Aromatization of the B-ring of 5,7-dienyl steroids by the electrophilic ruthenium fragment "[Cp*Ru]+"

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Aromatization of the B-Ring of 5,7-Dienyl Steroids by the Electrophilic Ruthenium Fragment "[Cp*Ru]$^+$"

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*Summary: Reaction of ergosterol or 7-dehydrocholesterol with the "Cp*Ru$^+$" fragment generated by the protonation of [Cp*Ru(OMe)]$_2$ by CF_3SO_3H leads to the high-yield selective aromatization of the B-ring of the steroid substrate via a C–C bond-cleavage process, affording near-quantitative yields of the mixed sandwich derivatives [Cp*Ru(η^6-aryl steroid)]$^+$. This reaction has been shown to proceed via an initial C–H bond activation step, yielding a [Cp*Ru(H)(η^5-cyclohexadienyl)]$^+$ intermediate, followed by elimination of CH_4.*

Even after the discovery of several pathways for the activation of C–H bonds in alkanes,[1] the activation of C–C bonds remained a mechanistic and synthetic challenge.[2] We, among others, have shown that the fragment "Cp*Ru$^+$" (1; Cp*$^-$ = $C_5Me_5^-$), prepared inter alia by the protonation of [Cp*Ru(OMe)]$_2$ by CF_3SO_3H in THF or CH_2Cl_2, shows an unusual affinity for aromatic hydrocarbons, forming mixed-sandwich [Cp*Ru(η^6-arene)]$^+$ complexes.[3,4] We have used this property, together with the electrophilicity of the fragment 1, for the aromatization of a variety of C_6 hydrocarbons via C–H, C–O, C–Cl, and even C–C bond activations, again affording η^6-arene derivatives as the final products.[5] As an extension of this work, we demonstrated that reaction of 1 with steroids containing an A-ring enone (testosterone or progesterone) or 3-hydroxyl-5-enyl functionality (cholesterol or dehydroisoandrosterone) results in selective high-yield aromatization of the A-ring of the steroid substrate,[6] yielding [Cp*Ru(η^6-aryl steroid)]$^+$ products analogous to those previously reported by Jaouen[7] and Moriarty.[8] In the case of cholesterol, we observed the initial dehydration of the A-ring of the steroid framework, formation of a triene, and homolytic cleavage of the C10–C19 bond to yield the A-ring aromatized product with total selectivity. Aromatization of the B-ring of a steroid substrate therefore appeared to be a challenging problem. To address this, we have studied the reactions of "Cp*Ru$^+$" with 7-dehydrocholesterol, which contains an additional unsaturation on the B-ring compared to cholesterol, and with ergosterol, which further shows unsaturation on the side chain (Figure 1). The results of these reactions are reported in this note.

The reaction of 1 with ergosterol in THF at 120 °C affords the single product 2 in virtually quantitative spectroscopic yield: recrystallization from THF/Et_2O yields off-white microcrystals of 2 in 47% yield. Gas-phase analysis of the reaction mixture shows the presence of methane as the sole gaseous byproduct. The ^{1}H NMR spectrum of 2 exhibits a singlet at δ 2.00 ppm (15H) due to the Cp* ligand and methyl resonances at δ 1.21, 1.08, 0.98 and 0.96 ppm (each 3H) from the side-chain CH_3 groups and δ 0.77 ppm (3H) for Me-18; no peak attributable to Me-19 was observed. An AB resonance at δ 5.93–5.87 ppm ($^3J_{H-H}$ = 5.9 Hz, 2H) deriving from H6 and H7 is also observed, approximately 0.35 ppm upfield from that shown by the steroid precursor; in contrast, the AB resonance at δ 5.42–5.38 ppm due to H22 and H23 is almost identical with that observed in free ergosterol, implying that no reaction occurs at the side chain of this steroid. The ^{13}C NMR spectrum of 2 shows coordinated aryl resonances at δ 103.27, 99.29, 98.95, and 98.58 ppm (s; C5, C8–C10) and δ 86.98, 86.08 ppm (d, $^1J_{C-H}$ = 174 Hz; C6, C7), in addition

(1) For recent reviews, see: (a) Shilov, A. E. *The Activation of Saturated Hydrocarbons by Transition Metal Complexes*; D. Reidel: Dordrecht, Holland, 1984. (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (c) Rothwell, I. P. *Polyhedron* **1985**, *4*, 177. (d) Ephritikhine, M. *New J. Chem.* **1986**, *10*, 9. (e) Sen, A. *Acc. Chem. Res.* **1988**, *21*, 421. (f) Shilov, A. E.; Shul'pin, G. B. *Russ. Chem. Rev. (Engl. Transl.)* **1990**, *59*, 853. See also: (g) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 2829. (h) Thompson, M. E.; Baxter, S. M.; Bulls, A. R.; Burger, B. J.; Nolan, M. C.; Santarsiero, B. D.; Schaefer, W. P.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 203. (i) Shul'pin, G. B.; Skripnik, S. Y.; Deiko, S. A.; Yatsimirskii, A. K. *Metallorg. Khin.* **1989**, *2*, 1301. (j) Labinger, J. A.; Herring, A. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1990**, *112*, 5628. (k) Kao, L. C.; Hutson, A. C.; Sen, A. *J. Am. Chem. Soc.* **1991**, *113*, 700. (l) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109. (m) Nomura, K.; Saito, Y. *J. Mol. Catal.* **1989**, *54*, 57. (n) Sakakura, T.; Sodeyama, T.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, *112*, 7221. (o) Maguire, J. A.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1989**, *111*, 7088. (p) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778. (q) Jordan, R. F.; Bradley, P. K.; Lapointe, R. E.; Taylor, D. F. *New J. Chem.* **1990**, *14*, 505. (r) Guram, A. S.; Jordan, R. F. *Organometallics* **1991**, *10*, 3470.

(2) See for example: (a) Benfield, F. W. C.; Green, M. L. H. *J. Chem. Soc., Dalton Trans.* **1974**, 1325. (b) Eilbracht, P. *Chem. Ber.* **1976**, *109*, 1429, 3136; **1980**, *113*, 542, 1033, 1420, 2211. (c) Suggs, J. W.; Cox, S. D. *J. Organomet. Chem.* **1981**, *221*, 199. (d) Crabtree, R. H.; Dion, R. B.; Gibboni, D. J.; McGrath, D. V.; Holt, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 7222. (e) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7346. (f) Geiger, W. E.; Salzer, A.; Edwin, J.; Von Philipsborn, W.; Piantini, V.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 7113. (g) Bunuel, E.; Burger, B. J.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 976.

(3) (a) Fagan, P. J.; Ward, M. D.; Caspar, J. V.; Calabrese, J. C.; Krusic, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 2981. (b) Fagan, P. J.; Ward, M. D.; Calabrese, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 1698. (c) Fagan, P. J.; Mahoney, W. S.; Calabrese, J. C.; Williams, I. D. *Organometallics* **1990**, *9*, 1843.

(4) (a) Chaudret, B.; Chung, G.; Huang, Y. S. *J. Chem. Soc., Chem. Commun.* **1990**, 749. (b) Chaudret, B.; Jalon, F.; Perez-Manrique, M.; Lahoz, F. J.; Plou, F. J.; Sanchez-Delgado, R. *New J. Chem.* **1990**, *14*, 331. (c) He, X. D.; Chaudret, B.; Dahan, F.; Huang, Y. S. *Organometallics* **1991**, *10*, 970.

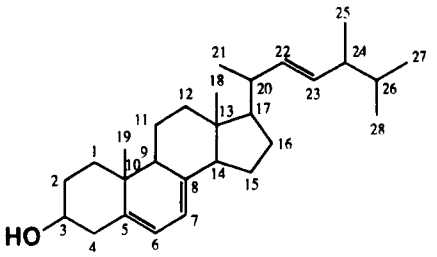
(5) (a) Chaudret, B.; Dahan, F.; He, X. D. *J. Chem. Soc., Chem. Commun.* **1990**, 1111. (b) Rondon, D.; Chaudret, B.; He, X. D.; Labroue, D. *J. Am. Chem. Soc.* **1991**, *113*, 5671. (c) Rondon, D.; He, X.-D.; Chaudret, B. *J. Organomet. Chem.* **1992**, *433*, C18.

(6) (a) Urbanos, F.; Fernandez-Baeza, J.; Chaudret, B. *J. Chem. Soc., Chem. Commun.* **1991**, 1739. (b) Urbanos, F.; Halcrow, M. A.; Fernandez-Baeza, J.; Labroue, D.; Dahan, F.; Chaudret, B. *J. Am. Chem. Soc.*, in press.

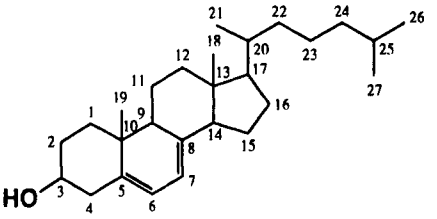
(7) (a) Jaouen, G.; Vessieres, A.; Top, S.; Ismail, A. A.; Butler, I. S. *J. Am. Chem. Soc.* **1985**, *107*, 4478. (b) Top, S.; Jaouen, G.; Vessieres, A.; Abjean, J. P.; Davoust, D.; Rodger, C. A.; Sayer, B. G.; McGlinchey, M. J. *Organometallics* **1985**, *4*, 2143. (c) Jaouen, G.; Vessières, A. *Pure Appl. Chem.* **1989**, *61*, 565. (d) El Amouri, H.; Gruselle, M.; Jackson, P. A.; Jaouen, G.; Vaissermann, J. *Organometallics* **1990**, *9*, 2871. (e) Vichard, D.; Gruselle, M.; El Amouri, H.; Jaouen, G. *J. Chem. Soc., Chem. Commun.* **1991**, 48.

(8) (a) Moriarty, R. M.; Ku, Y. Y.; Gill, U. S.; Gilardi, R.; Perrier, R. E.; McGlinchey, M. J. *Organometallics* **1989**, *8*, 960. (b) Moriarty, R. M.; Guo, L.; Ku, Y. Y.; Gilardi, R. *J. Chem. Soc., Chem. Commun.* **1990**, 1765.

0276-7333/93/2312-0955$04.00/0



Ergosterol



7-Dehydrocholesterol

Figure 1. Steroid substrates examined in this work.

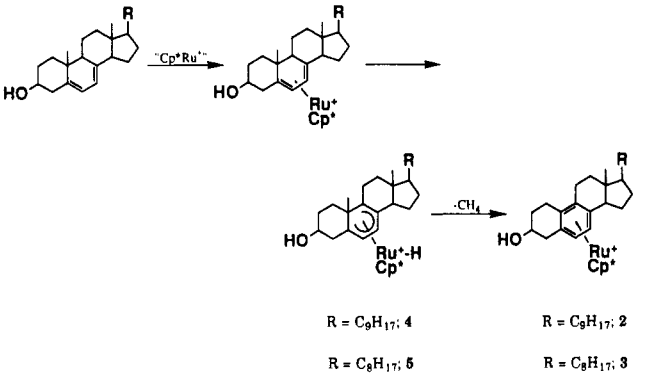
to quartets at δ 20.68, 19.59, 19.31, 17.27, and 10.76 ppm ($^1J_{C-H}$ = 124–126 Hz; C18, C21, C25, C27, C28) and δ 8.91 from the Cp* group. A doublet resonance at δ 63.26 ppm ($^1J_{C-H}$ = 144 Hz) is attributable to C3, showing the retention of the hydroxyl function at this carbon atom. These data are consistent with the aromatization of the B-ring of ergosterol by **1** with concomitant evolution of CH_4, yielding an η^6 complex of the resultant aromatized steroid.

The reaction of **1** with 7-dehydrocholesterol under conditions identical with those described above yielded **3**. The spectroscopic properties of **3** are very similar to those of **2**: ^{1}H NMR δ 5.93–5.87 (AB, $^3J_{H-H}$ = 5.9 Hz, 2H; H6, H7), 1.99 (s, 15H; Cp*), 1.13 (d, $^3J_{H-H}$ = 5.5 Hz, 3H; Me-21), 0.99 (d, $^3J_{H-H}$ = 6.5 Hz, 6H; Me-26, 27), 0.75 ppm (s, 3H; Me-18); ^{13}C NMR δ 103.41, 99.32, 99.07, 98.61 (C5, C8–C10), 87.02, 86.14 (C6, C7), 63.42 (C3), 22.46, 22.18 (C26, C27), 18.43 (C21), 10.58 (C18), 8.96 ppm (Cp*). Hence, product **3** was also formulated as a η^6 complex of $[Cp^*Ru]^+$ with the B-ring aromatized derivative of cholesterol. This reaction is in contrast with the previously reported formation of the A-ring aromatization product on reaction of cholesterol with **1**;[6] thus, we can control the site of attack on this complex organic molecule by **1** simply through the addition of one C=C double bond to the cholesterol substrate.

Interestingly, only one of the two possible isomers of **2** and **3** is observed; this is presumably the α-isomer,[8a] although this remains to be confirmed by X-ray crystallography. We have proposed that α ↔ β isomerization in this system occurs after the aromatization reaction is complete, via decoordination and migration of the Cp^*Ru^+ moiety between the two faces of the aromatic ligand.[6b] This being the case, such isomerization would be expected to be disfavored for **2** and **3**, since the increased steric crowding about the tetrasubstituted aromatized B-ring compared to a disubstituted aromatic A-ring should hinder migration of the Ru center about the steroid framework.

Reaction of **1** with ergosterol in THF at 293 K for 15 h affords a mixture of compounds, containing unreacted steroid and the new complex **4** in addition to other unidentified species. Similarly, reaction of **1** with 7-dehydrocholesterol under identical conditions yields **5**. We have been unable to isolate **4** and **5** as pure compounds; however, recrystallization of the reaction mixtures from THF/Et_2O affords brown solids containing **4** or **5** as the major components (ca. 70%), permitting their characterization by NMR spectroscopy. **4** and **5** give almost identical ^{1}H NMR spectra, each exhibiting an AB multiplet at δ 6.83 and 5.01 ppm ($^3J_{H-H}$ = 5.6 Hz, 2H) arising from H6 and H7, a singlet at δ 2.12 ppm (15H) from the Cp* ligand, singlets at δ 1.06 and 0.82 ppm (3H; Me-19 and Me-18), and a metal hydride at δ −4.66 ppm (br s, 1H). The ^{13}C NMR spectrum of **5** showed resonances at δ 103.83, 99.38, 97.35, 88.92, and 88.37 (C5–C9), 69.35 (C3), 38.76, 36.86 (C10, C19), 10.38 (C18), and 9.52 ppm (Cp*), in addition to other peaks expected from the steroid framework. These spectra are similar to those reported for $[Fe(CO)_3(\eta^5$-ergosteryl acetate$)]^+$ by McGlinchey et al.[9] and are consistent with a $[Cp^*Ru^{IV}(H)(\eta^5$-cyclohexadienyl steroid$)]^+$ formulation for **4** and **5**. When they are heated at 120 °C for 40 h or stand under Ar at 293 K for 2 weeks, **4** and **5** are quantitatively converted to **2** and **3**, respectively, consistent with the intermediacy of **4** and **5** in the aromatization processes.

Scheme I. Proposed Mechanism for the Formation of 2 and 3



The observation of **4** and **5** is consistent with a mechanism for the formation of **2** and **3** analogous to that observed in the aromatization of steroid enones by **1**, for which metal hydride containing intermediates were also detected[6b] (Scheme I). Initial coordination of the $[Cp^*Ru]^+$ fragment to the steroid diene is followed by rapid activation of the α-C–H bond C9–H9 to afford **4** and **5**. Cleavage of the C10–C19 bond and elimination of methane then yields **2** and **3**. Carbon–carbon bond activation reactions involving **1** are thought to follow a radical mechanism; this was proposed on the basis of the observation of trace amounts of C_2H_6 in addition to CH_4 in the gase phase of such reactions.[5b] The same mechanism presumably occurs here, although no trace ethane was detected. It is interesting that no competitive dehydration of the A-ring occurs during production of **2** and **3**, particularly since reaction of **1** with cholesterol leads to dehydration at C3–C4 as the first step of the reaction, resulting in aromatization of the A- rather than the B-ring.[6b] We have previously shown that C–O bond cleavage is preferred over C–H or C–C activation during the aromatization of simple cyclic hydrocarbons by **1**.[5b] Hence, introduction of an additional degree of unsaturation into the B-ring of the steroid framework increases the association constant for $[Cp^*Ru]^+$ with the B-ring to such

(9) Perrier, R. E.; Frampton, C. S.; McGlinchey, M. J. *J. Organomet. Chem.* **1992**, *435*, 357.

an extent that no competitive precoordination of the metal center to the A-ring hydroxyl group occurs.

In conclusion, we have now demonstrated the "Cp*Ru$^+$" can be used to selectively aromatize the A- or the B-ring of steroids, depending on the degree of unsaturation on the B-ring of the substrate. In addition, we have thus obtained stable cationic η^6 complexes of steroids aromatized on the B-ring, which to the best of our knowledge are the first such compounds to be reported: the single-crystal structure of [Fe(CO)$_3$(η^4-7-dehydrocholesteryl acetate)] has recently been reported.[9] 7-Dehydrocholesterol being readily available from cholesterol,[10] for example, our method therefore allows the controlled formation of novel aromatic steroids. Further transformation and functionalization of the coordinated steroids is possible, for example by alkylation at a benzylic position;[11] this is currently under investigation.

Experimental Section

All operations were performed under argon using standard Schlenk tube techniques. Microanalyses were performed by the "Centre de Microanalyse du CNRS" or in our laboratory. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer in acetone-d_6 solution. Activation experiments were carried out in closed Fischer–Porter bottles equipped with Swagelok fittings that can connect directly to the injection valve of an IGC 16 Intersmat GC.

Separation of CH_4, C_2H_6, and Ar was performed on a $^1/_8$-in. column: molecular sieve 5 Å (2 m); temperature 100 °C; carrier gas He, 20 mL/min; detector TCD; sample loop 0.3 mL.

The spectroscopic yields of reactions were determined by integration in both GC and ^{1}H NMR spectroscopy.

Reaction of 1 with Ergosterol. To a mixture of "Cp*Ru$^+$" (prepared from [Cp*Ru(OMe)]$_2$ (175 mg, 0.33 mmol) and CF_3SO_3H (60 μL, 0.66 mmol) in THF (20 cm^3) was added ergosterol (258 mg, 0.66 mmol). The resulting solution was transferred to a Fischer–Porter bottle and heated for 40 h at 120 °C. After the reaction mixture was cooled, the gases were analyzed, the solution was transferred into a Schlenk tube and evaporated to dryness, and the residue was analyzed by NMR spectroscopy. Recrystallization of the crude oily product from THF/Et_2O yielded **2** as an off-white solid: spectroscopic yield 100%; isolated yield 47%. Anal. Calcd for [$C_{37}H_{56}ORu$][CF_3SO_3]·2H_2O: C, 56.9; H, 7.41. Found: C, 57.1; H, 7.46. ^{1}H NMR spectrum: δ 5.93, 5.87 (AB, J = 5.8 Hz, 2H; H6, H7), 5.42, 5.38 (AB, J = 7.0 Hz, 2H; H22, H23), 2.00 (s, 15H; C_5Me_5), 1.21 (d, J = 6.6 Hz, 3H; Me-21), 1.06 (d, J = 6.9 Hz, 3H; Me-25) 0.98 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H; Me-27, 28), 0.77 ppm (s, 3H; Me-18). ^{13}C NMR spectrum: δ 135.36, 132.58 (C22, C23), 103.27, 99.29, 98.95, 98.58 (C5, C8-C10), 93.43 (C_5Me_5) 86.98, 86.08 (C6, C7), 63.26 (C3), 54.43, 49.04, 42.97, 40.38, 33.11 (C14, C17, C20, C24, C26), 42.03 (C13), 35.77, 34.82, 28.98, 26.57, 24.28, 23.10, 21.10 (C1, C2, C4, C11, C12, C15, C16), 20.68, 19.59, 19.31, 17.27 (C21, C25, C27, C28), 10.76 (C18), 8.91 (C_5Me_5).

Reaction of 1 with 7-Dehydrocholesterol. Reaction as above in THF at 120 °C for 40 h afforded **3**: spectroscopic yield 100%; isolated yield 42%. Anal. Calcd for [$C_{36}H_{56}ORu$][CF_3SO_3]·H_2O: C, 57.6; H, 7.44. Found: C, 57.9; H, 7.41. ^{1}H NMR spectrum: δ 5.93, 5.87 (AB, J = 5.9 Hz, 2H; H6, H7), 1.99 (s, 15H; C_5Me_5), 1.13 (d, J = 6.4 Hz, 3H; Me-21), 0.99 (d, J = 6.5 Hz, 6H; Me-26, 27), 0.75 ppm (s, 3H; Me-18). ^{13}C NMR spectrum: δ 103.41, 99.32, 99.07, 98.61 (C5, C8–C10), 93.50 (C_5Me_5), 87.02, 86.14 (C6, C7), 63.42 (C3), 54.80, 49.03, 36.10, 35.96 (C14, C17, C20, C25), 42.26 (C13), 39.53, 34.89, 30.39, 29.46, 28.68, 24.42, 27.98, 23.95, 23.18, 21.17 (C1, C2, C4, C11, C12, C15, C16, C22-C24), 22.46, 22.18 (C26, C27), 18.43 (C21), 10.58 (C18), 8.96 ppm (C_5Me_5).

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(10) Starka, D. L. *Pharmazie* **1962**, *17*, 126.

(11) (a) Top, S.; Vessières, A.; Abjean, J.-P.; Jaouen, G. *J. Chem. Soc., Chem. Commun.* **1984**, 428. (b) Jaouen, G.; Top, S.; Laconi, L.; Couturier, D.; Brocard, J. *J. Am. Chem. Soc.* **1984**, *106*, 2207. (c) Moriarty, R. M.; Ku, Y.-Y.; Gill, U.S. *Organometallics* **1988**, *7*, 660.