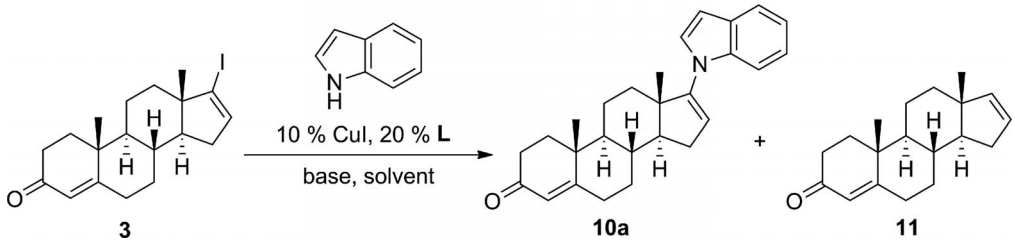
Scheme 3. Synthesis of 3-iodosteroids **8** and **9**.

9. The iodination of 3-hydrazones **6** and **7** followed by equilibration of the forming iododiene mixture in the presence of triflic acid[9a] afforded 3-iodosteroids **8** and **9** in moderate yields (Scheme 3).

Cu-Catalyzed C–N Coupling of Iodosteroids and Azoles

Conditions for the reaction between vinyliodides and azoles were optimized by using the cross-coupling of iodosteroid **3** with indole as a model reaction (Scheme 4). Initially we tried to apply one of the well-established protocols for Pd-catalyzed C–N coupling,[11] however, reaction conditions employing 4 mol-% [Pd(dba)$_2$], 5 mol-% BINAP, and 2 equiv. Cs_2CO_3 in dioxane at 100 °C only provided 9% of the reductive dehalogenation by-product **11** after 24 h, and none of the desired coupling product **10a** was detected. Cu-catalyzed systems are generally more effective than their Pd-catalyzed counterparts for the cross-coupling of azoles with aryl or vinyl iodides, so we decided to focus on the Cu-catalyzed variant of the C–N coupling and investigated the factors influencing the activity of the catalytic system.

Use of a ligand-free protocol[12] led to a mixture of 5% coupling product **10a** and 30% by-product **11**. Reductive dehalogenation reaction of iodosteroid **3** giving **11** was also observed in the absence of indole. This side-reaction is known to accompany Cu-catalyzed amination when the substrates used are sterically hindered.[13] Although the mechanism of reductive dehalogenation remains unclear,



Scheme 4. Amination of 17-iodosteroid **3** with indole.

possible pathways can include either protonation or homolytic cleavage of copper(III) intermediates.

The poor performance of the ligand-free system prompted us to study a number of *N*,*N*- (**L1**–**L7**[14]), N,O- (**L8**–**L11**[15]) and O,O-donating (**L12**–**L20**[16]) ligands (Figure 1). The choice of ligand indeed had a dramatic influence on the catalytic activity, and the use of different ligands resulted in levels of iodosteroid **3** conversion that varied over a wide range (from 14 to 93%, as shown in Table 1) and resulted in different selectivity towards products **10a** and **11**.

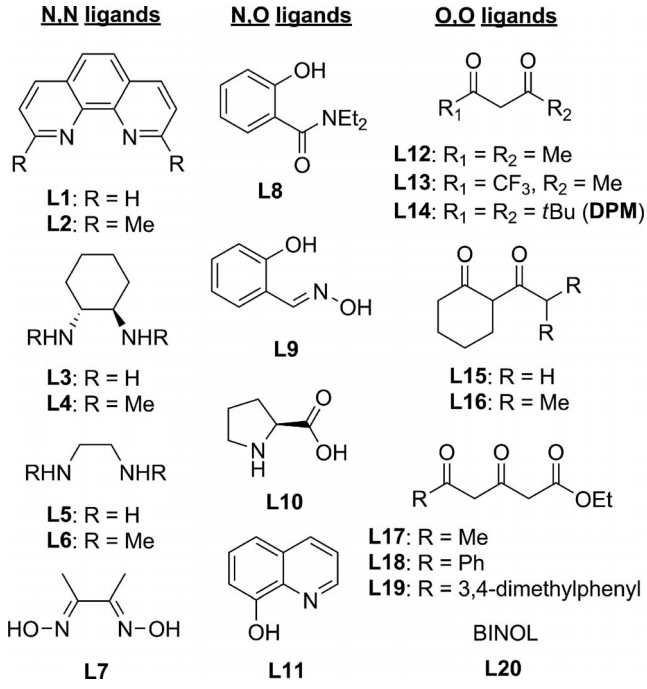


Figure 1. Ligands for the catalytic copper complex.

Table 1. Ligand effects on the Cu-catalyzed amination of **3** with indole.[a]

Ligand	Yield **10a/11** [%][b]	Ligand	Yield **10a/11** [%][b]
L1	22:14	**L11**	72:21
L2	4:12	**L12**[c]	41:30
L3	68:13	**L13**	7:23
L4	14:15	**L14 (DPM)**	79:10
L5	8:8	**L15**	9:7
L6	<5:60	**L16**	7:7
L7	8:72	**L17**	21:11
L8	5:27	**L18**	25:13
L9	4:16	**L19**	23:12
L10	24:20	**L20**	13:12

[a] Reaction conditions: CuI (10%), ligand (20%), indole (1.5 equiv.), K_2CO_3 (2 equiv.), DMSO, 100 °C, 24 h. [b] Based on ^{1}H NMR spectroscopic analysis. [c] $Cu(acac)_2$ was used.

Interestingly, the introduction of additional substituents, which usually improves the performance of Cu-catalyzed systems, in our case led to a decrease in the yields (see for example, **L2** vs. **L1**, and **L4** vs. **L3**) and loss of selectivity. The use of **L6** and **L7** led to high conversion of starting iodosteroid **3**, but undesired product **11** was formed almost exclusively.

Among the N,O ligands, 8-hydroxyquinoline **L11**[15e] furnished almost complete conversion, although a rather high amount of reduction product was formed. Salicylic acid/aldehyde derivatives **L8**[15d] and **L9**[15b] were shown to be ineffective.

The O,O ligands were mainly represented by 1,3-diketones. The use of ligands with an electron-withdrawing CF_3-group **L13** and cyclic ketones **L15** and **L16** led to low conversions; diketo esters **L17**–**L19** led to slightly better results, and a preformed copper(II) complex with the simplest 1,3-diketone, acetylacetone **L12**, demonstrated moderate activity. The highest yield of desired indolylsteroid **10a** was achieved by using dipivaloylmethane (DPM) **L14** as ligand.

As reported in Table 2, the reaction did not occur in nonpolar solvents such as toluene or dioxane (entries 1 and 2). The best conversion was observed in dimethyl sulfoxide (DMSO), and the addition of water had no significant effect (entries 5 and 6). Less polar solvents such as acetonitrile and *N*,*N*-dimethylformamide (DMF) appeared less effective (entries 3 and 4).

Table 2. Solvent effects on Cu-catalyzed amination of **3** with indole.[a]

Entry	Solvent	Yield **10a/11** [%][b]
1	toluene	0:0
2	dioxane	0:0
3	MeCN	21:1
4	DMF	58:3
5	DMSO/H_2O (9:1)	77:6
6	DMSO	79:10

[a] Reaction conditions: CuI (10%), DPM (20%), indole (1.5 equiv.), K_2CO_3 (2 equiv.), 100 °C, 24 h. [b] Based on ^{1}H NMR spectroscopic analysis.

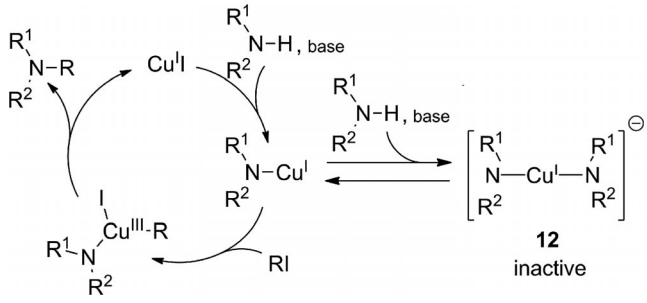
The best bases for the reaction were found to be K_2CO_3 and, unexpectedly, Et_3N (Table 3, entries 6 and 7). The latter is almost never used for C–N cross-coupling, either Pd- or Cu-catalyzed, and is commonly regarded as an ineffective base. The result obtained in our study can probably prompt a reevaluation of this simple and convenient base for amination methods. Curiously enough, most widely

Table 3. The effect of base and temperature on the Cu-catalyzed amination of **3** with indole.[a]

Entry	Base	Temperature [°C]	Yield **10a/11** [%][b]
1	K_3PO_4	100	7:3
2	Cs_2CO_3	100	9:2
3	NaOAc	100	15:10
4	Na_2CO_3	100	26:2
5	$KHCO_3$	100	49:4
6	Et_3N	100	78:6
7	K_2CO_3	100	79:10
8	K_2CO_3	130	74:15
9	K_2CO_3	80	29:0
10	*t*BuOK(Na) or KOH	100	0:0[c]

[a] Reaction conditions: CuI (10%), DPM (20%), indole (1.5 equiv.), base (2 equiv.), DMSO, 24 h. [b] Based on ^{1}H NMR spectroscopic analysis. [c] Partial decomposition of **3** was observed.

used bases such as K_3PO_4 and Cs_2CO_3 showed unsatisfactory results (Table 3, entries 1 and 2). Probably, these bases are too strong and promote the formation of inactive anionic copper complexes **12**,[17] thus effectively quenching the catalytic cycle (Scheme 5). Indeed, it was observed that the reaction of iodosteroid **3** with preformed indolylsodium instead of indole in the presence of 10 mol-% CuI and 20 mol-% DPM was suppressed almost completely.



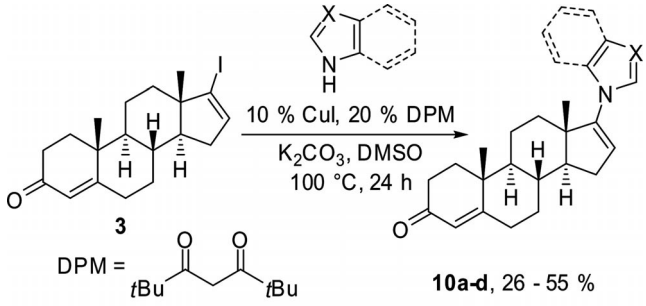
Scheme 5. Plausible mechanism of the Cu-catalyzed C–N coupling.

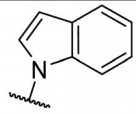
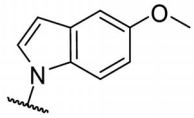
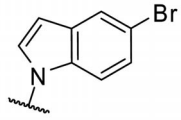
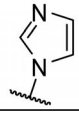
Increasing the reaction temperature from 100 to 130 °C led to practically the same conversion but increased the amount of by-product **11** (Table 3, entry 8). Decreasing the reaction temperature to 80 °C lowered the conversion considerably (Table 3, entry 9). Thus, a temperature of 100 °C was accepted as optimal.

We investigated the coupling of **3** with various azoles under the developed conditions and the yields of isolated compounds are presented in Table 4. Despite the high conversion and rather good selectivity reached with DPM as ligand, the formation of by-product **11** significantly complicated chromatographic isolation of the coupling product **10a** and, as a result, the isolated yield was only 55%. 5-Methoxyindole also gave a moderate yield of **10b** (55%), whereas the reaction of **3** with 5-bromoindole was complicated by competing amination of **10c** with 5-bromoindole. Thus, the reactivity of the C–I bond in **3** towards Cu-catalyzed amination is roughly comparable to that of the C–Br bond in 5-bromoindole. Coupling of **3** with indoles bearing electron-withdrawing substituents such as 3-formyl- and 4-cyano-indole gave very low yields together with the formation of significant amounts of reductive dehalogenation product **11**.

The amination of **3** proved to be very sensitive to steric effects exerted by the heterocycle. Thus, no coupling product was formed when 5-chloro-2-methylindole was used. Other azoles also gave lower yields with **3** than unsubstituted indole. For instance, pyrazole afforded 22% yield of the coupling product, whereas less than 10% yield of azolylsteroid was detected in the reaction with more sterically demanding indazole. The coupling of **3** with imidazole, although giving moderate yield of azolylsteroid (52%), clearly showed that the reaction was in fact inhibited by imidazole itself. The conversion with 3 equiv. imidazole was much lower than that obtained under the standard conditions for which 1.2 equiv. was employed (31 vs. 65%). Not unexpectedly, no product was observed in the reaction with benzimidazole.

Table 4. Yields of amination products in the reaction of **3** with azoles.



Entry	Azolyl substituent	Product	Isolated yield [%][a]
1		**10a**	55 (79)
2		**10b**	55 (67)
3		**10c**	26[b]
4		**10d**	52 (54)[c]

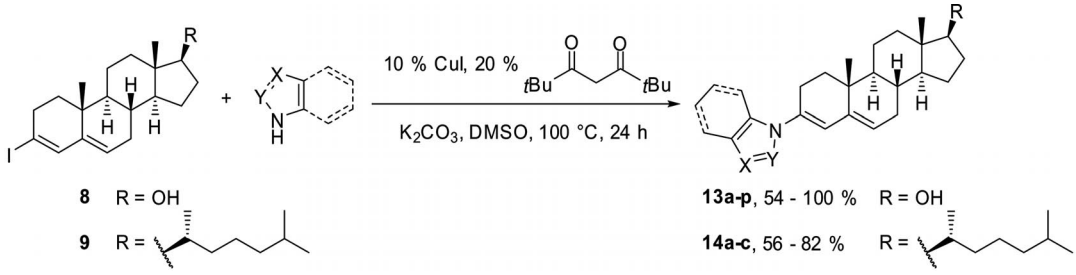
[a] ^{1}H NMR yield in parentheses. [b] Amination of **10c** with 5-bromoindole was also observed (22%). [c] Reaction time 48 h.

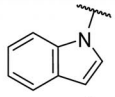
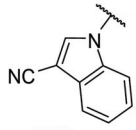
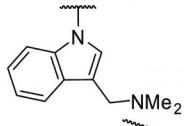
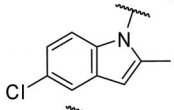
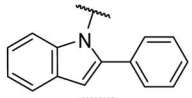
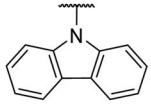
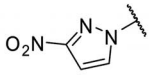
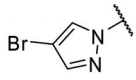
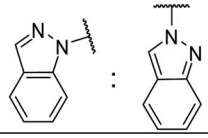
The developed procedure proved to be very efficient in coupling of less sterically hindered 3-iodosteroids **8** and **9**, with various NH-heterocycles giving azolyl-substituted steroids **13** and **14** in good to excellent yields (Table 5). The yields with cholestane derivative **9** were consistently lower than with **8**, reflecting significantly diminished solubility of this substrate in DMSO. The formation of reductive dehalogenation by-products was not observed at all, in contrast to the amination of substrate **3**.

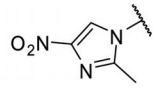
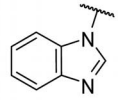
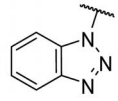
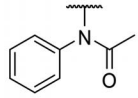
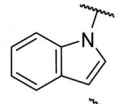
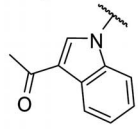
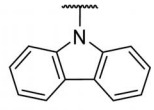
The dimethylamino group of gramine and the carbonyl group of 3-acetylindole were tolerated by this protocol (Table 5, entries 3 and 17). The presence of electron-withdrawing groups in azoles led to somewhat diminished yields, although the effect was not so catastrophic as for **3** even for substantially acidic azoles (entry 11). Carbazole (entries 6 and 18), 5-chloro-2-methylindole (entry 4), and 2-phenylindole (entry 5) did not exert enough steric hindrance to noticably impede coupling product formation. However, the combination of both steric bulk and increased acidity of azole was harmful to the coupling. Thus, only 46 and 13% yields were observed by ^{1}H NMR spectroscopic analysis in the reaction of 5-chloro-3-cyano-2-methylindole with **8** and **9**, respectively.

Coupling with ambident pyrazole and imidazole derivatives exclusively afforded vinylation of the less crowded ni-

Table 5. Yields of amination products in the reaction of **8** and **9** with N-nucleophiles.



Entry	Starting iodosteroid	Azolyl substituent	Product	Isolated yield [%][a]
1	**8**		**13a**	97
2	**8**		**13b**	82 (90)
3	**8**		**13c**	82
4	**8**		**13d**	99
5	**8**		**13e**	90
6	**8**		**13f**	92
7	**8**		**13g**	90
8	**8**		**13h**	66[b]
9	**8**		**13i/13j** (9:1)	100

Entry	Starting iodosteroid	Azolyl substituent	Product	Isolated yield [%][a]
10	**8**		**13k**	95
11	**8**		**13l**	54 (77)
12	**8**		**13m**	94
13	**8**		**13n**	89 (93)
14	**8**		**13o**	73 (88)
15	**8**		**13p**	60 (80)
16	**9**		**14a**	67
17	**9**		**14b**	56
18	**9**		**14c**	82

[a] ^{1}H NMR yield in parentheses. [b] Amination of **13h** with 4-bromopyrazole was observed (10%).

trogen atom (Table 5, entries 7 and 11). The structures of the obtained products **13g** and **13l** were confirmed by 1D NOESY and ^{13}C NMR spectroscopic data,[18] respectively. The reaction of **8** with benzotriazole gave solely more stable isomer **13n**, whereas the coupling with indazole afforded a 9:1 mixture of isomeric 1- and 2-substituted indazoles **13i** and **13j**, respectively. The structures of the major and the minor products were determined by comparison of their ^{13}C NMR spectra with data measured for 1- and 2-methylindazoles.[19] A similar regioselectivity of the Cu-catalyzed indazole and benzotriazole arylation favoring the 1-substituted isomer has been reported.[14b]

Other nitrogen nucleophiles were also screened for coupling with iodosteroids under the same conditions. Although no coupling product was observed in the reaction of **9** with pyrrolidine, the suggested conditions appear to be applicable to the preparation of enamides. The reaction of **8** with pyrrolidin-2-one and acetanilide afforded the desired products **13o** and **13p** in good yield (Table 5, entries 14 and 15). However, more acidic phthalimide failed to give any significant amount of product.

We are currently exploring the application of Cu-catalyzed couplings for attachment of other nucleophiles to the steroid core.

Conclusions

We have developed a highly efficient procedure for the synthesis of azolyl-substituted steroids by utilizing a catalyst system comprising CuI and dipivaloylmethane. A number of nitrogen heterocycles could be used in the vinylation process, affording the corresponding coupling products in good to excellent yields. The protocol is also applicable for a limited number of secondary amides.

Experimental Section

General: NMR spectra were recorded with a Bruker Avance 400 and an Agilent 400MR spectrometer (^{1}H 400 MHz, ^{13}C 100.6 MHz) at ambient temperature. Chemical shifts are presented in ppm (δ scale) and referenced to hexamethyldisiloxane (δ = 0.05 ppm) in the ^{1}H NMR spectra and to the solvent signal in the ^{13}C NMR spectra. MALDI-TOF spectra were recorded with a Bruker Daltonics UltraFlex instrument in dithranol matrix. Elemental analyses were performed with an Elementar Vario MICRO cube apparatus. Column chromatography was carried out on Macherey–Nagel silica gel 60 (0.040–0.063 mm).

3-Methoxyandrosta-3,5-dien-17-one Hydrazone (2): A suspension of **1** (15.00 g, 49.9 mmol) in a mixture of 95% ethanol (104 mL), hydrazine hydrate (28.5 mL, 586 mmol), and triethylamine (25 mL) was heated to reflux for 2 h with stirring. The resulting solution was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The product was used in the next step for the synthesis of **3** without further purification, yield 15.49 g (99%); white solid; m.p. 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22 (m, 1 H, 6-CH), 5.12 (d, J = 1.5 Hz, 1 H, 4-CH), 4.75 (br. s, 2 H, NH_2), 3.56 (s, 3 H, OCH_3), 2.34–2.03 (m, 5 H), 1.95–1.64 (m, 6 H), 1.54–1.02 (m, 6 H), 0.98 (s, 3 H, 19-CH_3), 0.88 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.9 (C(17)=NNH_2), 155.4 (*C*(3)OMe), 141.0 (5-C), 117.7 (6-CH), 98.4 (4-CH), 54.3, 54.1, 48.6, 43.9 (q), 35.3 (q), 34.1, 33.7, 31.2 (2 C), 25.2, 24.4, 23.3, 20.8, 18.9, 16.9 ppm.

17-Iodoandrosta-4,16-dien-3-one (3): Iodine (25.3 g, 99.7 mmol) was slowly added to a solution of **2** (15.49 g, 49.3 mmol) in a mixture of dioxane (300 mL) and triethylamine (66 mL). When gaseous products no longer evolved, the mixture was stirred for 30 min, treated with an aqueous solution of sodium sulfite, and extracted with CH_2Cl_2. The extract was washed with water, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The residue was mixed with 95% ethanol (130 mL) and conc. HCl (1.05 mL) and heated to reflux for 2.5 h with stirring. The resulting solution was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was subjected to column chromatography on silica gel (CH_2Cl_2/Et_2O, 20:1) and then recrystallized from methanol, yield 13.27 g (68%); yellow needles; m.p. 169 °C (MeOH) (ref. 169 °C).[9b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (dd, J = 6.6, 1.8 Hz, 1 H, 16-CH), 5.73 (m, 1 H, 4-CH), 2.49–2.25 (m, 4 H), 2.16 (ddd, J = 14.9, 6.6, 3.3 Hz, 1 H), 2.05–1.93 (m, 2 H), 1.87 (m, 1 H), 1.81–1.60 (m, 4 H), 1.56–1.41 (m, 2 H), 1.29–0.94 (m, 3 H), 1.20 (s, 3 H, 19-CH_3), 0.77 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.3 (C(3)=O), 170.6 (5-C), 137.4 (16-CH), 124.0 (4-CH), 112.1 (17-CI), 54.0, 53.9, 49.8 (q), 38.6 (q), 35.9, 35.5, 34.6, 33.9, 33.6, 32.6, 31.3, 20.7, 17.1, 15.2 ppm.

17β-Hydroxyandrost-4-en-3-one Hydrazone (6):[20] Obtained from **4** (3.391 g, 11.8 mmol) and hydrazine hydrate (6.7 mL, 140 mmol) according to the procedure used for the synthesis of **2** without addition of triethylamine. The product was used in the next step for the synthesis of **8** without further purification, yield 3.520 g (99%); white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (br. s, 1 H, 4-CH), 5.02 (br. s, 2 H, NH_2), 3.61 (t, J = 8.6 Hz, 1 H, 17-C*H*OH), 2.55 (m, 1 H), 2.42–0.71 (m, 19 H), 1.04 (s, 3 H, 19-CH_3), 0.76 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.7 (C(3)=NNH_2 or 5-C), 150.8 (C(3)=NNH_2 or 5-C), 121.0 (4-CH), 81.5 (17-CHOH), 53.7, 50.6, 42.7 (q), 37.5 (q), 36.5, 35.8, 34.8, 32.0, 31.7, 30.3, 23.3, 21.0, 18.8, 17.8, 11.0 ppm.

3-Iodoandrosta-3,5-dien-17β-ol (8): Iodine (6.9 g, 27 mmol) was slowly added to a solution of **6** (3.520 g, 11.6 mmol) in a mixture of dioxane (81 mL) and triethylamine (18 mL). When gaseous products no longer evolved, the mixture was stirred for 30 min, treated with an aqueous solution of sodium sulfite, and extracted with CH_2Cl_2. The extract was washed with water, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (CH_2Cl_2) to afford an equimolar mixture of $\Delta^{3,5}$- and $\Delta^{2,4}$-iodosteroids (by ^{1}H NMR). The product mixture was dissolved in anhydrous CH_2Cl_2 (10 mL), trifluoromethanesulfonic acid (20 mg) was added, and the mixture was stirred for 24 h at room temp. Triethylamine (1 mL) was added, the mixture was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4, and evaporated in vacuo. The residue was subjected to chromatography on silica gel (CH_2Cl_2) and then recrystallized from methanol, yield 2.60 g (56%); light-yellow crystals; m.p. 154–155 °C (MeOH) (ref. 155–157 °C).[9a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.54 (br. s, 1 H, 4-CH), 5.35 (m, 1 H, 6-CH), 3.64 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.70–2.53 (m, 2 H), 2.22–2.00 (m, 2 H), 1.83 (m, 1 H), 1.74–1.22 (m, 10 H), 1.15–0.91 (m, 3 H), 0.96 (s, 3 H, 19-CH_3), 0.76 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.3 (5-C), 139.2 (4-CH), 124.3 (6-CH), 94.9 (3-CI), 81.8 (17-CHOH), 51.4, 48.2, 42.9 (q), 37.2, 36.4, 36.3, 34.3 (q), 31.6, 31.1, 30.5, 23.3, 20.6, 18.9, 11.0 ppm.

Cholest-4-en-3-one Hydrazone (7):[21] Obtained from **5** (2.070 g, 5.20 mmol) and hydrazine hydrate (2.0 mL, 42 mmol) according to procedure used for the synthesis of **2** without addition of triethylamine. The product was used in the next step for the synthesis of **9** without further purification, yield 2.070 g (100%); white solid; m.p. 242–244 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (br. s, 1 H, 4-CH), 4.99 (br. s, 2 H, NH_2), 2.59–2.49 (m, 2 H), 2.38–2.12 (m, 3 H), 2.05–0.76 (m, 23 H), 1.03 (s, 3 H, 19-CH_3), 0.89 (d, J = 6.3 Hz, 3 H, 21-CH_3), 0.850 [d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.846 [d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.68 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.1 (C(3)=NNH_2 or 5-C), 150.9 (C(3)=NNH_2 or 5-C), 121.0 (4-CH), 56.2, 56.1, 53.7, 42.4 (q), 39.8, 39.5, 37.5 (q), 36.1, 35.9, 35.8, 34.8, 32.2 (2 C), 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.5, 18.9, 18.7, 17.8, 12.0 ppm.

3-Iodocholesta-3,5-diene (9): Obtained from **7** (2.000 g, 5.19 mmol) and iodine (2.667 g, 10.5 mmol) according to the procedure used for the synthesis of **8**. Eluent: hexanes, yield 1.085 g (42%); light-brown solid; m.p. 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (br. s, 1 H, 4-CH), 5.35 (m, 1 H, 6-CH), 2.70–2.52 (m, 2 H), 2.13 (m, 1 H), 2.00 (m, 1 H), 1.82 (m, 1 H), 1.72–0.62 (m, 21 H), 0.94 (s, 3 H, 19-CH_3), 0.90 (d, J = 6.4 Hz, 3 H, 21-CH_3), 0.850 [d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.847 [d, J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.68 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.3 (5-C), 139.3 (4-CH), 124.8 (6-CH), 94.8 (3-CI), 56.8, 56.1, 48.0, 42.4 (q), 39.6, 39.5, 37.3, 36.3, 36.2, 35.8, 34.2 (q), 31.6 (2 C), 28.2, 28.0, 24.1, 23.8, 22.8, 22.6, 21.0, 18.9, 18.7, 11.9 ppm. $C_{27}H_{43}I$ (494.53): calcd. C 65.57, H 8.76; found C 65.52, H 8.63.

C–N Coupling of Iodosteroids and Azoles. General Procedure: In a vial with a screw cap, iodosteroid (0.150 mmol), azole

(0.180 mmol), anhydrous K_2CO_3 (41.5 mg, 0.300 mmol), CuI (2.9 mg, 15 μmol, 10 mol-%), and dipivaloylmethane (6.3 μL, 30 μmol, 20 mol-%) were mixed under an Ar atmosphere in DMSO (0.5 mL). The reaction mixture was stirred at 100 °C for 24 h, then diluted with CH_2Cl_2 (25 mL) and washed with water (5 × 25 mL). The organic layer was dried with anhydrous Na_2SO_4, and the solvents were evaporated in vacuo. The residue was purified by column chromatography.

17-(1*H*-Indol-1-yl)androsta-4,16-dien-3-one (10a): Eluent: hexanes/EtOAc (4:1), yield 23.4 mg (55%); light-brown solid; m.p. 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 [d, J = 7.8 Hz, 1 H, 4- or 7-CH(indole)], 7.48 [d, J = 8.2 Hz, 1 H, 4- or 7-CH(indole)], 7.18 [m, 1 H, 5- or 6-CH(indole)], 7.14 [d, J = 3.3 Hz, 1 H, 2-CH(indole)], 7.10 [m, 1 H, 5- or 6-CH(indole)], 6.54 [d, J = 3.3 Hz, 1 H, 3-CH(indole)], 5.84 (dd, J = 2.9, 1.7 Hz, 1 H, 16-CH), 5.75 (br. s, 1 H, 4-CH), 2.51–2.28 (m, 5 H), 2.18 (ddd, J = 15.2, 11.2, 1.6 Hz, 1 H), 2.04–1.43 (m, 8 H), 1.31–1.02 (m, 3 H), 1.20 (s, 3 H, 19-CH_3), 0.99 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.3 (C(3)=O), 170.7 (5-C), 149.4 (17-C), 137.1 [7a-C(indole)], 128.4 [3a-C(indole)], 126.7, 124.1, 122.0, 121.6, 120.6, 120.0, 111.2 [7-CH(indole)], 102.5 [3-CH(indole)], 55.0, 54.1, 47.3 (q), 38.7 (q), 35.5, 34.8, 34.1, 33.9, 32.7, 31.3, 30.0, 20.7, 17.2, 16.0 ppm. $C_{27}H_{31}NO$ (385.24): calcd. C 84.11, H 8.10, N 3.63; found C 84.17, H 8.29, N 3.70.

17-(5-Methoxy-1*H*-indol-1-yl)androsta-4,16-dien-3-one (10b): Eluent: hexanes/EtOAc (4:1), yield 34.2 mg (55%); white solid; m.p. 147–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 [d, J = 8.9 Hz, 1 H, 7-CH(indole)], 7.12 [d, J = 3.3 Hz, 1 H, 2-CH(indole)], 7.05 [d, J = 2.4 Hz, 1 H, 4-CH(indole)], 6.83 [dd, J = 8.9, 2.4 Hz, 1 H, 6-CH(indole)], 6.46 [d, J = 3.3 Hz, 1 H, 3-CH(indole)], 5.80 (dd, J = 3.1, 1.7 Hz, 1 H, 16-CH), 5.75 (br. s, 1 H, 4-CH), 3.83 (s, 3 H, CH_3O), 2.51–2.28 (m, 4 H), 2.16 (ddd, J = 15.2, 11.2, 1.7 Hz, 1 H), 2.03–1.42 (m, 9 H), 1.27–1.03 (m, 3 H), 1.20 (s, 3 H, 19-CH_3), 1.00 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.3 (C(3)=O), 170.6 (5-C), 154.3 [5-C(indole)], 149.5 (17-C), 132.3 [7a-C(indole)], 128.8 [3a-C(indole)], 127.1 [2-CH(indole)], 124.1 (4-CH), 120.7 (16-CH), 112.2 [6- or 7-CH(indole)], 112.0 [6- or 7-CH(indole)], 102.3 [3- or 4-CH(indole)], 102.2 [3- or 4-CH(indole)], 55.8 (CH_3O), 55.0, 54.1, 47.2 (q), 38.7 (q), 35.6, 34.9, 34.1, 33.9, 32.7, 31.3, 29.9, 20.8, 17.2, 16.1 ppm. MALDI-TOF: m/z calcd. for $C_{28}H_{33}NO_2$ $[M]^+$ 415.2511; found 415.2574.

17-(5-Bromo-1*H*-indol-1-yl)androsta-4,16-dien-3-one (10c): Eluent: hexanes/EtOAc (4:1), yield 17.8 mg (26%); white solid; m.p. 187–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 [d, J = 1.5 Hz, 1 H, 4-CH(indole)], 7.33 [d, J = 8.8 Hz, 1 H, 7-CH(indole)], 7.24 [dd, J = 8.8, 1.5 Hz, 1 H, 6-CH(indole)], 7.13 [d, J = 3.0 Hz, 1 H, 2-CH(indole)], 6.48 [d, J = 3.0 Hz, 1 H, 3-CH(indole)], 5.82 (dd, J = 3.0, 1.5 Hz, 1 H, 16-CH), 5.75 (br. s, 1 H, 4-CH), 2.51–2.29 (m, 5 H), 2.18 (m, 1 H), 2.04–1.43 (m, 8 H), 1.27–1.04 (m, 3 H), 1.21 (s, 3 H, 19-CH_3), 0.98 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.3 (C(3)=O), 170.5 (5-C), 149.2 (17-C), 135.9 [7a-C(indole)], 130.1 [3a-C(indole)], 127.9, 124.9, 124.1, 123.1, 122.4, 113.2 [5-CBr(indole)], 112.6 [7-CH(indole)], 102.1 [3-CH(indole)], 55.1, 54.1, 47.3 (q), 38.7 (q), 35.6, 34.8, 34.1, 33.9, 32.6, 31.3, 30.0, 20.7, 17.2, 16.0 ppm. MALDI-TOF: m/z calcd. for $C_{27}H_{30}BrNO$ $[M]^+$ 463.1511; found 463.1535.

17-(1*H*-Imidazol-1-yl)androsta-4,16-dien-3-one (10d): Eluent: CH_2Cl_2/MeOH (20:1), yield 26.2 mg (52%); light-brown solid; m.p. 168–171 °C (ref. 147–150 °C).[2a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 [br. s, 1 H, CH(imidazole)], 7.15 [br. s, 2 H, CH(imidazole)], 5.74 (br. s, 1 H, 4-CH), 5.68 (dd, J = 3.3, 1.5 Hz, 1 H, 16-CH), 2.51–2.23 (m, 5 H), 2.11–1.46 (m, 9 H), 1.27–1.03 (m, 3 H), 1.22 (s, 3 H, 19-CH_3), 1.01 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.2 (C(3)=O), 170.2 (5-C), 148.6 (17-C), 137.0 [v. br., 2 C, CH(imidazole)], 129.7 [v. br., CH(imidazole)], 124.2 (4-CH), 118.9 (16-CH), 55.4, 53.9, 46.2 (q), 38.6 (q), 35.5, 34.6, 33.84, 33.82, 32.5, 31.2, 29.6, 20.7, 17.1, 15.9 ppm. MALDI-TOF: m/z calcd. for $C_{22}H_{29}N_2O$ $[M + H]^+$ 337.2280; found 337.2311.

3-(1*H*-Indol-1-yl)androsta-3,5-dien-17β-ol (13a): Eluent: CH_2Cl_2/MeOH (100:1), yield 56.2 mg (97%); white solid; m.p. 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 [d, J = 7.8 Hz, 1 H, 4- or 7-CH(indole)], 7.52 [d, J = 8.3 Hz, 1 H, 4- or 7-CH(indole)], 7.22–7.15 [m, 2 H, CH(indole)], 7.10 [t, J = 7.4 Hz, 1 H, 5- or 6-CH(indole)], 6.55 [dd, J = 3.3, 0.6 Hz, 1 H, 3-CH(indole)], 6.19 (br. s, 1 H, 4-CH), 5.50 (m, 1 H, 6-CH), 3.66 (t, J = 8.4 Hz, 1 H, 17-C*H*OH), 2.71–2.50 (m, 2 H), 2.24 (m, 1 H), 2.15–1.96 (m, 2 H), 1.87 (m, 1 H), 1.79–1.57 (m, 4 H), 1.54–0.98 (m, 8 H), 1.10 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.3 (5-C), 135.6 [7a-C(indole)], 133.2 (3-C), 129.0 [3a-C(indole)], 126.3 (4-CH), 124.2 [2-CH(indole)], 121.94 [6-CH or 5-CH(indole)], 121.85 [6-CH or 5-CH(indole)], 120.9 [4-CH(indole)], 119.9 [6-CH(indole)], 111.4 [7-CH(indole)], 102.7 [3-CH(indole)], 81.8 (17-CHOH), 51.4, 48.2, 42.9 (q), 36.5, 35.0 (q), 33.9, 31.9, 31.5, 30.5, 26.4, 23.4, 20.8, 19.1, 11.1 ppm. $C_{27}H_{33}NO$ (387.56): calcd. C 83.68, H 8.58, N 3.61; found C 83.60, H 8.56, N 3.61.

3-(3-Cyano-1*H*-indol-1-yl)androsta-3,5-dien-17β-ol (13b): Eluent: CH_2Cl_2/MeOH (100:1), yield 50.7 mg (82%); white solid; m.p. 197–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 [dd, J = 6.8, 2.0 Hz, 1 H, 4- or 7-CH(indole)], 7.65 [s, 1 H, 2-CH(indole)], 7.50 [dd, J = 6.6, 1.9 Hz, 1 H, 4- or 7-CH(indole)], 7.35–7.25 [m, 2 H, 5- and 6-CH(indole)], 6.21 (d, J = 1.6 Hz, 1 H, 4-CH), 5.59 (m, 1 H, 6-CH), 3.67 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.65 (m, 1 H, 2-CH^{β}), 2.47 (dd, J = 17.6, 4.9 Hz, 1 H, 2-CH^{α}), 2.26 (m, 1 H), 2.15–1.97 (m, 2 H), 1.88 (m, 1 H), 1.81–0.98 (m, 12 H), 1.09 (s, 3 H, 19-CH_3), 0.81 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 139.5 (5-C), 135.3 [7a-C(indole)], 133.5 [2-CH(indole)], 131.6 (3-C), 127.8 [3a-C(indole)], 127.0, 125.4, 124.1, 122.4, 119.9, 115.6 (C≡N), 112.1 [7-CH(indole)], 87.1 [3-C(indole)], 81.7 (17-CHOH), 51.4, 48.2, 42.9 (q), 36.5, 34.9 (q), 33.8, 31.8, 31.6, 30.5, 26.4, 23.3, 20.8, 19.1, 11.1 ppm. MALDI-TOF: m/z calcd. for $C_{28}H_{32}N_2O$ $[M]^+$ 412.2515; found 412.2542.

3-{3-[(Dimethylamino)methyl]-1*H*-indol-1-yl}androsta-3,5-dien-17β-ol (13c): Eluent: CH_2Cl_2/MeOH (10:1), yield 54.7 mg (82%); light-brown solid; m.p. 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 [d, J = 7.8 Hz, 1 H, 4- or 7-CH(indole)], 7.52 [d, J = 8.2 Hz, 1 H, 4- or 7-CH(indole)], 7.31 [s, 1 H, 2-CH(indole)], 7.20 [t, J = 7.6 Hz, 1 H, 5- or 6-CH(indole)], 7.13 [t, J = 7.3 Hz, 1 H, 5- or 6-CH(indole)], 6.19 (m, 1 H, 4-CH), 5.50 (m, 1 H, 6-CH), 3.80 [br. s, 2 H, CH_2N$(CH_3)_2$], 3.66 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.71–2.51 (m, 2 H), 2.40 [br. s, 6 H, N$(CH_3)_2$], 2.24 (m, 1 H), 2.13–1.95 (m, 2 H), 1.87 (m, 1 H), 1.78–0.76 (m, 12 H), 1.09 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.2 (5-C), 135.9 [7a-C(indole)], 132.8 (3-C), 128.8 [3a-C(indole)], 126.8, 124.4, 122.2, 122.0, 120.2, 119.0, 111.6 [7-CH(indole)], 81.7 (17-CHOH), 53.7 [*C*H_2N$(CH_3)_2$], 51.5, 48.2, 44.4 [2 C, N$(CH_3)_2$], 42.9 (q), 36.5, 35.0 (q), 33.9, 31.9, 31.6, 30.5, 26.4, 23.4, 20.8, 19.1, 11.1 ppm. MALDI-TOF: m/z calcd. for $C_{30}H_{41}N_2O$ $[M + H]^+$ 445.3219; found 445.3207.

3-(5-Chloro-2-methyl-1*H*-indol-1-yl)androsta-3,5-dien-17β-ol (13d): Eluent: CH_2Cl_2/MeOH (100:1), yield 65.0 mg (99%); white solid; m.p. 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 [d, J = 1.7 Hz, 1 H, 4-CH(indole)], 7.05 [d, J = 8.7 Hz, 1 H, 7-CH(indole)], 7.01 [dd, J = 8.7, 1.7 Hz, 1 H, 6-CH(indole)], 6.20 [s, 1 H, 3-CH(in-

dole)], 6.05 (d, J = 2.0 Hz, 1 H, 4-CH), 5.54 (m, 1 H, 6-CH), 3.67 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.50–2.38 (m, 1 H), 2.32 (br. s, 3 H, CH_3), 2.30–2.19 (m, 2 H), 2.09 (m, 1 H), 1.97 (m, 1 H), 1.87 (m, 1 H), 1.79–0.99 (m, 12 H), 1.11 (s, 3 H, 19-CH_3), 0.81 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.1 (5-C), 138.1 [7a-C(indole)], 135.6 [2-*C*Me(indole)], 131.9 (3-C), 129.7 (4-CH), 129.2 [3a-C(indole)], 126.4 (6-CH), 125.1 [5-CCl(indole)], 120.8 [4-CH(indole)], 118.9 [6-CH(indole)], 110.8 [7-CH(indole)], 100.0 [3-CH(indole)], 81.8 (17-CHOH), 51.4, 48.2, 42.9 (q), 36.5, 34.8 (q), 34.0, 31.9, 31.5, 30.5, 26.7, 23.4, 20.8, 19.1, 12.9, 11.1 ppm. $C_{28}H_{34}ClNO$ (436.03): calcd. C 77.13, H 7.86, N 3.21; found C 76.98, H 7.94, N 3.30.

3-(2-Phenyl-1*H*-indol-1-yl)androsta-3,5-dien-17β-ol (13e): Eluent: CH_2Cl_2/MeOH (100:1), yield 62.7 mg (90%); white solid; m.p. 198–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 [d, J = 7.3 Hz, 3 H, 2,6-CH(Ph), 4- or 7-CH(indole)], 7.41–7.33 [m, 3 H, 3,5-CH(Ph), 4- or 7-CH(indole)], 7.29 [t, J = 7.2 Hz, 1 H, 4-CH(Ph)], 7.17 [t, J = 7.2 Hz, 1 H, 5- or 6-CH(indole)], 7.11 [t, J = 7.3 Hz, 1 H, 5- or 6-CH(indole)], 6.67 [s, 1 H, 3-CH(indole)], 6.32 (br. s, 1 H, 4-CH), 5.55 (m, 1 H, 6-CH), 3.64 (t, J = 8.4 Hz, 1 H, 17-C*H*OH), 2.25 (m, 1 H), 2.16–2.00 (m, 2 H), 1.94–0.90 (m, 15 H), 0.99 (s, 3 H, 19-CH_3), 0.77 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.5 (5-C), 139.8 (q), 138.4 (q), 133.4 (q), 133.3 (q), 128.6, 128.4 [2 C, CH(Ph)], 128.2 (q), 127.8 [2 C, CH(Ph)], 127.5, 125.3, 121.9, 120.4, 120.3, 110.6 [7-CH(indole)], 102.9 [3-CH(indole)], 81.8 (17-CHOH), 51.4, 48.0, 42.8 (q), 36.5, 34.8 (q), 33.9, 31.8, 31.5, 30.4, 27.0, 23.3, 20.7, 19.1, 11.0 ppm. $C_{33}H_{37}NO$ (463.65): calcd. C 85.48, H 8.04, N 3.02; found C 85.07, H 8.17, N 2.73.

3-(9*H*-Carbazol-9-yl)androsta-3,5-dien-17β-ol (13f): Eluent: CH_2Cl_2/MeOH (100:1), yield 60.5 mg (92%); white solid; m.p. 268–269 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + [D_6]DMSO): δ = 8.06 [d, J = 7.7 Hz, 2 H, 4,5-CH(carbazole)], 7.39 [m, 2 H, 2,7-CH(carbazole)], 7.34 [d, J = 8.0 Hz, 2 H, 1,8-CH(carbazole)], 7.20 [m, 2 H, 3,6-CH(carbazole)], 6.24 (m, 1 H, 4-CH), 5.58 (m, 1 H, 6-CH), 4.24 (br. s, 1 H, OH), 3.56 (m, 1 H, 17-C*H*OH), 2.61–2.39 (m, 2 H), 2.25 (m, 1 H), 2.07–1.84 (m, 3 H), 1.81–0.97 (m, 11 H), 1.19 (s, 3 H, 19-CH_3), 0.78 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ + [D_6]DMSO): δ = 138.7 [2 C, 8a,9a-C(carbazole)], 138.5 (5-C), 129.8 (3-C), 127.5 (4-CH), 124.6 (6-CH), 124.3 [2 C, 2,7-CH(carbazole)], 121.2 [2 C, 4a,4b-C(carbazole)], 118.6 [2 C, CH(carbazole)], 117.9 [2 C, CH(carbazole)], 108.4 [2 C, 1,8-CH(carbazole)], 79.0 (17-CHOH), 49.8, 46.6, 41.3 (q), 35.1, 33.3 (q), 32.3, 30.2, 30.0, 28.6, 23.4, 21.8, 19.2, 17.6, 9.9 ppm. $C_{31}H_{35}NO$ (437.62): calcd. C 85.08, H 8.06, N 3.20; found C 85.29, H 8.20, N 3.17.

3-(3-Nitro-1*H*-pyrazol-1-yl)androsta-3,5-dien-17β-ol (13g): Eluent: CH_2Cl_2/MeOH (50:1), yield 51.7 mg (90%); yellow solid; m.p. 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 [d, J = 2.6 Hz, 1 H, 5-CH(pyrazole)], 6.96 [d, J = 2.6 Hz, 1 H, 4-CH(pyrazole)], 6.52 (d, J = 1.9 Hz, 1 H, 4-CH), 5.67 (m, 1 H, 6-CH), 3.66 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.80 (dd, J = 17.7, 5.0 Hz, 1 H, 2-CH^{α}), 2.63 (m, 1 H, 2-CH^{β}), 2.27 (m, 1 H), 2.13–1.99 (m, 2 H), 1.87 (m, 1 H), 1.78–0.98 (m, 12 H), 1.00 (s, 3 H, 19-CH_3), 0.79 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.0 [3-C(pyrazole)], 139.2 (5-C), 132.8 (3-C), 128.3, 128.0, 119.1, 103.5 [4-CH(pyrazole)], 81.7 (17-CHOH), 51.4, 48.0, 42.8 (q), 36.4, 34.9 (q), 33.2, 31.7, 31.7, 30.4, 23.3, 23.0, 20.7, 18.9, 11.0 ppm. MALDI-TOF: m/z calcd. for $C_{22}H_{29}N_3O_3$ $[M]^+$ 383.2209; found 383.2275.

3-(4-Bromo-1*H*-pyrazol-1-yl)androsta-3,5-dien-17β-ol (13h): Eluent: CH_2Cl_2/MeOH (100:1), yield 41.4 mg (66%); white solid; m.p. 204–206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 [br. s, 1 H, CH(pyrazole)], 7.53 [br. s, 1 H, CH(pyrazole)], 6.36 (d, J = 1.5 Hz, 1 H, 4-CH), 5.55 (m, 1 H, 6-CH), 3.65 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.73 (dd, J = 17.6, 4.9 Hz, 1 H, 2-CH^{α}), 2.56 (m, 1 H, 2-CH^{β}), 2.23 (m, 1 H), 2.13–1.95 (m, 2 H), 1.86 (m, 1 H), 1.77–0.96 (m, 12 H), 0.99 (s, 3 H, 19-CH_3), 0.78 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.4 [CH(pyrazole)], 139.6 (5-C), 133.1 (3-C), 126.1, 125.6, 115.6, 94.4 [4-CBr(pyrazole)], 81.8 (17-CHOH), 51.4, 48.1, 42.9 (q), 36.5, 35.0 (q), 33.4, 31.8, 31.6, 30.5, 23.3, 23.0, 20.8, 19.0, 11.1 ppm. MALDI-TOF: m/z calcd. for $C_{22}H_{30}BrN_2O$ $[M + H]^+$ 417.1542; found 417.1544.

3-(1*H*-Indazol-1-yl)androsta-3,5-dien-17β-ol (13i) and 3-(2*H*-Indazol-2-yl)androsta-3,5-dien-17β-ol (13j): Eluent: CH_2Cl_2/MeOH (100:1). According to ^{1}H NMR, a 9:1 inseparable mixture of isomers **13i** and **13j** was obtained, yield 58.2 mg (100%); white solid; m.p. 146–151 °C.

3-(1*H*-indazol-1-yl)androsta-3,5-dien-17β-ol (13i, major isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 [s, 1 H, 3-CH(indazole)], 7.72 [d, J = 8.1 Hz, 1 H, 4- or 7-CH(indazole)], 7.69 [d, J = 8.6 Hz, 1 H, 4- or 7-CH(indazole)], 7.37 [t, J = 8.1 Hz, 1 H, 5- or 6-CH(indazole)], 7.16 [t, J = 7.5 Hz, 1 H, 5- or 6-CH(indazole)], 6.31 (d, J = 1.9 Hz, 1 H, 4-CH), 5.54 (m, 1 H, 6-CH), 3.67 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 3.00 (dd, J = 18.2, 5.1 Hz, 1 H), 2.70 (m, 1 H), 2.25 (m, 1 H), 2.14–1.99 (m, 2 H), 1.87 (m, 1 H), 1.79–1.57 (m, 4 H), 1.55–0.99 (m, 8 H), 1.10 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.3 (5-C), 138.6 [7a-C(indazole)], 134.5 (3-C), 134.3 [CH(indazole)], 126.6 (4-CH), 124.9 [3a-C(indazole)], 124.5 (6-CH), 121.2 [CH(indazole)], 121.1 [CH(indazole)], 119.1 [CH(indazole)], 111.4 [CH(indazole)], 81.8 (17-CHOH), 51.5, 48.2, 42.9 (q), 36.5, 35.1 (q), 33.7, 31.9, 31.6, 30.5, 25.1, 23.4, 20.8, 19.1, 11.1 ppm.

3-(2*H*-indazol-2-yl)androsta-3,5-dien-17β-ol (13j, minor isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ (main signals) = 8.15 [s, 1 H, 3-CH(indazole)], 7.62 [d, J = 8.5 Hz, 1 H, 4- or 7-CH(indazole)], 7.69 [d, J = 8.3 Hz, 1 H, 4- or 7-CH(indazole)], 7.26 [dd, J = 8.6, 6.9 Hz, 1 H, 5- or 6-CH(indazole)], 7.04 [dd, J = 8.0, 7.0 Hz, 1 H, 5- or 6-CH(indazole)], 6.78 (br. s, 1 H, 4-CH), 5.68 (m, 1 H, 6-CH), 3.67 (t, J = 8.5 Hz, 1 H, 17-C*H*OH), 2.94 (dd, J = 17.7, 5.2 Hz, 1 H), 2.79 (m, 1 H), 1.05 (s, 3 H, 19-CH_3), 0.79 (s, 3 H, 18-CH_3) ppm. $C_{26}H_{32}N_2O$ (388.55): calcd. C 80.37, H 8.30, N 7.21; found C 80.18, H 8.34, N 7.39.

3-(1*H*-Imidazol-1-yl)androsta-3,5-dien-17β-ol (13k): Eluent: CH_2Cl_2/MeOH (20:1), yield 48.1 mg (95%); white solid; m.p. 224–225 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.01 [br. s, 1 H, CH(imidazole)], 7.56 [br. s, 1 H, CH(imidazole)], 7.00 [br. s, 1 H, CH(imidazole)], 6.28 (br. s, 1 H, 4-CH), 5.53 (m, 1 H, 6-CH), 4.46 [d, J = 4.6 Hz, 1 H, OH], 3.45 (m, 1 H, 17-C*H*OH), 2.67–2.51 (m, 2 H), 2.17 (m, 1 H), 1.99–0.99 (m, 14 H), 0.94 (s, 3 H, 19-CH_3), 0.67 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 139.5 (5-C), 134.6 [2-CH(imidazole)], 130.6 (3-C), 129.1 [5-CH(imidazole)], 124.5 (4-CH), 116.6 [4-CH(imidazole)], 115.4 (6-CH), 79.9 (17-CHOH), 51.0, 47.8, 42.4 (q), 36.3, 34.3 (q), 32.9, 31.4, 31.1, 29.8, 23.6, 23.0, 20.4, 18.7, 11.3 ppm. $C_{22}H_{30}N_2O$ (338.49): calcd. C 78.06, H 8.93, N 8.28; found C 78.14, H 8.80, N 8.11.

3-(2-Methyl-4-nitro-1*H*-imidazol-1-yl)androsta-3,5-dien-17β-ol (13l): Eluent: CH_2Cl_2/MeOH (50:1), yield 32.3 mg (54%); white solid; m.p. > 300 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ = 7.72 [br. s, 1 H, 5-CH(imidazole)], 6.07 (d, J = 1.6 Hz, 1 H, 4-CH), 5.66 (m, 1 H, 6-CH), 3.65 (t, J = 8.6 Hz, 1 H, 17-C*H*OH), 2.55 (m, 1 H, 2-CH^{β}), 2.38 (br. s, 3 H, CH_3), 2.34–2.19 (m, 3 H), 2.12–1.97 (m, 2 H), 1.88 (m, 1 H), 1.78–1.57 (m, 4 H), 1.54–0.98 (m, 7 H), 1.03 (s, 3 H, 19-CH_3), 0.80 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ + CD_3OD): δ = 146.5 [2- or 4-C(imidazole)], 144.6 [2- or 4-C(imidazole)], 138.7 (5-C), 129.9 (3-C), 129.3 (4- or 6-CH), 128.5

(4- or 6-CH), 119.5 [5-CH(imidazole)], 81.4 (17-CHOH), 51.3, 47.9, 42.8 (q), 36.3, 34.6 (q), 33.5, 31.6, 31.5, 30.1, 26.8, 23.2, 20.7, 18.9, 13.6 [*C*H$_3$C(imidazole)], 11.0 ppm. MALDI-TOF: *m*/*z* calcd. for $C_{23}H_{32}N_3O_3$ [M + H]$^+$ 398.2444; found 398.2452.

3-(1*H*-Benzimidazol-1-yl)androsta-3,5-dien-17β-ol (13m): Eluent: CH_2Cl_2/MeOH (20:1), yield 55.0 mg (94%); white solid; m.p. 245–247 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 [br. s, 1 H, 2-CH(benzimidazole)], 7.85 [br. s, 1 H, 4-CH(benzimidazole)], 7.60 [br. s, 1 H, 7-CH(benzimidazole)], 7.27 [m, 2 H, 5- and 6-CH(benzimidazole)], 6.23 (d, *J* = 1.5 Hz, 1 H, 4-CH), 5.59 (m, 1 H, 6-CH), 3.66 (t, *J* = 8.5 Hz, 1 H, 17-C*H*OH), 2.70 (m, 1 H, 2-CH$^\beta$), 2.56 (dd, *J* = 17.9, 5.1 Hz, 1 H, 2-CH$^\alpha$), 2.32–1.98 (m, 4 H), 1.89 (m, 1 H), 1.79–1.41 (m, 7 H), 1.32 (qd, *J* = 12.1, 5.9 Hz, 1 H), 1.19–0.98 (m, 3 H), 1.09 (s, 3 H, 19-CH$_3$), 0.81 (s, 3 H, 18-CH$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 141.8 [v. br., 2- and 3a-C(benzimidazole)] 139.6 (5-C), 135.1 [v. br., 7a-C(benzimidazole)], 130.4 (3-C), 126.4 (6-CH), 123.3 [5- or 6-CH(benzimidazole)], 123.2 [5- or 6-CH(benzimidazole)], 122.3 (4-CH), 120.4 [4-CH(benzimidazole)], 111.5 [br., 7-CH(benzimidazole)], 81.6 (17-CHOH), 51.4, 48.2, 42.9 (q), 36.5, 34.9 (q), 33.7, 31.8, 31.5, 30.4, 26.1, 23.3, 20.7, 19.0, 11.1 ppm. MALDI-TOF: *m*/*z* calcd. for $C_{26}H_{33}N_2O$ [M + H]$^+$ 389.2593; found 389.2582.

3-(1*H*-1,2,3-Benzotriazol-1-yl)androsta-3,5-dien-17β–ol (13n): Eluent: CH_2Cl_2/MeOH (100:1), yield 52.0 mg (89%); white solid; m.p. 202–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 8.07 [d, *J* = 7.8 Hz, 1 H, 4-CH(benzotriazole)], 7.72 [d, *J* = 7.8 Hz, 1 H, 7-CH(benzotriazole)], 7.48 [t, *J* = 7.8 Hz, 1 H, 5- or 6-CH(benzotriazole)], 7.36 [t, *J* = 7.8 Hz, 1 H, 5- or 6-CH(benzotriazole)], 6.43 (br. s, 1 H, 4-CH), 5.65 (m, 1 H, 6-CH), 3.66 (t, *J* = 8.5 Hz, 1 H, 17-C*H*OH), 3.08 (dd, *J* = 18.4, 4.9 Hz, 1 H, 2-CH$^\alpha$), 2.86 (m, 1 H, 2-CH$^\beta$), 2.28 (m, 1 H), 2.15–1.42 (m, 11 H), 1.32 (m, 1 H), 1.20–0.98 (m, 3 H), 1.11 (s, 3 H, 19-CH$_3$), 0.81 (s, 3 H, 18-CH$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$ + [D$_6$]DMSO): δ = 146.4 [3a-C(benzotriazole)], 139.6 (5-C), 132.2 (3-C), 132.0 [7a-C(benzotriazole)], 127.6, 127.1, 124.1, 121.0, 120.0, 111.2 [7-CH(benzotriazole)], 81.6 (17-CHOH), 51.4, 48.1, 42.8 (q), 36.5, 35.0 (q), 33.5, 31.8, 31.6, 30.4, 25.0, 23.3, 20.7, 19.0, 11.0 ppm. MALDI-TOF: *m*/*z* calcd. for $C_{25}H_{32}N_3O$ [M + H]$^+$ 390.2545; found 390.2454.

3-(2-Oxopyrrolidin-1-yl)androsta-3,5-dien-17β-ol (13o): Eluent: CH_2Cl_2/MeOH (20:1), yield 39.0 mg (73%); white solid; m.p. 214–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (d, *J* = 1.4 Hz, 1 H, 4-CH), 5.35 (m, 1 H, 6-CH), 3.68–3.51 (m, 3 H, 17-C*H*OH, CH_2N), 2.81–2.63 (m, 2 H, 2-CH_2), 2.46 [t, *J* = 8.0 Hz, 2 H, CH_2C(O)], 2.18 (m, 1 H), 2.11–1.97 (m, 3 H), 1.90–1.81 (m, 2 H), 1.74–0.94 (m, 12 H), 0.97 (s, 3 H, 19-CH$_3$), 0.77 (s, 3 H, 18-CH$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.1 (C=O), 140.7 (5-C), 135.2 (3-C), 122.4 (6-CH), 114.5 (4-CH), 81.8 (17-CHOH), 51.5, 48.5 (CH_2N), 48.3, 42.9 (q), 36.5, 34.6 (q), 33.9, 32.9 [*C*H$_2$C(O)], 31.8, 31.5, 30.5, 24.2, 23.3, 20.7, 18.9, 18.0 [4-CH_2(pyrrolidine)], 11.0 ppm. MALDI-TOF: *m*/*z* calcd. for $C_{23}H_{34}NO_2$ [M + H]$^+$ 356.2590; found 356.2490.

3-[Acetyl(phenyl)amino]androsta-3,5-dien-17β-ol (13p): Eluent: CH_2Cl_2/MeOH (50:1), yield 36.6 mg (60%); white solid; m.p. 237–238 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.10 [m, 5 H, CH(Ph)], 6.03 (br. s, 1 H, 4-CH), 5.53 (br. s, 1 H, 6-CH), 3.64 (t, *J* = 8.4 Hz, 1 H, 17-C*H*OH), 2.21 [br. s, 3 H, CH$_3$C(O)], 2.15–0.90 (m, 18 H), 0.95 (s, 3 H, 19-CH$_3$), 0.77 (s, 3 H, 18-CH$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.0 (C=O), 140.4 (5-C), 129.0 (br.), 126.1 (v. br.), 81.8 (17-CHOH), 51.5, 48.1, 42.9 (q), 36.5, 34.7 (q), 33.9, 31.8, 31.5, 30.5, 25.4, 23.3 (2 C), 20.8, 19.0, 11.1 ppm [3-C, 1-C(Ph) and 5-C ^{13}C NMR signals were not observed due to signal broadness]. MALDI-TOF: *m*/*z* calcd. for $C_{27}H_{36}NO_2$ [M + H]$^+$ 406.2746; found 406.2723.

3-(1*H*-Indol-1-yl)cholesta-3,5-diene (14a): Eluent: hexanes, yield 48.5 mg (67%); white solid; m.p. 144–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 [d, *J* = 7.8 Hz, 1 H, 4- or 7-CH(indole)], 7.52 [d, *J* = 8.2 Hz, 1 H, 4- or 7-CH(indole)], 7.22–7.14 [m, 2 H, CH(indole)], 7.09 [t, *J* = 7.5 Hz, 1 H, 5- or 6-CH(indole)], 6.54 [d, *J* = 3.2 Hz, 1 H, 3-CH(indole)], 6.18 (br. s, 1 H, 4-CH), 5.50 (m, 1 H, 6-CH), 2.69–2.48 (m, 2 H), 2.22 (m, 1 H), 2.09–1.93 (m, 2 H), 1.84 (m, 1 H), 1.77–0.96 (m, 20 H), 1.08 (s, 3 H, 19-CH_3), 0.92 (d, *J* = 6.6 Hz, 3 H, 21-CH_3), 0.859 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.856 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.72 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.2 (5-C), 135.6 [7a-C(indole)], 133.1 (3-C), 129.0 [3a-C(indole)], 126.3 (4-CH), 124.7 [2-CH(indole)], 122.1 [6-CH or 5-CH(indole)], 121.8 [6-CH or 5-CH(indole)], 120.9 [4-CH(indole)], 119.9 [6-CH(indole)], 111.4 [7-CH(indole)], 102.6 [3-CH(indole)], 56.9, 56.1, 48.1, 42.5 (q), 39.7, 39.5, 36.2, 35.8, 34.9 (q), 33.9, 32.0, 31.8, 28.2, 28.0, 26.4, 24.2, 23.8, 22.8, 22.6, 21.2, 19.1, 18.7, 12.0 ppm. $C_{35}H_{49}N$ (483.77): calcd. C 86.90, H 10.21, N 2.90; found C 86.69, H 10.09, N 2.77.

3-(3-Acetyl-1*H*-indol-1-yl)cholesta-3,5-diene (14b): Eluent: CH_2Cl_2, yield 44.2 mg (56%); white solid; m.p. 186–187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 [m, 1 H, CH(indole)], 7.79 [s, 1 H, 2-CH(indole)], 7.45 [m, 1 H, CH(indole)], 7.31–7.21 [m, 2 H, CH(indole)], 6.23 (s, 1 H, 4-CH), 5.59 (m, 1 H, 6-CH), 2.74–2.46 (m, 2 H), 2.53 [s, 3 H, CH$_3$C(O)], 2.25 (m, 1 H), 2.09–1.96 (m, 2 H), 1.85 (m, 1 H), 1.79–0.96 (m, 20 H), 1.10 (s, 3 H, 19-CH_3), 0.93 (d, *J* = 6.4 Hz, 3 H, 21-CH_3), 0.862 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.857 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.73 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (APT) (100.6 MHz, $CDCl_3$): δ = 193.1 (C=O), 139.6 (5-C), 136.8 [7a-C(indole)], 133.5 (CH), 132.0 (3-C), 127.0 (CH), 126.4 [3a-C(indole)], 125.3 (CH), 123.5 (CH), 122.8 (CH), 122.6 (CH), 117.8 [3-C(indole)], 111.4 [7-CH(indole)], 56.8 (CH), 56.1 (CH), 48.1 (CH), 42.5 (q), 39.7 (CH_2), 39.5 (CH_2), 36.2 (CH_2), 35.8 (CH), 34.9 (q), 33.8 (CH_2), 32.0 (CH_2), 31.8 (CH), 28.2 (CH_2), 28.0 (CH), 27.7 [*C*H$_3$C(O)], 26.5 (CH_2), 24.2 (CH_2), 23.8 (CH_2), 22.8 [CH(*C*H$_3$)$_2$], 22.6 [CH(*C*H$_3$)$_2$], 21.2 (CH_2), 19.1 (19-CH_3), 18.7 (21-CH_3), 12.0 (18-CH_3) ppm. $C_{37}H_{51}NO$ (525.81): calcd. C 84.52, H 9.78, N 2.66; found C 84.84, H 9.89, N 2.58.

3-(9*H*-Carbazol-9-yl)cholesta-3,5-diene (14c): Eluent: hexanes/EtOAc (50:1), yield 65.4 mg (82%); white solid; m.p. 148–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 [d, *J* = 7.7 Hz, 2 H, 4,5-CH(carbazole)], 7.39 [m, 2 H, 2,7-CH(carbazole)], 7.34 [d, *J* = 7.8 Hz, 2 H, 1,8-CH(carbazole)], 7.20 [m, 2 H, 3,6-CH(carbazole)], 6.26 (m, 1 H, 4-CH), 5.55 (m, 1 H, 6-CH), 2.60–2.42 (m, 2 H), 2.23 (m, 1 H), 2.09–1.94 (m, 2 H), 1.84 (m, 1 H), 1.78–0.97 (m, 20 H), 1.17 (s, 3 H, 19-CH_3), 0.92 (d, *J* = 6.6 Hz, 3 H, 21-CH_3), 0.863 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.859 [d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$], 0.73 (s, 3 H, 18-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.5 [2 C, 8a,9a-C(carbazole)], 140.3 (5-C), 131.7 (3-C), 129.1 (4-CH), 126.2 (6-CH), 125.6 [2 C, 2,7-CH(carbazole)], 123.1 [2 C, 4a,4b-C(carbazole)], 120.2 [2 C, CH(carbazole)], 119.3 [2 C, CH(carbazole)], 109.9 [2 C, 1,8-CH(carbazole)], 56.9, 56.1, 48.2, 42.5 (q), 39.7, 39.5, 36.2, 35.8, 34.9 (q), 34.0, 32.0, 31.8, 28.2, 28.0, 25.0, 24.2, 23.8, 22.8, 22.6, 21.2, 19.2, 18.7, 12.0 ppm. $C_{39}H_{51}N$ (533.83): calcd. C 87.75, H 9.63, N 2.62; found C 87.74, H 9.73, N 2.43.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **7**–**9**, **10a**–**d**, **13a**–**p** and **14a**–**c**.

Acknowledgments

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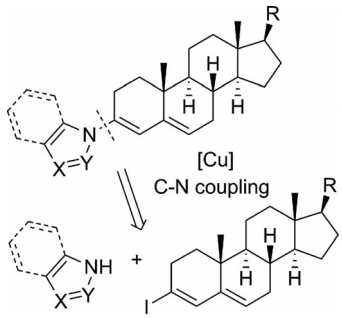
Copper Catalysis

A facile synthetic route to azolyl-substituted steroids has been developed on the basis of Cu-catalyzed cross-coupling of steroidal vinyliodides and aromatic NH-heterocycles. The protocol has been shown to be convenient and highly efficient, affording coupling products in good to excellent yields.



Keywords: Steroids / Nitrogen heterocycles / Cross-coupling / Amination / Copper

