Selective Aromatization of the A-Ring of Steroids through C–C, C–H, and C–O Bond Activation by an Electrophilic Ruthenium Complex

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Abstract: The Cp^*Ru^+ fragment (**1**) generated by the protonation of $[Cp^*Ru(OMe)]_2$ by CF_3SO_3H reacts with oestradiol and oestrone in THF or CH_2Cl_2 at 293 K to form mixed sandwich $[Cp^*Ru(\eta^6\text{-aryl steroid})]^+$ products. Reaction of **1** with testosterone, progesterone, cholesterol, dehydroisoandrosterone, or androsterone at 90–120 °C leads to selective and (except for androsterone) near-quantitative aromatization of the A-ring of the steroid substrates via C–O, C–H and C–C bond activation, affording η^6-aryl derivatives as above and CH_4, H_2, and/or H_2O as byproducts. The reactions with testosterone and progesterone proceed through a hydrido cyclohexadienyl intermediate, whereas those with cholesterol and dehydroisoandrosterone occur via a triene intermediate. In the latter case, the triene has been trapped by reaction with NaOMe, which leads to addition of a methoxo group to the carbon C6 of the steroid; the single crystal X-ray structure of the resultant metal complex is presented. Cp^*Ru^+ forms a 1:1 adduct with prednisolone; reaction of 2 equiv of **1** with prednisolone causes fragmentation of the steroid.

Introduction

While the creation of new chemical bonds is obviously more important to the organic synthesist, the discovery of new bond activation reactions has led to several new developments in organic chemistry.[1] For example, activation of C–H bonds[2] has been achieved by oxidative addition to low-valent electron-rich complexes in the presence or absence of an alkene as hydrogen acceptor,[3] using electrophilic early transition-metal complexes via a σ-bond metathesis mechanism,[4] or even in the presence of cationic platinum(IV) or palladium(II) derivatives,[5–8] both of which were able to activate methane.[2a,2e] These elementary processes are now used for productive organic transformations such as dehydrogenation,[9,10] carbonylation,[9–11] or silylation[10] of alkanes using a rhodium complex as photocatalyst, alkylation of pyridine by zirconium derivatives,[12] and chlorination of alkanes by platinum salts.[2f]

At the same time, another important challenge for the organometallic chemist has been the activation of carbon–carbon bonds.[13] While cleavage of strained C–C bonds is common,[13] the reaction is rare for unstrained C–C bonds,[13] whether using electron-rich or electrophilic transition-metal centers. Only highly Lewis acidic species such as scandium(III)[14] or dicationic palladium(II)[2e] derivatives have been shown to initiate reactions such as isomerization of pentadiene or *tert*-butylethene.

We have recently demonstrated that the protonation of $[Cp^*Ru(OMe)]_2$ ($Cp^{*-} = C_5Me_5^-$) by triflic acid affords the electrophilic fragment Cp^*Ru^+ (**1**), in fact a mixture of complexes exhibiting varying degrees of solvation and/or triflate ion coordination which react instantaneously and quantitatively with acetonitrile or benzene to give the expected triacetonitrile or η^6-benzene derivatives.[15] The fragment **1** is able to aromatize C_6 hydrocarbons through activation of C–H, C–O, C–Cl, or even C–C bonds, a driving force for these reactions being the high affinity of **1** for aromatic hydrocarbons.[16,17] In particular, we showed that enones containing two geminal methyl substituents (e.g., isophorone or 4,4′–dimethylcyclohexenone) were selectively demethylated under relatively mild conditions to form the corresponding substituted phenols.[15b]

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Whilst examining possible applications for this novel organometallic process, we considered the reactions of **1** with steroids. Steroids are large multifunctional molecules with a great diversity of structures; however, the A-ring of steroids generally contains alcohol, enone, or similar functionality which can coordinate to a transition-metal center as well as a quaternary carbon atom linked to a methyl group. Aromatization of the A-ring requires rupture of this latter carbon–carbon bond. This is a difficult process, which is achieved in nature by a cytochrome P-450 enzyme (P-450 aromatase) via successive oxidation steps:[18] a model study of this process was recently reported.[19] Reductive aromatization by reaction with lithium has been used to aromatize the A-ring of dienone-containing steroids.[20]

The pioneering work of Birch and colleagues has shown that attachment of $[Fe(CO)_3]$ fragments could favor the cleavage of C–H and C–O bonds of hexadienes using various chemical reagents.[21] η^4-π-Complexes of dienyl steroids with organometallic fragments such as $[Fe(CO)_3]$ have been widely studied for synthetic purposes, the metal fragment acting both as a protecting group for the diene functionality and to control the site of attack at the dienyl moiety by incoming nucleophiles.[21d,22,23] More recently, a number of η^6-complexes of oestrogens with Cr, Ru, or Rh moieties have been prepared by the groups of Jaouen and Moriarty,[24–28] who studied the functionalization of the steroid ligands by nucleophilic attack at the benzylic position of the π-coordinated A-ring[26] as well as the potential utility of these substances in biological systems. For example, the π-arene complex $[Cr(CO)_3(\eta^6$-oestradiol)] has been used as a marker in molecular biology.[24] Other known examples of reactions of organometallics with steroids include dehydrogenation of the alcohol function of the A-ring through hydrogen transfer catalyzed by ruthenium complexes,[29] aromatization by cleavage of a C–O bond,[30] and the formation of clusters containing 17-α-alkynyl steroidal moieties.[31]

We report in this paper new reactions leading to coordination of the $[Cp^*Ru]^+$ fragment to estrone and estradiol, selective aromatization of the A-ring of steroid enones via elimination of CH_4, and selective aromatization of the A-ring of sterols through multistep reactions involving elimination of CH_4, H_2O, and/or H_2. A preliminary report of some of these reactions has been published:[32a] aromatization at the B-ring of 5,7-dienyl steroids by **1** is also described in a companion paper.[32b]

Results and Discussion

(1) Coordination of Cp^*Ru^+ (1) to Estrogens. As discussed above, Jaouen et al. have coordinated Cp^*Ru^+ (**1**) to estradiol and some of its derivatives using either the cationic precursor $[Cp^*Ru(NCMe)_3]^+$ or zinc reduction of $[Cp^*RuCl_2]_n$ followed by anion exchange.[27] Since the activation reactions reported hereafter were expected to lead to π-complexes of estradiol or estrone derivatives, we first investigated the simple coordination of **1** to these steroids using our methodology, i.e., protonation of $[Cp^*Ru(OMe)]_2$ by CF_3SO_3H in THF followed by addition of the aromatic steroid, in order to prepare and study the spectroscopic properties of authentic samples of these products.

The reaction of **1** with estradiol at room temperature for 5 h is quantitative and yields a 60:40 mixture of the previously reported complexes α- and β-$[Cp^*Ru(\eta^6$-estradiol)$]CF_3SO_3$[27] (**2**α and **2**β) by ^1H NMR spectroscopy. Recrystallization from THF/Et_2O affords an analytically pure sample showing some enrichment in the α-isomer (**2**α:**2**β, 2:1). This differs significantly from Jaouen's result (**2**α:**2**β, 85:15)[27] and probably originates from the increased rate of coordination of **1** compared to $[Cp^*Ru(NCMe)_3]CF_3SO_3$. In refluxing THF or acetonitrile, the formation of the thermodynamically more stable α-isomer is probably favored.

We have previously reported the reaction of $[Cp^*Ru(OMe)]_2$ with phenol, which leads to a π-bonded phenoxo derivative.[17c] The same reaction using estradiol leads to an analogous estradionyl derivative $[Cp^*Ru(\eta^6$-estradionyl)] (**3**; **3**α:**3**β, 80:20) which are the deprotonated forms of **2**α and **2**β. As observed for simple phenoxo[33] and alkoxo[34] adducts and in agreement with similar observations by Jaouen,[27,28] compound **3** is hydrogen-bonded to a free estradiol molecule, whose ^1H NMR spectrum differs slightly in the aromatic region from that of free estradiol (δ 7.16, d, J = 8.5 Hz, H1; 6.74, dd, J = 8.5 and 1 Hz, H2; 6.59, d, J = 1 Hz, H4).

The complexation of estrone by Cp^*Ru^+ is similar to that of estradiol. Thus reaction of **1** with estrone in CH_2Cl_2 is quantitative, yielding $[Cp^*Ru(\eta^6$-estrone)$]CF_3SO_3$ (**4**; **4**α:**4**β, 2:1). Recrystallization from THF/Et_2O affords a 60% yield of a 9:1 mixture of **4**α and **4**β, a good separation of the isomers. As for similar π-arene derivatives, the ^1H NMR spectrum of **4**α shows the coordinated aromatic ring protons near δ 6 (δ 6.15, d, J = 6.3 Hz, H1; 5.88, dd, J = 6.3 and 1.8 Hz, H2; 5.84, d, J = 1.8 Hz, H4), the hydrogen atoms bound to C6 near δ 3 (δ 3.1, m, H6α; 2.8, dd, H6β), the 18-methyl group at δ 1.02 (s), and the Cp^* ligand at δ 2.04 (s). ^{13}C NMR data are listed in the Experimental Section, together with assignments where these could be made. As observed in similar systems, there is an upfield shift of ca. 40 ppm for the π-coordinated ring carbons (δ 130.13, C3; 100.57 and 94.33, C5 and C10; 84.34, 76.87, and 76.39, C1, C2, and C4).

As with estradiol, estrone reacts with $[Cp^*Ru(OMe)]_2$ to yield the corresponding π-complexes of the deprotonated form of estrone, namely **5**α and **5**β, which exhibit properties similar to those of **3**α and **3**β. In particular, hydrogen bonding of **5** to a free estrone molecule is also observed. These hydrogen bonds are important not only for the biological properties of these

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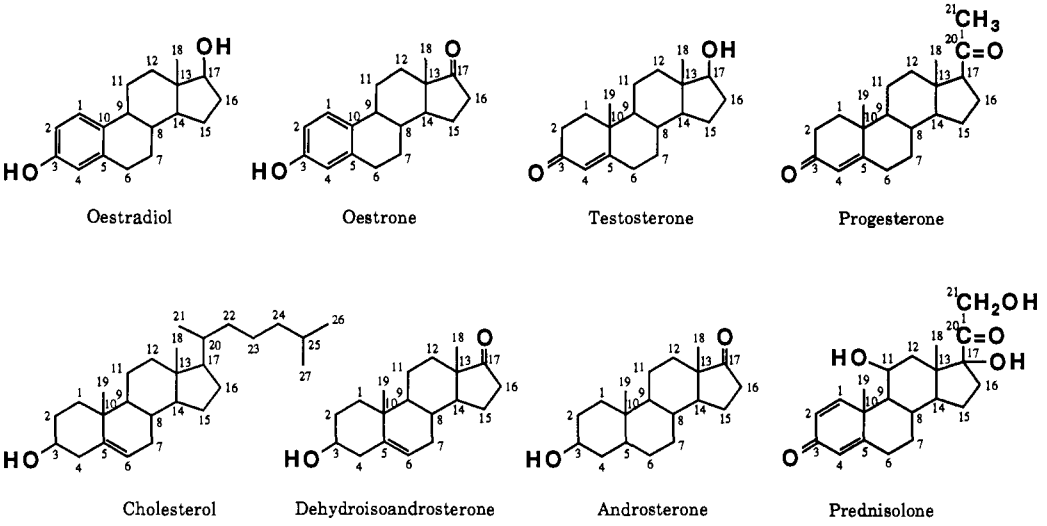


Figure 1. Steroid substrates used in this work with atom numbering scheme employed.

Table I. Conditions Employed and Yields Obtained for Reactions Discussed in This Paper

steroid	solvent	T (K)	reaction time (h)	gases detected	ligand transformation (%)	products	spectroscopic yields (%)	isolated yields (%)
estradiol	THF[a]	293	5		100	**2α**	60	45
						2β	40	22
	THF[b]	293	16		50	**3α**	79[d]	61[d]
						3β	21[d]	12[d]
estrone	CH_2Cl_2[a]	293	5		100	**4α**	67	54
						4β	33	6
	THF[b]	293	16		50	**5α**	75[d]	56[d]
						5β	25[d]	16[d]
testosterone	CH_2Cl_2[a]	393	40	CH_4	30	**2α**	22	
						6α	8	
	THF[a]	413	70	CH_4	100	**2α**	62	42
						2β	8	
						6α	27	18
						6β	3	
progesterone	THF[a]	413	40	CH_4	95	**7α**	66	55
						7β	7	6
						8α	19	16
						8β	3	2
cholesterol	THF[a]	383	24	$H_2 + CH_4$	100	**13α**	68	40
						14α	32	18
	CH_2Cl_2[a]	383	40	CH_4	100	**13α**	100	
	THF[a]	393	40	CH_4	100	**13α**	100	30
	THF[a]	413	40	CH_4	100	**13α**	100	48
dehydroisoandrosterone	THF[a]	393	40	$H_2 + CH_4$	80	**16α**	52	36
						17α	28	4
	THF[a]	413	40	CH_4	80	**16α**	56	46
						16β	24	5
androsterone	THF[a]	433	40	$H_2 + CH_4$	15	**16α**	15	
prednisolone	THF[a]	293	5		100	**18**	100	72
	CH_2Cl_2[a]	393	40	CO	100	*e*		
	THF[a]	413	40	CO	100	*e*		
	THF[c]	413	40		100	**19**	75	35

[a] Reaction with **1**. [b] Reaction with $[Cp^*Ru(OMe)]_2$. [c] Reaction with 2 molar equiv of **1**. [d] Yields with respect to initial weight of steroid. [e] Complex mixture of products.

molecules,[27b] but they also control the self-assembly of organic and organometallic compounds in the solid state. The NMR spectra of **5** resemble those of **3** (**5α**: δ 5.54, d, J = 6.5 Hz, H1; 4.75, dd, J = 1.7 and 6.5 Hz, H2; 4.70, d, J = 1.7 Hz, H4. **5β**: δ 5.40, d, J = 6.6 Hz, H1; 4.60, d, J = 1.8 Hz, H4; 4.50, dd, J = 1.8 and 6.6 Hz, H2).

As with other known π-phenoxo complexes, protonation of **3** and **5** with CF_3SO_3H yields **2** and **4** without changing the α:β isomer ratio.

(2) Reactions of Cp^*Ru^+ (1) with Steroids Containing an Enone Function on the A-Ring. We have previously shown that demethylation of cyclic enones by **1** leads to coordinated phenol derivatives.[15b] It was of interest to test this type of reaction with important biological compounds such as testosterone and progesterone, both of which possess other reactive functionalities (Figure 1). Furthermore, demethylation of testosterone would yield estradiol in one step, a transformation usually achieved using multistep oxidation.

The reaction conditions employed and yields obtained are summarized in Table I. All the reactions examined afforded methane, the presence of which was confirmed and quantified by GC. The highest yields of aromatized products were obtained in THF because of competitive C–Cl activation reactions in CH_2Cl_2 which lead to chloromethylidene clusters.[15b] The highest yield was obtained at a temperature of 120 °C for a reaction time of 70 h, in which case the testosterone was quantitatively converted to estradiol and derivatives.

NMR analysis of the reaction products shows, in addition to

Table II. Bond Lengths (Å) for **15** with Estimated Standard Deviations in Parentheses

Ru–C(1)	2.201(4)	Ru–C(29)	2.196(4)
Ru–C(2)	2.160(4)	Ru–C(3)	2.198(4)
Ru–C(3)	2.159(5)	Ru–C(31)	2.171(7)
Ru–C(4)	2.163(4)	Ru–C(32)	2.161(6)
Ru–C(5)	2.222(4)	Ru–C(33)	2.173(6)
C(1)–C(2)	1.417(7)	C(11)–C(12)	1.536(7)
C(2)–C(3)	1.388(6)	C(12)–C(13)	1.525(7)
C(3)–C(4)	1.397(7)	C(13)–C(14)	1.516(6)
C(4)–C(5)	1.410(7)	C(13)–C(17)	1.552(6)
C(5)–C(10)	1.525(6)	C(13)–C(18)	1.551(6)
C(10)–C(1)	1.513(6)	C(14)–C(15)	1.517(6)
C(5)–C(6)	1.519(6)	C(15)–C(16)	1.535(7)
C(6)–C(7)	1.521(7)	C(16)–C(17)	1.551(6)
C(6)–O	1.426(5)	C(17)–C(20)	1.546(7)
O–C(28)	1.388(6)	C(20)–C(21)	1.501(6)
C(7)–C(8)	1.526(6)	C(20)–C(22)	1.564(6)
C(8)–C(9)	1.531(6)	C(22)–C(23)	1.479(8)
C(9)–C(10)	1.539(7)	C(23)–C(24)	1.524(7)
C(10)–C(19)	1.546(7)	C(24)–C(25)	1.520(7)
C(8)–C(14)	1.533(6)	C(25)–C(26)	1.474(7)
C(9)–C(11)	1.527(6)	C(25)–C(27)	1.516(8)
C(29)–C(30)	1.400(8)	C(29)–C(34)	1.489(7)
C(30)–C(31)	1.398(9)	C(30)–C(35)	1.495(7)
C(31)–C(32)	1.409(11)	C(31)–C(36)	1.514(9)
C(32)–C(33)	1.388(10)	C(32)–C(37)	1.463(7)
C(33)–C(29)	1.410(8)	C(33)–C(38)	1.499(8)

the byproduct **6** (vide infra), the presence of **2**α and **2**β in a ratio of 6:1 for reaction at 100 °C and 8:1 at 120 °C. These product ratios are different from that observed in the simple room-temperature complexation of estradiol discussed earlier and are now similar to that obtained by Jaouen in refluxing MeCN of 85:15. This may imply that equilibration between the isomers occurs at high temperatures (vide infra) or alternatively that attack on the α-face of testosterone is preferred because of the steric hindrance created by the 19-methyl group on the β-face of the molecule. In the latter case the carbon–carbon bond activation step would occur when the ruthenium center is bound to the α-face of the steroid, opposite the 19-methyl group, consistent with homolytic rupture of the carbon–carbon bond. The observed presence of 10–15% ethane in addition to methane in the gas phase is in agreement with this proposal, which was previously formulated for the aromatization of cyclic enones purely on the basis of gas-phase analysis.

Together with compound **2**, another very similar complex (**6**) is formed during these reactions in ca. 30% yield with respect to **2**. **6** is present as a mixture of isomers in a ratio similar to that of **2** (**6**α:**6**β, ca. 8:1). The ^{1}H NMR spectrum of **6**α resembles that of **2**α (δ 2.07, C_5Me_5; 0.91, Me-18) except in the phenyl region, which consists of a complex multiplet at δ 6.0–6.3 and a singlet at δ 3.97 attributed to a methoxy group. **6**β is a very minor component of the reaction mixture but is still identifiable by ^{1}H NMR (δ 4.00, OMe; 2.09, C_5Me_5; 1.05, Me-18). Recrystallization from THF/Et_2O produces a microcrystalline solid in ca. 60% yield. While the α:β ratio is enhanced by recrystallization, the **2**:**6** ratio is unaffected; we have been unable to separate **2** and **6**. **6** was thus identified as a π-complex of the methyl ether derivative of estrone; such methyl ether derivative byproducts were also observed in the aromatization of simple cyclic enones by **1**.[15b] For that reaction, it was shown that formation of the ether functionality occurred at an early stage of the aromatization process, before the C–C activation step.

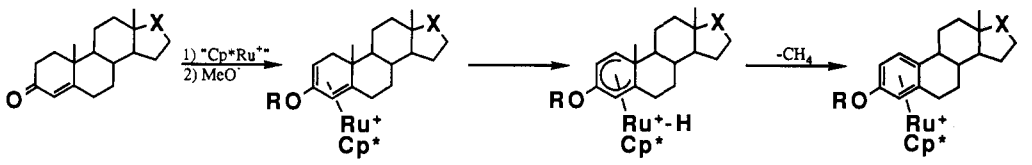
Analogous reactions were carried out using progesterone, which differs from testosterone by the presence of an acyl functionality at the 17-carbon atom compared to an hydroxyl group (Figure 1). This reaction is smoother than that observed for testosterone, and complete transformation of progesterone occurs after 40 h at 120 °C. As for the preceding reaction, four products are observed, viz. the products of aromatization at the A-ring (**7**; **7**α:**7**β, 8:1) and their methyl ether derivatives (**8**; **8**α:**8**β, 8–10:1; **7**α:**8**α, 10:3). The ^{1}H and ^{13}C NMR data for **7** and **8** are very similar to those of **2** and **4** and are given in the Experimental Section. No side reactions such as decarbonylation of the acyl group are observed: GC analysis of the reaction mixture shows the presence of methane and ethane as before but no carbon monoxide.

Reaction of **1** with testosterone in THF at 293 K for 15 h clearly shows by ^{1}H NMR spectroscopy, in addition to unreacted steroid, the presence of two metal hydride species (**9** and **10**) at δ 5.21 (d, J = 6.7 Hz, H2), 5.17 (s, H4), and –5.70 (br s), and at δ 4.96 (d, J = 7.1 Hz, H2), 4.91 (s, H4), and –6.96 (d, J = 6.6 Hz), respectively. A similar reaction of **1** with progesterone allowed the observation of **11** and **12** at δ 5.22 (d, J = 6.7 Hz, H2), 5.19 (s, H4), 3.47 (d, J = 6.7 Hz, H1), and –5.68 (br s) and at δ 4.98 (d, J = 6.9 Hz, H2), 4.93 (s, H4), 3.29 (dd, 6.9, J = 6.1 Hz, H1), and –6.96 (d, J = 6.1 Hz). These hydride resonances are very similar to those observed for the intermediates $[Cp^*Ru^{IV}(H)(\eta^5\text{-}4,4\text{-}Me_2C_6H_4OR)]^+$ (R = H, Me) in the aromatization of 4,4′-dimethylcyclohexenone by **1**[15b] and are in agreement with the formation of a hydrido η^5-complex on which the C10–C19 bond cleavage has not yet occurred. Given this evidence, together with the similarity of the products observed in the two cases (CH_4 and C_2H_6 in the gas phase, methyl ether derivatized byproducts), we propose that an analogous mechanism operates for these steroid transformations, i.e., coordination of Cp^*Ru^+ to the dienol form of the steroid enone, partial attack of methanol at the hydroxyl functionality of the coordinated dienol to form the methoxy derivative, activation of a C–H bond to give the observed cyclohexadienyl hydride species, and finally rupture of the C10–C19 bond to yield methane and a π-arene complex (Figure 2).

(3) Reactions of Cp^*Ru^+ (1) with Cholesterol and Dehydroisoandrosterone. The reactions described in the preceding section were an extension of previous work on cyclic enones and involved only a short sequence of mechanistic steps. In order to extend the scope of the aromatization reactions, we considered the case of sterols bearing unsaturation on the B-ring, such as cholesterol and dehydroisoandrosterone (Figure 1). In this case, aromatization of the A-ring could involve migration of the C5=C6 double bond, dehydrogenation, or dehydration as well as demethylation.

The reaction of **1** with cholesterol under various conditions (CH_2Cl_2 at 90 °C, THF at 100 or 120 °C) invariably yields one product (**13**) in quantitative spectroscopic yield. Recrystallization from THF/Et_2O affords microcrystals of **13** in 48% yield. Gas-phase analysis indicates the presence of methane and ethane as before but not of hydrogen. The ^{1}H NMR spectrum of **13** is clean, specifically showing the Cp* group at δ 2.08, the 18-methyl group at δ 0.85, two doublets for the isopropyl and methyl groups of the steroid side chain at δ 0.99 and 1.08, respectively, and a complex aromatic signal between δ 6.0 and 6.3. The ^{13}C NMR spectrum is also clean (see Experimental Section) and exhibits aromatic resonances at δ 104.46 and 101.34 (C5, C10) and δ 87.28, 87.01, 86.80, and 85.38 (C1, C2, C3, and C4).

The absence of hydrogen in the gas phase and the presence of four aryl C–H groups in the ^{13}C NMR spectrum are strong indications for the involvement of a dehydration rather than a dehydrogenation step in the aromatization process. In order to confirm this and to assign more thoroughly the ^{1}H NMR spectrum of **13** we undertook two-dimensional proton–proton and carbon–proton NMR experiments (Figure 3). The most important result from this is the demonstration that four protons contribute to the complex ^{1}H NMR signal near 6 ppm. One of these resonances is a doublet at δ 6.27 ($^3J_{H-H}$ 5.9 Hz) which corresponds to the carbon peak at δ 85.38. This carbon is distinct from the others and could be assigned to C1 or C4: we propose that it corresponds to C1, since this aromatic carbon should be the most perturbed by the rest of the molecule. The other aromatic carbons and protons (C2, C3, C4 and H2, H3, and H4) were not assigned.



R = H, Me

X = CH-OH, R = H; **9**
R = Me; **10**
X = C(O)Me, R = H; **11**
R = Me; **12**

X = CH-OH, R = H; **2**
R = Me; **6**
X = C(O)Me, R = H; **7**
R = Me; **8**

Figure 2. Proposed mechanism for the aromatization of steroid enones by **1**.

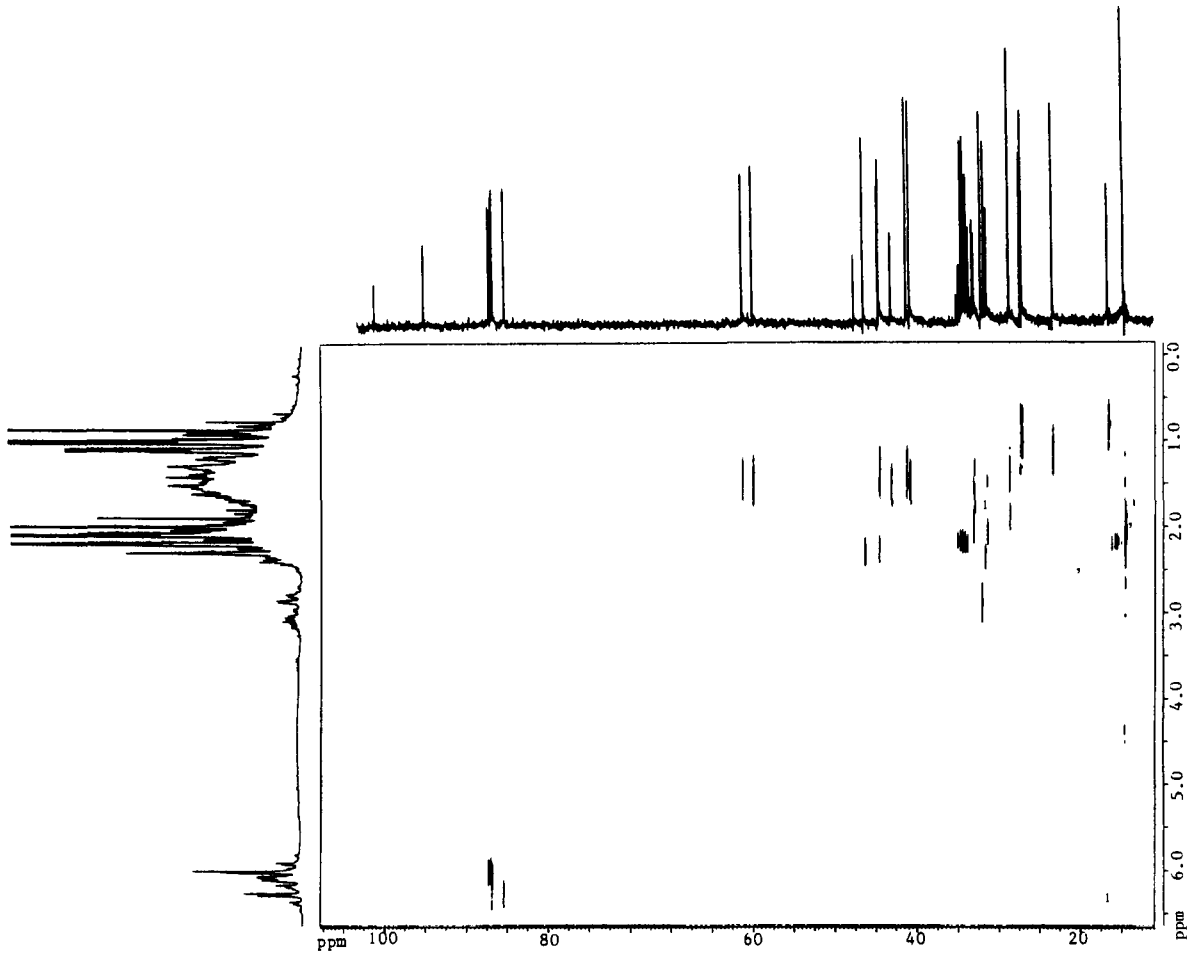


Figure 3. $^1H/^{13}C$ δ–δ heteronuclear correlation NMR spectrum of **13** (acetone-d_6; ^1H, 250.13 MHz; ^{13}C, 61.89 MHz).

Additional information from these experiments includes the observation of C6 at δ 27.13, H6α and H6β resonating at δ 2.8 and 3.1, respectively, and confirmation of the methyl group assignments. The chemical shifts of C1 and H1 in **13** are close to those of the analogous atoms in **2**α; this, together with the observation of two well-separated multiplets for H6α and H6β also suggests an α-conformation for compound **13**.[25a]

To gain insight into the mechanism of this transformation, we analyzed by ^1H NMR the crude products of the reaction of **1** with cholesterol under varying conditions. After reaction in THF at 90 °C for 24 h we observed, together with **13**, the presence of another compound (**14**) characterized by peaks at δ 2.07 from the Cp* moiety, δ 0.80 and 0.82 for the 18- and 19-methyl groups, and olefinic protons at δ 6.45 (dd, J = 5.2 and 5.5 Hz; H3), 5.34 (d, J = 6.6 Hz; H6), 5.29 (t, J = 5.6 Hz; H2), 5.02 (d, J = 5.2 Hz; H4), and 3.65 (d, J = 5.6 Hz; H1); both H_2 and CH_4 were observed in the gas phase of this reaction. It proved impossible to isolate **14**, but upon reaction of a mixture of **13** and **14** with sodium methoxide we were able to extract and crystallize a new compound (**15**) resulting from the addition of a methoxo group to the carbon C6 of **14**. Complex **15** was extracted with pentane and recrystallized from diethyl ether, affording off-white crystals. The single crystal X-ray structure of **15** (Figure 4 and Tables II, III) shows the ruthenium center to be bound to an η^5-Cp* ligand and the α-face of an η^5-cholestadienyl group. The cholestadienyl group is bonded to the Ru atom by carbons C1–C5, C10 bearing the 19-methyl group. The methoxy substituent is linked to C6 and appears on the β-face of the steroid. All bond distances and angles are in the usual ranges for such compounds. The NMR spectra of **15** clearly show the absence of carbon–carbon bond activation in this compound. The 19-methyl group resonates at δ 0.31, the methoxo group at δ 3.28, signals corresponding to H1–H4 respectively at δ 2.23 (d, J = 6.2 Hz), 3.96 (dd, J = 4.8 and 6.2 Hz), 5.28 (t, J = 4.8 Hz), and 4.22 (d, J = 4.8 Hz), and H6 at δ 3.05. The ^{13}C NMR spectrum of **15** is given in the Experimental Section; the five cholestadienyl Ru-bound carbons are observed at δ 97.27 (C5), 82.25, 81.97, 80.16, and 79.81 (C1–C4), C6 at δ 51.27, and the methoxy group at δ 55.33.

The formation of **15** clearly results from the addition of MeO^- to **14** and provides strong additional evidence for the triene

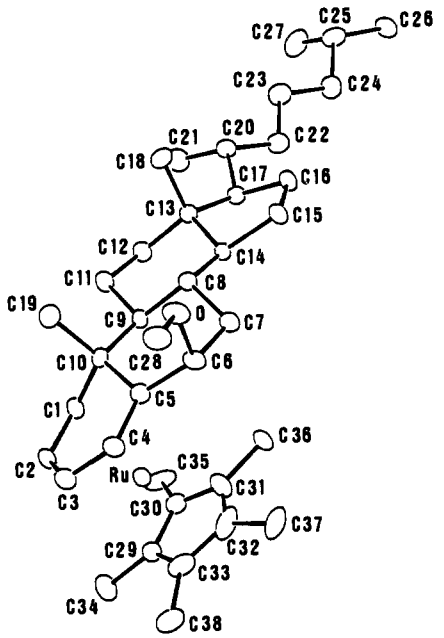


Figure 4. ORTEP view of **15** with ellipsoids drawn at 20% probability. All hydrogen atoms are omitted.

structure of **14** itself. This triene is never observed in high quantity during the reaction of **1** with cholesterol, and reaction under more forcing conditions produces **13** only. In addition, heating a mixture of **13** and **14** in THF under H_2 at 120 °C for 24 h results in the quantitative formation of **13**, showing that **14** is a genuine intermediate in the aromatization process; interestingly, an analogous reaction under Ar resulted in only ca. 50% transformation of **14** and the observation of additional aromatic resonances from an unknown byproduct at δ 6.61 (t), 6.55 (d), 6.43 (d), and 6.22 (m). Figure 5 summarizes our proposed mechanism for the aromatization of the A-ring of cholesterol. An initial dehydration step transforms cholesterol into conjugated cholesta-3,5-diene, which then coordinates in η^4-fashion to the ruthenium center. Dehydrogenation of this diene leads to the η^4- or η^6-cholesta-1,3,5-triene complex **14**; the formation of an analogous η^4-cholesta-1,3,5-triene complex has been reported from the reaction of $[Fe(CO)_3(\eta^4\text{-cholesta-1,3-diene})]$ with Ph_3C^+ followed by base-catalyzed hydrolysis.[23a] Further heating leads to homolytic cleavage of the C10–C19 bond and rearrangement of the molecule to an aromatic A-ring. This final aromatization step consumes H_2 and can be written as:

$$\mathbf{14} + H_2 \rightarrow \mathbf{13} + CH_4$$

This consumption of H_2 could occur in two ways. Elimination of $CH_3^\bullet$ from **14** would afford an A-ring-aromatized radical centered on C6, which could then be quenched by H_2, H_2O, or MeOH present in the medium (Scheme I). It is possible that a significant proportion of the methyl radicals thus produced would further attack **14**, affording ethane and establishing the propagation step of a radical chain reaction. This would explain the relatively large amount of ethane observed in this reaction. Alternatively, **14** may be in equilibrium at higher temperatures with $[Cp^*Ru(\eta^5\text{-cyclohexadienyl})(H)]^+$ intermediates of the type described in Section 2 (Scheme I):

$$[Cp^*Ru(1,3,5\text{-triene})]^+ + H_2 \rightleftharpoons [Cp^*Ru(\eta^5\text{-cyclohexadienyl})(H)]^+$$

This type of equilibrium has been observed previously by Shvo et al. in the catalytic hydrogenation of ketones by ruthenium tetraphenylcyclopentadienone complexes.[35] While we did not detect any cyclohexadienyl hydride species in the reactions of **1** with cholesterol, the relatively high temperatures required to generate **14** and **17** may preclude their observation; it is noteworthy that every other C–C bond cleavage reaction by **1** which has been successfully characterized mechanistically has involved this type of intermediate (vide supra).[15b,32b] Attempts to trap radical intermediates in this reaction using ^{t}BuNO$^\bullet$ were unsuccessful, possibly due to the high temperatures involved.

Analogous reactions were performed using dehydroisoandrosterone as substrate, a steroid showing the same A- and B-ring functionality as cholesterol but possessing an oxo group on C17 of the D-ring instead of an alkyl chain (Figure 1). The reaction of **1** with dehydroisoandrosterone in THF at 100 °C for 72 h results in the detection of hydrogen as the major product in the gas phase, whereas reaction at 120 °C for 40 h produces methane as the main gaseous product.

The difference in the reactions carried out at these two temperatures can be observed by ^{1}H NMR. After reaction at 120 °C, a new complex (**16**) similar to **13** could be isolated, while reaction at 100 °C produced a mixture of **16** and a triene complex (**17**) similar to **14**. Furthermore, in contrast to the formation of **13**, compound **16** is present as a mixture of two isomers after the

Table III. Selected Bond Angles (deg) for **15** with Estimated Standard Deviations in Parentheses

C(1)–Ru–C(2)	37.9(2)	C(1)–Ru–C(3)	67.0(2)
C(1)–Ru–C(4)	77.1(2)	C(1)–Ru–C(5)	62.9(1)
C(1)–Ru–C(29)	120.3(2)	C(1)–Ru–C(30)	106.6(2)
C(1)–Ru–C(31)	123.5(2)	C(1)–Ru–C(32)	160.0(3)
C(1)–Ru–C(33)	155.6(2)	C(2)–Ru–C(3)	37.5(2)
C(2)–Ru–C(4)	67.1(2)	C(2)–Ru–C(5)	78.1(1)
C(2)–Ru–C(29)	106.4(2)	C(2)–Ru–C(30)	118.5(2)
C(2)–Ru–C(31)	152.8(2)	C(2)–Ru–C(32)	161.6(3)
C(2)–Ru–C(33)	125.1(2)	C(3)–Ru–C(4)	37.7(2)
C(3)–Ru–C(5)	67.4(2)	C(3)–Ru–C(29)	116.6(2)
C(3)–Ru–C(30)	147.7(2)	C(3)–Ru–C(31)	169.1(2)
C(3)–Ru–C(32)	131.2(3)	C(3)–Ru–C(33)	109.5(2)
C(4)–Ru–C(5)	37.5(2)	C(4)–Ru–C(29)	144.6(2)
C(4)–Ru–C(30)	174.2(2)	C(4)–Ru–C(31)	136.9(2)
C(4)–Ru–C(32)	112.0(2)	C(4)–Ru–C(33)	115.8(2)
C(5)–Ru–C(29)	175.4(2)	C(5)–Ru–C(30)	140.1(2)
C(5)–Ru–C(31)	113.3(2)	C(5)–Ru–C(32)	112.9(2)
C(5)–Ru–C(33)	140.0(2)	Ru–C(1)–C(2)	69.5(2)
Ru–C(1)–C(10)	97.3(3)	Ru–C(2)–C(1)	72.6(2)
Ru–C(2)–C(3)	71.2(3)	Ru–C(3)–C(2)	71.3(3)
Ru–C(3)–C(4)	71.3(3)	Ru–C(4)–C(3)	71.0(2)
Ru–C(4)–C(5)	73.5(2)	Ru–C(5)–C(4)	69.0(2)
Ru–C(5)–C(6)	128.0(3)	Ru–C(5)–C(10)	96.1(2)
C(10)–C(1)–C(2)	121.7(4)	C(1)–C(2)–C(3)	118.2(4)
C(2)–C(3)–C(4)	118.3(5)	C(3)–C(4)–C(5)	120.1(4)
C(4)–C(5)–C(10)	119.6(4)	C(4)–C(5)–C(6)	117.0(4)
C(10)–C(5)–C(6)	117.4(4)	C(5)–C(6)–C(7)	112.8(4)
C(5)–C(6)–O	112.5(4)	C(7)–C(6)–O	104.3(4)
C(6)–O–C(28)	117.0(4)	C(6)–C(7)–C(8)	112.1(4)
C(7)–C(8)–C(9)	110.8(4)	C(7)–C(8)–C(14)	110.1(3)
C(9)–C(8)–C(14)	108.1(3)	C(8)–C(9)–C(11)	111.1(4)
C(10)–C(9)–C(11)	113.8(4)	C(8)–C(9)–C(10)	114.1(3)
C(1)–C(10)–C(5)	98.8(4)	C(1)–C(10)–C(9)	109.1(3)
C(1)–C(10)–C(19)	113.2(4)	C(5)–C(10)–C(9)	110.6(4)
C(5)–C(10)–C(19)	112.2(4)	C(9)–C(10)–C(19)	112.1(4)
C(9)–C(11)–C(12)	113.1(4)	C(11)–C(12)–C(13)	111.7(4)
C(12)–C(13)–C(14)	107.3(4)	C(12)–C(13)–C(17)	116.5(3)
C(12)–C(13)–C(18)	111.0(4)	C(14)–C(13)–C(17)	99.0(3)
C(14)–C(13)–C(18)	113.2(3)	C(17)–C(13)–C(18)	109.5(4)
C(8)–C(14)–C(13)	115.0(3)	C(8)–C(14)–C(15)	118.3(3)
C(13)–C(14)–C(15)	104.4(4)	C(14)–C(15)–C(16)	104.2(4)
C(15)–C(16)–C(17)	105.7(4)	C(13)–C(17)–C(16)	103.5(3)
C(13)–C(17)–C(20)	120.6(3)	C(16)–C(17)–C(20)	111.6(4)
C(17)–C(20)–C(21)	113.5(4)	C(17)–C(20)–C(22)	108.1(3)
C(21)–C(20)–C(21)	110.9(4)	C(20)–C(22)–C(23)	115.2(4)
C(22)–C(23)–C(24)	113.7(5)	C(23)–C(24)–C(25)	114.3(4)
C(24)–C(25)–C(26)	111.0(4)	C(24)–C(25)–C(27)	109.7(5)
		C(26)–C(25)–C(27)	111.7(4)

(35) (a) Shvo, Y.; Czarkie, D.; Rahamin, Y.; Chodosh, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400. (b) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885.

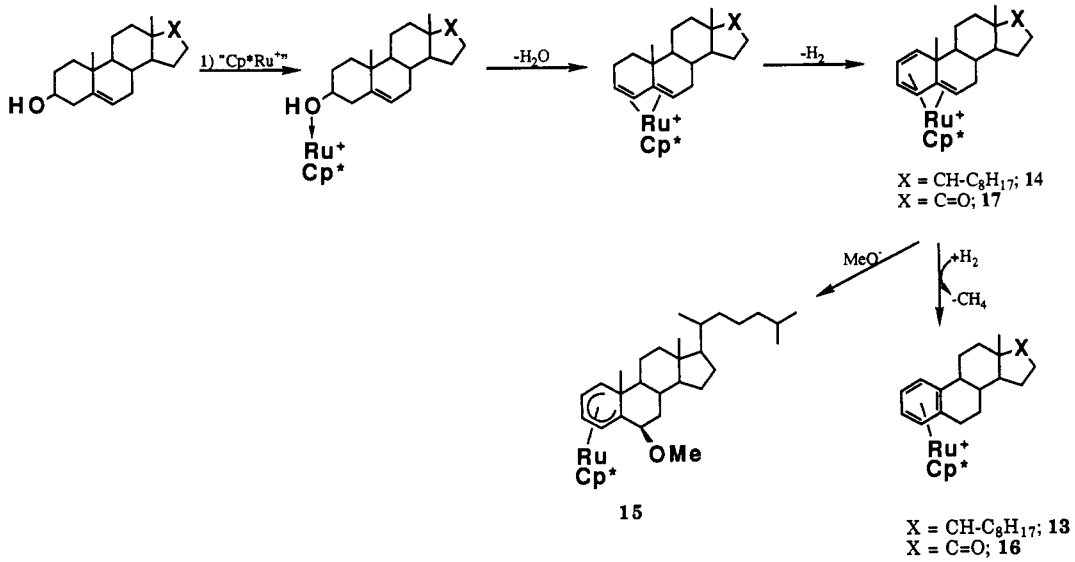
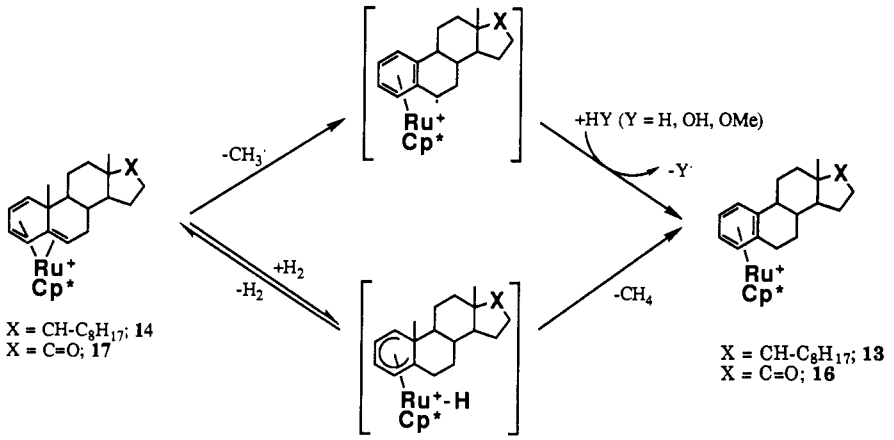


Figure 5. Proposed mechanism for the aromatization of cholesterol and dehydroisoandrosterone by **1**.

Scheme I. Possible Pathways for Conversion of Trienes **14** and **17** into **13** and **16**



120 °C reaction, which we propose to be **16**α and **16**β. The ^{1}H NMR spectrum of **16**α shows the aromatic protons at δ 6.30 (d, J = 5.7 Hz, 1 H) and 6.02–6.07 (complex multiplet, 3 H), **16**β being observed at slightly higher field (δ 6.25, d, 5.95–6.00). Compound **17** possesses a ^{1}H NMR spectrum almost identical to that of **14** in the olefinic region, i.e., δ 6.48 (td, H3), 5.40 (d, H6), 5.32 (t, H2), 5.06 (d, H4), and 3.70 (d, H1). Significantly, we did not observe **16**β after reaction at 100 °C, nor did we detect a β-isomer of **17**, implying that isomerization may occur after the final aromatization step via decoordination of ruthenium.

It is noteworthy that a dehydrogenation + demethylation aromatization process for dehydroisoandrosterone would lead to the estrone complex **5**. We did not detect **5** at any stage of the reaction, giving further evidence for an initial C–O bond cleavage step.

In summary, we have demonstrated here that it is possible to aromatize the A-ring of a steroid containing unsaturation on the B-ring. In contrast to the expected mechanism implying initial migration of the C=C double bond, the aromatization step occurs on a triene complex still bearing unsaturation at the B-ring. Unexpectedly, these reactions involving complex organic molecules have allowed us to gain further insight into the carbon–carbon bond cleavage step in our system. Furthermore, to the best of our knowledge, the aromatization of this type of molecule has no precedent.

(4) Reaction of Cp*Ru$^+$ (1) with Androsterone. While looking for more challenging reactions, we considered the case of androsterone, which contains a hydroxyl group on the A-ring but no unsaturation (Figure 1). Reaction of **1** with androsterone is difficult, since little or no activation occurs at 100 or 120 °C in THF. However, at 140 °C a transformation is observed, affording **16**. The gas phase of the reaction mixture consists mainly of hydrogen after reaction at 120 °C and of both hydrogen and methane for the reaction at 140 °C. The high quantity of H_2 observed could also originate from a side dehydrogenation of methanol. Unfortunately, we could not identify the intermediates from this reaction: a broad peak near δ 5.7 in the ^{1}H NMR spectrum of the crude reaction mixture may belong to a polyene intermediate but could not be definitively assigned.

After 40 h at 140 °C, the spectroscopic yield of **16** from androsterone is modest (15%). Nonetheless, this reaction demonstrates that the aromatization of fully saturated steroids by **1** is possible.

(5) Reaction of Cp*Ru$^+$ (1) with Prednisolone. Considering the remarkable activity and selectivity of **1** toward aromatization of the A-ring of various steroids, it was of interest to examine more and more unfavorable compounds in order to reach the limits of the method. Prednisolone looked attractive in this regard, since it contains both a quinoid structure on the A-ring and three oxygenated functions on the D-ring side chain, to which Cp*Ru$^+$ would likely coordinate (Figure 1).

1 was reacted with prednisolone at 100 and 120 °C in THF or CH_2Cl_2. The gas phase of these reaction mixtures contained purely carbon monoxide (ca. 60% of the theoretical amount required from complete decarbonylation of the $C(O)CH_2OH$ group on the D-ring of the steroid). This implies that **1** reacts

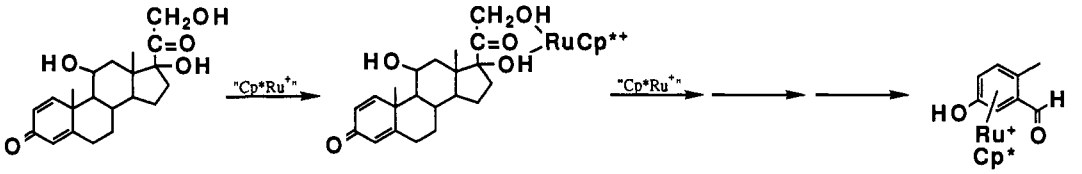


Figure 6. Observed reactions of **1** with prednisolone.

with the D-ring of prednisolone, rather than the A-ring. To test this conclusion, the reaction was carried out at room temperature, affording the 1:1 adduct $[Cp^*Ru(prednisolone)]CF_3SO_3$ (**18**) in 72% yield. It is clear from the ^1H and ^{13}C NMR spectra of this product that the A-ring of prednisolone is little perturbed by adduct formation and hence that **1** does not coordinate to it. Thus, H1, H2, and H4 resonate at δ 6.05, 6.30, and 7.65, respectively, while C1, C2, and C4 are observed at δ 121.9, 127.3, and 157.3 by ^{13}C NMR. In contrast, the resonances assigned to the CH_2OH group of free prednisolone are shifted from δ 4–5 in the free ligand to between δ 2.5 and 3.5 on coordination. The IR carbonyl absorptions of **18** ($\nu_{C=O}$ = 1715, 1655) are very similar to those of free prednisolone. In conclusion, while we cannot precisely assign the mode of coordination of **1** to prednisolone, it is clear that it involves the hydroxyl O-donor functions attached to C17 of the D-ring of the steroid. The coordination of ruthenium to the D-ring could explain the above-described carbon monoxide evolution although the exact reaction is not known.

These results led us to attempt to aromatize the A-ring of prednisolone using 2 equiv of **1**, 1 equiv to act as a protecting group for the D-ring functionality and 1 equiv to react with the A-ring. This reaction proceeds smoothly in THF at 100 °C, affording a compound (**19**) exhibiting a single Cp^* ^1H resonance, an aromatic multiplet near 5.9 ppm (3 H) and singlet peaks at δ 9.93 (1 H) and 2.28 (3 H); no methyl resonances near 1.0 ppm are observed. ^{13}C NMR spectroscopy affords a relatively simple spectrum, showing resonances at δ 130.52, quaternary aromatic carbons at δ 102.07 and 95.68, aromatic C–H centers at δ 88.44, 78.14, and 76.98 and a methyl resonance at δ 14.97, in addition to peaks from the Cp^* ligand. IR spectroscopy shows a carbonyl absorption at 1 716 cm^{-1}. The arene ring coordinated to **19** was thus identified as 2-methyl-5-hydroxybenzaldehyde.

The mechanism of formation of **19** from prednisolone is unclear. However, prednisolone contains a quinoid structure on the A-ring and steric congestion on the α-face: we have previously shown that coordination of Cp^*Ru^+ to quinone leads to the intermediate formation of a biradical quenched as hydroquinone.[36] We therefore propose that attack of a second molecule of **1** on prednisolone occurs on the β-face, causing homolytic rupture of the C9–C10 bond and leading to a biradical centered on the oxygen functionality at C3 and the carbon C10 (Figure 6). Further transformation would then produce the observed benzaldehyde derivative through an unknown mechanism.

Concluding Remarks

To the best of our knowledge, the work reported in this paper is the first synthetic application of a transition-metal-induced carbon–carbon bond activation reaction. This study demonstrates that, rather unexpectedly, the reactions of Cp^*Ru^+ with non-aromatic steroids lead to a clean, selective, and in most cases quantitative cleavage of one carbon–carbon bond (C10–C19). It is remarkable that this method allows us to achieve in one step a reaction that requires a multistep oxidation process in nature.

The reactions of **1** with steroid enones resemble those observed previously for simple cyclic enones, as shown by mechanistic studies and by the products obtained (phenol or anisole derivatives). This aromatization involves methane elimination from a hydrido η^5-cyclohexadienyl derivative and thus conserves the C3–O bond.

It is interesting to note that complicating the system by using sterols unsaturated on the B-ring led to a clearer understanding of the mechanism of the aromatization process and in particular of the important carbon–carbon bond cleavage step. The observation of triene intermediates, trapped as a methoxo adduct in the case of cholesterol, also led to an understanding of the early steps of the reaction. Thus, initial dehydration leads to a conjugated cholestadiene derivative which then readily transforms into cholestatriene. The important points of this mechanism are first that this triene is an intermediate in the aromatization process and that hydrogen initially produced in the gas phase of the reaction mixture disappears and is replaced by methane. The second point is that aromatization occurs when the ruthenium moiety and the 19-methyl group are located on opposite faces of the steroid substrate, strongly suggesting the intermediacy of free radicals in this process. We had previously proposed a radical mechanism for this C–C activation step on the basis of the observation of ethane in the gas phase of the reaction mixtures. The third point concerns the regioselectivity of the complexation by **1**. The triene intermediates observed from cholesterol or dehydroisoandrosterone both exist as single isomers (α), as does the final aromatized product derived from cholesterol. However, the final aromatization of dehydroisoandrosterone, which requires higher temperature (120 °C), results in a 9:1 mixture of the α and β isomers. This suggests that $\alpha \leftrightarrow \beta$ isomerization occurs at higher temperatures as a result of partial or complete decoordination of the ruthenium moiety.

Finally, we have also demonstrated that a saturated sterol could be aromatized, although in this case the reaction is more difficult, and that potentially chelating O-donor substituents on the steroid side chain prevent the attack of **1** on the A-ring of prednisolone. Reaction of an excess of **1** with prednisolone allows attack at the quinoid A-ring, causing an unusual fragmentation of the steroid framework.

Among the challenges that still have to be met to make this process genuinely useful to the organic chemist are (i) decoordination of the aromatized ring; (ii) catalytic recovery of ruthenium; (iii) selective attack on other parts of steroid substrates, such as aromatization of the B-ring or dehydrogenation of the D-ring; and (iv) functionalization of the aromatized products. We have addressed the first of these points: using the method described by Mann et al., i.e., photolysis of a $[Cp^*Ru(arene)]^+$ compound in acetonitrile,[37] we have successfully decoordinated the aromatized fragment derived from cholesterol in ca. 50% yield. We have also reported aromatization at the B-ring of 5,7-dienyl sterols by **1** in a separate publication.[32b] The rest of the above aims are currently being addressed in our laboratory.

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. ^1H and ^{13}C NMR spectra were recorded on Bruker AC200 or WM250 spectrometers in acetone-d_6 solution. Infrared spectra were obtained in CH_2Cl_2 solution or as KBr disks using a Perkin-Elmer 1725X Fourier-transform spectrometer.

(36) Huang, Y-S.; Sabo-Etienne, S.; He, X-D.; Chaudret, B.; Boubekeur, K.; Patail, B. *Organometallics* **1992**, *11*, 3031.

(37) Schrenk, J. L.; McNair, A. M.; McCormick, F. B.; Mann, K. R. *Inorg. Chem.* **1986**, *25*, 3501.

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 H_2, CH_4, C_2H_6, and Ar was performed on a $^1/_8$-in. column: molecular sieve 5 Å (2m); 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. Details of the reaction conditions employed and yields obtained in this study are summarized in Table I.

Reaction of [Cp*Ru(OMe)]$_2$ with Estradiol. Estradiol (153 mg, 0.56 mmol) was added to a solution of [Cp*Ru(OMe)]$_2$ (150 mg, 0.28 mmol) in THF (10 mL). The resultant reaction mixture was stirred at room temperature for 16 **h**. The solvent was removed under vacuum, and the crude solid residue was recrystallized from THF/Et_2O, yielding a white solid product three. Spectroscopic yields: **3**α, 79%; **3**β, 21%. Isolated yields: **3**α, 61%; **3**β, 12%. Anal. Calcd for $[C_{28}H_{38}O_2Ru][C_{18}H_{24}O_2]\cdot 2H_2O$: C, 67.7; H, 8.15. Found: C, 64.7; H, 7.98. ^{1}H NMR: **3**α, δ 5.40 ppm (d, J = 6.5 Hz, 1 H; H1), 4.59 (dd, J = 6.5, 1.6 Hz, 1 H; H2), 4.54 (d, J = 1.6 Hz, 1 H; H4), 1.91 (s, 15 H; C_5Me_5), 0.91 (s, 3 H; Me-18); **3**β, δ 5.36 (d, J = 6.5 Hz, 1 H; H1), 4.47 (d, J = 1.6 Hz, 1 H; H4), 4.37 (dd, J = 6.5, 1.6 Hz, 1 H; H2), 1.92 (s, 15 H; CMe), 1.00 (s, 3 H, Me-18); H-bonded estradiol, 7.16 (d, J = 8.5 Hz, 1 H; H1), 6.74 (dd, J = 8.5, 1.0 Hz, 1 H; H2), 6.59 (d, J = 1.0 Hz, 1 H; H4), 0.89 (s, 3 H, Me-18). ^{13}C NMR: **3**α, δ 151.24 (C3), 99.74, 89.79 (C5, C10), 93.08 (C_5Me_5), 84.43, 77.31, 77.04 (C1, C2, C4), 80.86 (C17), 49.92, 42.56, 39.35 (C8, C9, C14), 43.41 (C13), 37.06, 27.39, 26.55, 23.12 (from C6, C7, C11, C12, C15, C16), 11.03 (C18), 9.47 (C_5Me_5); **3**β, δ 81.09, 79.09, 76.72 (C1, C2, C4), 9.90 (C_5Me_5); H-bonded estradiol, δ 126.06, 115.63, 113.40 (C1, C2, C4), 11.01 (C18).

Reaction of [Cp*Ru(OMe)]$_2$ with Estrone. An analogous procedure to that described above afforded **5**. Spectroscopic yields: **5**α, 75%; **5**β, 25%. Isolated yields: **5**α, 56%; **5**β, 16%. Anal. Calcd for $[C_{28}H_{36}O_2Ru][C_{18}H_{22}O_2]\cdot H_2O$: C, 69.6; H, 7.62. Found: C, 69.5; H, 7.76. ^{1}H NMR: **5**α, δ 5.54 (d, J = 6.5 Hz, 1 H, H1), 4.75 (dd, J = 6.5, 1.7 Hz, 1 H, H2), 4.70 (d, J = 1.7 Hz, H4), 1.93 (s, 15 H, C_5Me_5), 1.04 (s, 3 H, Me-18); **5**β, δ 5.44 (d, J = 6.5 Hz, 1 H, H1), 4.64 (d, J = 1.8 Hz, 1 H, H4), 4.52 (dd, J = 6.5, 1.8 Hz, 1 H, H2), 1.12 (s, 3 H, Me-18); H-bonded oestrone, δ 7.18 (d, J = 8.3 Hz, 1 H, H1), 6.75 (d, J = 8.3 Hz, 1 H, H2), 6.71 (s, 1 H, H4), 1.01 (s, 3 H, Me-18). ^{13}C NMR: **5**α, δ 148.24 (C3), 99.80, 90.55 (C5, C10), 94.23 (C_5Me_5), 84.44, 77.44, 77.17 (C1, C2, C4), 49.93, 42.41, 38.54 (C8, C9, C14), 47.40 (C13), 35.97, 31.83, 26.38, 25.75, 24.48 (from C6, C7, C11, C12, C15, C16), 13.97 (C18), 9.46 (C_5Me_5); **5**β, δ 9.94 (C_5Me_5); H-bonded estrone, δ 156.73 (C3), 137.20, 129.70 (C5, C10), 126.17, 115.66, 113.77 (C1, C2, C4), 13.53 (C18).

Activation Reactions. A typical activation reaction was carried out as follows. 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 mL) was added cholesterol (255 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 and the solution was transferred into a Schlenk tube, evaporated to dryness, and analyzed by NMR spectroscopy. Recrystallization of the crude oily product from THF/Et_2O yielded an off-white solid.

This procedure was also used for the aromatization reactions with testosterone, progesterone, dehydroisoandrosterone, androsterone, and prednisolone. The same procedure, but in a Schlenk tube at room temperature, was used for the direct complexation reactions of Cp*Ru$^+$ with estradiol, estrone, and prednisolone.

Reaction of 1 with Estradiol. Reaction as above in THF at 20 °C for 5 h afforded **2**. Spectroscopic yields: **2**α, 60%; **2**β, 40%. Isolated yields: **2**α, 45%; **2**β, 22%. Anal. Calcd for $[C_{28}H_{39}ORu][CF_3SO_3]\cdot H_2O$: C, 51.5; H, 6.12. Found: C, 50.9; H, 5.93. ^{1}H NMR: **2**α, δ 6.15 (d, J = 6.3 Hz, 1 H; H1), 5.88 (dd, J = 6.3, 1.8 Hz, 1 H; H2), 5.84 (d, J = 1.8 Hz, 1 H; H4), 2.04 (s, 15 H; C_5Me_5), 1.08 (s, 3 H; Me-18); **2**β, δ 6.05 (d, J = 6.3 Hz, 1 H; H1), 5.68 (dd, J = 6.3, 1.7 Hz, 1 H; H2), 2.08 (s, 15 H; C_5Me_5), 1.01 (s, 3 H; Me-18). ^{13}C NMR: **2**α, δ 129.98 (C3), 100.40, 94.47, 94.12 (C5, C10 + C_5Me_5), 84.30, 76.70, 76.39 (C1, C2, C4), 80.61 (C17), 50.36, 43.18, 38.07 (C8, C9, C14), 43.76 (C13), 37.56, 28.01, 27.15, 26.73, 25.95, 22.95 (C6, C7, C11, C12, C15, C16), 11.36 (C18), 9.53 (C_5Me_5); **2**β, δ 9.81 (C_5Me_5).

Reaction of 1 with Estrone. Reaction as above in CH_2Cl_2 at 20 °C for 5 h afforded **4**. Spectroscopic yields: **4**α, 67%; **4**β, 33%. Isolated yields: **4**α, 54%; **4**β, 6%. Anal. Calcd for $[C_{28}H_{37}O_2Ru][CF_3SO_3]\cdot 2H_2O$: C, 50.4; H, 5.97. Found: C, 50.4; H, 5.77. ^{1}H NMR: **4**α, δ 6.30 (dd, J = 6.3, 1.8 Hz, 1 H; H2), 6.16 (d, J = 6.3 Hz, 1 H; H1), 5.84 (d, J = 1.8 Hz, 1 H; H4), 2.04 (s, 15 H; C_5Me_5), 1.03 (s, 3 H; Me-18); **4**β, δ 6.09 (d, J = 6.4 Hz, 1 H; H1), 5.73 (dd, J = 6.4, 1.8 Hz, 1 H; H2), 5.91 (d, J = 1.8 Hz, 1 H; H4), 2.04 (s, 15 H; C_5Me_5), 1.13 (s, 3 H; Me-18). ^{13}C NMR: **4**α, δ 130.13 (C3), 100.57, 94.33 (C5, C10), 84.34, 76.87, 76.52 (C1, C2, C4), 49.72, 41.74, 37.78 (C8, C9, C14), 47.58 (C13), 35.34, 31.64, 27.45, 26.30, 25.41, 21.42 (C6, C7, C11, C12, C15, C16), 13.42 (C18), 9.35 (C_5Me_5).

Reaction of 1 with Testosterone. Reaction in THF at 120 °C for 70 h afforded a mixture of **2** and **6**. Spectroscopic yields: **2**α, 62%; **2**β, 8%; **6**α, 27%; **6**β, 3%. Isolated yields: **2**α, 42%; **6**α, 18%. ^{1}H NMR: **6**α, δ 6.28–6.03 (m, 3 H; H1, H2, H4), 3.97 (s, 3 H; OMe), 2.07 (s, 15 H; C_5Me_5), 0.91 (s, 3 H; Me-18); **6**β, δ 4.00 (s, 3 H; OMe), 2.09 (s, 15 H; C_5Me_5), 1.05 (s, 3 H; Me-18). ^{13}C NMR: **6**α, δ 131.55 (C3), 100.70, 94.12 (C5, C10), 86.99, 75.55, 75.28 (C1, C2, C4), 80.61 (C17), 61.58 (OMe), 11.57 (C18), 9.28 (C_5Me_5).

Reaction of 1 with Progesterone. Reaction as above in THF at 120 °C afforded a mixture of **7** and **8**. Spectroscopic yields: **7**α, 66%; **7**β, 7%; **8**α, 19%; **8**β, 3%. Isolated yields: **7**α, 55%; **7**β, 6%; **8**α, 16%; **8**β, 2%. Anal. Calcd for $[C_{30}H_{41}ORu][CF_3SO_3]\cdot H_2O$: C, 53.0; H, 5.97. Found: C, 53.3; H, 6.39. ^{1}H NMR: **7**α, δ 6.14 (d, J = 6.3 Hz, 1 H; H1), 5.87 (dd, J = 6.3, 1.7 Hz, 1H; H2), 5.81 (d, J = 1.7 Hz, 1 H; H4), 2.04 (s, 15 H; C_5Me_5), 1.09 (s, 3 H; Me-18); **7**β, H1 obscured, δ 5.76 (br, 1 H; H4), 5.70 (dd, J = 6.5 Hz, 1 H; H2), 2.07 (s, 15 H; C_5Me_5), 0.88 (s, 3 H; Me-18); **8**α, δ 6.26–6.07 (m, 3 H; H1, H2, H4), 3.98 (s, 3 H; OMe), 2.02 (s, 15 H; C_5Me_5), 1.10 (s, 3 H; Me-18); **8**β, δ 4.01 (s, 3 H; OMe), 2.05 (s, 15 H; C_5Me_5), 1.22 (s, 3 H; Me-18). ^{13}C NMR: **7**α, δ 207.66 (C20), 129.98 (C3), 100.39, 94.14 (C5, C10), 94.50 (C_5Me_5), 84.28, 76.68, 76.37 (C1, C2, C4), 63.04 (C17), 54.75, 41.30, 38.07 (C8, C9, C14), 45.42 (C13), 38.34, 30.74, 27.37, 26.88, 26.39, 23.90 (C6, C7, C11, C12, C15, C16), 22.69 (C21), 12.86 (C18), 9.27 (C_5Me_5); **7**β, δ 9.76 (C_5Me_5); **8**α, δ 132.27 (C3), 101.46, 94.66 (C5, C10), 87.64, 75.54, 75.28 (C1, C2, C4), 60.62 (OMe), 13.47 (C18), 9.49 (C_5Me_5); **8**β, δ 10.01 (C_5Me_5). IR: 1703 cm^{-1}.

Reaction of 1 with Cholesterol. Reaction as above in CH_2Cl_2 at 90 °C or in THF at 120 °C, for 40 h afforded **13**α only. Spectroscopic yield: 100%. Isolated yield: 48%. Anal. Calcd for $[C_{36}H_{55}Ru][CF_3SO_3]\cdot 2H_2O$: C, 57.4; H, 7.68. Found: C, 57.3; H, 7.46. ^{1}H NMR: δ 6.34–5.88 (m, 4 H; H1-H4), 2.08 (s, 15 H; C_5Me_5), 1.08 (d, J = 6.4 Hz, 3 H; Me-21), 0.99 (d, J = 6.5 Hz, 6 H; Me-26, 27), 0.85 (s, 3 H; Me-18). ^{13}C NMR: δ 104.46, 101.34 (C5, C10), 95.26 (C_5Me_5), 87.28, 87.01, 86.80, 85.38 (C1–C4), 56.32, 55.03, 41.48 39.69, 39.56, 35.81 (C8, C9, C14, C17, C20, C25), 42.68 (C13), 36.21, 28.27, 28.14, 28.01, 27.13, 26.77, 26.48, 23.75 (2C) (C6, C7, C11, C12, C15, C16, C22-C24), 22.18 (2C; C26, C27), 18.42 (C21), 11.60 (C18), 9.65 (C_5Me_5).

Reaction of 1 with Dehydroisoandrosterone. Reaction as above in THF at 120 °C for 40 h afforded **16**. Spectroscopic yields: **16**α, 56%; **16**β, 24%. Isolated yields: **16**α, 46%; **16**β, 5%. Anal. Calcd for $[C_{28}H_{37}ORu][CF_3SO_3]\cdot 2H_2O$: C, 51.5; H, 6.12. Found: C, 51.5; H, 6.05. ^{1}H NMR: **12**α, δ 6.31–6.02 (m, 4 H; H1–H4), 2.10 (s, 15 H; C_5Me_5), 1.03 (s, 3 H; Me-18). ^{13}C NMR: **12**α; δ 104.17, 101.33 (C5, C10), 95.44 (C_5Me_5), 87.73, 87.43, 86.84, 85.40 (C1–C4), 49.76, 41.76, 37.57 (C8, C9, C14), 47.54 (C13), 35.31, 31.60, 27.16, 26.02, 25.40, 21.36 (C6, C7, C11, C12, C15, C16), 13.37 (C18), 9.68 (C_5Me_5). IR: 1740 cm^{-1}.

Reaction of 1 with Androsterone. Reaction as above in THF at 140 °C for 40 h afforded **16**. Spectroscopic yield: 15%.

Reaction of 1 with Prednisolone at 20 °C. Reaction as above in THF at 20 °C for 5 h afforded **18**. Spectroscopic yield: 100%. Isolated yield: 72%. Anal. Calcd for $[C_{31}H_{43}O_5Ru][CF_3SO_3]\cdot 2H_2O$: C, 49.2; H, 6.06. Found: C, 49.0; H, 5.88. ^{1}H NMR: δ 7.66 (d, 1 H; H2), 6.44 (d, 1 H; H1), 6.19 (s, 1 H; H4), 2.01 (s, 15 H; C_5Me_5), 1.03 (s, 3 H), 0.64 (s, 3 H; Me-18, 19). ^{13}C NMR: δ 157.31, 127.31, 121.95 (C1, C2, C4), 123.84 (C5), 94.39 (C_5Me_5), 69.62 (C11), 56.37 (C17), 51.71, 34.48, 32.05 (C8, C9, C14), 44.76 (C13), 39.41 (C21), 34.24 (C10), 33.80, 31.67, 30.33, 23.95, 20.96 (C6, C7, C12, C15, C16), 16.93, 14.89 (C18, C19), 9.28 (C_5Me_5). IR: 1715, 1655 cm^{-1}.

Reaction of 2 molar equiv of 1 with Prednisolone at 100 °C. Reaction as above in THF at 100 °C for 40 **h** yielded **19**. Spectroscopic yield: 75%. Isolated yield: 35%. Anal. Calcd for $[C_{18}H_{23}O_2Ru][CF_3SO_3]\cdot 2H_2O$: C, 40.9; H, 4.88. Found: C, 41.1; H, 4.98. ^{1}H NMR: δ 9.93 (s, 1 H; C*H*O), 5.97–5.80 (m, 3 H; H1, H2, H4), 2.28 (s, 3 H; Me), 2.03 (s, 15 H; C_5Me_5). ^{13}C NMR: δ 130.52 (C3), 102.07, 95.68 (C5, C6), 94.39 (C_5Me_5), 88.44 (C1), 78.14, 76.98 (C2, C4), 14.97 (Me), 9.32 (C_5Me_5). IR: 1716 cm^{-1}.

Reaction of 14 with NaOMe. A 1:1 mixture of **9** and **10** (269 mg, 0.34 mmol) was added to a solution of Na (20 mg, 0.86 mmol) in MeOH (10 mL), and the mixture was stirred at room temperature for 2 h. The solution was then evaporated to dryness, and the resultant brown oil was extracted with pentane (2 × 20 mL). Evaporation of the extracts afforded a crude brown solid product **15**, which was recrystallized from acetone at 253 K. Isolated yield: 24%. Anal. Calcd for $[C_{38}H_{60}ORu]$: C, 72.0; H, 9.54. Found: C, 71.8; H, 9.83. ^{1}H NMR: δ 5.28 (td, J = 4.8, 0.8 Hz, 1 H; H2), 4.23 (dd, J = 4.8, 0.8 Hz, 1 H; H1), 3.96 (ddd, J = 6.2, 4.8, 0.8 Hz, 1 H; H3), 3.28 (s, 3 H; OMe), 2.23 (d, J = 6.2 Hz; H3), 1.97 (s, 15 H; C_5Me_5), 1.09 (d, J = 6.4 Hz, 3 H; Me-21), 1.00 (d, J = 6.4 Hz, 6 H; Me-26, 27), 0.80 (s, 3 H; Me-18). ^{13}C NMR: δ 97.27 (C5), 88.77 (C_5Me_5), 82.25, 81.97, 80.16, 79.81 (C1–C4), 56.78, 56.60, 51.27, 44.39, 43.08 (C6, C8, C9, C14, C17), 55.33 (OMe), 48.83, 41.14 (C10, C13), 39.64, 36.35, 36.01, 35.15, 26.80 (2C), 24.37, 23.92 (C7, C11, C12, C15, C16, C22-C24), 22.44 (2C; C26, C27), 22.21 (C19), 18.53 (C21), 11.85 (C18), 10.83 (C_5Me_5).

Single Crystal X-ray Structure of 15. Single crystals were grown from an acetone solution of the complex at 253 K. A brown plate of dimensions 0.50 × 0.40 × 0.10 mm was mounted on a glass fiber and transferred to an Enraf–Nonius CAD-4 diffractometer. Cell constants were obtained from the least-squares fitting of the setting angles of 25 reflections in the range $10 < \theta < 13°$. A summary of crystal and intensity collection data is given in Table IV. Intensity standards, monitored every 2 h, showed no significant crystal decay during data collection. Data were corrected for Lorentz polarization and empirical absorption[38] (T_{min} = 0.91, T_{max} = 1.05) using the MolEN package.[39]

The structure was solved by direct methods using SHELXS86[40] and developed by iterative cycles of full-matrix least-squares refinement and difference Fourier synthesis on a Digital Equipment MicroVAX 3400 computer with the SHELX76 program,[41] using 4067 reflections with $F_o^2 \geq 3\sigma(F_o^2)$. The asymmetric unit consists of one molecule of **15**. Anisotropic thermal parameters were refined for all non-hydrogen atoms. All hydrogen atoms were placed in fixed, calculated positions (C–H = 0.97 Å) with separate isotropic U values for methyl and other hydrogens which could be refined. The atomic scattering factors used were those of Cromer and Waber with anomalous dispersion effects.[42] Scattering factors for hydrogen were taken from reference 43.

Refinement for both possible enantiomers was achieved; the one giving the lowest R factor was adopted for the final model (from Bijvoet pairs hkl and $\bar{h}\bar{k}\bar{l}$). The final full-matrix least-squares refinement, minimizing the function $\sum w(|F_o| - |F_c|)^2$, converged to R = 0.024 and R_w = 0.026. An analysis of variance showed no unusual trends. In the last cycle of refinement the maximum observed shift was 0.11 σ, and the final difference Fourier map showed a maximum residual electron density of 0.36 e Å^{-3}.

An ORTEP[44] plot showing the molecular structure of **15** is shown in Figure 4.

Table IV. Crystal Data and Data Collection Details for **15**

chemical formula	$C_{38}H_{60}RuO$
formula weight	633.97
T, K	293(1)
space group	$P2_1$
a, Å	14.936(1)
b, Å	7.877(1)
c, Å	15.246(1)
β, deg	103.84(1)
V, Å	1741.6(4)
Z	2
d_{calcd}, g cm^{-3}	1.21
μ, cm^{-1}	4.7
$F(000)$	680
diffractometer	Enraf–Nonius CAD-4
radiation	Mo Kα, graphite monochromated
λ, Å	0.710 73
$2\theta_{max}$, deg	46
scan type	ω–2θ
scan width	0.80 + 0.35 tan θ
h range	$-16 \leq h \leq 16$
k range	$-8 \leq k \leq 8$
l range	$0 \leq l \leq 16$
total data collected	5044
unique data collected	4667 (R_{int} = 0.016)
data with $I > 3\sigma(I)$	4067
weighting scheme	unit weights
R	0.024
R_w	0.026
number of parameters	362

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Supplementary Material Available: Final atomic coordinates (Tables SI, SII), anisotropic thermal parameters (Table SIII), and complete bond distances and angles (Table SIV) (5 pages); list of observed and calculated structure factors (Table SV) (18 pages). Ordering information is given on any current masthead page.

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