Published in final edited form as:
Chem Commun (Camb). 2012 June 14; 48(47): 5838–5840. doi:10.1039/c2cc31973j.

Convenient method for the functionalization of the 4- and 6-positions of the androgen skeleton

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Abstract

The preparation and reactivity of steroidal vinyldiazo compounds is reported, providing a convenient, substituent tolerant, chemo- and stereoselective entry into 4- and 6-substituted androgen analogues from a common precursor. Under dirhodium catalysis, O—H insertion occurs at the carbenoid site, leading to 4-substituted steroids, but under silver catalysis, O—H insertion occurs at the vinylogous position, leading to 6-substituted steroids.

The steroid skeleton is one of Nature's privileged motifs.[1] The ubiquity of this structure throughout a variety of human biochemical pathways has made it a target of considerable interest to a range of drug discovery programs.[2] These efforts have revolved around either total syntheses of specific analogues[3] or hemisynthesis as a means of accessing the tetracyclic core.[4]

Aromatase cytochrome P450 is the enzyme responsible for the oxidation of androgens to estrogens. It is the only mammalian enzyme capable of converting an aliphatic six-membered ring to an aromatic ring. As such it is essential to the modulation of steroidal biogenesis. However, it has been found to be over-expressed in >75% of postmenopause breast cancer cells.[5] Consequently, it has been a significant clinical target.[6] Until recently, the mechanism of aromatization was not completely understood, and many current medications have been designed without the benefit of access to a detailed structural analysis of the active site of the enzyme.[7]

The first X-ray crystal structure of aromatase P450 was solved by Ghosh *et al.* in 2009.[8] As part of a collaborative program with the Ghosh group we have sought to construct a series of androgen analogues to futher probe the active site and ultimately develop, through informed design, highly selective aromatase P450 inhibitors. In order to achieve this goal, we required ready access to 4- and 6-functionalized alkoxy analogues. This paper describes a carbene approach that allows selective 4- or 6-functionalization by exploiting the complementary dirhodium(II)- or silver(I)-catalyzed donor/acceptor carbene O—H insertion chemistry that has recently been developed.[9]

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†Electronic Supplementary Information (ESI) available: [Experimental details and spectral data]. See DOI: 10.1039/b000000x/

Our investigations began by developing an efficient method for the installation of the diazo functionality at the 4-position (Scheme 1). The synthesis of the diazo compounds **2** and **4** was achieved through a three-step process. The synthesis began from the commercially available 1,4-androstadienedione **1** and 1,4-androstenedione **3**. Radical bromination[10] followed by zinc promoted de-bromination and concommitent de-conjugation[11] afforded the diazo precursors. Use of a water-soluble diazo-transfer reagent[12] was essential in the preparation of the steroidal diazo compounds **2** and **4** as removal of the water-soluble by-products greatly facilitated their isolation.

We then examined the optimization of the O—H insertion of the rhodium carbenes derived from these diazo compounds (Table 1). Formation of the rhodium carbene from **2** and subsequent insertion into the O—H bond of ethanol afforded the 4-ethoxy substituted steroid **5a,** the product of direct OH insertion. The product was found to exist as a mixture of tautomers, predominantly favoring the enol form, likely due to internal H-bonding stabilization. Low yields were obtained when the alcohol was used as the solvent (entry 1). When hexane was used low conversion was observed (entry 2), presumeably due to solubility issues. However, effective OH insertion was observed when the reaction was conducted in trifluorotoluene (TFT) with ten equivalents of alcohol (entry 3 *vs* 4). The reaction was found to be catalyzed by a range of dirhodium(II) catalysts, though Rh_2(*S*-DOSP)$_4$ proved to be the most efficient (entry 4).

With conditions established for the efficient O—H insertion, our focus turned to the scope of this transformation. The reaction with a range of alcohols and acids is described in Table 2. The O—H insertion of the rhodium carbene derived from diazoketone **2** proved to be general, with a range of aliphatic and aromatic 4-substituted ethers and esters **5a-f** afforded in moderate to good yield (41–68%). Sterically and electronically diverse alcohols are suitable for this reaction system. The O—H insertion reaction proceeds with excellent regioselectivity. The 6-substituted androgens, which arise from vinylogous reaction of the rhodium carbene, were generally observed in only trace amounts.

The rhodium carbene arising from the decomposition of **4** was also found to be capable of O—H bond insertion reactions (Table 3). The 4-substituted ethers **6a-c** were prepared in moderate yield (entries 1–3; 44–53%). The regioselectivity of the reaction was high, with only trace amounts of the 6-substituted analogues detected.

The nature of the metal catalyst employed to form the stabilized donor/acceptor carbene has been established to have a profound effect on the reaction outcome.[9] Previous studies on the donor/acceptor vinyldiazoacetate functionality have demonstrated that while rhodium carbenes typically react at the carbene carbon, the silver(I) salts promote reactions predominantly at the vinylogous position *via* a carbene intermediate.[9] We chose to exploit this to provide an expedient entry into 6-substituted androgens from the same vinylcarbenoid precursors **2** and **4**. Indeed, by employing 10 mol% of silver triflate, reaction of the carbene derived from **2** afforded the 6-substituted analogues **7a-g**, arising from vinylogous insertion (Table 4). The scope of the reaction is general, affording both the 6-substituted ethers and esters in moderate to good yield (39–71%). The insertion proceeds with excellent diastereoselectvity, favoring the 6-β-isomer, and regioselectivity, with the 4-substituted analogues generally present in only trace amounts.

The silver triflate promoted vinylogous reaction was also efficient in the saturated system. The O–H insertion of the silver carbene derived from **4** led to essentially exclusive formation of the corresponding 6-substituted ethers **8a-d** with only trace amounts of the 6-substituted analogues detected (Table 5). The ethers were prepared in moderate yield (39–61%), with high levels of both regio- and diastereoselectivity. The 6-β-androgens again

were found to be highly favored. Attempts at preparing the acetate derivative **8e** were unsuccessful as the compound appeared to be unstable and prone to elimination.

The remarkable diastereoselectivity of the O—H insertion reaction of the silver carbenes derived from **2** and **4**, deserves further comment. In all instances the 6-β-androgen product was strongly favored. The stereochemical assignment was initially made on the basis of the distinctive coupling constants for the C-6 proton, which indicated that the alkoxy group was in the 6-β-position. This assignment was then confirmed by the single crystal X-ray analysis of **7d** (Figure 1).[13]

An inspection of the parent diazo structures might suggest that substrate-controlled stereoselection would be dictated by the C-19 β-methyl groups; this would direct the reaction to the α-face. We can account for the observed stereoselectivity if we consider the transition state (**9**) (Figure 2). While pathway **b** reduces the steric clash with the C–19 methyl group, pathway **a** is favored on stereoelectronic grounds, representing axial attack to form the conformationally preferred chair product.

In summary, we have developed a convenient procedure to regioselectively functionalize the steroid skeleton at the 4-and 6-positions, with a broad range of analogues accessible *via* common intermediates. The regioselectivity of the reaction was controlled effectively through choice of metal catalyst employed. Rhodium-catalyzed reactions result in selective reactions at the carbenoid site, whereas silver catalyzed reactions preferentially functionalize the vinylogous position of the carbenoid. Substrate-controlled diastereoselectivity was observed in the vinylogous reaction mediated by silver triflate, allowing the preparation of 6-β-substituted analogues. These compounds are currently being used to probe the active site of the aromatase P450 enzyme, the results of which will be disclosed in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institutes of Health (R01GM086893). We thank Dr. Kenneth I. Hardcastle for the X-ray crystallographic structure determination.

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13. The crystal structure of 8d has been deposited at the Cambridge Crystallographic Data Centre under deposition number CCDC 829542A.

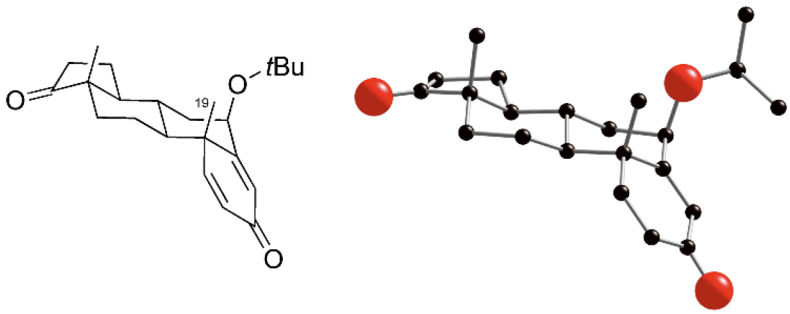


Fig. 1.
Single crystal X-ray analysis of 6-β androgen **7d**

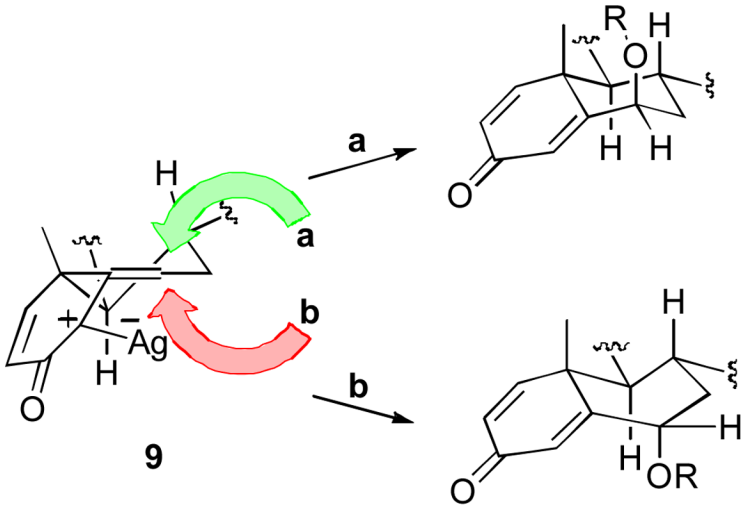
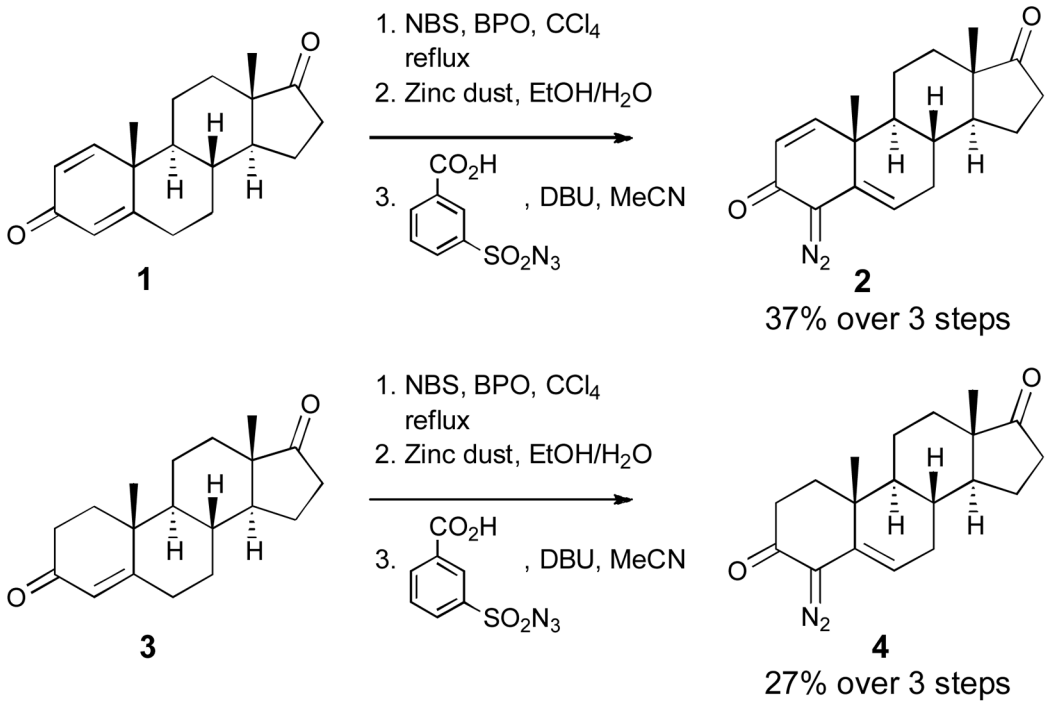


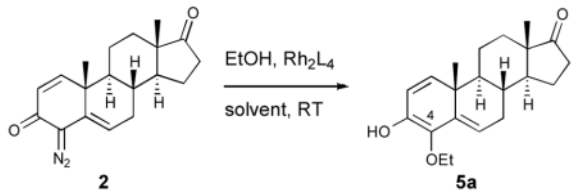
Fig. 2.
Stereoelectronic rationalization of the formation of the 6-β substituted ethers and esters



Scheme 1.
Synthesis of vinyldiazo steroids **2** and **4**

Table 1

Optimization of the catalyst and solvent



2 **5a**

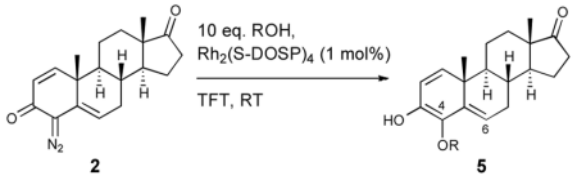
entry	Rh_2L_4[a]	solvent[b]	equiv. EtOH	yield (%)
1	Rh_2(*S*-DOSP)$_4$	neat	10	12
2	Rh_2(*S*-DOSP)$_4$	hexanes	10	8
3	Rh_2(*S*-DOSP)$_4$	TFT	5	51
4	**Rh_2(*S*-DOSP)$_4$**	**TFT**	**10**	**61**
5	Rh_2(Ooct)$_4$	TFT	10	48
6	Rh_2(*S*-PTAD)$_4$	TFT	10	38
7	Rh_2(OAc)$_4$	TFT	10	50

[a] In all reactions 1 mol% of catalyst was employed. The reaction was allowed to react for 4h after addition of the solution of **2**.

[b] All reactions were run at a concentration of 0.15 M with respect to **2**.

Table 2

Rhodium-catalyzed O—H insertion



2 **5**

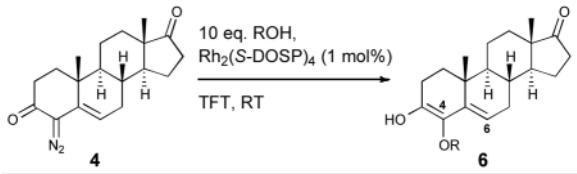
entry	R	product	time (h)	C-4:C-6[a]	yield (%)[b]
1	-CH_2CH_3	**5a**	6	>95:5	61
2	-CH_3	**5b**	6	76:24	49
3	-CH_2Ph	**5c**	12	>95:5	52
4	-$(CO)CH_3$	**5d**	8	92:8	68
5	-$(CO)CH_2CH_3$	**5e**	6	88:12	55
6	-$(CO)CH_2Ph$	**5f**	16	>95:5	41

[a]Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. All reactions were run at a concentration of 0.15 M with respect to **2**.

[b]Isolated yield of the C-4 regioisomer

Table 3

Rhodium-catalyzed O—H insertion of **4**



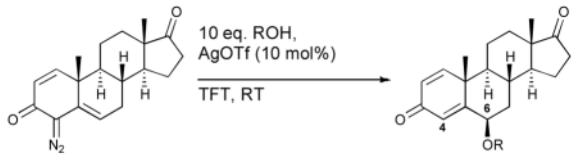
entry	R	product	time (h)	C-4:C-6[a]	yield (%)[b]
1	-CH_2CH_3	**6a**	8	90:10	53
2	-CH_3	**6b**	10	93:7	44
3	-CH_2Ph	**6c**	10	>95:5	45

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. All reactions were run at a concentration of 0.15 M with respect to **2**.

[b] Isolated yield of the C-4 regioisomer

Table 4

Silver-catalyzed O—H insertion of **2**



2 **7-β**

entry	R	product	time (h)	C-4:C-6[a]	α:β[a]	yield (%)[b]
1	-CH_2CH_3	**7a**	4	10:90	15:85	41
2	-CH_3	**7b**	4	8:92	12:88	46
3	-CH_2Ph	**7c**	6	5:>95	22:78	39
4	-C(CH_3)	**7d**	3	5:>95	8:92	70
5	-(CO)CH_3	**7e**	4	5:>95	5:>95	66
6	-(CO)CH_2CH_3	**7f**	10	5:>95	11:89	71
7	-(CO)CH_2Ph	**7g**	6	5:>95	5:>95	38

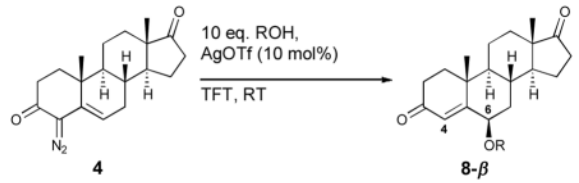
[a]Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. All reactions were run at a concentration of 0.15 M with respect to **2**.

[b]Isolated yield of the **7-β** diastereomer

Chem Commun (Camb). Author manuscript; available in PMC 2013 June 14.

Table 5

Silver-catalyzed O—H insertion of **4**



entry	R	product	time (h)	C-4:C-6[a]	*α*:*β*[a]	yield (%)
1	-CH_2CH_3	**8a**	6	5:>95	12:88	42
2	-CH_3	**8b**	8	8:92	10:90	39
3	-CH_2Ph	**8c**	12	5:>95	5:>95	61
4	-$C(CH_3)$	**8d**	10	5:>95	5:>95	46
5	-$(CO)CH_3$	**8e**	16	-	-	<5

[a]Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. All reactions were run at a concentration of 0.15 M with respect to **2**.

[b]Isolated yield of the **8**-β diastereomer

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