Transition-Metal-Catalyzed Reactions in Steroid Synthesis

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1. Introduction

Organo-transition-metal chemistry, after an unbelievable expansion in the last half of the century,

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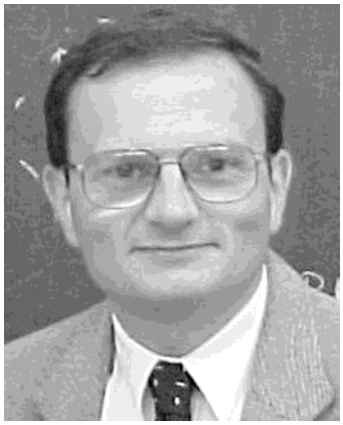
Rita Skoda-Földes was born in Várpalota, Hungary. She studied chemical engineering at the University of Veszprém and graduated in 1987. From 1987 to 1990, she carried out her Ph.D. research under the guidance of Bálint Heil and László Kollár, being involved in the hydrosilylation of olefins. In 1991, she started with transition-metal-catalyzed reactions of steroids including homogeneous catalytic coupling and carbonylation reactions, as well as further functionalization of these key intermediates and the synthesis of the steroidal skeleton possessing the E ring. She was appointed Associate Professor in 1998 at the University of Veszprém. One of the novel topics of her current research is the synthesis of various ferrocene derivatives via a palladium-catalyzed carbonylation reaction.



László Kollár was born in Kaposvár, Hungary. He studied chemical engineering at the University of Veszprém, where he received his diploma in 1979 and the doctoral degree in 1983, working under the direction of László Markó and Bálint Heil on the enantioselective hydrogenation of ketones with rhodium complexes. For postdoctoral studies, he spent two years with Piero Pino and Giambattista Consiglio at the ETH, Zurich, being involved in the enantioselective hydroformylation of unsaturated esters with the platinum–phosphine–tin(II)chloride system. He began independent research on the asymmetric hydroformylation of vinyl aromatics and some mechanistic investigations of platinum–phosphine–tin(II)chloride systems, as well as the transition-metal-catalyzed functionalization of steroids. He was appointed Associate Professor at the University of Veszprém in 1993. In 1996, he moved to Pécs (southern Transdanubia, Hungary), where he has been Full Professor since 1997 at the University of Pécs. The main focuses of his current research are platinum, palladium, and rhodium complexes of heterobidentate and multidentate ligands, mechanistic aspects of insertion reactions, and coordination chemistry in ionic liquids.

reached the stage of general application in synthetic organic chemistry. The recognition of the carbon−metal bonding properties and the mechanistic understanding of the basic catalytic reactions, as well as the definition of the scope and limitations, have rendered many of the transition-metal-catalyzed reactions the most efficient solution to practical problems. In many recent reviews organo-transition metals are considered to be the most important source of new reactions. As Seebach published a decade ago and is cited more and more often among chemists interested in organometallic chemistry directed toward organic synthesis ("OMCOS people"), "The discovery of truly new reactions is likely to be limited to the realm of transition metal organic chemistry, which will almost certainly provide us with additional 'miracle reagents' in the years to come."[1] Many general treatises[2−5] and reviews, as well as an increasing number of papers, demonstrate the increasing role of transition metals in the field of organometallic synthesis.

Overcoming the fear of a novel type of reactants and the myth of using transition-metal complexes in a different way than "classical" organic reagents, as well as laying aside the prejudice of "expensive reagents" and that of "just an intellectual exercise", some of these systems are used routinely as a tool for the functionalization of various skeletons with potential practical applications.

The enhanced selectivities, well-defined mechanism, and applicability of standard techniques are the main features that also make the homogeneous catalytic reactions attractive in the synthesis of steroids. Although some homogeneous catalytic reactions with steroidal substrates have already been the subject of several reviews and book chapters since the 1970s,[6−9] to the best of our knowledge there is no precedence of a review showing the strength of homogeneous catalytic transformations by using a biologically important backbone such as a steroidal skeleton.

There is increasing interest in developing new strategies to introduce functional groups into specific positions of steroidal nuclei to modify their biological properties. Transition-metal-catalyzed reactions have proven to be versatile tools both for the construction of the steroid framework from easily available building blocks and for the functionalization of the steroidal skeleton.

The above facts have prompted us to summarize the most important achievements in the field of steroid synthesis in the presence of transition-metal catalysts. Our goal is to show how efficiently these systems can be used for the introduction of a desired functionality and how rather complex synthetic processes can be accomplished with organo-transition-metal reagents. The advantage of the consecutive use of some homogeneous catalytic syntheses over conventional multistep synthesis will also be shown in some cases.

Although the collection of references is intended to be comprehensive, it is not simple to cover all references that might be of some interest in the context of the potential of homogeneous catalysis in steroid synthesis. The difficulty in maintaining a satisfactory overview arises from the fact that relevant papers may appear in general, organic, inorganic, organometallic, or even more specialized journals and that fine details concerning the application

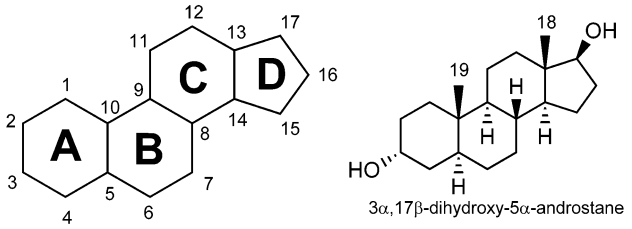


Figure 1. Numbering of the steroidal skeleton and nomenclature of an androstane derivative.

of steroids might be "hidden" in a paper on a rather different topic. The list of references covers the most important ones published through end of 2002.

The basic skeleton of a steroid consists of three fused cyclohexane rings and a cyclopentane ring ("cyclopentano perhydrophenantrene structure"): rings A, B, C, and D, respectively. In most cases (steroids belonging to the cholestane, androstane, and pregnane families), there are two angular methyl groups at C-10 and C-13. (For numbering, see Figure 1.). The substituents on the same side as these methyl groups are β substituents; the others are α substituents. In most cases, the four rings are trans-anti, trans-anti, and trans anellated (as indicated in Figure 1) resulting in a substantially flat skeleton. The hydrogens at the stereogenic centers are in 5α, 8β, 9α, and 14α positions. In the schemes in this paper, in agreement with the chemical literature, the ring hydrogens attached to C-5, C-8, C-9, and C-14 stereogenic centers are omitted. (In case of any differences in ring fusion, the positions of these hydrogens are clearly indicated.)

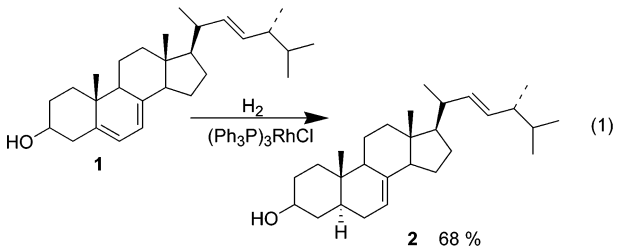
2. Homogeneous Catalytic Hydrogenation of Steroids

Among the homogeneous catalytic reactions, as in the case of many classes of other compounds of practical importance, hydrogenation and hydroformylation (vide infra) were also the first ones used for the synthesis of steroids. Although no novel functionalities are introduced through the hydrogenation of steroidal olefins, the stereochemistry of various positions of the skeleton can be influenced. This renders hydrogenation to the fundamental transition-metal-catalyzed reactions of steroids.

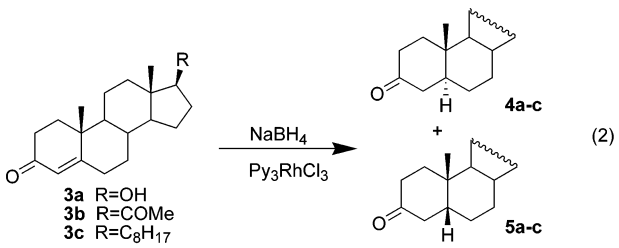
2.1. Hydrogenation of the Carbon–Carbon Double Bonds

2.1.1. Hydrogenation of Δ^4 and Δ^5 Double Bonds Resulting in A/B cis- and trans-Fused Skeletons

Both the "preformed" rhodium catalyst, $(Ph_3P)_3$-RhCl, and in situ systems derived from a rhodium-diene precursor and tertiary phosphines proved to be efficient catalysts in the hydrogenation of steroids. The Δ^5 double bond of ergosterol (**1**) was reduced selectively to give 5α-7-ene derivative **2** in the presence of the Wilkinson-type catalyst (eq 1). [10,11] Less-hindered double bonds (Δ^1, Δ^2, Δ^3) were readily hydrogenated, but double bonds attached to C-5 (Δ^4 and Δ^5) were inert under the conditions used. Accordingly, the Δ^1 double bond of a 1,4-diene-3-one derivative was reduced selectively with the $(Ph_3P)_3$-RhCl catalyst.[12] The Δ^4 double bond of a 4-en-3-one system (e.g., in cholesta-4-en-3-one) could also be reduced but at a much slower rate.[13] The reduction of both Δ^4 and Δ^5 double bonds results in 5α products (i.e., the hydrogen enters from the α face). Higher catalytic activities were reported with iridium catalysts.[14]



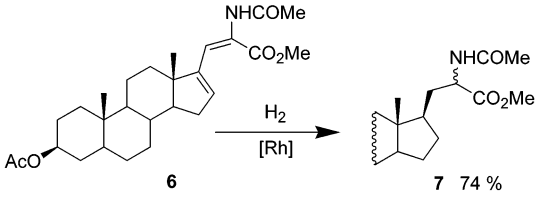
The application of the $(Py_3)RhCl_3$-$NaBH_4$ catalyst resulted in the reduction of the conjugated double bonds of the 4-en-3-one system of steroids **3a**−**c**; therefore, rather complex mixtures of 5α (**4a**−**c**) and 5β derivatives (**5a**−**c**) were obtained (eq 2). [15] The reduction of testosterone (**3a**) and progesteron (**3b**) led to 3.5:1 mixtures of the 5α (**4a**, **4b**) and 5β (**5a**, **5b**) compounds, and the same reaction of cholestenone (**3c**) resulted in the formation of **4c**/**5c** in a 1:3 ratio. The carbon−carbon double bonds of similar systems (androst-4-en-3,17-dione, androsta-1,4-diene-3,17-dione, cholest-4-en-3-one) were reduced selectively with rhodium-tertiary phosphine in situ catalyst while the carbonyl group remained intact. (Interestingly, the reduction of a similar A-ring system of 17α-ethynyl-testosterone results in the partial reduction of the carbonyl group, too.) The stereochemistry of the reaction could be influenced substantially by the appropriate choice of the monodentate phosphine. The results can be rationalized as rhodium-dihydrides favors α selectivity and monohydrides obtained upon the addition of a base attack preferentially from the β face.[16]



2.1.2. Hydrogenation of Carbon–Carbon Double Bonds

The carbon−carbon double bond in the α,β-unsaturated position was reduced selectively in cholesteryl cynnamate by the potassium formate/palladium(II) acetate system in high yields.[17] Steroidal dehydroamino acid esters were stereoselectively hydrogenated with molecular hydrogen under a hydrogen atmosphere of up to 110 bars in the presence of rhodium-phosphine in situ catalysts.[18] Whereas the hydrogenation was highly chemoselective in the case

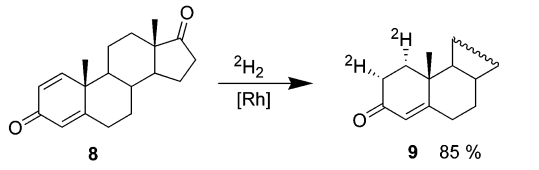
of 3,5-dienes (reduction took place exclusively in the side chain), both double bonds were hydrogenated when the 17-acetamidoacrylate moiety was bonded to steroids possessing Δ^{16} (**6**, eq 3). The systematic variation of the phosphine ligands revealed that the diastereoselectivity of hydrogenation was mainly determined by the steroid skeleton itself.



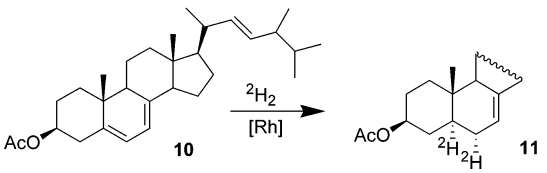
6 **7** 74 % (3)

2.1.3. Isotope Labeling of Steroids via Deuteration and Tritiation

The cis addition of deuterium to the Δ^2 double bond of 5α-cholest-2-ene resulted in the saturated 2ξ,3ξ-d_2-5α-cholestane. The product exhibits high isotopic purity unlike those obtained with heterogeneous catalysts.[19,20] Selective deuteration of the Δ^1 double bond of androsta-1,4-diene-3,17-dione (**8**) takes place from the α face; consequently, deuterium labels are in 1α,2α positions (eq 4).[21] In contrast to heterogeneous systems that produce a preferential *β*-side attack, the deuteration of 17*β*-hydroxy-androst-4-en-3-one with homogeneous systems show α-side selectivity.[13] The Δ^5 double bond of ergosterol acetate (**10**) was deuterated selectively (eq 5). The α configuration of the incorporated deuteriums can be established easily from the ^{1}H NMR.[10] Homogeneous catalytic deuteration also proved to be an excellent tool for the preparation of side-chain-labeled steroids. The saturation of the double bonds at positions $\Delta^{20(21)}$, Δ^{23}, and Δ^{24} provided the corresponding deuterated compounds in high isotopic purity. [12] Deuterium labeling was also applied to the solution of stereochemical problems in the steroidal sapogenine series.[21]

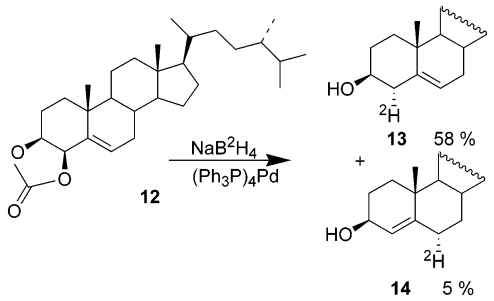


8 **9** 85 % (4)



10 **11** (5)

Highly stereoselective deuteration has been performed in the palladium(0)-mediated sodium borodeuteride reduction of readily available cholest-5-en-3*β*,4*β*-diol cyclic carbonate (**12**). A $^{12}/_1$ mixture of [4α-^2H]-cholesterol (**13**) and [6α-^2H]-Δ^4-cholesterol (**14**) was obtained (eq 6). A similar approach was used for the synthesis of the corresponding ^3H-labeled compounds. However, the use of $Pd_2(dba)_3$ resulted in the loss of the borotritide reagent because of the reduction of the dibenzylideneacetone ligand.[22]



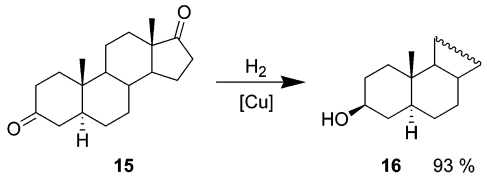
12 **13** 58 % + **14** 5 % (6)

2.2. Reduction of the Carbonyl Group in Steroidal Ketones

2.2.1. Hydrogenation of the Carbonyl Group

Despite the high importance of 3-hydroxy and 17-hydroxy epimers, unlike the heterogeneous hydrogenation case, relatively little work has been published on the homogeneous catalytic hydrogenation (with molecular hydrogen) of 3-keto and 17-keto derivatives, respectively.

The 3-keto functionality of 5α- (**15**) and 5*β*-androst-3,17-dione was reduced chemoselectively with the preference of the 3*β*- (**16**) and the 3α-alcohols, respectively (eq 7). Very similar stereoselectivities were observed for the reduction of 5α- and 5*β*-cholestanones to the corresponding 3-hydroxy epimer mixtures.[23] A hydrido-copper catalyst, $[(Ph_3P)CuH]_6$, in the presence of more basic Me_2PhP proved to be an active hydrogenation catalyst under atmospheric hydrogen.

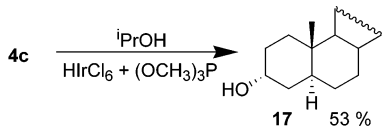


15 **16** 93 % (7)

2.2.2. Transfer Hydrogenation of the Carbon–Oxygen Double Bond

The reduction of steroidal ketones (especially at the 3 position) is of high interest because the conventional stoichiometric reduction with hydrides provides the formation of the thermodynamically favored equatorial (i.e., in case of 3-keto derivatives the 3*β*) alcohol. However, a catalytic method has been developed that gives the axial (3α) alcohol. The reduction of cholestanone (**4c**) was carried out with a chloroiridic acid/trimethyl phosphite catalyst with the predominant formation (92%) of the axial alcohol **17** (eq 8).[24,25] The transfer hydrogenation involves the transfer of hydrogen from 2-propanol to the carbonyl functionality. Ketones at the 2 and 3 positions were reduced to the corresponding axial alcohols by a similar methodology.[26,27] Steroidal carbonyl groups at the 4, 6, 7, 11, 12, 17, and 20 positions were not affected under the same reaction conditions. Replacement of the iridium precursor by $(Ph_3P)_3RhCl$ resulted in even higher 3α/3*β* stereoselectivity; however, the removal of the catalyst proved to be more complicated in the rhodium case. Whereas the iri-

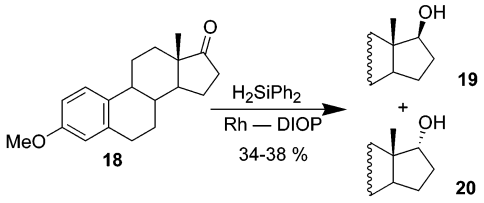
dium catalyst was removed simply by extraction, the removal of the Wilkinson catalyst required chromatography.



(8)

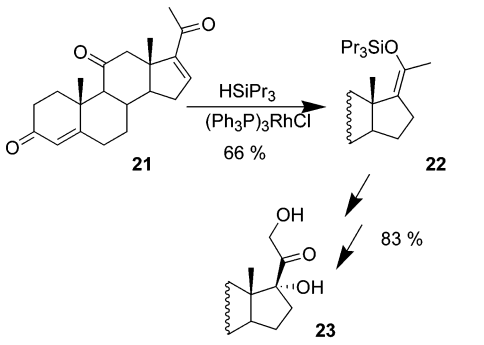
2.2.3. Hydrosilylation of the Carbon–Oxygen Double Bond

The need for steroidal 17-alcohols as pure epimers also led to an intensive search for an appropriate catalytic system. Whereas the application of conventional hydrides for the reduction of 17-ketones results in an almost exclusive formation of 17β-OH in most cases, the homogeneous catalytic hydrosilylation with the chiral rhodium-DIOP system allowed some stereoselectivity toward the relatively inaccessible 17α-alcohols.[28] Estrone and estrone methyl ether (**18**) were reduced to the corresponding 17β/17α-hydroxy epimeric mixture (**19**, **20**) in a $^1/_1$ ratio in the best cases (eq 9).[29] However, no effect of the use of the two catalytic systems containing different DIOP enantiomers on stereoselectivity was observed with pregna-3,5-dien-20-one. This was attributed to the free rotation of the 20-carbonyl function around the C-17−C-20 σ bond. The isomeric distribution of the 17-alcohol diastereoisomers obtained during the hydrosilylation of 3-methoxy-16α-methyl-5α-androstan-17-one and 3-methoxy-16,16-dimethyl-5α-androstan-17-one with the Wilkinson catalyst was found to be similar to that observed with the $LiAlH_4$ stoichiometric reagent (17α/17β = $^{15}/_{85}$). [30] However, the 17α/17β diastereomeric ratio could be shifted to $^{53}/_{47}$ by the rhodium-DIOP in situ system.



(9)

During the total synthesis of (±)-cortisone, the hydroxy functionalities of the side chain were formed using Rh-catalyzed hydrosilylation as the key step. The selective reaction of pregna-4,16-dien-3,11,20-trione (**21**) with tripropylsilane gave the 20-silyloxy-17(20)-en derivative (**22**) as the main product (eq 10). The oxidation of this compound led to cortisone silyl

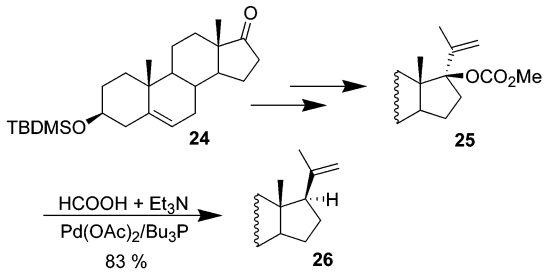


(10)

ether, which lost its silyl group upon acidic workup to afford cortisone (**23**). The same procedure was used during the synthesis of cortexolone.[31]

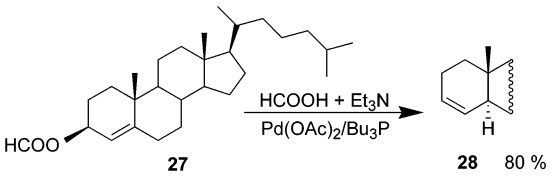
2.3. Hydrogenolysis

The 17α-isopropenyl-17β-OH steroidal allylic alcohol, obtained by the reduction of steroidal 17-ketone **24** with isopropenyllithium, was converted to the corresponding carbonate **25**. Its hydrogenolysis with triethylammonium formate affords 17β-isopropenyl derivative **26**, an appropriate intermediate of compounds of practical importance (eq 11).[32,33] Previous studies have shown the efficiency of this palladium-catalyzed hydrogenolysis of C-20 (*E*) and (*Z*) allylic carbonates to produce natural and unnatural epimers at C-20 on a steroidal side chain.[34]



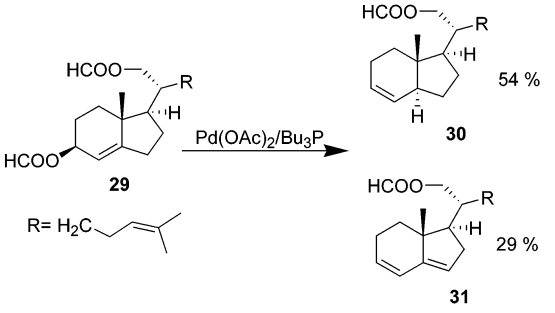
(11)

The allylic formates (such as cholesteryl formate) underwent palladium-catalyzed hydrogenolysis influencing the A/B ring junctions. The hydrogenolysis of 3β- (**27**) or 3α-formate results in a stereoselective formation of 5α- (trans fusion) (**28**) or 5β-cholest-3-ene (cis fusion), respectively.[35,36] This is due to the formation of a key π-allyl-palladium formate intermediate that rearranges to the σ-allyl-palladium formate complex. The selective hydrogen transfer of "formate hydrogen" affords the steroidal olefin.



(12)

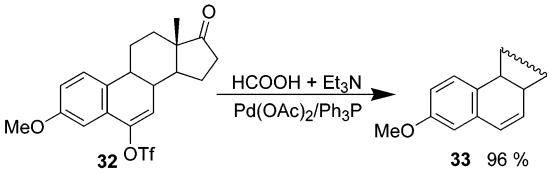
The hydrogenolysis of allyl formates (eg. **29**) resulted in the *trans*-hydrindan ring junction in a multistep synthesis of a vitamin D_3 building unit (eq 13).[37] The stereoselective hydrogenolysis with double bond migration, developed by Tsuji, was catalyzed by the $Pd(OAc)_2$−Bu_3P in situ catalyst.



(13)

Various enol triflates were converted into the corresponding alkenes by a reaction with tributylammonium formate in the presence of $(Ph_3P)_2Pd(OAc)_2$.[38] A valuable feature of this method is the regioselective and quantitative introduction of a deuterium atom when the reaction is carried out in DCO_2D instead of formic acid. This method was extended to the hydrogenolysis and deuteration of 3-triflyloxy-estrone by changing the catalyst to $Pd(OAc)_2$ + dppf (dppf: 1,1′-bis(diphenylphosphino)ferrocene).[39]

The treatment of estrogens possessing the 6-triflyloxy-6-ene (enol triflate) moiety (eg., **32**) with triethylammonium formate as a hydrogen donor gave the corresponding 6,7-didehydroestrogens (eg., **33**) in high yields (eq 14). The preparation of the above substrates was carried out from the easily accessible 6-keto-estrogens.[40]



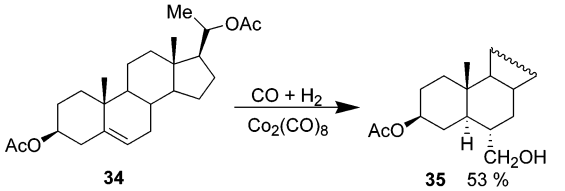
32 **33** 96 % (14)

3. Homogeneous Catalytic Carbonylation Reactions of Carbon–Carbon Double Bonds

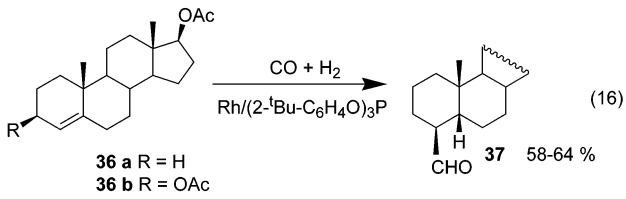
3.1. Hydroformylation

3.1.1. Hydroformylation of Carbon–Carbon Double Bonds in the Ring System

Despite ongoing interest in the hydroformylation of various substrates, this reaction has been only scarcely reported for unsaturated steroids. In the case of the hydroformylation of steroids possessing a carbon−carbon double bond in the ring system, the synthetic applicability could be diminished by both the low reactivity and the low regio- and stereoselectivity. Although the first reports were published in the 1950s, there are only a few papers in this field. This pioneering work reports on the hydroformylation of 3β-acetoxy-pregn-5-en-20-one and 3β,20β-diacetoxy-pregn-5-ene (**34**) with the aim of synthesizing the 6α-methyl steroids.[41,42] Because cobalt catalysts were used under severe conditions, the newly introduced formyl groups were reduced immediately to the corresponding alcohol (eq 15). In both cases, 6α-hydroxymethylpregnanes were isolated in about 60% yield. The trans A/B ring fusion reflects an α-side hydroformylation. The hydroformylation of carbon−carbon double bonds in similarly sterically hindered positions was published after only approximately four decades.[43] Δ^4-Androstenes (eg., **36a**, **b**) were hydroformylated with the rhodium-tris(2-*tert*-butylphenyl)-phosphite catalyst to the corresponding 4β-formyl-androstane derivatives (eq 16). As in many other homogeneous catalytic reactions, β-side attack has been observed in contrast to the Δ^5 derivatives (vide supra), where an almost exclusive α attack was observed.

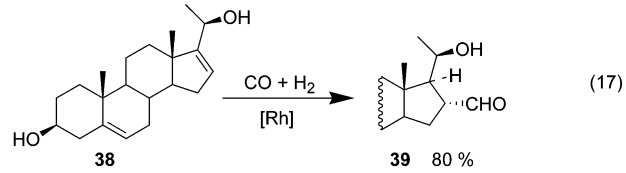


34 **35** 53 % (15)



36 a R = H
36 b R = OAc
37 58-64 % (16)

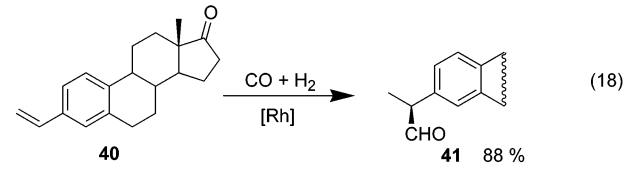
In the case of steroidal olefins containing a carbon−carbon double bond in the ring skeleton, the less hindered Δ^{16} derivatives such as (20*R*)-3β,20β-dihydroxy-pregna-5,16-diene (**38**) or 3β-hydroxy-androst-16-ene preferentially give the corresponding formyl derivatives arising from an α-side attack of the catalyst (eq 17). The reactivity difference between Δ^5 and Δ^{15} was also clearly demonstrated by the hydroformylation of 3β,17β-dihydroxy-androsta-5,15-diene: the double bond in the D ring was hydroformylated to a mixture of four aldehydes in the ratio 45/45/5/5, whereas that in the B ring remained intact.[44]



38 **39** 80 % (17)

3.1.2. Hydroformylation of Carbon–Carbon Double Bonds in the Substituents

The steroids containing double bonds in the side chain underwent a facile hydroformylation reaction. The hydroformylation of pregna-16,20-diene resulted in a rather complex mixture with various rhodium catalysts because of competing hydrogenation that also influenced the stereochemistry at the 17 position.[45] Both chemo- and stereoselectivities obtained with 3-vinyl-estrone (**40**) are of synthetic importance.[46] The branched aldehyde [3-(2′-formylethyl-estra-1,3,5(10)-trien-17-one, **41**] was formed with up to 92% regioselectivities (eq 18). High diastereoselectivities were also observed for this compound both with achiral (Ph_3P) and chiral (PROPHOS [1,2-bis-(diphenylphosphino)propane], CHIRAPHOS [2,3-bis-(diphenylphosphino)butane]) ligand-containing rhodium catalysts.



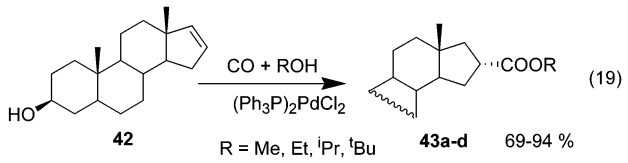
40 **41** 88 % (18)

3.2. Hydroalkoxycarbonylation of Carbon–Carbon Double Bonds

Various androst-16-enes (e.g., **42**) were converted to the 16α-alkoxycarbonyl derivatives (**43a**−**d**) with

high chemo- and regioselectivity in the presence of alcohols and a catalytic amount of $(Ph_3P)_2PdCl_2$ under 120 bars of CO pressure (eq 19). However, a Δ^5 double bond remained intact even under more severe conditions.[47] The selective formation of 16α-monoesters of similar substrates was observed using α,ω-diols with two to four carbon atoms.[48]

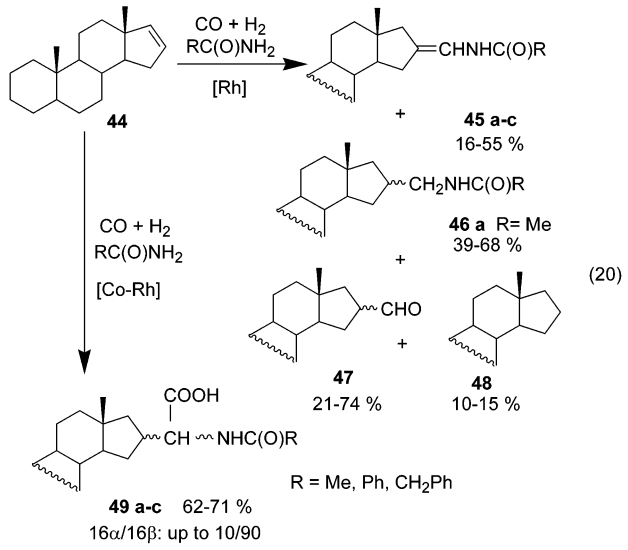
As the result of the hydroethoxycarbonylation of vinyl-estrone in the presence of Pd(II)-phosphine systems, the formation of the branched ester possessing a new stereogenic center was preferred. However, the ratio of the two epimers (approximately $^{80}/_{20}$) could not be influenced by the use of either chiral or achiral phosphines.[49]



(19)

3.3. Other Carbonylation Reactions

A domino hydroformylation−amidocarbonylation reaction sequence was carried out with steroidal substrates. The reaction of various androst-16-ene derivatives (e.g., **44**) with acetamide or benzamide under hydroformylation conditions led to a mixture of an unsaturated methylidene compound (**45**), an amido-methylene (**46**), and a formyl derivative (**47**), together with the hydrogenated product (**48**) in the presence of an Rh-Ph_3P catalyst (eq 20). The use of rhodium−cobalt bimetallic systems resulted in the formation of steroidal *N*-acyl-α-amino acids (**49**) with good selectivity.[50]



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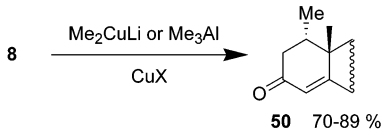
4. 1,4 and 1,6 Additions to Enones

The 1,4 addition of various organometallics to enones, usually by using low-order or high-order cuprates, is a widely used synthetic reaction. A copper-catalyzed 1,4 addition of trialkylaluminum derivatives on 1,4-dien-3-one (**8**) and 1-en-3-one moieties of steroids resulted in 1α-alkyl-3-one derivatives (**50**) with high stereoselectivities (eq 21).[51−53] In the case of 1,4-dien-3-one derivatives, the reaction also proceeds with high regioselectivity toward 1-ene (i.e., 1-methyl-derivatives predominate over 5-methyl derivatives).



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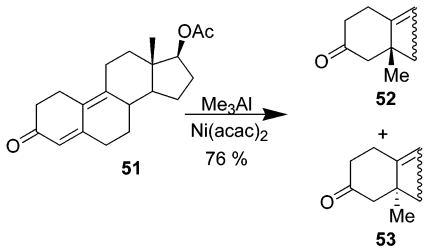
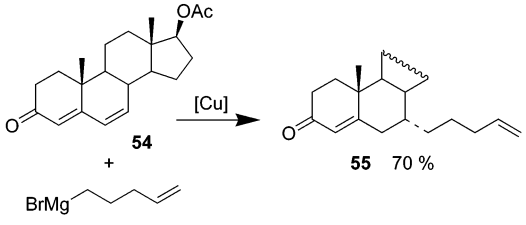
A reversal of the regioselectivity in favor of position 5 could be achieved by a variation in the nature of the reagent system. In the presence of $Ni(acac)_2$, conjugate addition may occur at the sterically hindered C-5 of androsta-1,4-dien-3-one derivatives by the application of ate complexes of aluminum or titanium.[53] 5β-Methyl derivatives were produced with high regioselectivity when steroidal 4-en-3-ones were treated with trimethyl-aluminum[54,55] or organotitanate compounds[56] under nickel catalysis. However, a similar reaction of 17β-acetoxy-19-norandrosta-4,9-dien-3-one (**51**) resulted in the formation of the 5β/5α-methyl derivatives (**52**, **53**) in a $^2/_1$ ratio (eq 22).[55]



(22)

Aryl groups were transferred selectively to the 1α position of both 5α-androst-1-en-3-one and 1,4-dien-3-one derivatives from dialkyl(aryl)alanes in the presence of $Ni(acac)_2$.[57] An excess of arylalanes had to be used to produce optimal yields. In the reaction of androst-1,4-diene-3,17-dione (**8**) with dimethylphenylalane, 3% of the 5β-methyl compound as a 1,4-methylation side product was also formed. Copper(I) catalysts were also used for the introduction of an alkyl group to the 7 position of 4,6-dien-3-one derivative **54**. The 1,6 conjugate addition of a Grignard reagent proceeds with the preferential formation of 7α-alkyl-4-en-3-one derivative **55** with up to 4.5/1 7α/7β stereoselectivity (eq 23).[58] 7α-Substituted estradiols of practical importance are delivered by dehydrogenation at the Δ^1 position followed by demethylation at position 10. A modification of the conjugate addition process was used by Wüst et al. with a CuCN catalyst instead of CuI.[59]



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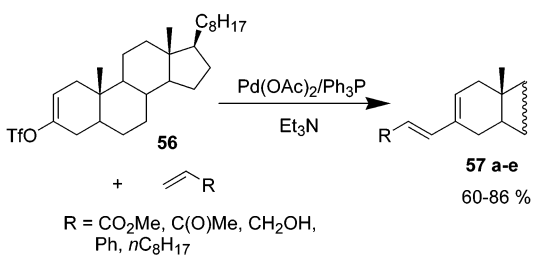
5. Carbon–Carbon Bond-Forming Reactions on Enol Triflates and Iodo Alkenes (Excluding Carbonylation Reactions)

5.1. Coupling Reactions of Steroidal Enol Triflates/Iodo Alkenes with Alkenes (Heck Reaction)

The palladium-catalyzed coupling reaction of vinyl (or aryl) triflates (or halides) with electron-deficient alkenes (Heck reaction) in the presence of a base has become one of the most important homogeneous catalytic reactions for the generation of new carbon−carbon bonds.

This methodology is extensively used both for the functionalization of the steroidal skeleton and for the construction of the steroid framework. (See also Chapter 8). In the first group of these reactions, discussed in this chapter, the main advantage of the Heck reaction is the attachment of various side chains to the steroidal skeleton from readily available keto derivatives. First, the steroidal ketones are converted either to the corresponding enol triflates[60,61] or vinyl iodides,[62,63] which are coupled with alkenes using a catalytic amount of a Pd salt, usually $Pd(OAc)_2$, or a Pd complex ($(Ph_3P)_2Pd(OAc)_2$) and excess base (Et_3N, KOAc, or K_2CO_3). In most cases, the incorporation of the unsaturated side chains with the appropriate functional groups makes possible further transformations leading to compounds of potential pharmacological importance.

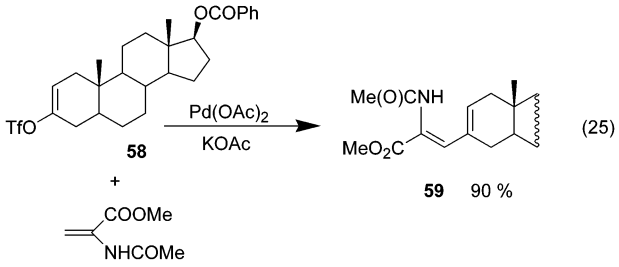
A great number of publications concerning the coupling of steroidal enol triflates with alkenes have appeared since the pioneering work of Cacchi et al.[60] Cacchi reported that steroidal enol triflates (3-triflyloxy-cholest-2-ene (**56**), 3β-acetoxy-17-triflyloxy-5α-androst-16-ene, and 17β-acetoxy-3-triflyloxy-androsta-3,5-diene) could be converted to the corresponding substituted α,β-unsaturated dienes (or trienes) (eq 24) in good yields using various olefins (methyl acrylate, 1-buten-3-one, allyl alcohol, 1-decene, or styrene) as reagents. The use of the $Pd(OAc)_2 + 2Ph_3P$ catalyst precursor and triethylamine as a base resulted in products in 65−86% isolated yield. In the absence of Ph_3P, the yield of the products dropped considerably. The coupling of methyl acrylate, 1-buten-3-one, and styrene was regioselective. The reaction of the allyl alcohol and 1-decene resulted in the formation of a mixture of regioisomers, though β-vinylation was favored, as observed later in the coupling of vinyl acetate and steroidal enol triflates.[64]



(24)

Unsaturated side chains were attached to various positions (C-3, C-17,[65] and C-4[66]) of the steroidal skeleton starting from enol triflates and α,β-unsaturated ketones,[65] α,β-unsaturated esters,[66] or *N*-protected allylamines.[67] The reactions were highly stereo- and regioselective in each case.

Various steroidal β-vinyl-α,β-didehydro-α-amino acids (e.g., **59**, eq 25) were produced in 60−90% isolated yield with α-acetoamidoacrylate as the Heck reagent.[68] The best yields were achieved by the use of the $Pd(OAc)_2$ catalyst in the presence of KOAc.



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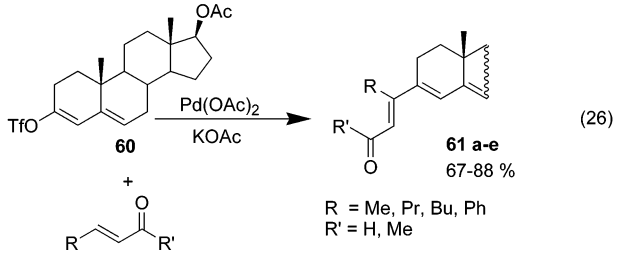
Enol triflates were reacted with α-methylene-γ-butyrolactone to yield a mixture of furan-2(5*H*)-ones and α-alkylidene-γ-butyrolactones that were converted by hydrogenation into the corresponding 3-substituted-γ-butyrolactones in approximately 80% yield without the isolation of the coupling products.[69]

Enol ethers of β,γ-unsaturated α-keto esters with the *Z* configuration were produced in the reaction of enol triflates and methyl α-methoxyacrylate in the presence of the $Pd(OAc)_2 + 2Ph_3P$ catalytic system under phase-transfer conditions.[70]

Vinylation of various primary, secondary, and tertiary allylic alcohols with enol triflates furnished the conjugated dienols as the major products.[71] The regioselectivity for substitution at the terminal carbon of the olefin was generally good. For primary and secondary alcohols, the best results were obtained with $[(o\text{-Tol})_3P]_2Pd(OAc)_2$ as the catalyst and triethylamine as a base. However, the reactions with 2-methyl-3-buten-2-ol required the use of the ligandless $Pd(OAc)_2$ catalyst and K_2CO_3 as a base to get satisfactory yields.

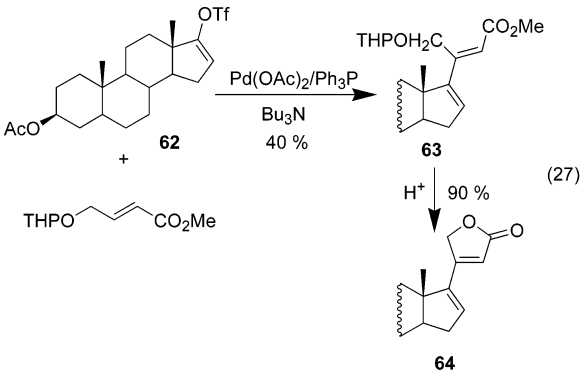
β-Substituted α,β-unsaturated carbonyl compounds[72] and esters[73] were also used as Heck reagents in the Pd-catalyzed coupling with steroidal enol triflates. The coupling was highly regio- and stereoselective. The products (e.g., **61a**−**e**) were formed via preferential attack at the β carbon of the olefin, and trans disposition of the steroidal moiety toward the carbonyl group was observed (eq 26). Comparing various β-substituted α,β-unsaturated esters, a decrease in the yield with increasing size of the β substituent was evident.



(26)

Although attempts to couple 3β-acetoxy-17-triflyloxy-5α-androst-16-ene (**62**) directly with 2(5*H*)-

furanone failed, the Heck reaction of this substrate with (*E*)-3-(methoxycarbonyl)-2-propenyl tetrahydropyranyl ether produced a useful intermediate (**63**) of the synthesis of cardenolides (**64**, eq 27), as reported by Harnisch et al.[73]

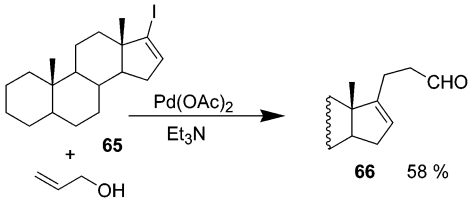


(27)

In some cases, steroidal aryl triflates or vinyl iodides were also used as substrates in the Heck reaction.

In the reaction of 3-triflyloxy-estra-1,3,5(10)-trien-17-one with α-acetoamidoacrylate, special conditions [$Pd(OAc)_2$/*n*-Bu_3N/dppf/LiCl] and a longer reaction time (20 h) compared to those of the coupling of enol triflates (2−7 h) had to be used to achieve a satisfactory yield of the product (62%).[68] The reaction of the same compound with methyl-α-methoxyacrylate required similar conditions.[70]

Steroidal vinyl iodides (17-iodo-5α-androst-16-ene (**65**), 17-iodo-4-aza-5α-androst-16-en-3-one, and 17-iodo-4-aza-4-methyl-5α-androst-16-en-3-one) were successfully used as substrates during the coupling with allyl acetate or methyl acrylate in the presence of the $Pd(OAc)_2$ catalyst and triethylamine as a base.[74] With methyl acrylate, in contrast to the coupling of enol triflates,[60] a lower yield of the diene was obtained, especially at higher temperature, because of the Diels−Alder reaction of the product with the starting olefin. Also, unlike the reaction of enol triflates,[71] the coupling of allyl alcohol with the steroidal alkenyl iodides (e.g., **65**) led to the exclusive formation of 21-formyl-pregn-16-enes (e.g., **66**) (eq 28).



(28)

Steroidal methyl ketones were produced via the Heck reaction of the corresponding vinyl iodides or enol triflates, and ethyl vinyl ether followed by acidic hydrolysis of the product α-alkoxy-vinyl derivatives.[75] Although the coupling of enol triflates gave better overall yields (75−78%) than those of vinyl iodides (45−50%), a byproduct, formed via the attack of the β carbon of the vinyl group of ethyl-vinyl ether, could be isolated in one of these reactions.

A steroidal 3-enol sulfonate, instead of triflate, was also converted to the 3-acetyl derivative via coupling with ethyl-vinyl ether.[76]

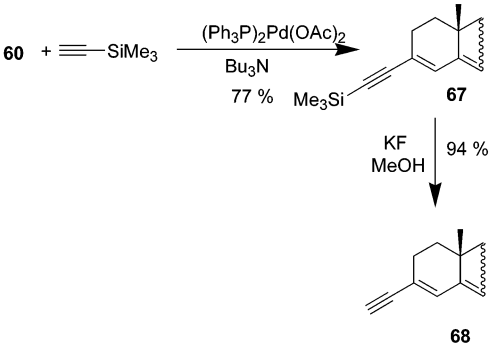
Hydrovinylation can also accompany palladium-catalyzed C−C coupling reactions in the presence of proton donors (e.g., AcOH formed from KOAc, which is usually used as a base). As an example, the coupling of 3β-acetoxy-17-triflyloxy-androst-16-ene and butenal afforded 3β-acetoxy-21-formyl-20-methyl-pregn-16-ene exclusively. The reaction of the same steroid with methyl 2-butenoate furnished the vinylic substitution product selectively. Therefore, it can be concluded that the vinylic substitution/hydrovinylation ratio depends on an intriguing combination of steric and electronic effects of the reaction partners.[72]

5.2. Coupling Reactions of Steroidal Enol Triflates/Iodo Alkenes with Alkynes

Enol-triflates undergo carbon−carbon bond-forming reactions not only with alkenes but also with terminal alkynes to produce conjugated enynes. When a catalytic amount of CuI is used together with the usual Pd catalyst ($(Ph_3P)_4Pd$ or $(Ph_3P)_2Pd(OAc)_2$), the reaction proceeds smoothly even at room temperature.

Various enol-triflates (3-triflyloxy-androsta-3,5-diene, 3β-acetoxy-17-triflyloxy-androsta-5(6),16-diene, 3-triflyloxy-cholesta-3,5-diene, and 3-methoxy-17-triflyloxy-estra-1,3,5(10),16-tetraene) were converted to the corresponding steroidal enynes in good yield (71−96%) using a number of terminal alkynes (e.g., ethynylbenzene, ethynyltrimethylsilane, ethyl propynoate, 3-hydroxy-3-methyl-1-butyne, and 3,3-dimethyl-1-butyne) as reagents.[77] The use of triethylamine as the base gave satisfactory results in most cases, with the exception of the reactions of ethyl propynoate. Here, good conversions could be achieved by substituting sodium acetate for the amine.

A variety of steroids containing 1-hydroxy-3-yn-5-ene[78] and 5-vinyl-4-pentynoic acid moieties[79] were obtained in excellent yield (85−95% in most cases) in the coupling of enol-triflates and 1-butyn-4-ol and 4-pentynoic acid, respectively. Even terminal steroidal alkynes such as 3-ethynyl-17β-acetyl-androsta-3,5-diene (**68**) were synthesized in this way by the desilylation of the coupling product of trimethylsilylacetylene with 17β-acetoxy-3-triflyloxy-androsta-3,5-diene (**60**) (eq 29).[80]



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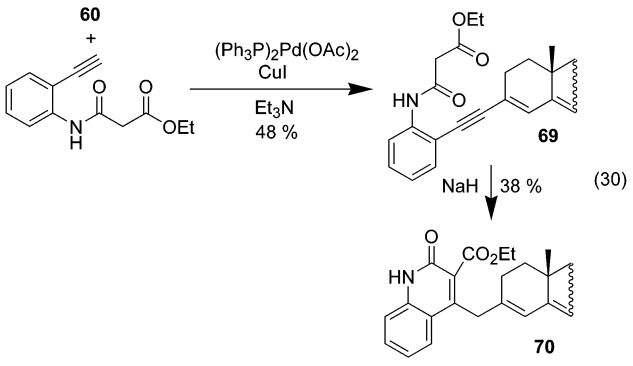
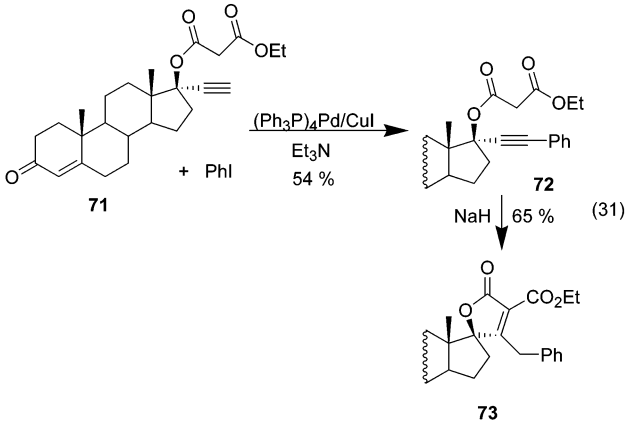
Steroidal alkynes with fluorescent labels, which can serve as probes in biological systems, were also obtained by coupling reactions.[81] In this case, the label-molecule is connected to the steroidal moiety through a predominantly hydrocarbon spacer arm

that is supposed to be more resistant to enzymatic hydrolysis compared to functional groups such as esters or amides, which result from standard labeling protocols.

Steroidal alkynes of more complex structure can be used for the construction of heterocyclic derivatives because the alkynyl moiety can provide new carbon−carbon and carbon−heteroatom bonds by simple transformations. (Palladium-catalyzed reactions of enol triflates leading directly to cyclic compounds are discussed in Chapter 8.) The cyclization of coupling products of ethyl *N*-(*o*-ethynyl))malonanilide (**69**)[82] and propargyl ethyl malonates (**72**)[83] led to 3,4-disubstituted-2(1*H*)-quinolones (**70**, eq 30) and substituted butenolides (**73**, eq 31), respectively. Various 2-alkynyl-anilines, intermediates for the Pd-catalyzed synthesis of steroidal 2-substituted indoles (Chapter 8), were obtained by the coupling of triflates with 2-ethynylaniline in 85−98% isolated yield.[84]





Preformed heterocyclic rings with alkynyl side chains can also be attached to the steroidal backbone via palladium catalysis. Steroidal alkynylpyrroles and 1*H*-pyrrol-2(3*H*)-ones were obtained by the coupling of steroidal triflates with the corresponding terminal alkynes.[85]

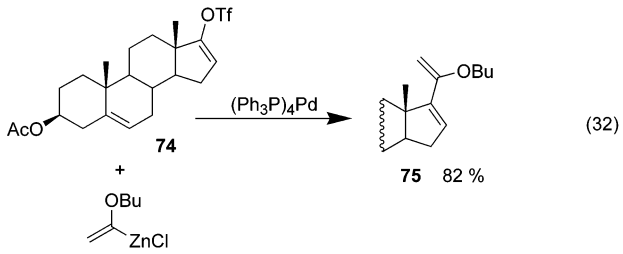
As in the Heck reaction, here it was also demonstrated that steroidal enol sulfonates can be used as substrates during the coupling with alkynes.[76]

When the palladium-catalyzed reaction of steroidal enol triflates with internal acetylenes was carried out in the presence of trialkylammonium formate reagents, a hydrovinylation reaction instead of substitution took place. The reaction of triflates with diphenylacetylene[86] and a tertiary 3-(*o*-acetoxyaryl)-propynol derivative[87] led to the corresponding conjugated dienes in moderate to good yield. All of the reactions were stereoselective, affording the cis adducts. In the case of the propynol derivative, the regioselectivity of the reaction was controlled by the directing effect of the tertiary hydroxy group, leading to C−C coupling at the C-3 position of the propynol. The product was used as starting material for a zinc chloride-mediated cyclization following the cleavage of the ester group that resulted in the formation of a steroidal 4-vinylchromene.

5.3. Coupling Reactions of Steroidal Enol Triflates/Iodo Alkenes with Organometallics

Beside the reactions discussed in the above two chapters, the palladium-catalyzed cross coupling of enol/aryl triflates or halides with organometallic reagents also serves as a versatile method for carbon−carbon bond formation. Among the numerous organometallics that can be used as coupling partners, organozinc, boron, and tin derivatives were employed in the functionalization of steroids.

This approach has been successfully used in the synthesis of 3β-acetoxy-21-hydroxy-pregna-5,16-dien-20-one.[88] Efforts to produce intermediate enol ether **75** via Heck coupling of 3β-acetoxy-17-triflyloxy-androsta-5,16-diene (**74**) and butyl vinyl ether were fruitless because of the low regioselectivity of the reaction. However, coupling between the same triflate and (α-methoxyvinyl)tributyltin in the presence of the $Pd(OAc)_2 + 2Ph_3P$ catalyst and 3 equiv of LiCl afforded the steroid with the desired 2-methoxy-1,3-diene moiety in 54% yield. Even better results were obtained by coupling triflate **74** with a zinc reagent, α-butoxy-ethenyl zinc chloride, using $(Ph_3P)_4Pd$ (eq 32). The desired enol ether (**75**) could be produced in 82% yield.

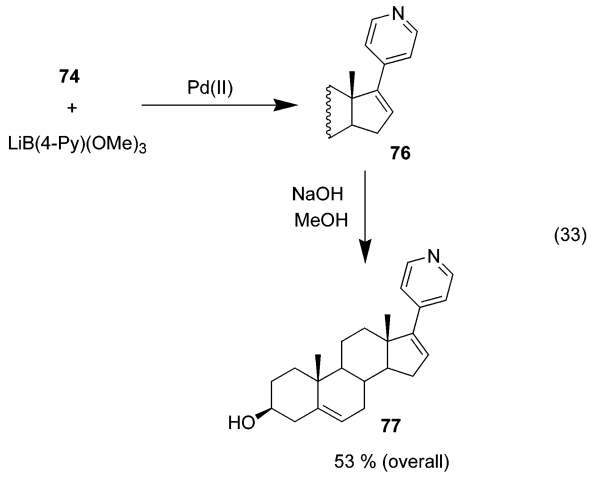


Furan rings were attached to C-3 or C-17 positions of various steroids via cross coupling of enol triflates and 2-furylzinc chloride.[89]

The palladium-catalyzed coupling of 17-iodo-6β-methoxy-3α,5α-cyclo-androst-16-ene and 17-iodo-androsta-5,16-dien-3β-ol with various arylzinc chlorides, which were generated from aryl bromides (1-bromomethylbenzene, *O*-(triethylsilyl-2-bromophenyl)-propan-2-ol, 4-bromobenzonitrile, 4-bromobenzoic acid *tert*-butyl ester, and 3-bromopyridine) via aryllithium derivatives, was examined. The respective cross-coupling products were obtained in good yields.[90]

During the quest for efficient inhibitors of human cytochrome $P450_{17\alpha}$ (17α-hydroxylase-$C_{17,20}$-lyase), which is a key enzyme in androgen hormone biosynthesis, a number of 17-pyridyl-androstenes were synthesized.[91] The question was how the pyridyl substituent could be incorporated into the steroidal

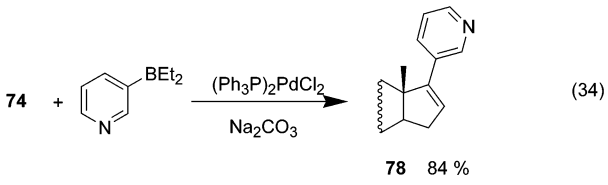
skeleton such that the pyridyl nitrogen would coordinate to the iron atom of the heme cofactor of the active site of the enzyme. 2-Pyridyl- and 2-picolyl derivatives were produced by coupling 3β-acetoxy-17-triflyloxy-androsta-5,16-diene with 2-pyridyl- and 2-picolylzinc chloride, respectively. The same method led to the 4-pyridyl steroid in low yield, probably because of the instability of 4-bromopyridine used for the in situ synthesis of the organozinc compound. However, the coupling of another organometallic reagent, lithium trimethoxy(4-pyridyl)boronate, to 3β-acetoxy-17-triflyloxy-androsta-5,16-diene **74** led to 3β-acetoxy-17-(4-pyridyl)androsta-5,16-diene (**76**, eq 33), which after hydrolysis gave **77** in satisfactory yield.



(33)

In the syntheses of the 2- and 4-pyridyl derivatives, a novel palladium catalyst, bromo-(isopropenyl)bis-(triphenylphosphine)palladium(II), prepared from 2-bromopropene and $(Ph_3P)_4Pd$ was used. This catalyst enabled the coupling to proceed at ambient temperature, thereby avoiding side reactions.

The most potent inhibitors of the target enzyme, the 17-(3-pyridyl)-16-ene derivatives (e.g., **78**) were obtained by the coupling of the corresponding triflates with diethyl(3-pyridyl)borane (eq 34).[91] In this reaction, good results were achieved even with 0.001 equiv of catalyst $(Ph_3P)_2PdCl_2$. This method turned out to be more efficient and higher-yielding than a previous route, the reaction of 3-pyridyl-lithium with a 17-keto steroid and the dehydration of the resulting tertiary alcohol. Other 3-pyridyl compounds with further structural variations in rings A and B were also produced by the same method.



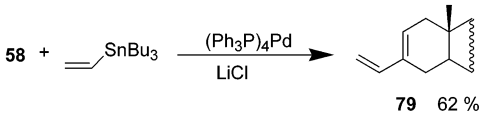
(34)

Because of some problems concerning the synthesis of the starting 17-enol triflate derivative, the possible use of 3β-hydroxy-17-iodo-androsta-5,16-diene was investigated.[92] The cross coupling of this vinyl iodide with diethyl(3-pyridyl)borane proceeded without the need to protect the 3-hydroxyl function, but the reaction was much slower, requiring 4 days at 80 °C compared to 1 h with the enol triflate.

Functional groups in the para position of the aromatic group of 11β-aryl-substituted steroidal derivatives were introduced via a palladium-catalyzed coupling reaction of the corresponding aryl triflates and diethyl(3-pyridyl)borane or tributyl(1-ethoxyethenyl)stannane during the synthesis of antiprogestins.[93]

$NaBPh_4$ was used as a phenylating agent in the palladium-catalyzed cross coupling of steroidal triflates.[94] The reaction of enol triflates with $NaBPh_4$ in DMF in the presence of $(Ph_3P)_4Pd$ and in the absence of a base proceeded even at room temperature to produce the corresponding phenyl-substituted steroids in 67−73% isolated yield in 1−3 h. It was proven that in the presence of a base (Et_3N) more then two phenyl groups were available for transfer to the vinylic moiety, so the reactions could be conducted with a borate/triflate ratio of $^{0.5}/_{1}$. Other tetraarylborates ($NaB(4\text{-}MeC_6H_4)_4$ and $NaB(4\text{-}FC_6H_4)_4$) were also successfully employed as reagents. The reaction of the aryl triflate 3-triflyloxy-estra-1,3,5-(10)-trien-17-one was again more sluggish, but the use of $K_3PO_4 \cdot 3H_2O$ as a base in toluene led to a satisfactory yield of the 3-phenyl derivative.

Conjugated steroidal dienes (e.g., **79**) that could be good starting materials for further functionalization of the steroidal skeleton were produced by the coupling of enol triflates (e.g., **58**) and vinyltributyltin (Stille coupling) (eq 35).[95] Yields 62−65% have been obtained in the presence of the $(Ph_3P)_4Pd$ catalyst and LiCl, which had been reported to act as a ligand exchanger in the initially formed organopalladium triflates.[96] In some cases, vinyltributyltin had to be used in excess because some of this organometallic reagent was consumed in a side reaction with LiCl, leading to the formation of Bu_3SnCl without coupling with the steroid.



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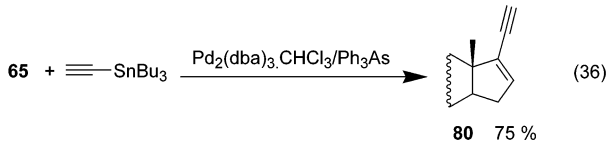
3-Triflyloxy-estra-1,3,5(10)-trien-17-one[46] and 17β-(*N-tert*-butylcarboxamido)-3-triflyloxy-estra-1,3,5(10)-triene[97] were converted to the corresponding aryl-alkenes using $(Ph_3P)_4Pd$ and $(Ph_3P)_2PdCl_2$ catalysts, respectively, in the presence of LiCl.

Steroidal alkenyl iodides were also effectively used as starting material in the absence of LiCl, giving cleaner reactions compared to those of triflates.[98] The aza derivatives (17-iodo-4-aza-5α-androst-16-en-3-one and 17-iodo-4-aza-4-methyl-5α-androst-16-en-3-one) were less reactive than 17-iodo-5α-androst-16-ene but could be successfully converted to the products in a longer reaction time. In the case of 17-bromo-5α-androsta-2,16-diene, the addition of a new portion of $(Ph_3P)_4Pd$ during the reaction was necessary because of a partial decomposition of the catalyst and the precipitation of palladium metal.

Conjugated steroidal enynes were produced by reacting the same substrates with ethynyltributyltin. Using the $Pd_2(dba)_3 \cdot CHCl_3 + 8Ph_3As$ catalyst system,

90% conversion of 17-iodo-5α-androst-16-ene (**65**) was achieved in half an hour even at 0 °C (eq 36).



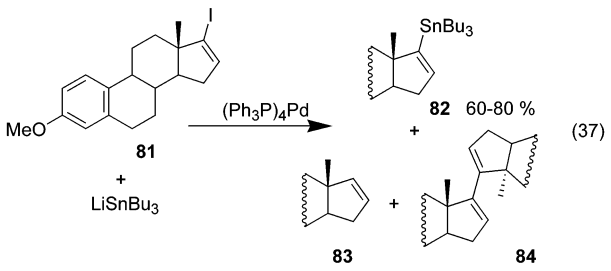
(36)

The use of the above catalyst was essential to the production of steroidal 3-indoles in high yield in the coupling reactions of enol triflates with 1-tosyl-3-tributylstannylindoles. Unsatisfactory results were obtained by employing either $(Ph_3P)_4Pd$ or the $Pd_2(dba)_3$ + tri(2-furyl)phosphine system both in the presence and in the absence of LiCl.[99]

The coupling of alkenyl iodides with vinyltributyltin was also carried out using microwave irradiation.[100] Reactions were complete in minutes compared to the 3−5 h that was needed in the case of conventional heating.

As an alternative to the Heck reaction, palladium-catalyzed coupling of 17-iodo-16-enes with (α-ethoxyvinyl)tributyltin was used for the synthesis of coupling products that after hydrolysis furnished the 17-acetyl derivatives in 60% yield.[101]

The reaction of similar substrates (e.g., **81**) with lithium(tributyl)stannate led to the 17-tributylstannyl-16-enes (**82**) in 60−80% yield in the presence of electron-rich complexes of nickel and palladium. The formation of side products 16-enes (**83**) and steroidal dimers (**84**) emerging from the cross coupling of the 17-iodo-16-enes and the tributylstannyl steroids (eq 37) was also observed.[101]



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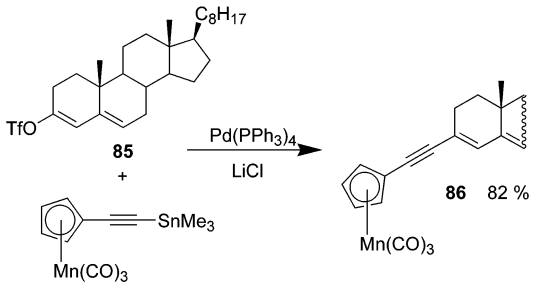
The palladium-catalyzed Stille cross-coupling reaction of *N-Boc*-4-trimethylstannyl-L-phenylalanine methyl ester with 3-triflyloxy-cholesta-3,5-diene afforded the corresponding steroidal phenylalanine in 78% yield.[102]

The effect of the A-ring substitution of 2,4-disubstituted estradiol derivatives was investigated by Cummins. It has been stated that the ortho substituents could provide a mechanism for altering conjugation chemistry and that their presence could slow or prevent metabolic catechol estrogen formation.[103] He found that 2,4-dibromo analogues of estrone or ethynylestradiol or various protected forms of the two compounds could not be converted to the 2,4-dimethyl derivatives by a halogen−metal exchange process with a methyl iodide quench. However, the coupling of 3-acetoxy-2,4-dibromo-estra-1,3,5(10)-trien-17-one with tetramethyltin in the presence of $(Ph_3P)_2PdCl_2$ led to the 2,4-dimethyl derivative in 83% yield.

Steroids were labeled with the ethynylcyclopentadienyl-manganese-tricarbonyl moiety by Stille coupling (eq 38).[104] The metal carbonyl complexes can be used as FTIR markers in biological studies as an alternative to radioactive markers in immunoassays. Various enol and aryl triflates (e.g., **85**) were coupled with {η^5-[(trimethyltin)ethynyl]cyclopentadienyl}-manganesetricarbonyl in the presence of the $(Ph_3P)_4$-Pd catalyst and 7 equiv of lithium chloride in THF. Coupling products (**86**) of enol triflates were isolated in 80−85% yield after 12−14 h of reflux. The aryl triflate was less reactive, but the same yield was obtained after prolonged interaction (20−24 h). However, steroidal allyl and vinyl bromides failed to couple with the organometallic reagent.



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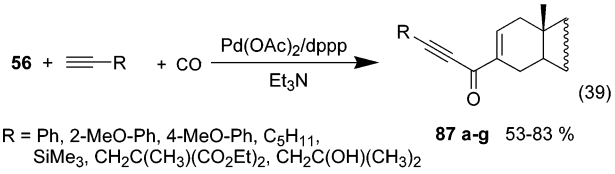
5.4. Carbonylative Coupling Reactions

When some of the reactions discussed in Chapters 5.2 and 5.3 are carried out under atmospheric CO pressure, the starting enol triflates or alkenyl halides can be converted into unsaturated carbonyl compounds. Acylpalladium(II) complexes are formed in the reaction of the substrates with the palladium precursor and carbon monoxide. These intermediates are very active acylating agents and lead to the products by reacting with an alkyne or an organometallic compound.

Various steroidal alkynyl ketones were obtained starting from enol triflates (e.g., **56**) and a number of terminal alkynes (phenylacetylene, (2-methoxyphenyl)acetylene, (4-methoxyphenyl)acetylene, 1-hexyne, 4-hydroxy-4-methyl-1-pentyne, etc.) in the presence of $(dppp)PdCl_2$ (dppp: 1,3-bis(diphenylphosphino)propane)) at 60 °C in 73−83% yield (eq 39).[105] In the case of 3β-acetoxy-17-triflyloxy-5α-androst-16-ene, a CuI cocatalyst had to be used to avoid the side reaction of direct coupling. However, 3-triflyloxy-estra-1,3,5(10)-trien-17-one was recovered practically unchanged even using a higher reaction temperature or a CuI cocatalyst.

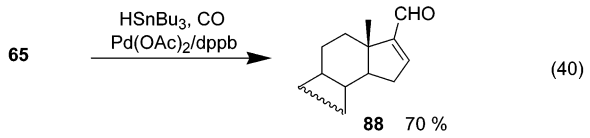


(39)

The palladium-catalyzed carbonylative coupling of enol triflates or vinyl iodides and vinyltributyltin in the presence of $(Ph_3P)_4Pd$ led to the corresponding vinyl ketones in good yield.[95,98] For the conversion of enol triflates, the use LiCl was essential. As observed

by Ciattini during the coupling with alkynes, 3-triflyloxy-estra-1,3,5(10)-trien-17-one was unreactive in this reaction, too. The reactivity order of alkenyl halides was the same as that observed in direct coupling. No carbonylative coupling of the same substrates was observed with ethynyltributyltin. In a CO atmosphere, only a small amount of the directly coupled products were obtained but with considerably lower yields than under argon.

17-Formyl-androst-16-ene (**88**) and its analogues were synthesized from the corresponding 17-iodo-16-ene derivatives (e.g., **65**) in palladium-catalyzed formylation (eq 40). Tributyltin hydride was used as a hydrogen source under mild reaction conditions (1 bar carbon monoxide, 50 °C). The formylation is accompanied by hydrogenolysis, resulting in 16-ene derivatives and their isomerization products. The extent of the side reactions can be controlled by the reaction conditions and the use of the appropriate ligand in the catalyst precursor.[106]



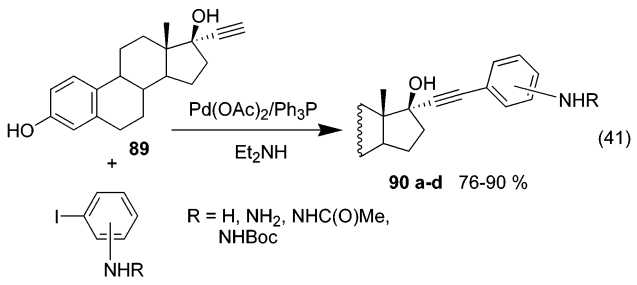
(40)

Both iodovinyl- and triflyloxyvinyl substrates were used as starting materials for the synthesis of phenyl ketones via carbonylation in the presence of $NaBPh_4$.[107] The activity of the $(Ph_3P)_4Pd$ catalyst was similar to that of the $Pd(OAc)_2 + 2Ph_3P$ system. The use of the former complex suppressed side reactions and made it possible to decrease the borate/steroid ratio even to $^{0.25}/_{1}$ without the loss of selectivity.

5.5. Coupling Reactions of Steroidal Alkenes/Alkynes

Steroids with unsaturated side chains may undergo palladium-catalyzed coupling reactions with aryl/alkenyl halides.

Various nitrogen-containing moieties were incorporated into the 17α side chain of 17α-ethynylestradiol (**89**) via the palladium(0)/copper(I)-catalyzed reaction of the steroid and iodoaniline or (iodophenyl)hydrazine derivatives (eq 41). The amino group of halogenated benzylamines had to be protected before coupling to avoid competing ortho palladation of the benzylamine substrates.[108]

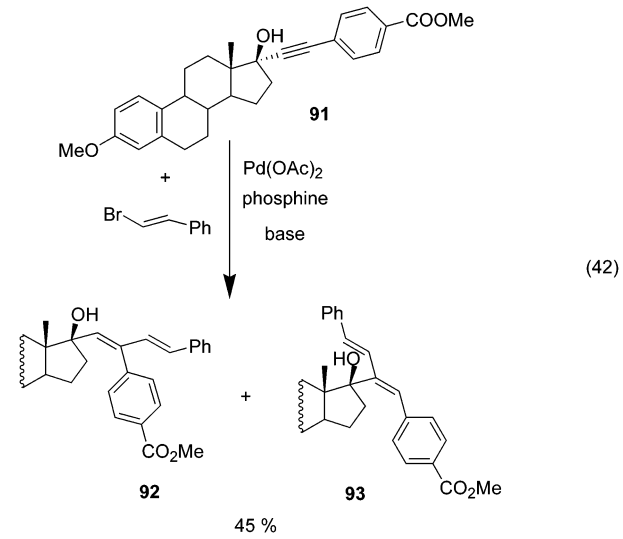


(41)

Palladium-catalyzed cross-coupling of 4-bromo-2,6-bis-((alkylthio)methyl)pyridine derivatives and 4-bromo-2,6-pyridinedicarboxylate diethyl ester with 17α-ethynyl-estradiol was accomplished to produce delivery vectors that facilitate the controlled transport of metal ions to tissues rich in estrogen receptors.[109]

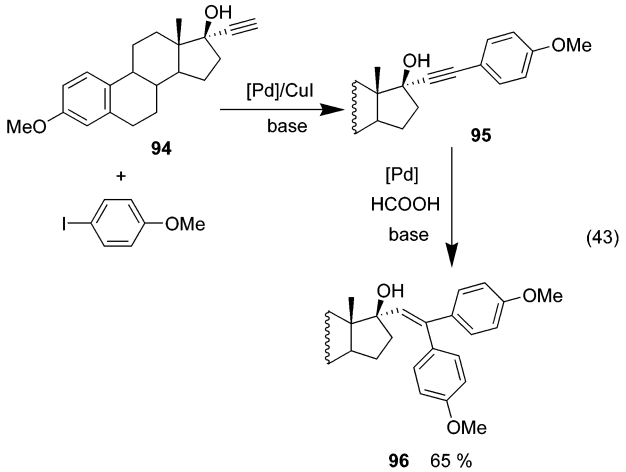
Palladium-catalyzed reductive addition of aryl or vinyl halides to carbon−carbon multiple bonds takes place in the presence of trialkylammonium formate reagents.

Various steroidal arylethynyl-dialkylcarbinols (e.g., **91**) were converted to steroids with α,β-unsaturated side chain (**92**, **93**) by the reductive addition of vinyl halides in the presence of $Pd(OAc)_2$, phosphines, formic acid, and a base. The configuration of the vinyl partner was retained. In the presence of Et_3N, the addition of the vinyl unit to the less crowded carbon atom was found to be favored (eq 42). This result was rationalized in terms of steric hindrance and hydroxyl coordination that affected the direction of the addition of the Pd-alkenyl complex, formed from the vinyl halide and the palladium precursor, to the carbon−carbon triple bond. The regioisomeric ratio ranged from 3.2 to 1.3 depending on the nature of the phosphine ligand (Ph_3P, $(o\text{-Tol})_3P$). A tendency to favor reverse addition and higher overall yields were obtained using Bu_3N as a base.[110]



(42)

17α-Ethynyl-3-methoxy-estra-1,3,5(10)-trien-17β-ol (**94**) was subjected to a subsequent Pd-catalyzed addition−reductive addition sequence using 4-methoxy-phenyl iodide as a reagent (eq 43). The first step



(43)

leading to coupling product **95** was accelerated by the presence of a catalytic amount of a Cu(I) salt. The reductive arylation was carried out by simply adding the palladium catalyst, the base (piperidine), the formic acid, and an excess of the aryl iodide to the reaction mixture derived from palladium-catalyzed coupling filtered through a short column of florisil. Again, the aryl moiety tended to react with the less crowded carbon atom of the triple bond in the second step, and the reaction produced **96** in 65% yield.[111]

A similar reductive addition of 4-hydroxyphenyl iodide to a steroidal 16,20-dien-22-one led to the exclusive formation of the 20-aryl derivative in moderate yield.[65]

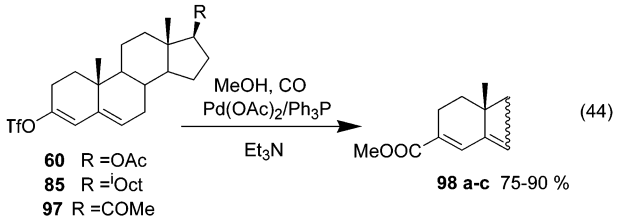
Steroids with the 17-acetyl-16-ene moiety were synthesized by the palladium-catalyzed coupling of the corresponding 17-tributylstannyl compounds with acetyl chloride. The drawback of this method was the cleavage of protecting groups (tetrahydropyranyl- or ethyl-) of androst-5,16-dien-3-ol derivatives. This reaction was found to be accompanied by the formation of the 16-ene compounds instead of 17-acetyl-16-enes as the main products.[75]

6. Carbonylation Reactions of Enol Triflates and Related Structures

Aryl triflates or alkenyl triflates/halides can be oxidatively added to Pd(0) precursors, resulting in the formation of arylpalladium(II) or alkenylpalladium-(II) complexes, respectively. The reaction with carbon monoxide produced the corresponding acylpalladium-(II) derivatives. These complexes serve as very active acylating agents and give various carboxylic acid derivatives upon reaction with nucleophiles. The carbonylation can be made catalytic in the presence of a base that converts the hydrido-palladium(II) complex produced in the above reaction back to the starting Pd(0) species. This method was effectively used for the incorporation of carboxylic acid, ester, or amide functionalities into various positions in the steroidal skeleton.

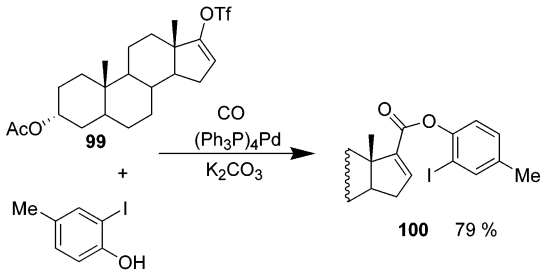
6.1. Alkoxycarbonylation and Hydroxycarbonylation Reactions

Cacchi and co-workers found that the carbonylation of enol triflates (**60**, **85**, **97**) provided a practically useful route to the corresponding α,β-unsaturated methyl esters (**98a**−**c**) (eq 44).[112] The use of the $Pd(OAc)_2 + 2Ph_3P$ catalyst and triethylamine as the base led to products in 69−90% yield at room temperature in 1−6 h. Even isopropyl alcohol was successfully used as a nucleophile. The method was extended to 3-triflyloxy-estra-1,3,5(10)-trien-17-one, but in this reaction, the application of dppf instead of Ph_3P was essential.[113] Furthermore, an increased amount of phosphine (2 moles per mole of palladium) was also necessary to obtain the 3-methoxycarbonyl-estra-1,3,5(10)-trien-17-one in 81% yield at 60 °C. Another palladium complex, $(dppp)Pd(OAc)_2$, was also reported to be a useful catalyst in the conversion of 17-(*tert*-butyl-dimethylsiloxy)-3-triflyloxy-estra-1,3,5(10)-triene to the 3-methylester.[114]



(44)

The carbonylation of steroidal enol triflates (e.g., **99**) with 2-iodo-4-methyl-phenol in anhydrous MeCN in the presence of a catalytic amount of $(Ph_3P)_4Pd$ and K_2CO_3 as a base afforded *o*-iodophenyl α,β-unsaturated esters (**100**) in high yield (eq 45).[115] It is worth mentioning that under these reaction conditions the oxidative insertion of the catalyst took place chemoselectively into the =C−OTf bond and the aryl iodide moiety remained unchanged.

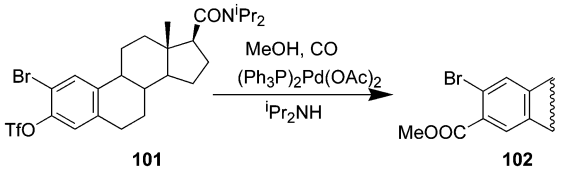


(45)

Several publications and patents show the effectiveness of carbonylation in the synthesis of a number of 5α-reductase inhibitors. (Steroid 5α-reductase is an enzyme responsible for the NADPH-dependent conversion of testosterone to dihydrotestosterone (DHT). Elevated DHT levels have been proven to result in several human endocrine diseases such as benign prostatic hyperplasia, prostatic carcinoma, male pattern baldness, etc. The inhibition of steroid 5α-reductase can diminish the formation of DHT in the tissues, thus steroid 5α-reductase inhibitors such as finasteride, epristeride, etc. can be used as pharmacological therapy for these diseases.)

Holt and co-workers reported the preparation of steroidal 3-carboxylic acid derivatives via the vinyl/aryl triflate-carboxylic acid ester-carboxylic acid sequence.[97,116−118] The first step involved the palladium-catalyzed carbonylation of vinyl or aryl triflates in the presence of methanol. Then the methyl esters were converted to carboxylic acids by hydrolysis.

It is worth mentioning that the carbonylation of 17β-(*N*,*N*-diisopropylcarbamoyl)-2-bromo-3-triflyloxy-estra-1,3,5(10)-triene (**101**) and the analogous 4-bromo derivative furnished the 2-bromo- (**102**) and 4-bromo-3-carboxylic acid derivatives, respectively, which shows the higher reactivity of the aryl triflate moiety compared to that of the aryl bromide (eq 46).[116]

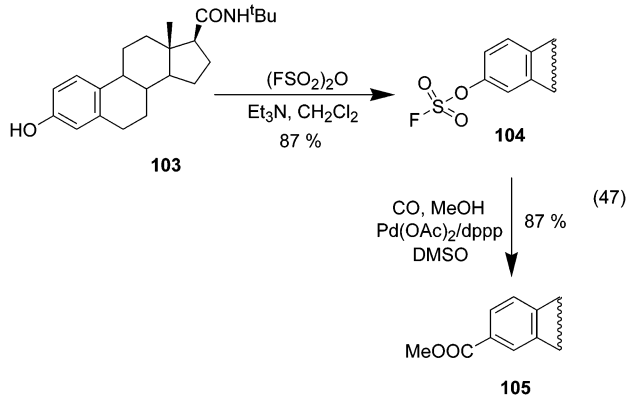


(46)

However, this method suffers from some drawbacks. The first problem concerns the production of the starting materials, the triflate derivatives. The synthesis requires the use of relatively expensive and moisture-sensitive triflic anhydride. Besides, according to Tian and co-workers, during the direct conversion of 17β-(*N*-*tert*-butylcarbamoyl)androst-4-en-3-one to the corresponding dienol-triflate with triflic anhydride, a 2:1 mixture of the awaited 3-triflyloxy-3,5-diene and its 17-nitrile byproduct was obtained.[119] The second problem may arise in the last, hydrolytic step of the sequence. In some cases, a considerable amount of a byproduct is formed by epimerization at C-17 during the basic hydrolysis to the acid.[120]

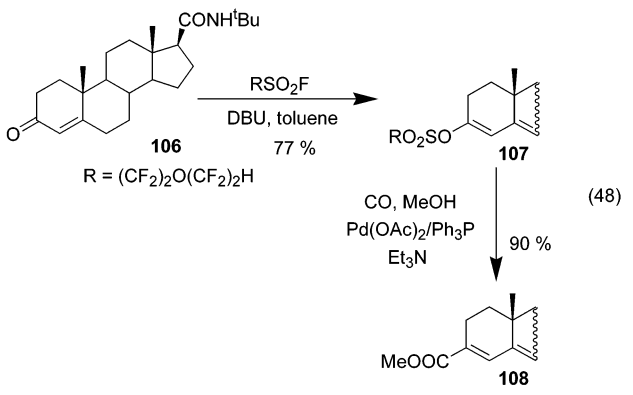
The first drawback can be overcome by the incorporation of other leaving groups into the desired positions of the steroidal skeleton. Fluorosulfonate esters or halides might serve as attractive alternatives to triflates.

The fluorosulfonation of 17β-(*N*-*tert*-butylcarbamoyl)estra-1,3,5(10)-trien-3-ol (**103**) with fluorosulfonic anhydride resulted in the formation of 3-(fluorosulfonate)ester **104** in 87% yield. The methoxycarbonylation of this compound led to 17β-(*N*-*tert*-butylcarbamoyl)-3-metoxycarbonyl-estra-1,3,5(10)-triene (**105**, eq 47). The reaction has been reported to proceed at a faster rate when only 4 to 5 equiv of methanol is present. The carbonylation could be run effectively with 0.5−1.0 mol % catalyst, even on a large scale. Probably because of superior mixing, the reaction was complete in 15 min (87%), compared to the 1−4 h reaction time that was required on a smaller scale.[121]



(47)

Polyfluoroalkanesulfonyl fluorides are structurally similar to the triflating agents, but they are less expensive and much easier to handle. Steroid 3-ketones (e.g., **106**) were chemo- and regioselectively converted to the corresponding enol sulfonates (**107**) using these compounds as reagents. For example, the reactions of 5*H*-3-oxa-octafluoropentanosulfonyl fluoride and steroid-3-ones with various other substituents at different positions occurred exclusively at the C-3 position. Other functional groups, such as amide or ketal and more interestingly C-6, C-17, and C-20 carbonyls, were not affected. The palladium-catalyzed carbonylation of such enol sulfonates in dimethylformamide and methanol at 70 °C produced the steroid-3-carboxylates (**108**) in 90% yield (eq 48).[76,119,122]



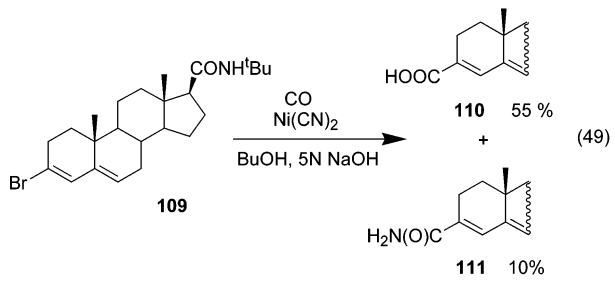
(48)

Some methods for the direct synthesis of steroidal carboxylic acids via palladium-catalyzed carbonylation have been developed.

A steroidal carboxylic acid was produced from 3-methoxy-17-triflyloxy-estra-1,3,5(10),16-tetraene by treatment with triethylammonium formate and carbon monoxide.[112]

Enol triflates were converted to the α,β-unsaturated acids in 77−84% isolated yield in the presence of $(Ph_3P)_2Pd(OAc)_2$, KOAc, and CO in DMF in 2 h. The acetate anion was found to play a crucial role in the success of the reaction. The conversion of aryl triflates required somewhat more forced conditions; 3-hydroxycarbonyl-estra-1,3,5(10)-trien-17-one was obtained from the corresponding 3-triflyloxy compound in 84% isolated yield after 18 h in DMSO at 60 °C using the $Pd(OAc)_2$ + dppf catalytic system.[123]

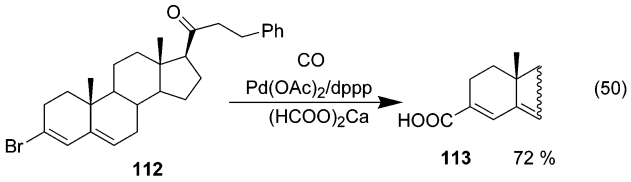
The hydroxycarbonylation of 3-bromo-17β-(*N*-*tert*-butylcarbamoyl)-androsta-3,5-diene (**109**) and 3-bromo-17β-(2-phenylethyl)carbonyl-androsta-3,5-diene (**112**) led to 5α-reductase inhibitors epristeride (**110**, SK&F 105657) and a 3-carboxy-20-keto steroid **113** (SB 209963), respectively. The nickel-catalyzed carbonylation of the first bromodiene in *n*-butanol/5N NaOH/$Ni(CN)_2$ under atmospheric carbon monoxide with cetyl trimethylammonium bromide as a phase-transfer catalyst resulted in the formation of product **110** in 55% yield together with a 3-primary amide byproduct (**111**, eq 49).[124] The formation of the latter compound was probably due to the displacement of the dienyl bromide with cyanide and subsequent hydrolysis with aqueous base. At the same time, the carbonylation of the same bromodiene substrate employing the usual $Pd(OAc)_2$ + $2Ph_3P$ catalyst system under similar phase-transfer conditions led to epristeride in 77% yield.



(49)

The hydroxycarbonylation of 3-bromo-17β-(2-phenylethyl)carbonyl-androsta-3,5-diene (**112**) was carried out with calcium formate in DMSO/toluene in the presence of the $Pd(OAc)_2$ + dppp catalyst in 72% yield (eq 50).[120] Tian et al reported the direct

synthesis of a steroidal carboxylic acid starting from enol sulfonates under the same conditions used for methoxycarbonylation but in the absence of methanol.[122] The source of OH is uncertain, but the mechanism is probably the same as in the formation of carboxylic acids under similar conditions starting from alkenyl iodides. Here, the carboxylic acids were produced via the primary formation of carboxylic anhydrides under carbonylation conditions in the presence of the water impurity of the solvent.[125]

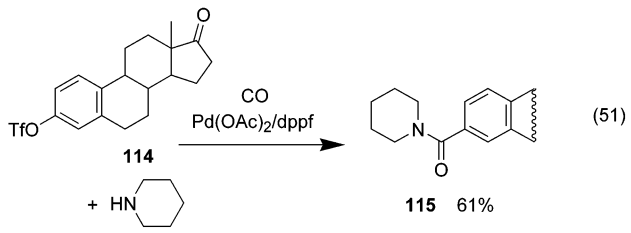


(50)

6.2. Aminocarbonylation and Related Reactions

The carbonylation of enol/aryl triflates or alkenyl halides in the presence of amines as nucleophiles leads to the formation of amides. The same substrates and similar conditions to those in the alkoxycarbonylation reactions were used by Cacchi et al. for the production of amides in the presence of Et_2NH and piperidine as nucleophiles.[112]

For the conversion of 3-triflyloxy-estra-1,3,5(10)-trien-17-one (**114**) to corresponding amide **115**, a higher reaction temperature (80 °C) and a higher phosphine ratio (9 mol % instead of 6 mol %) compared to those for the alkoxycarbonylation reaction of the same substrate had to be used (eq 51).[113] At 60 °C, the amide was formed in only 24% yield even after 7 h.

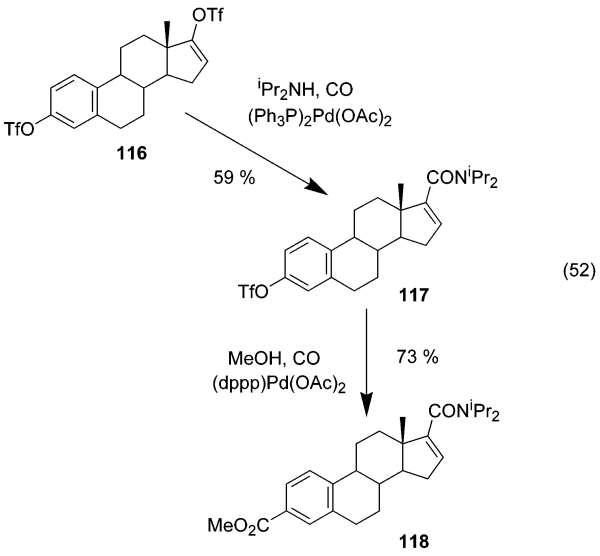


(51)

Not only the 3-carboxylic or phosphinic acid functionality but also the 17-carboxamido moiety was introduced to the steroidal skeleton to produce various 5α-reductase inhibitors by Holt et al.[97,116,117,126−128] Using 3,17-bis-triflyloxy-estra-1,3,5(10),16-tetraene (**116**) as the substrate, 3,17-heterosubstituted derivative **118** was obtained selectively in two subsequent carbonylation steps. The greater propensity for Pd insertion into the vinyl triflate over the aryl triflate allowed for the chemoselective introduction of the D-ring carboxamide using the $(Ph_3P)_2PdCl_2$ catalyst. Subsequent A-ring carbomethoxylation was accomplished at higher temperature by employing the more active $(dppp)Pd(OAc)_2$ catalyst (eq 52).[97,116]

As in the alkoxycarbonylation reactions, steroidal enol sulfonates were successfully used as substrates for the synthesis of carboxamides.[76,122]

Carbonylation reactions of enol and aryl triflates with hexamethyldisilazane as the nucleophilic partner, in the presence of $PdCl_2 + 2Ph_3P$ or $PdCl_2 + 2$

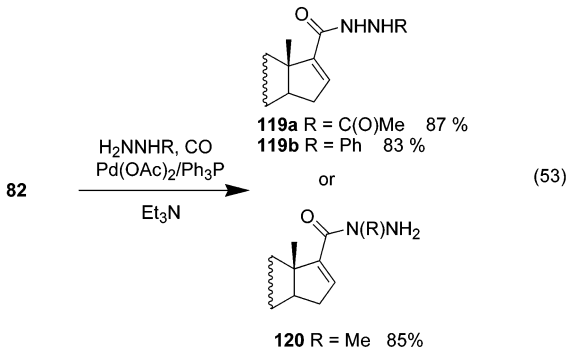


(52)

dppp catalytic systems, respectively, afforded the corresponding primary amides after the hydrolytic workup.[129]

17-Carboxamido-androstanes possessing crown ether moieties attached to the amide functionality were synthesized from the corresponding 17-iodo-androst-16-enes.[130]

Various steroidal hydrazides[131−133] and hydroxamic acid derivatives[134,135] were obtained by aminocarbonylation reactions using mono- or disubstituted hydrazines and either *N*- or *O*-substituted hydroxylamines as nucleophiles. As mentioned before, these reactions can be regarded as the acylation of the nucleophiles by the acylpalladium complex formed by consecutive oxidative addition−CO insertion reactions. When reagents with two nucleophilic centers (monosubstituted hydrazines or *N*-substituted hydroxylamines) have been used, the site of acylation is determined mainly by the electronic and steric properties of the nucleophiles. Acetyl- or phenylhydrazine is acylated at the unsubstituted nitrogen (products **119a**, **b**), but the acylation of methylhydrazine occurs exclusively on the substituted one (product **120**, eq 53).



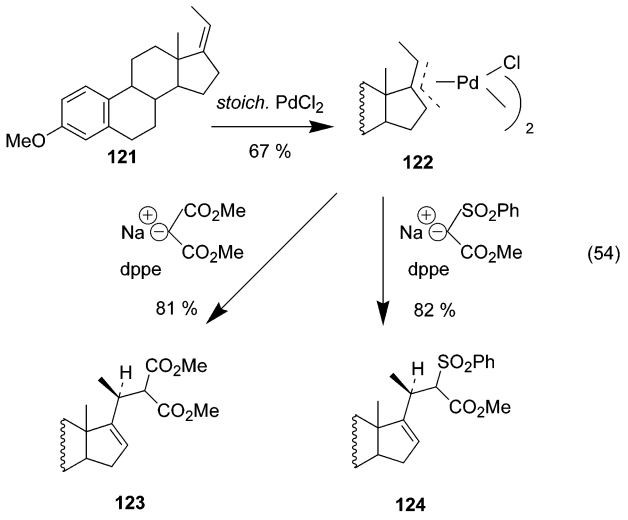
(53)

Similarly, the use of *N*-*tert*-butylhydroxylamine or *N*-acetylhydroxylamine led to *O*-acylated products in 93 and 100% yield, respectively. Interestingly, the site of acylation is greatly influenced by reaction conditions (solvent, substrate structure, temperature) in the case of *N*-methylhydroxylamine. Both *N*- and

O-acylated derivatives were synthesized in moderate to good yield by tuning the reaction conditions.

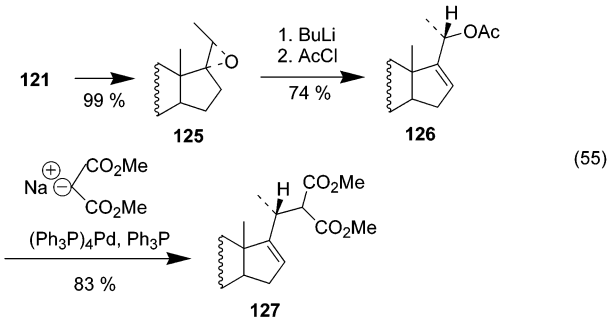
7. Stereocontrolled Introduction of an Acyclic Substituent onto a 4-Ring Skeleton via π-Allylpalladium Chemistry

The stereocontrolled introduction of side chains at C-20 in (*Z*)-$\Delta^{17,20}$ compounds was reported by Trost.[136,137] 3-Methoxy-*cis*-19-norpregna-1,3,5(10),17(20)-tetraene (**121**), obtained from estrone methyl ether by the Wittig reaction, was converted to its π-allyl-palladium complex (**122**), which underwent C-20 alkylation by dimethyl malonate and methyl phenylsulfonyl acetate nucleophiles in 81 and 82% yield, respectively, in the presence of a phosphine, favorably dppe (dppe: 1,2-bis(diphenylphosphino)-ethane) (eq 54). The reaction could be carried out catalytically,



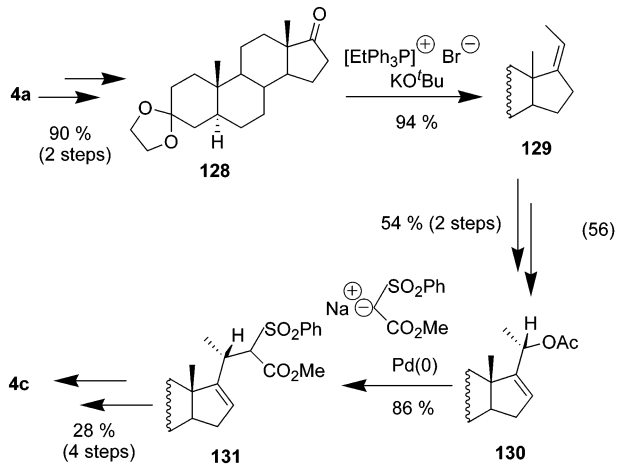
(54)

starting from allylic acetate **126** (eq 55). Interestingly, the two pathways, using stoichiometric and



(55)

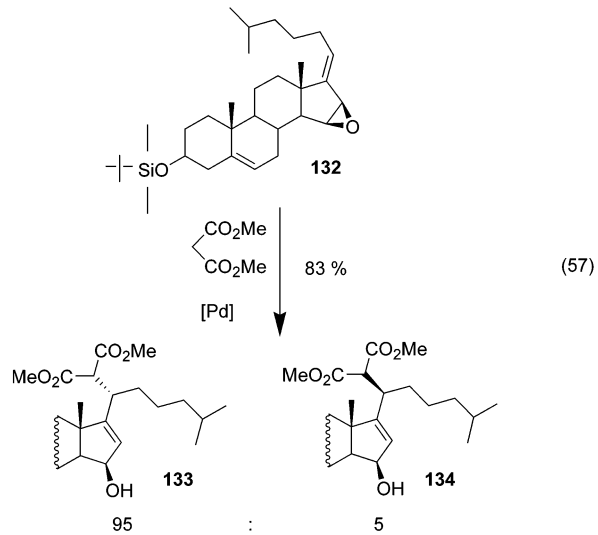
catalytic amounts of palladium, respectively, led to products with opposite stereochemistry at C-20. A similar reaction sequence was used for the synthesis of **131**, epimerically pure at C-20 using 4,5α-dihydrotestosterone (**4a**) as starting material. By subjecting **131** to further alkylation, desulfonylation, decarboxylation, and hydrogenation, 5α-cholestanone (**4c**) was obtained (eq 56).



(56)

The alkylation of the allylic carboxylate functionality of the 17β-alkenyl side chain of an androst-4-en-3-one derivative was carried out with the $(Ph_3P)_4Pd$ catalyst in the presence of NaH using dimethyl propargylmalonate as the reagent. The reaction resulted in the formation of an enyne that turned out to be a suitable starting material for a palladium-catalyzed cyclization leading to a five-membered carbocyclic ring in the 17β side chain.[138]

In the reaction of a 1,3-diene monoepoxide (**132**) with the dimethyl malonate nucleophile, the 1,4 adducts (**133**, **134**) were obtained in 83% yield (eq 57). The reaction with sulfonyl acetate was slow, and no reaction takes place with disulfone.[139,140] The high stereoselectivity was explained by the favorable initial attack of Pd(0) from the opposite face of the epoxide, resulting in the most stable syn π-allylpalladium species. Because syn−anti izomerization is supposed to be very slow due to the location of Pd on the congested β-face of the steroid, the following favorable attack of the malonate nucleophile proceeds again from the opposite (β) face of the syn-π-allylpalladium species. As staring material for the steroid diene monoepoxide, a 15-en-17-one derivative was synthesized by the reaction of the corresponding enol acetate with allyl methyl carbonate by using $Pd(OAc)_2$ and tributyltin methoxide as a bimetallic catalyst.



(57)

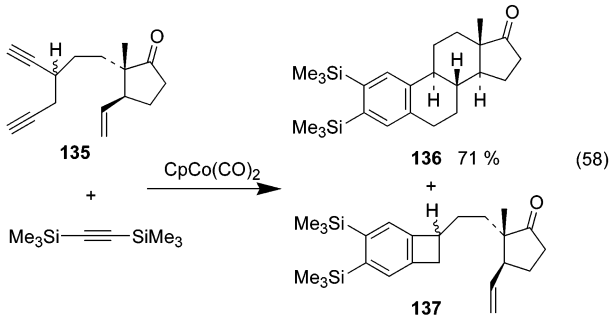
Copper(I) chloride was shown to catalyze the addition of Grignard reagents to 5α,10α-epoxy-$\Delta^{9(11)}$-19-norsteroids. The reactions led to the 11β-substituted derivatives exclusively, in nearly quantitative yields. Although the uncatalyzed reactions furnished the 10β-substituted steroids, in the copper-catalyzed addition no such compounds could be detected.[141]

8. Transition-Metal-Catalyzed Cyclization Reactions

8.1. Stereoselective Formation of the Basic Steroidal Skeleton via Cyclization Reactions

Although most of the publications discussed in this review deal with partial synthesis or selective functionalization of various positions of steroids, there are a number of elegant transition-metal-catalyzed total syntheses. There are several strategies for the construction of the steroid nucleus, including the cyclization of polyenes or polyynes, coupling, and ring-expansion reactions.

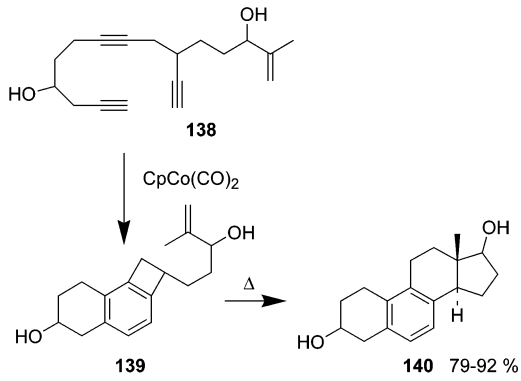
The cyclization of polyunsaturated compounds can take place in the presence of either stoichiometric or catalytic amounts of $CpCo(CO)_2$.[142,143] Racemic 2,3-bis(trimethylsilyl)estra-1,3,5(10)-trien-17-one (**136**) was obtained in a catalytic reaction of 1,5-hexadiyne precursor **135** with bis(trimethylsilyl)ethyne (eq 58). During this transformation, five bonds are made in one step, and the ABC portion of the steroid is fused to the preformed D ring. Primarily, the reaction leads to a mixture of the product and the benzocyclobutene derivative. The latter compound is cyclized to the product upon further heating.[144] The method was extended to other 2,3-substituted estrone derivatives and to *dl*-estrone. The latter compound was obtained in six steps from the 1,5-hexadiyne in 15% overall yield.[145,146]



(58)

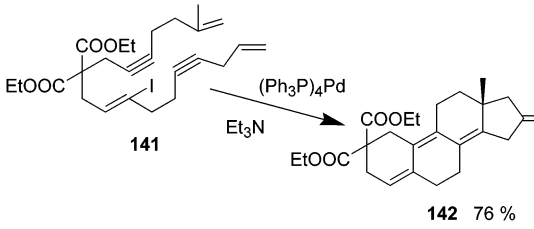
All four rings were assembled directly to give aromatic B-ring derivatives (**140**) with 100% trans stereochemistry of the C,D-ring juncture. The cobalt-catalyzed cyclization of starting enetriyne **138** could be performed in one step (79−92% yield) or could be interrupted at the benzocyclobutene stage (**139**, eq 59). The heating of the latter compounds also furnished the steroidal products.[147]

An elegant tetracyclization reaction involving the carbopalladation of an acyclic polyunsaturated precursor (**141**) was published by Negishi et al. The $(Ph_3P)_4Pd$-catalyzed cyclization furnished tetracyclic triene **142** as a suitable intermediate for steroids of various ring junctions in 76% isolated yield (eq 60).



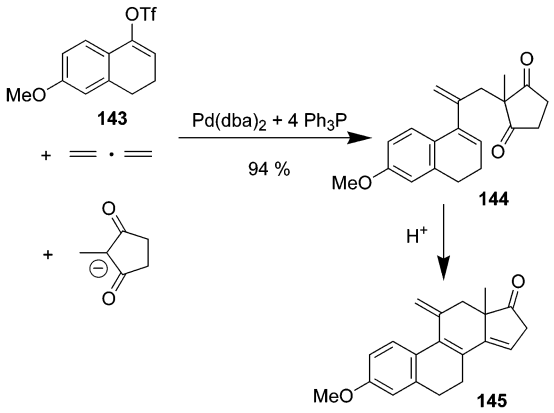
(59)

(The polyunsaturated starting material is depicted in a way that expresses the prospective tetracycle.[148])



(60)

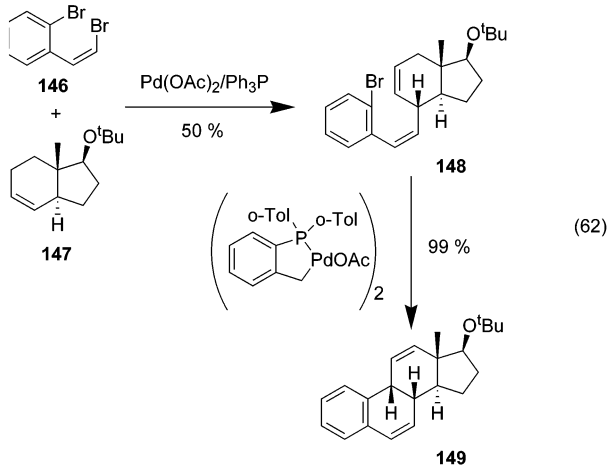
Another carbopalladation reaction as the key step in the construction of the steroid framework was also published. A three-component mixture consisting of the enol triflate of an α-tetralone derivative (**143**), 1,2-propadiene, and the enolate of 2-methyl-cyclopentan-1,3-dione was heated in the presence of the $Pd(dba)_2 + 4Ph_3P$ catalytic system to give tricyclic compound **144** (corresponding to the ABD rings) in 94% yield (eq 61). The product was converted to tetracyclic derivative **145** by acid-promoted cyclization. The yield of the carbopalladation step was found to be strongly dependent on the nature of the triflate and the 1,3-dione reaction partners.[149]



(61)

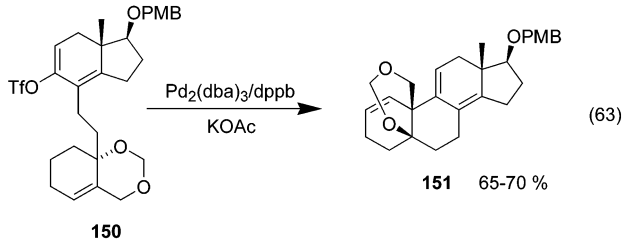
An efficient total synthesis of the steroidal framework was achieved using two successive Heck reactions as key steps in the construction of the B ring (eq 62).[150] Although this reaction sequence resulted in the formation of cis-fused B/C rings, selective hydrogenation of the primary products led to steroid derivatives with the usual trans-ring junction. A doubly functionalized arene (**146**) with two functions of different reactivity was used as starting material.

Because vinyl bromides turned out to be more reactive in the Heck reaction than aryl bromides, the CD-ring synthon (**147**), which is a chiral hydrindene, reacted easily with the bromovinyl moiety of arene **146**. The reaction proceeded with high stereo- and regioselectivity. The high stereoselectivity could be explained by the shielding of the upper face of the hydrindene by the angular methyl group. The high regioselectivity is thought to be due to a stereoelectronic effect that forces the attack of palladium at C-5 from the α face to allow a chairlike transition state with subsequent syn addition of the vinyl group at C-4. The next step, the intramolecular coupling, led to a single diastereomer of tetracyclic compound **149**. The same approach was used for the synthesis of enantiopure estrone and its derivatives,[151] a novel D-homosteroid,[152] 19-nor-steroids,[153] and structurally simplified cephalostatin analogues.[154]



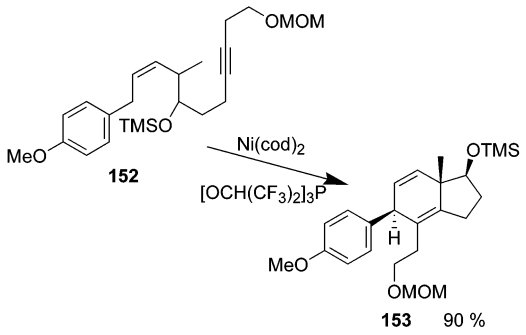
(62)

Complex cardenolides are challenging targets for total synthesis because of the high degree of oxidation of the steroidal skeleton and the cis A/B and C/D ring fusions. As can be seen from the previous reactions, Heck coupling is an ideal tool for the construction of cis-fused polycyclic products. This approach was used by Deng et al. to build up the B ring and establish the cis A/B fusion of cardenolides. Besides, the functional groups at C-5 and C-19 of the product could lead easily to the target molecules (eq 63).[155]



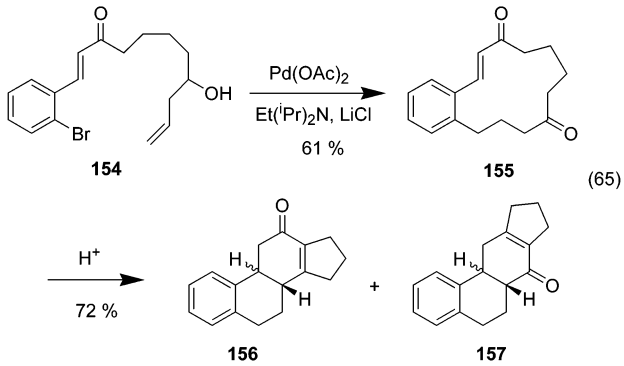
(63)

A nickel-catalyzed cycloaddition of a dienyne (**152**), obtained in five steps starting from the commercially available 3-butyn-1-ol, resulted in a tricyclic product (**153**) corresponding to the ACD rings of an A-ring aromatic steroid in 90% yield. The product was found to possess natural steroidal stereochemistry at the pro-C-9, C-13, and C-17 centers (eq 64). It should be mentioned that in the absence of the catalyst the reaction provided decomposition products only.[156]



(64)

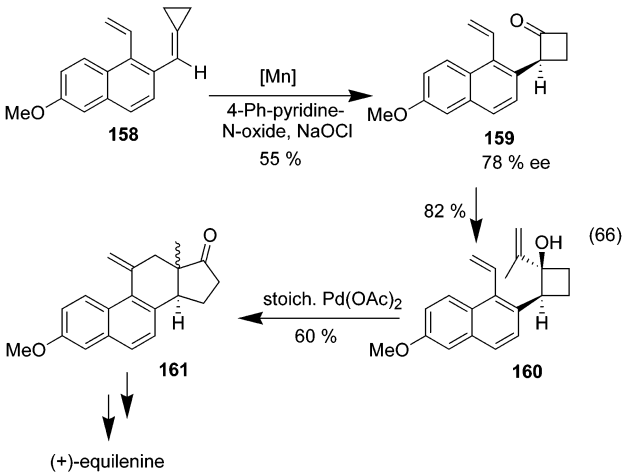
The intramolecular Heck reaction of a compound bearing aryl bromide and homoallylic alcohol moieties (**154**) led to macrocycle **155**, which is suitable for a double transannular cyclization. This cyclization gave four stereo- and regioisomers of a steroidal framework (**156**, **157**, eq 65).[157]



(65)

A catalytic enantioselective Torgov cyclization was achieved in 72% yield and up to 70% ee using a Ti complex of a bis-steroidal ligand as a catalyst.[158]

The asymmetric total synthesis of (+)-equilenin was accomplished via two subsequent cascade ring-expansion reactions.[159,160] The first (catalytic) step involved the asymmetric epoxidation of a naphthyl-substituted cyclopropylidene derivative (**158**) to form a chiral oxaspiropentane, followed by its enantiospecific rearrangement to chiral cyclobutanone **159**. The asymmetric epoxidation reaction was carried out by using a chiral (salen)Mn(III) complex, and the



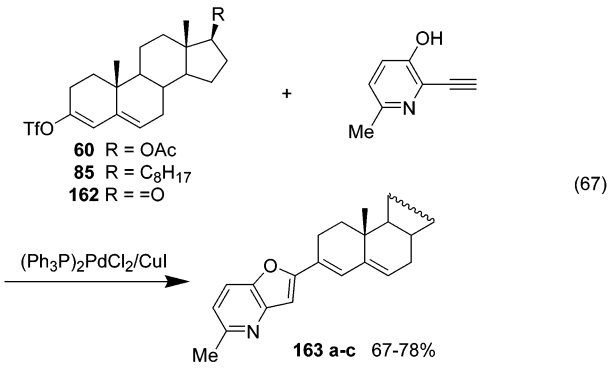
(66)

desired cyclobutanone derivative (**159**) was obtained in 55% yield in 78% ee (eq 66). Equilenin was synthesized through another ring-expansion−cyclization step by using a stoichiometric amount of $Pd(OAc)_2$ in this case. It should be mentioned that another transition-metal-catalyzed reaction, the Stille coupling, was also employed to produce the 9-vinyl-naphthyl derivative that is necessary for the cyclization of the C ring.[159−161]

8.2. Synthesis of Cyclic Systems Attached to the 4-Ring Skeleton

Various five- and six-membered rings were constructed in the side chains of the steroidal skeleton. These reactions mostly involve the palladium-catalyzed coupling of two reaction partners, a vinyl/aryl triflate or halide and an unsaturated compound with a suitable functional group that ensures in situ cyclization after the coupling.

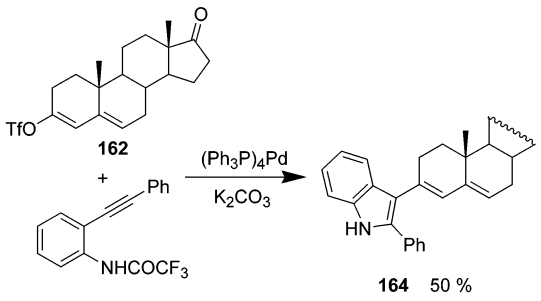
A benzofuran or a furopyridine ring was attached to C-3 of various steroidal skeletons via coupling of steroid enol triflates (**60**, **85**, **162**) and 2-alkynyl-phenols or 2-alkynyl-pyridinols (eq 67), respectively, in the presence of the $(Ph_3P)_2Pd(OAc)_2$/CuI catalytic system that was usually employed in triflate−alkyne couplings (Chapter 5.2). The formation of the products was explained by the following mechanism. 2-Alkynyl-phenol (or 2-alkynyl-pyridinol) reacts with the L_2XPdR-type complex generated in situ from zero-valent palladium species and the unsaturated triflates, followed by cyclization of the coupling intermediates through the intramolecular nucleophilic attack of the ortho oxygen on the carbon−carbon triple bond. The cyclization step is thought not to require the presence of the transition metal.[80,162]



(67)

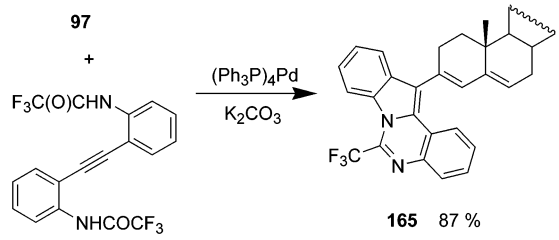
Some reactions with variations in the substitution pattern of the reactants gave similar products. The reaction of 17α-ethynyl-17β-hydroxy-3-methoxy-estra-1,3,5(10)-triene and 2-iodophenol furnished the steroidal benzofuran in 70% yield.[163] The same cyclization took place on reacting steroid-substituted alkynylphenols with enol triflates.[80]

A steroidal indole derivative (**164**) was produced via the palladium-catalyzed heteroannulation of 2-ethynyl-trifluoroacetanilide and 3-triflyloxy-androsta-3,5-dien-17-one (**162**) (eq 68). Because no indoles were obtained using aniline derivatives with free amino or an acetamido group, the acidity of the nitrogen−hydrogen bond might be an important feature in this heteroannulation. The best results were obtained with $(Ph_3P)_4Pd$ as the catalyst and K_2CO_3 as the base.[164]



(68)

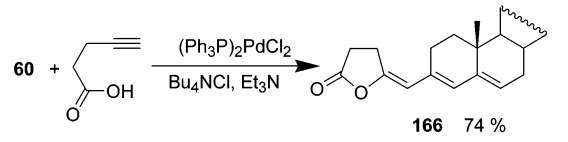
A similar coupling and subsequent cyclization led to indol[1,2-*c*]quinazoline derivatives (such as **165**) using bis(*o*-trifluoroacetamidophenyl)acetylene) and steroidal triflates (e.g., **97**) as reactants (eq 69). The reaction was thought to proceed via an aminopalladation/reductive elimination domino pathway followed by cyclization of the 3-substituted indole to give the tetracylic derivative that afforded indole-quinazoline product **165** via the elimination of trifluoroacetic acid.[165]



(69)

Quinolidine and coumarine derivatives were produced in moderate yields (20−72%) by the reaction of steroidal triflates and 4-(*o*-acetamidophenyl)-3-buten-2-one and ethyl 4-(*o*-hydroxyphenyl)-3-propenoate, respectively, in the presence of the ligandless $Pd(OAc)_2$ catalyst and KOAc as the base.[166]

Regio- and stereoselective syntheses of steroidal (*E*)-δ-vinyl-γ-methylene-γ-butyrolactones (**166**, eq 70)[167] and (*E*)-alkenylidene-3-tosyloxazolidin-2-ones (**167**, eq 71)[168] were carried out by the reaction of enol triflates (e.g., **60** or **97**) and 4-alkynoic acids and propargyl tosylcarbamates, respectively. The use of Bu_4NCl to convert the intermediate alkenyl-palladium triflate complexes into the more reactive alkenyl-palladium chlorides was essential for the formation of the products in both cases. The *E* selectivity of the reactions might be the consequence



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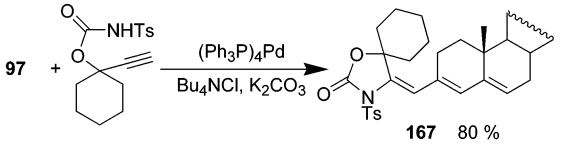
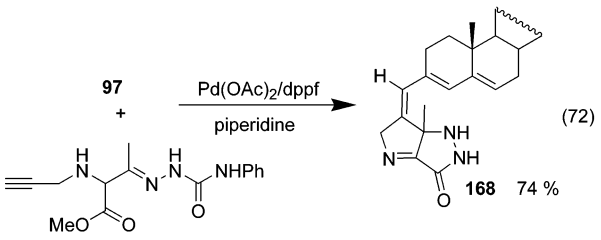


(71)

of the trans addition of the carboxylate anion or trans aminometalation across the carbon−carbon triple bond. The reaction of enol triflates and 4-alkynoic acids led to simple coupling under different conditions (the use of DMSO and room temperature instead of MeCN and 60 °C and the omission of $^{n}Bu_4NCl$; see Chapter 5.2[79]).

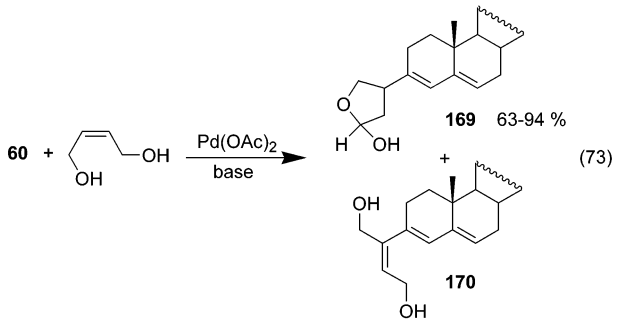
1*H*-Pyrazol-5(2*H*)-ones obtained by the piperidine-promoted annulation of α-propargyl-aminohydrazones followed by solvolytic cleavage at N-1 underwent palladium-catalyzed domino vinylation/carbocyclization with steroidal enol triflates such as **97** in the presence of the $Pd(OAc)_2$ + dppf catalytic system (eq 72). The *Z* geometry of the exocyclic double bond was proved by various NMR techniques.[169]



(72)

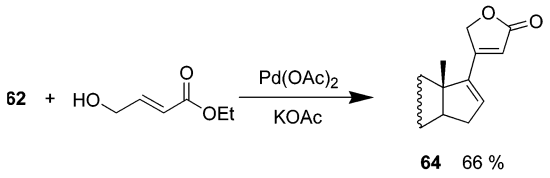
2,3,5-Trisubstituted furans were produced by a similar process reacting steroidal enol triflates with 3-acetyl-5-hexyn-2-one in the presence of $(Ph_3P)_4Pd$ and K_2CO_3 as the base.[170]

β-Substituted *γ*-butyrolactols (**169**), which are precursors of *γ*-butyrolactones, were produced in 63−94% yield by the reaction of (*Z*)-2-buten-1,4-diol with steroidal enol triflates (e.g., **60**) (eq 73). The best results were obtained using K_2CO_3 or $NaHCO_3$ as the base, Bu_4NCl as the chloride source, and catalytic amounts of $Pd(OAc)_2$. Employing Et_3N as the base favored the formation of 2-substituted diol **170**. It was assumed that in the absence of phosphine ligands and amines, hydroxyl coordination to palladium occurred in the initial adduct, favoring the formation of a five-membered cyclic intermediate, and this led to the formation of the lactol.[171]



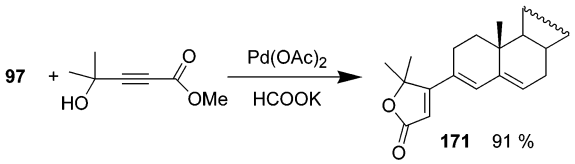
(73)

A palladium-catalyzed vinylic substitution followed by in situ cyclization was used as a key step in the synthesis of cardenolide **64** starting from 3-acetoxy-17-triflyloxy-androst-16-ene (**62**) and ethyl 4-hydroxy-2-pentenoate (eq 74). The reaction conditions played a decisive role in this synthesis. Whereas the use of the $Pd(OAc)_2$ catalyst and the KOAc base turned out to be an effective combination, no butenolide was formed with either the $Pd(OAc)_2/Ph_3P/Et_3N$ or $Pd(OAc)_2/Ph_3P/K_2CO_3/^{n}Bu_4NCl$ system.[72]



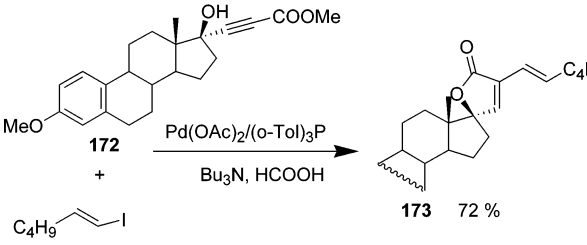
(74)

The sequential palladium-catalyzed hydrovinylation-cyclization of methyl 4-hydroxy-2-butynoates (e.g., methyl 4-hydroxy-4-methyl-pentynoate (eq 75)) in the presence of steroidal enol triflates (e.g., **97**) produced 3-vinylfurane-2(5*H*)-ones (**171**) in good to high yield. The regiochemistry of the carbopalladation step was governed by the strong directing effect of the tertiary alcohol group.[86]



(75)

The reaction of steroidal carbomethoxyethynyl-dialkylcarbinols (e.g., **172**) with alkenyl halides led to 3-alkenyl-spirobutenolides (**173**) in high yield in the presence of the $Pd(OAc)_2$ + P(*o*-Tol)$_3$ catalyst and tributylammonium formate (eq 76). The acyclic 1,3-dienes, the main products of the same reaction of arylethynyl-dialkycarbinols (Chapter 5.5), could not be isolated in this case.[110]

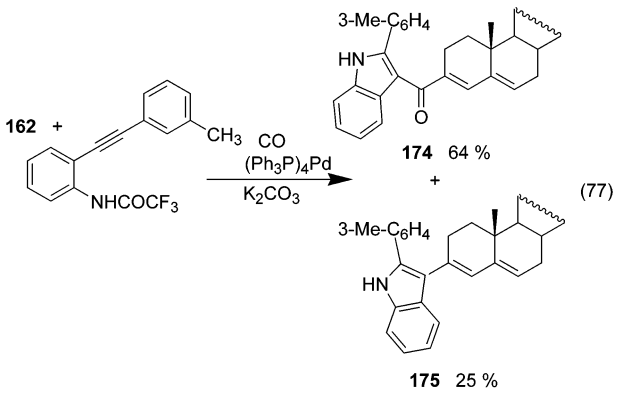


(76)

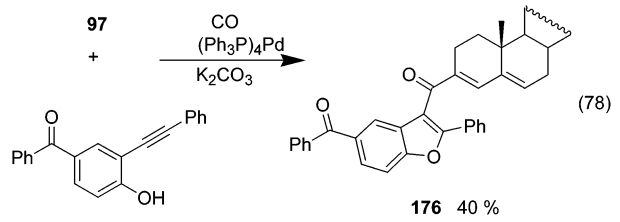
3-Spiro-fused steroidal benzofuran-2(3*H*)-ones were produced by an intramolecular Heck reaction starting from α,*β*-unsaturated *o*-iodophenyl esters. (For the transition-metal-catalyzed synthesis of these substrates, see Chapter 6.1.) Regioselective 5-*exo*-*trig* cyclization of the esters was accomplished in the presence of the $(Ph_3P)_2Pd(OAc)_2$ catalyst and 1.2 equiv of TlOAc.[115]

Some of the reactions discussed above were carried out under a carbon monoxide atmosphere and led to various heterocycles with acyl substituents.

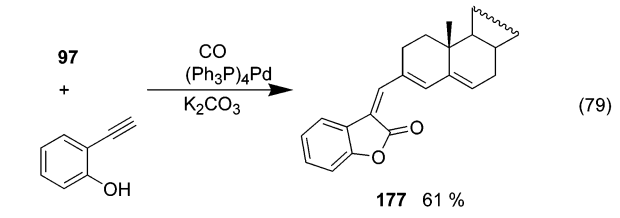
2-Phenyl-3-(17-oxo-androsta-3,5-dienyl-3-carbonyl)-indole (**174**) was isolated in 64% yield in the reaction of 3-triflyloxy-androst-3,5-dien-17-one (**162**) and 2-(3-methylphenyl) ethynyltrifluoroacetanilide under atmospheric carbon monoxide pressure. The corresponding 2-substituted 3-vinylindole (**175**) that was formed via direct coupling without the incorporation of CO was obtained in 25% yield (eq 77).[172]



A steroidal 3-acylbenzofuran (**176**) was obtained in 40% yield during the carbonylative coupling and in situ cyclization of 3-triflyloxy-pregna-3,5-dien-20-one (**97**) and 4-benzoyl-2-(phenylethynyl)-phenol (eq 78).[80]

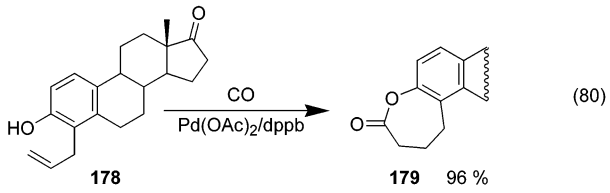


Interestingly, the same reaction of 2-ethynylphenol and steroidal triflates followed a completely different pathway to produce 3-alkylidene-2-coumaranones (**177**, eq 79). This reaction probably involves the intramolecular addition of the carbonylpalladium fragment of an alkoxycarbonyl-palladium intermediate to the triple bond with syn stereochemistry. The resulting σ-vinylpalladium species undergoes reductive elimination of Pd(0) to give the 2-coumaranone derivative. Contrary to the reaction of other substrates, steroidal triflates afforded the (*Z*)-alkylidene isomers with good selectivity. These derivatives were probably generated through a thermal isomerization of the reductive elimination product arising from the syn adduct formed initially.[173]



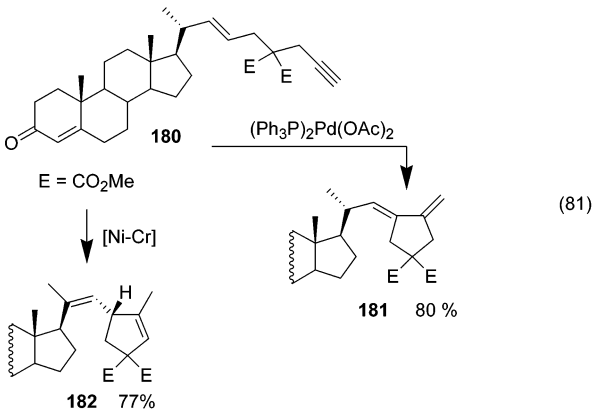
Spironolactone, an aldosterone antagonist, was produced in good yield starting from ethisterone. The key step of the synthesis was a hydroformylation reaction to achieve the formation of the lactol ring. Because the reduction of the Δ^4 bond also took place as a side reaction, ethisterone was converted first to a ketal derivative with an isolated double bond. This compound gave a clean reaction upon hydroformylation in the presence of $Rh_2(OAc)_4$ and Ph_3P. The oxidation of the lactol to the corresponding lactone proceeded quantitatively in the presence of $(Ph_3P)_3RuCl_2$.[174]

Seven-membered lactones attached to the A ring of an estrone derivative (**179**) were synthesized by regioselective cyclocarbonylation of the corresponding 4-allylsteroid **178** (eq 80).[175]



17α-Ethynyl-17β-hydroxy steroids ("ethynylcarbinols") were carbonylated to the corresponding 21-methoxycarbonyl-20-yne derivatives ("methyl 4-hydroxy-2-alkynoates"), which underwent a one-pot hydrogenation/cyclization reaction. The steroidal spirobutenolides obtained by this methodology are of potential pharmacological interest and could also serve as starting material for more complex structures.[176]

Two methods for the construction of carbocyclic rings in the 17-side chain of a steroid have been published. The cyclizations took place via intramolecular carbometalation of the 1,6-enyne functionality. In the presence of $(Ph_3P)_2Pd(OAc)_2$, the cyclopentane derivative with two exocyclic double bonds (**181**) was formed (eq 81).[138] The other method that used a nickel−chromium catalyst differed from this cyclization in terms of the regioselectivity of the hydrogen migration and led to cyclopentene product **182** with high diastereoselectivity.[177]



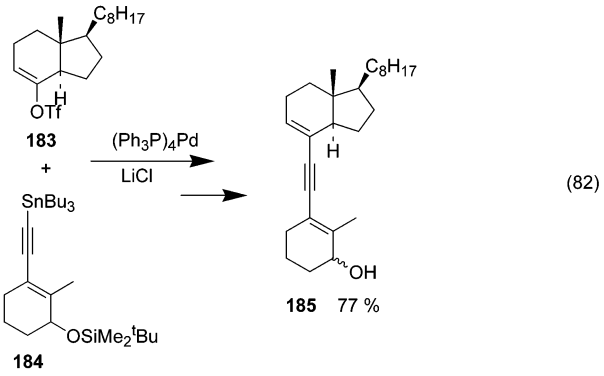
Steroids with a 1,3-dihydropyrrol-2-one ring system attached to the D ring were produced via the ruthenium-catalyzed reaction of steroidal α,β-unsaturated imines with carbon monoxide and ethylene. In this reaction, a new stereogenic center at C-3 of the pyrrolone ring was formed. A different reactivity of 16- and 17-imino derivatives was observed. In the first case, the products could be synthesized in nearly quantitative yields but with poor diastereoselectivity except for the reaction of the 16β-imino-17β-silyloxy derivative where complete diastereoselectivity could be achieved. The sterically more hindered 17-imino steroids were less reactive, but the products were formed with good diastereoselectivities.[178]

A lactol ring was attached to the A ring of a tetracyclic A-nor,B-nor-steroidal derivative by the

palladium-catalyzed ring closure of an organomercurial compound. This was obtained by regio- and stereoselective ring-opening of the cyclopropane ring of 3α,5-cyclo-5α-cholestan-6α-ol by Hg(II) followed by skeletal rearrangement.[179]

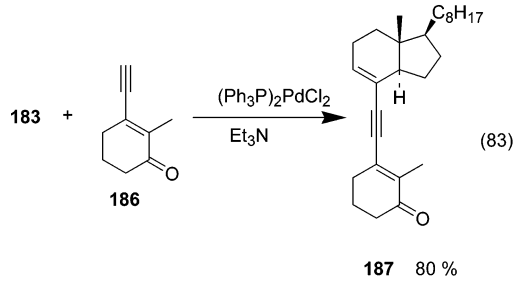
8.3. Synthesis of Vitamin D Derivatives

Two strategies were developed for the construction of dienyne precursors of the vitamin D_3 triene system by palladium-catalyzed reactions. The first method involved the coupling of a triflyloxy derivative of a *trans*-hydrindene (**183**) and an alkynyl stannane derivative of a substituted cyclohexene (**184**) in the presence of LiCl and a catalytic amount of $(Ph_3P)_4Pd$. The desired epimeric mixture of dienyne alcohols **185** was obtained in 77% yield after 20 h of reflux in THF and subsequent deprotection of the hydroxyl group (eq 82).



(82)

The other route, the direct coupling of triflate **183** with an unsaturated acetylenic ketone (3-ethynyl-2-methyl-cyclohex-2-enone, **186**) in the presence of $(Ph_3P)_2PdCl_2$ afforded dienynone **187** in 80% yield after 4 h at 75 °C (eq 83).[180]



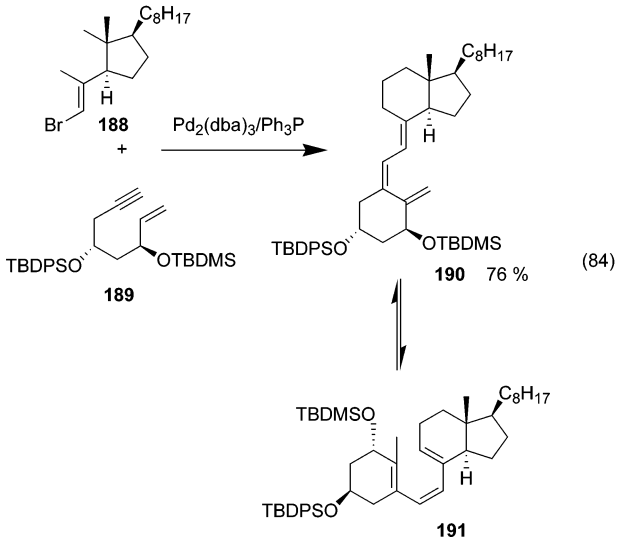
(83)

This last approach was used during the synthesis of several vitamin D_3 derivatives, e.g., for that of the most potent metabolite 1α,25-dihydroxyvitamin D_3[181,182] and also for some of its analogues. The great interest in developing these methods for the synthesis of vitamin D_3 derivatives can be explained by the finding that in addition to the role of 1α,25-dihydroxyvitamin D_3 as a regulator of calcium homeostasis it was shown to promote normal cell differentiation and proliferation.

The previtamin of 1α,25-dihydroxyvitamin D_3 and its pentadeuterio analogue were synthesized by the coupling of the CD- and A-ring fragments using the procedure of Ortar (Chapter 5.2[77]). The application of the Cu(I) cocatalyst made it possible to run the reaction at room temperature.[183]

To produce such derivatives that are capable of selective biological responses, various side-chain derivatives were synthesized both in the Mouriño and the Okamura group.[184,185] Other compounds, such as A-ring diastereomers of 1α,25-dihidroxyvitamin D_3,[186] an oxa analogue,[187] a C-11-functionalized derivative,[188] and 1α,24(*R*)-dihydroxyvitamin D_3,[189] were obtained similarly.

All of the above cases involve the "preformation" of the A ring followed by its coupling to the CD unit. Another reaction sequence was used by Trost during the synthesis of the vitamin D metabolites alphacalcidiol and calcitriol, where A-ring formation is concomitant with its attachment to the appropriate CD fragment. As an example, the alkylative cyclization of enantiomerically pure 1,7-enyne **189** with bromoolefin **188** as a CD ring synthon in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and Ph_3P gave a 9:1 mixture of the silylated alphacalcidiol (**190**) and its tautomer (**191**) (eq 84). Purification resulted in the silylated vitamin in 76% yield for this step.[190,191]

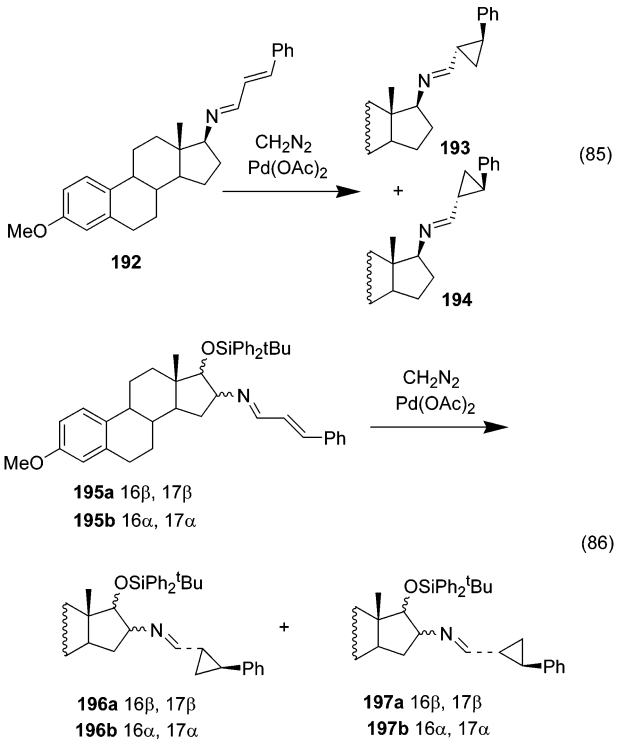


(84)

8.4. Cyclopropanation

Chiral cyclopropanocarbaldehydes were synthesized by Pd-catalyzed cyclopropanation using steroids as chiral auxiliaries. Steroidal cinnamic aldimines (**192**; **195a**, **b**) obtained from 17β-amino-3-methoxyestra-1,3,5(10)-triene or steroidal 16,17-*cis*-amino alcohols were reacted with diazomethane using $Pd(OAc)_2$ as a catalyst (eqs 85 and 86). The reactions proceeded with high chemoselectivity at the C=C double bond, and a mixture of diastereomeric trans-substituted steroidal cyclopropanes (**193**; **194** and **196a**, **b**; **197a**, **b**) were isolated in high yield (no definite data are given) in each case. After the hydrolysis of diastereomeric products **193** and **194**, a mixture of the enantiomeric *trans*-phenyl-cyclopropanocarbaldehydes was obtained. The chiral auxiliaries could be recovered by column chromatography. Good stereoselectivity was obtained only in the cyclopropanation of the 16,17-substituted derivatives (e.g., 17β-(*tert*-butyl-diphenyl)silyloxy-16β-cinnamic aldimine (**195a**, eq 86)) probably because one face of

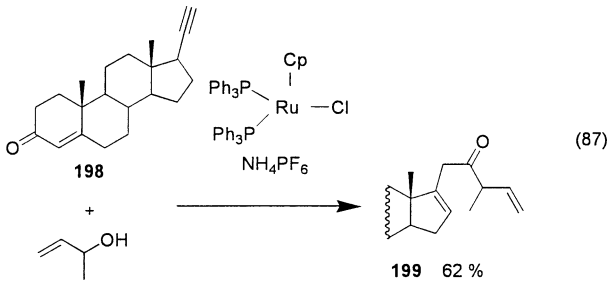
the unsaturated imine was blocked by the 13β-methyl and the 17β-silyloxy group. After hydrolysis, the two *trans*-phenyl-cyclopropanocarbaldehydes were obtained in a (*1S,2S*)/(*1R,2R*) = 98.6/1.4 ratio. Similarly good results were obtained by the cyclopropanation of the steroid with opposite configurations at C-16 and C-17 (**195b**), and after hydrolysis, the (*1R,2R*)-cyclopropane derivative was formed in 82% yield and 90% ee. This observation showed that the other stereogenic centers of the steroid core did not affect the stereochemistry of cyclopropanation.[192]



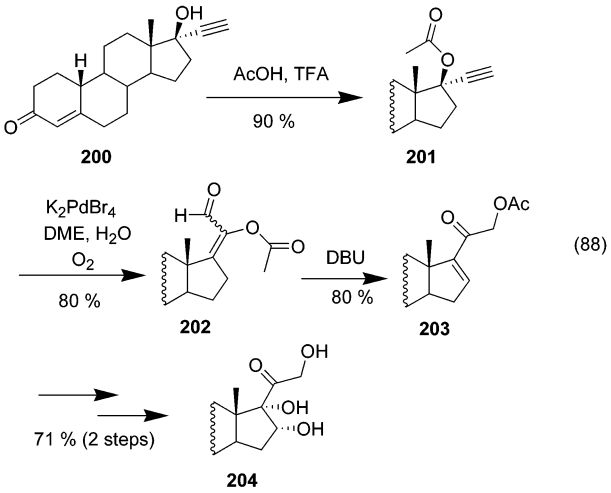
9. Catalytic Rearrangements

The selective demethylation at C-10 of various unsaturated 3-keto- (e.g., testosterone) and 3-hydroxy steroids (e.g., cholesterol) followed by dehydrogenation leads to the aromatization of the A ring with and without 3-hydroxy functionality, respectively. The carbon−carbon bond activation reaction (i.e., the "splitting" of the C-10−C-19 bond) proceeds via the Ru-Cp* cationic species. The synthetic importance of this reaction arises from the fact that steroids belonging to the androstane, cholestane, or pregnane series can be selectively converted to the corresponding estrane derivative.[193]

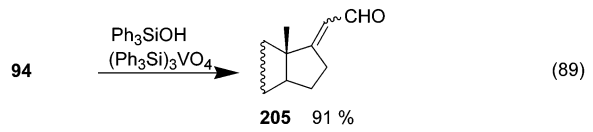
A direct condensation of terminal acetylenes and allylic alcohols to produce β,γ-unsaturated ketones was reported by Trost et al. The transformation was successfully used for the selective synthesis of the 21-keto derivative (**199**) starting from the 17-ethynyl derivative (**198**) and 3-hydroxy-1-butene (eq 87). Although the reaction mechanism is not completely solved, ruthenium-vinylidene complexes are formed from acetylene as probable key intermediates, which react with the alcohol to form a ruthenium carbene species. Its rearrangement and reductive elimination provide the ketone.[194]



A key intermediate toward the synthesis of fluoro furanyl norprogesterone (FFNP) was synthesized in a Pd(II)-catalyzed oxidative rearrangement followed by a base-catalyzed acetate rearrangement furnishing the requisite corticosteroid side chain as a keto-acetate moiety. The palladium-catalyzed route starting from norethindrone (**200**, eq 88) was found to be considerably more efficient for the synthesis of 16α,-17α,21-triol **204** than the dioxene approach using 19-nor-androst-4-en-3,17-dione as starting material.[195]



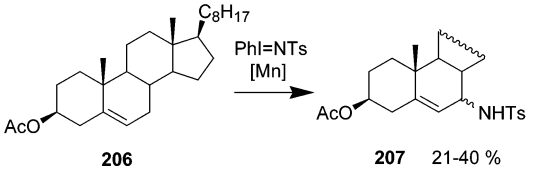
As key intermediates of corticosteroid synthesis, 17(20)-en-21-al derivatives (**205**) were produced via the catalytic isomerization of 17α-ethynyl-17β-hydroxy steroids (e.g., **94**) with tris[triphenylsilyl]-vanadate (eq 89). The formyl derivatives were obtained as mixtures of geometrical isomers at the 17(20)-olefinic linkage. Heating the isomeric mixture in the presence of a catalytic amount of tri-*n*-propyl vanadate afforded the product as the single *E* isomer.[196]



10. Introduction of Heteroatoms to the Steroidal Backbone

10.1. Amidation of Saturated C–H Bonds

The amidation of 3β-acetoxy-cholest-5-ene (**206**) at the allylic C−H bonds at C-7 was investigated using chiral manganese porphyrins as catalysts (eq 90).[197] The reaction of the substrate with (*N*-tosylimino)-phenyliodinane or using the commercially available reagents $Ph(IOAc)_2$ and NH_2R (R = Ts, *p*-nitrophenyl-sulfonyl) afforded the C-7-substituted derivatives (e.g., **207**) with 81−92% chemoselectivity and moderate yield. The amidation was α-selective with $^{\alpha}/_{\beta}$ ratios ranging from 1.2:1 to 4.2:1.

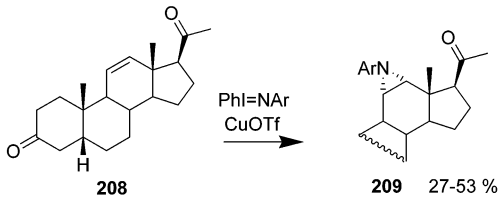


206 **207** 21-40 % (90)

The reaction of equilenin acetate with the (*N*-tosylimino)phenyliodinane reagent in the presence of a manganese porphyrin complex led to the 11β-amidation product in 47% yield with complete stereoselectivity. The 11β-hydroxy- and 6-hydroxy derivatives were also formed as byproducts in 5 and 30% yield, respectively.[198]

10.2. Aziridination

Aziridino steroids are of interest as inhibitors of various enzymes, but they can also be considered to be reactive intermediates leading to amino steroids after nucleophilic ring opening. 11-Pregnen-3,20-dione (**208**) was converted to corresponding aziridinyl-steroid **209** in the presence of a copper(I) triflate catalyst and various aryliminoiodinanes as reagents (eq 91). The use of [*N*-(2-trimethylsilyl-ethanesulfonyl)imino]phenyliodinane was found to be the most effective, affording the product in 53% yield with complete α selectivity.[199]



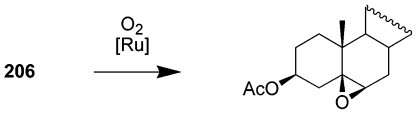
208 **209** 27-53 % (91)

10.3. Epoxidation

Epoxides are extremely useful for further elaboration because their facile ring opening allows the introduction of various substituents in a stereospecific manner, so there has been a great interest in developing methods for the stereoselective epoxidation of unsaturated steroids.

Various Δ^5 steroidal derivatives were converted to the 5β,6β-epoxides with high stereoselectivity by aerobic oxidation in the presence of a ruthenium(VI) porphyrin[200−202] and a ruthenium(II) bisoxazoline catalyst.[203] It should be mentioned that because of the presence of the C-10 angular methyl group usual epoxidation methods (e.g., the use of peracids) lead to the 5α,6α-epoxides as major products.

In the first case, cholesterol was found to inhibit the catalytic system, presumably through the protonation of the oxo ligand of the active species.[200] Cholest-5-ene was slowly converted to the epoxide (45% yield after 3 days), but some minor unidentified byproducts were also obtained. The oxidation of cholesteryl chloride resulted in a 90% yield of the product in 7 days at room temperature with 91% β selectivity. High yields were obtained in the facile epoxidation of cholesteryl esters. The selectivities (>99%) are also of practical importance.[201] The reaction of 3β-acetoxy-cholest-5-ene (**206**, eq 92) was complete in 5 h, but the conversion of other ester derivatives of 3β-hydroxy-cholest-5-ene (e.g., formic, pivalic, and benzoic esters) required longer reaction times (3−5 days). It is worth mentioning that the epoxidation of 3α-acetoxy-cholest-5-ene led also to the 5β,6β-epoxide in 62% yield and >99% selectivity.[202]



206 **210** 85 % (92)

The epoxidation of other Δ^5 steroids (androstenone acetate, pregnenolone acetate, cholest-4-en-3-one) was also examined. According to the results, the presence of a keto group in the steroid nucleus did not affect the epoxidation process, with the exception of the α,β-unsaturated compound. In the case of cholest-4-en-3-one, 85% of the starting material was recovered after 9 days.[201]

No profound effect of the substituent at C-3 on the epoxidation of cholesteryl esters was observed in the presence of the Ru(II)-bisoxazoline catalyst.[203] The products were obtained in 85−95% yield in 4−8 h at room temperature. Both 3α- and 3β-benzoyloxy-cholest-5-ene and even cholest-5-ene gave the 5β,6β-epoxides with high selectivity.

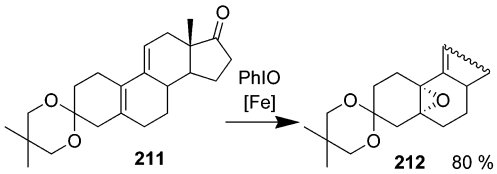
The epoxidation of cholesteryl esters with 2,6-dichloropyridine *N*-oxide was also carried out in the presence of dendritic ruthenium porphyrins.[204] The β stereoselectivities were comparable to those obtained with the Ru(VI)-porphyrin system (<20) discussed above, whereas the catalyst turnover numbers were much higher (up to 820). The reaction of 3-methoxy-17-methylidene-estra-1,3,5(10)-triene also afforded the 17,20-epoxide in 95% yield with complete β stereoselectivity in 2 days under the same conditions.

Magnesium monoperoxyphthalate, which is a good oxidant for the α-stereoselective epoxidation of cholest-5-ene derivatives, showed an inverse stereoselectivity when it was used together with a manganese porphyrin catalyst.[205]

Iron(III) and manganese(III) steroidal porphyrins in bilayer assemblies were used as regioselective epoxidation catalysts for steroidal substrates. Epoxidation took place exclusively in the side chain.[206]

The 5α,10α-epoxy-9(11)-estrene derivative (**212**), a key intermediate for the synthesis of 11β-aryl deriva-

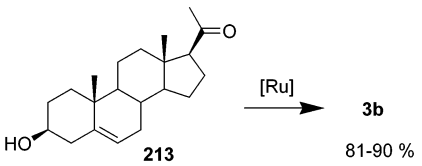
tives with high antiprogestational activity, was produced in 80% yield and 92% stereoselectivity by the epoxidation of diene **211** with iodosobenzene as the oxidant in the presence of an Fe(II)-phthalocyanine catalyst (eq 93).[207]



(93)

10.4. Oxidation

A ruthenium-catalyzed Oppenauer-type oxidation was used for the formation of the enone moiety, a typical feature of steroidal hormones, starting from 5-en-3β-ol derivatives (e.g., **213**, eq 94). The reaction could be performed efficiently in the presence of a catalytic system consisting of either $(Ph_3P)_3RuCl_2$ and K_2CO_3 or $[(C_4Ph_4COHOCC_4Ph_4)(\mu\text{-}H)][(CO)_4Ru_2]$ using acetone as the solvent. The mechanism involved a hydrogen transfer from the alcohol substrate to acetone via ruthenium alkoxide intermediates. The reaction tolerates the presence of double bonds, keto and ester groups, tertiary hydroxyl groups, and protected corticoid side chains. Various alcohols such as cholesterol, stigmasterol, and pregnenolone were converted selectively into the products. Only the reaction of a corticoid substrate led to a mixture of the desired cortexolone acetate and the isomeric 5,6-unsaturated ketone.[208]



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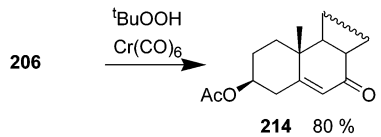
Steroid 5-en-7-one derivatives are known inhibitors of sterol biosynthesis and can also be of use in cancer chemotherapy because they are more toxic toward tumorous than nontumorous cells. These compounds were traditionally synthesized from the Δ^5 steroids by allylic oxidation using a great excess of toxic chromium reagents, which makes these methods unattractive. Pearson showed that cholesteryl acetate (**206**) could be oxidized in 80% yield to corresponding enone **214** with *tert*-butyl hydroperoxide and 0.5 equiv of chromium hexacarbonyl (eq 95).[209] Clean oxidation of 3β-acetoxy-pregn-5-en-20-one and diosgenin acetate indicated that the reaction was selective in the presence of relatively sensitive functional groups. Direct oxidation of stigmasterol gave the 3β-hydroxy-7-one derivative without the oxidation of the secondary alcohol functionality. However, the oxidation system was found to convert secondary alcohols to ketones in the absence of a double bond. As an example, the treatment of methyl cholate under similar conditions gave the corresponding triketone.[210]

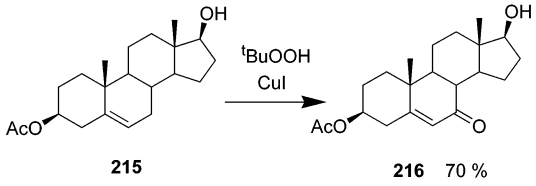


(95)

Muzart used a 5 mol % CrO_3 catalyst for the conversion of Δ^5 steroids to 5-en-7-ones. The products were obtained in 32−61% yield together with some epoxides as byproducts. The presence of a keto group at C-3 in cholest-5-en-3-one induced the migration of the Δ^5 double bond with the formation of cholest-4-en-3,6-dione. Disubstitution of the C-4 methylene of the substrates led to better yields and lower quantities of the epoxides.[211]

Various steroidal 5-en-7-ones were synthesized in 51−75% yield by $RuCl_3$-catalyzed oxidation with *tert*-butyl hydroperoxide. In the case of 3β-acetoxy-16α-hydroxy-androst-5-ene, quick oxidation of the hydroxyl function together with allylic oxidation was observed. At the same time, cholesterol was oxidized preferentially at the 7 position.[212]

The reaction of Δ^5-3β-acetoxy steroids with *tert*-butyl hydroperoxide led to the allylic oxidation products in high yield (75−84%) in the presence of either Cu(II) or Cu(I) salts or metallic copper. The best results were obtained with copper powder that was transformed in situ to a soluble copper compound. The oxidation was shown to occur with good selectivity even in the presence of a secondary hydroxyl group. 3β-Acetoxy-17β-hydroxy-androst-5-ene (**215**) was converted to the 3β-acetoxy-17β-hydroxy-androst-5-en-7-one (**216**) in 70% yield using CuI as a catalyst (eq 96).[213]

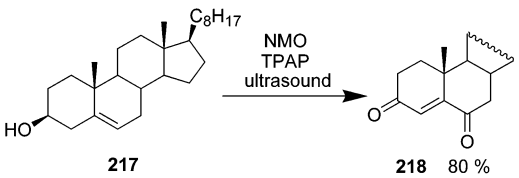


(96)

These reactions were very selective compared to the use of $Fe(acac)_3$ as a catalyst, where epimeric 7-alcohols and 7-alkylhydroperoxides were also formed.[214] The use of $Mo(CO)_6$ has also been described, but this reaction resulted in the formation of epoxides.[215,216]

Cobalt acetate both in homogeneous and supported forms was also used as a catalyst for the high-yielding (70−86%) synthesis of allylic oxidation products from steroidal substrates. In the heterogeneous reactions, the reuse of the catalyst led only to a small reduction in the yields.[217]

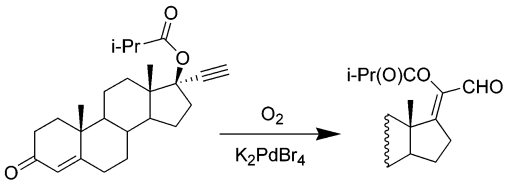
Although the oxidation of cholesterol (**217**) with 4-methylmorpholine *N*-oxide (NMO) as the oxidant gave only a low yield of cholest-4-ene-3,6-dione (**218**) in the presence of the tetra-*n*-propylammonium perruthenate (TPAP) catalyst, ultrasonic irradiation of the reaction mixture led to an almost quantitative



(97)

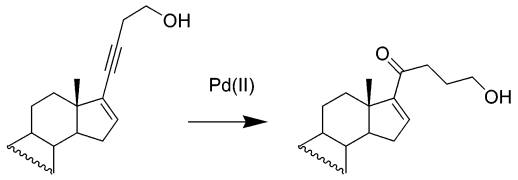
reaction in 90 min (eq 97). The method was successfully used for the conversion of various 3β-hydroxy-Δ^5-pregnenes and -androstenes to the corresponding 4-ene-3,6-diones.[218]

As key intermediates in the synthesis of 21-hydroxy-16-ene-20-keto steroids, which are immediate precursors of the clinically important 16-substituted glucocorticoids, 20-acyloxy-pregna-4,17(20)dien-3-on-21-al derivatives (**220**) were obtained in 90−95% isolated yield by the K_2PdBr_4-catalyzed oxidative rearrangement of 17α-ethynyl-17β-acyloxy-androst-4-en-3-ones (**219**, eq 98).[219]



219 **220** 95 % (98)

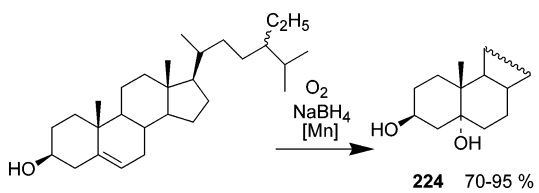
Various steroidal γ'-hydroxy conjugated enynes of type **221** were converted to the corresponding γ'-hydroxy-α,β-enones (**222**, eq 99), which are useful intermediates for the preparation of five-membered hetero- and carbocycles, under an acidic CH_2Cl_2/3N HCl two-phase system in the presence of Bu_4NCl and using $PdCl_2$ as the catalyst. The substrates were obtained by the coupling of steroidal enol triflates and 1-butyn-4-ol (Chapter 5.2). It was possible to prepare the enones through a one-pot process without the isolation of the intermediate enyne.[78]



221 **222** 62-87 % (99)

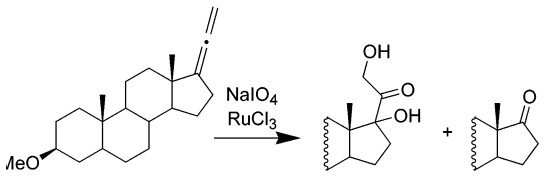
$RuCl_3$-catalyzed cis dihydroxylation of cholesteryl acetate using the acetone−acetonitrile−water solvent system was reported by Shing et al. The reaction resulted in the formation of the 5α,6α-diol in 68% yield together with some 5α-hydroxy-6-one derivatives.[220]

The metalloporphyrin-catalyzed oxidation of steroidal olefins (e.g., sitosterol **223**) in the presence of a reductant produced the corresponding 5α derivatives selectively (eq 100). Manganese complexes showed higher efficiency than the iron derivatives because of the difference in metal−porphyrin orbital interactions.[221]



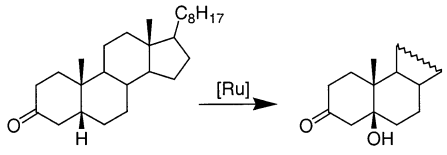
223 **224** 70-95 % (100)

Although nonsteroidal trisubstituted allenic systems were easily oxidized to α,α′-dihydroxyketones, steroid **225** could be converted to dihydroxyketone **226** only in moderate yield because oxidative cleavage of the unsaturated side chain leading to **227** prevailed (eq 101).[222]



225 **226** 16 % **227** 49 % (101)

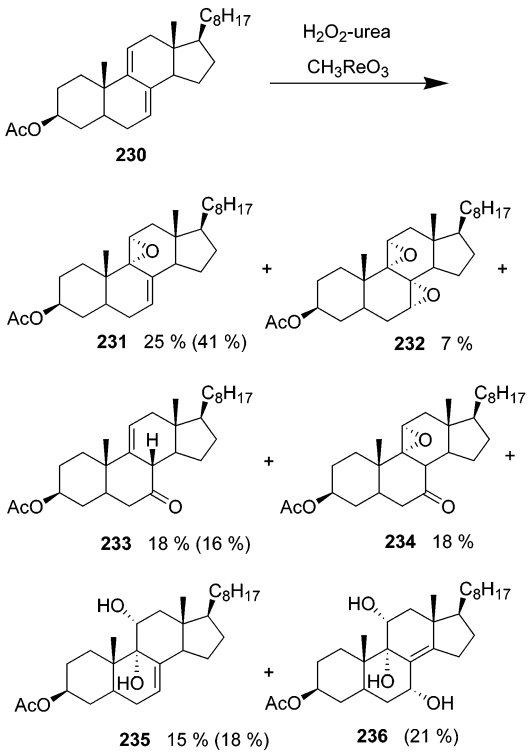
Nagano et al. observed that ruthenium porphyrins catalyzed oxygen transfer from 2,6-dichloropyridine *N*-oxide to tertiary carbons of steroids with the retention of the configuration of the asymmetric centers. 5β-Steroids (e.g., **228**) were oxidized to the corresponding 5β-hydroxy derivatives (**229**) in good yield (42−70%) (eq 102), but the 5α substrates gave considerably poorer results (14−28% yield of the 5α-hydroxy products).[223]



228 **229** 64 % (102)

Some conjugated diene steroids were oxidized with hydrogen peroxide in the presence of catalytic amounts of methyltrioxorhenium to afford unsaturated 1,2- or 1,4-diols possibly derived from allylic epoxides.[224]

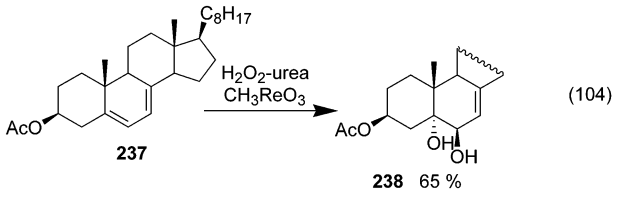
The oxidation of cholesta-3,5-diene and 3β-acetoxy-5α-cholesta-7,9(11)-diene (**230**) with a urea−hydro-



230 **231** 25 % (41 %) **232** 7 % **233** 18 % (16 %) **234** 18 % **235** 15 % (18 %) **236** (21 %) (103)

gen peroxide oxidant was investigated in the presence of a catalytic amount of methyltrioxorhenium. The stereoselectivity of the reaction of the first substrate was generally low because of the less hindered position of the Δ^3 double bond. The oxidation of cholesta-3,5-diene at 25 °C afforded cholest-5-en-3α,4α-diol, cholest-5-en-3α,4β-diol, cholest-4-en-3α,6α-diol, and cholest-4-en-3α,6β-diol in almost equal amounts and in 62% total yield. At 0 °C, the formation of isomeric epoxy-steroids was also observed. The oxidation of 3β-acetoxy-5α-cholesta-7,9-(11)-diene (**230**, eq 103) was not affected by the temperature. In $CHCl_3$, 9α,11α-epoxy-5α-cholest-7-en-3β-yl acetate (**231**) was obtained as the main product in 25% yield, together with 7α,8α,9α,11α-diepoxy-5α-cholestan-3β-yl acetate (**232**), a keto steroid (7-oxo-5α-cholest-9(11)-en-3β-yl acetate **233**), an epoxy ketone (9α,11α-epoxy-7-oxo-5α-cholestan-3β-yl acetate **234**), and a diol (9α,11α-dihydroxy-5α-cholest-7-en-3β-yl acetate **235**). The use of diethyl ether as a solvent led to a higher yield of the first product (**231**, eq 103, yields in parentheses), but keto steroid **233**, diol **235**, and new 7α,9α,11α- triol **236** were also formed.[225]

Oxygenated functions were introduced in the 15 and 9 positions on the steroid rings by the same method starting from 5α-cholesta-8,14-dien-3β-yl acetate.[226] A more selective reaction was observed for cholesta-5,7-dien-3β-yl acetate (**237**). In this case, the oxidation of the substrate led to the 5α,6β-diol (**238**) in 65% yield (eq 104).[227]

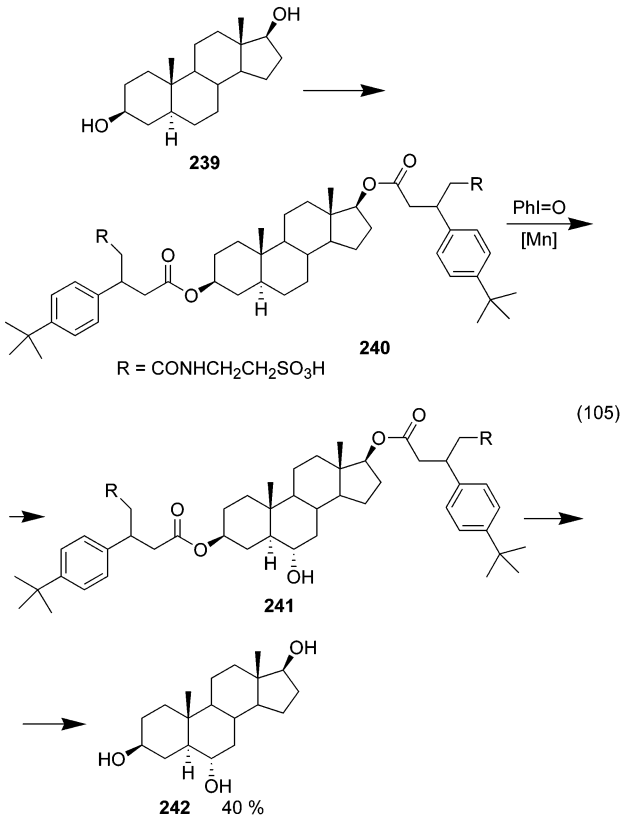


237 **238** 65 % (104)

Equilenin acetate was oxidized with iodosobenzene in the presence of a manganese porphyrin complex, resulting in the formation of the 6-hydroxy derivative as the major product and the 11β-ol compound as the minor product in 42 and 15% yield, respectively.[198]

Various manganese−porphyrin catalysts carrying cyclodextrin binding groups were employed for hydroxylations at C-6 and C-9 positions of particular practical interest. The main feature of this reaction is the stereoselective introduction of a hydroxyl group at geometrically accessible carbon atoms in the presence of secondary OH groups and carbon−carbon double bonds, as in enzymatic reactions.

The first catalyst had phenyl linkers holding the cyclodextrin to the porphyrin. The substrate (androstan-3β,17β-diol, **239**) was converted to diester **240**, which carried *tert*-butyl groups for binding to the cyclodextrins and sulfonate groups for water solubility. Oxidation with iodosobenzene in the presence of the Mn−porphyrin catalyst resulted in the selective formation of the 3β,6α,17β-triol (**242**, eq 105) after hydrolysis, but only three to five turnovers were achieved before the catalyst was oxidatively destroyed.[228] By introducing tetrafluorophenyl rings[229] and then a nitrophenyl group into the porphyrin,[230] turnover numbers were raised to 180 and 3000, respectively.



(105)

To change the position of hydroxylation by changing the relative position of the steroid backbone with respect to the metalloporphyrin, binding groups with different lengths were introduced at C-3 and C-17. With appropriate linkers, it was possible to move the preferred position of hydroxylation to C-15, but selectivity was poorer than in the previous cases.[231]

Selective oxidation at C-9 was achieved by the introduction of a third binding interaction into the substrate. The triester of androstan-3β,6α,17β-triol was oxidized by the catalyst containing pentafluorophenyl groups on the porphyrin with 10 turnovers.[232] By omitting the binding at C-17 and by using a catalyst with trifluoropyridyl rings on the porphyrin, essentially complete hydroxylation was observed at C-9 with 90 turnovers.[233]

Because not only the porphyrin system but also the cyclodextrin binding of the catalyst seemed to be destroyed by oxidation, cyclodextrins were replaced by synthetic cyclophanes during the construction of new manganese−porphyrin catalysts. Although hydroxylation occurred preferably at the C-6 and C-9 positions of the substrates with 400 and 70 turnovers, respectively, in the first case a 15α-hydroxylated product was also obtained in 10% yield, and C-9 hydroxylation was accompanied by the formation of other derivatives with hydroxyl groups at various positions.[234]

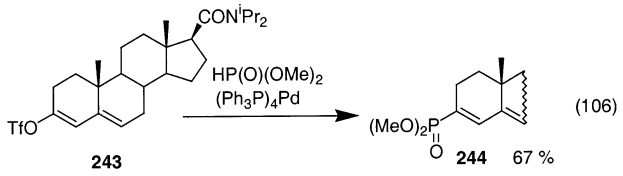
Some 14β-H antiprogestins were synthesized starting from the 14α-H-17-keto compounds. The intermediate 17-silyl-14,16-dienol ethers were obtained from the Δ^{14}-17-keto compounds by the deconjugation of the double bonds of Δ^{15}-17-keto derivatives that

were produced by the modified Saegusa oxidation of the starting compounds in the presence of $Pd(OAc)_2$.[93]

10.5. Phosphonation and Amination

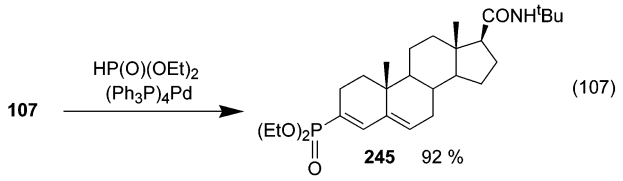
Steroidal enol triflates or alkenyl iodides were used as starting material for the synthesis of steroidal phosphonates, phosphines, and amines by transition-metal-catalyzed C−P or C−N coupling.

Various estra-1,3,5(10)-triene and androsta-3,5-diene phosphonic acid derivatives were shown to inhibit 5α-reductase (Chapter 6.1). They were synthesized by the hydrolysis of the coupling products obtained by the reaction of the corresponding 3-triflyloxy derivatives (e.g., **243**) with dialkyl phosphites in the presence of a catalytic amount of $(Ph_3P)_4Pd$ and Et_3N as the base (eq 106).[126,235]



243 **244** 67 % (106)

Diethyl 17β-(*N*-*tert*-butylcarboxamido)-androsta-3,5-dien-3-phosphonate (**245**), which was produced by the coupling of diethyl phosphite and the steroid 3-enol sulfonate (**107**), was also found to exhibit remarkable activity on rat 5α-reductase (eq 107).[76,122]

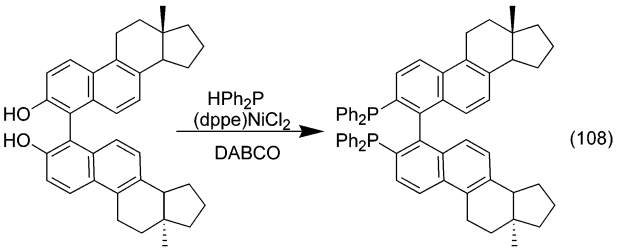


245 92 % (107)

Alkenyl triflates were also found to undergo Pd(0)-catalyzed coupling either with dialkyl phosphites or with hypophosphorous acid at room temperature to provide alkenyl phosphonates or phosphinates, respectively, in high yield.[128,236]

Steroidal alkenyl iodides could also be used as substrates. The best results were obtained with the $Pd_2(dba)_3 \cdot CHCl_3$ catalyst employing the phosphites as solvents.[237]

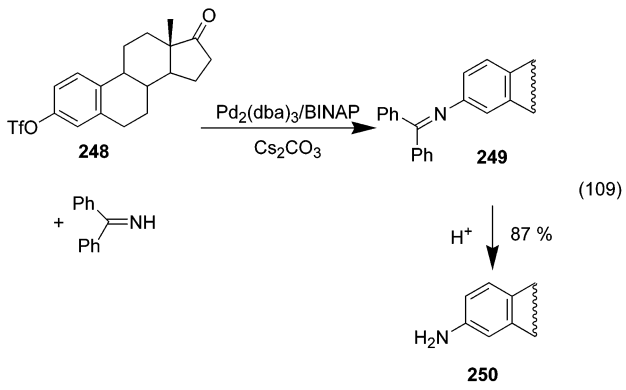
Palladium- and nickel-catalyzed C−P coupling reactions were also employed in the synthesis of steroidal phosphines. A bis-steroid (**246**, eq 108) derived from equilenin was converted to BINAP analogue bis-phosphine **247** by a nickel mediated coupling of the aryl triflate functionalities of the substrate with diphenylphosphine.[238] The same coupling reaction was used as the key step during the synthesis of a new bis-steroidal phosphine of similar structure but with the cis configuration at the CD-ring junctions.[239]



246 **247** 70 % (108)

The reaction of steroidal alkenyl halides and diphenylphosphine also gave the corresponding diphenylphosphino derivatives in the presence of $Pd(OAc)_2$. The products were obtained in high yield starting from alkenyl iodides, but the use of 17-bromo-androsta-2,16-diene resulted in the formation of the 17-diphenylphosphino steroid in only 44% yield.[240]

3-Amino-estrone (**250**) was produced by a C−N coupling reaction. The amination of estrone-triflate (**248**) was carried out using benzophenone imine as an ammonia equivalent in the presence of a catalytic amount of the $Pd_2(dba)_3$/(*S*)-(−)-BINAP system and Cs_2CO_3 as the base (eq 109). The overall yield starting from estrone was 60%, in comparison with 43% obtained from a "classical" route involving thermal rearrangement and subsequent acidic hydrolysis of the estrone-derived 4-aryloxy-2-phenylquinazoline.[241]



248 **249** (109)

250

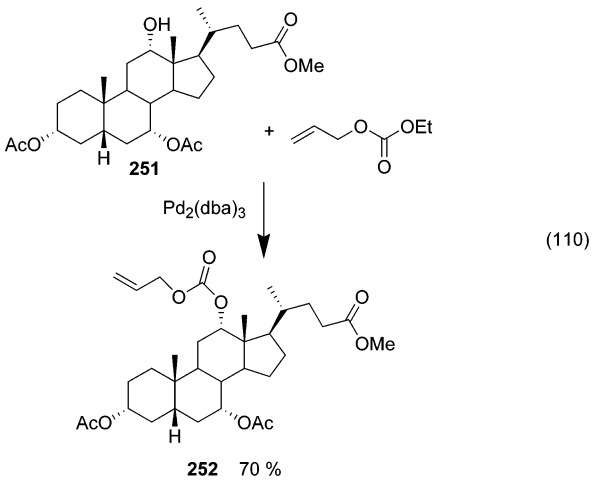
11. Formation of the Carbon–Oxygen Bond

11.1. *O*-Acylation

Quantitative acetylation of various secondary and tertiary steroidal alcohols was carried out using vanadyl(IV)-acetate as the catalyst. Under the reaction conditions, selective acetylation of hydroxy carbonyl compounds was achieved without the formation of α,β-unsaturated compounds because of the elimination of the resulting acetate. Because the catalyst was practically insoluble in the acetonitrile solvent, it could be reused in several cycles without a considerable loss of activity.[242]

11.2. *O*-Vinylation, Allylation

The treatment of hindered steroidal alcohols, such as 12α-hydroxy- and 7α,12α-dihydroxy-5β-androstane (**251**) derivatives, with allyl ethyl carbonate in the presence of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and phosphine ligands (Ph_3P, dppb or dppe) led to the formation of steroidal allyl carbonates (**252**, eq 110) instead of the expected allyl ethers. The reaction was exceptional in that carbon dioxide was not lost from the carbonate, as is usual in such reactions.[243]

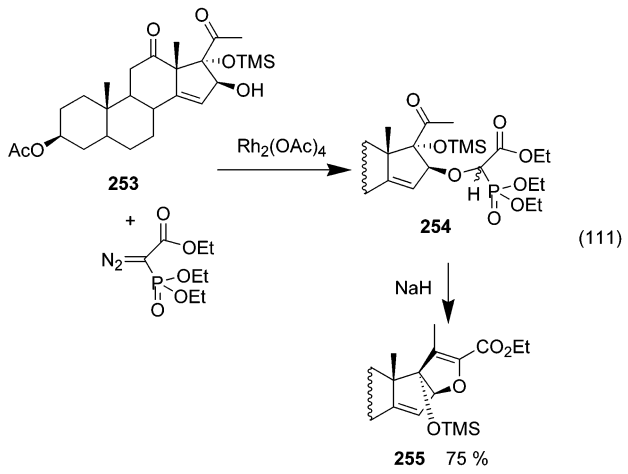


(110)

Primary and secondary steroidal O-vinyl ethers were synthesized from the corresponding alcohols and ethyl vinyl ether in the presence of bis(acetato)-(1,10-phenantroline-N^1,N^{10})palladium as the catalyst.[244]

11.3. *O*-Alkylation

A number of trisdecacyclic pyrazines, so-called cephalostatins, exhibit high potency against a number of cancer cell lines. The E rings of "north" and "south" hexacyclic steroidal units of various members of this family were constructed using a rhodium-catalyzed alkylation of steroidal alcohols (e.g., **253**) with ethyldiazophosphonates as the key step (eq 111). The α-alkoxyphosphonoacetates (**254**) were obtained as 1:1 diastereomeric mixtures in high yield and were converted to the pentacyclic derivatives (**255**) via an intramolecular Wadsworth-Emmons reaction.[245−247]



(111)

12. Steroid-Based Ligands in Homogeneous Catalysis

Despite the large number of chiral ligands derived from easily available optically active natural products, there are only a few examples for those obtained from steroids. Therefore, functionalized steroids are not only of biological importance but might also serve as potential ligands in homogeneous catalysis. (Theoretically, the ligands can be formed in homogeneous reactions catalyzed by transition-metal−steroidal ligand catalysts, i.e., the steroids acting as ligands might be produced in a 'breeder cycle".)

12.1. Steroidal Ligands with Phosphorus Donors

Achiwa incorporated a steroidal moiety into a pyrrolidine-derived chiral bisphosphine ((*2S*,*4S*)-*N*-cholesteryloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine, CPPM, Figure 2, **256**) to increase both the solubility of the ligand in aliphatic hydrocarbons and its lipophilic interaction with the substrates. The in situ-formed Rh complex of the ligand was actually freely soluble in cyclohexane, and the asymmetric hydrogenation of pyruvates and dimethyl itaconate gave 63−67% and 29.5% optical yields, respectively. However, these results are the same or only slightly better than those obtained with the use of a similar ligand with a *N*-*tert*-butoxycarbonyl group, indicating that the steroidal moiety had very little effect on the stereoselectivity of the reaction.[248]

Gladiali et al. synthesized the first chiral phosphine, 3α-diphenylphosphino-5α-cholestane ((+)-DICOL, **257**), that contained a steroid backbone as the only source of chirality. This ligand and the DIOP analogue 2,3-*O*-(5′α-cholestan-3′,3′-ylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((−)-DIOCOL, **258**) were tested in Rh-catalyzed asymmetric hydrogenation and hydroformylation and Pd-catalyzed hydrocarbethoxylation reactions. The catalysts based on the monodentate phosphine gave unsatisfactory stereoselectivity results in these reactions. Optical purities of the products obtained in hydroformylation and hydrocarbalkoxylation reactions in the presence of (−)-DIOCOL were similar to those obtained with (−)-DIOP.

The best results were obtained using (−)-DIOCOL as the ligand during the hydrogenation of (*Z*)-α-acetylaminocinnamic acid. The reaction gave *N*-acetyl (*R*)-phenylalanine in 91−93% optical yield, which was better than the results achieved by using the (−)-DIOP-derived catalyst.[249]

The Rh-catalyzed hydroformylation of various dehydroamino acid derivatives was carried out using a Rh/(−)-DIOCOL catalyst. Although the reaction was highly chemo- and regioselective, enantioselectivities were modest (around 30%) and of the same order as those obtained using (−)-DIOP.[250]

Steroidal 1,4-diphosphines 3α- (Figure 2, **259**) and 3*β*-diphenylphosphino-2α-(2′-diphenylphosphinoethyl)5α-androstanes and the corresponding dibenzophosphole derivatives were prepared and used as chiral ligands in the rhodium-catalyzed hydrogenation of (*Z*)-α-acetamidocinnamic acid, rhodium-catalyzed hydroformylation of vinyl acetate, and palladium-catalyzed addition of hydrogen cyanide to norbornene. Interestingly, the 3α- and 3*β*-epimers led to opposing enantioselection preferences in enantioselective hydrogenation.[251]

BINAP-type steroidal bis-phosphines with trans (**260**) and cis CD-ring junctions (**261**) were tested in ruthenium-catalyzed asymmetric hydrogenation reactions.[238,239] When compared to BINAP, the asymmetric induction of these catalysts was only slightly lower during the hydrogenation of methyl aceto-

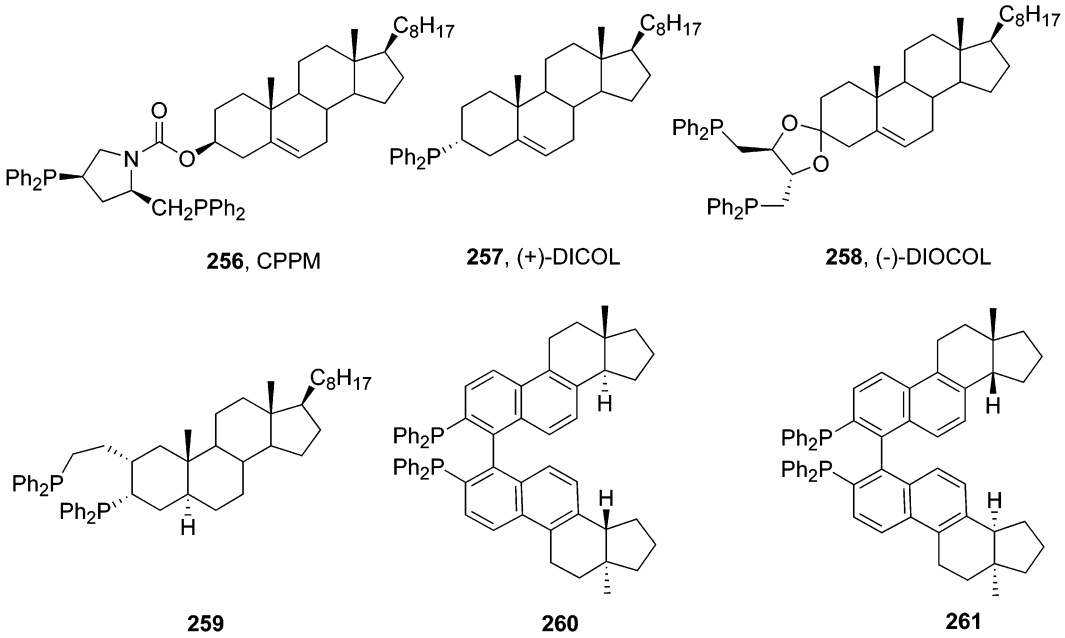


Figure 2. Steroidal ligands possessing P donors.

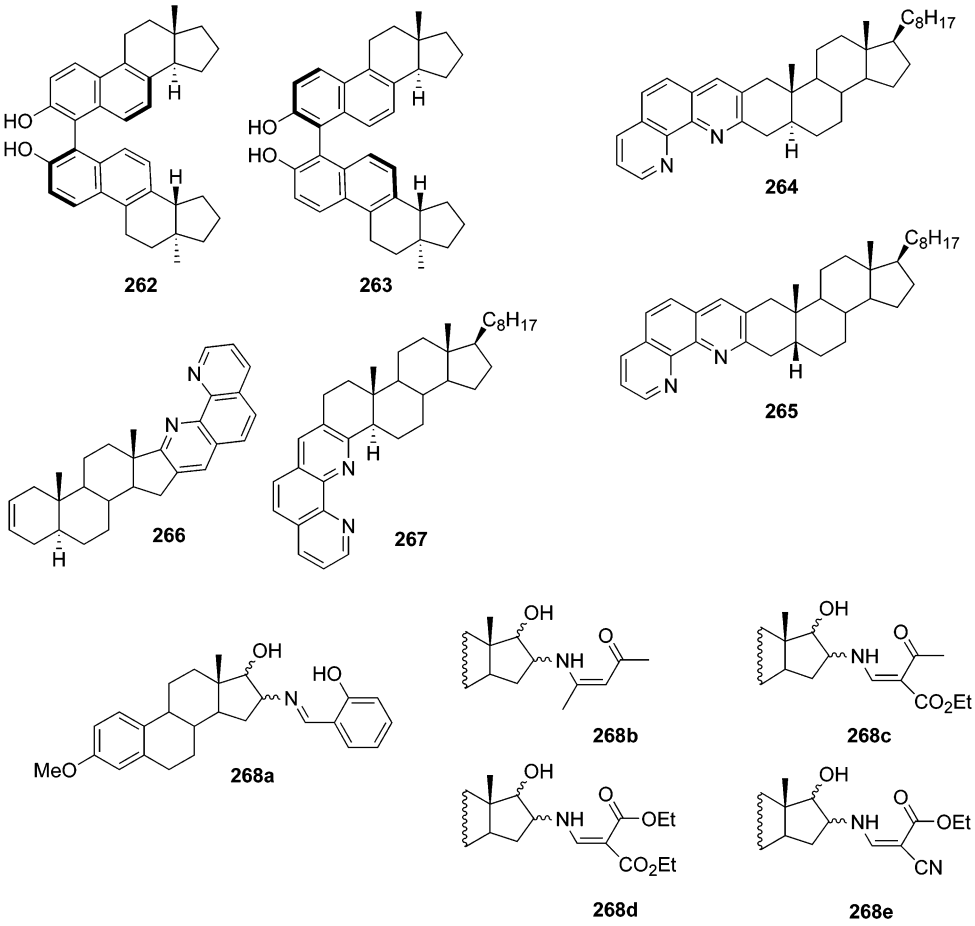


Figure 3. Steroidal ligands possessing O and N donors.

acetate but was considerably higher in the hydrogenation of α-acetocinnamic acid or tiglic acid. However, after a detailed investigation of the properties of these new catalysts, it was concluded that these selectivity differences could not be ascribed to the chirality of the steroid backbone but rather to the different electronic properties of the bis-steroidal ligands and BINAP.

12.2. Steroidal Ligands with Other Donors

Two diastereomeric binaphthol-type bis-steroidal ligands were used in a Ti-catalyzed Torgov cyclization to produce the C ring of a steroidal framework. In the presence of the (R_{ax},S_c)-bis-steroid (**262**, Figure 3), an increased level of enantiocontrol (70% ee (*S*)) compared to that for other nonsteroidal ligands (up

to 47%) was observed. Interestingly, the use of the diastereomeric (S_{ax},S_c)-bis-steroid (**263**) resulted in the formation of the opposite enantiomer with only 54% *R* selectivity. This is in contrast to the enantioselective reactions carried out in the presence of catalysts containing bis-steroidal phosphines of similar structure, where the use of diastereomeric ligands led to enantioselection of a similar magnitude.[158]

The same and similar steroidal axially chiral diol ligands induced moderate to high enantioselectivities (up to 82%) in the Ti-catalyzed addition of Et_2Zn to aldehydes.[252]

Chiral C_1-symmetric phenantrolines incorporated in a steroidal backbone were used as ligands in the enantioselective palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. 1,3-Diphenylprop-2-enyl malonate was obtained in high yield using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a catalyst precursor and epimeric phenantrolines derived from 5α- (**264**) and 5β-cholestan-3-one (**265**), respectively. Interestingly, both ligands led to the product possessing the same sense of chirality and a low enantiomeric excess, indicating that the different configuration at C-5 has little effect on the stereoselectivity of the process. 5α-Androst-2-en-[17,16-*b*]-1,-10-phenantroline (**266**) derived from 5α-androst-2-en-17-one was expected to exert a greater induction because in the intermediate π-allylpalladium complex the steroid backbone could get closer to the allylic termini. However, this ligand also afforded a moderate level of stereoselectivity (54%). The best derivative turned out to be 5α-cholestan[4,3-*b*]-1,10-phenantroline (**267**) obtained from 5α-cholestan-4-one, which gave a much higher enantioselectivity (94%).[253]

The catalytic activity of copper complexes of a series of aldimines and β-ketoenamines (**268a**−**e**) produced from the four diastereomeric 16-amino-17-hydroxy-3-methoxy-estra-1,3,5(10)-triene derivatives was tested in the bioanalogous oxidation of 3,5-di-*tert*-butyl-catechol to the corresponding quinone. The ligands formed dinuclear complexes when treated with copper acetate. Most of the complexes of the β-ketoenamine-type steroids were found to be suitable catalysts. The complexes of the trans isomers showed an activity 1 magnitude higher than that of the cis isomers. The main reason for this could be the nearly planar environment of the copper ions in the case of the cis ligands, which had been shown not to be ideal for a possible catechol oxidase catalyst and/or the higher stability of the dinuclear structure of the cis compounds.[254]

13. Concluding Remarks

This review compiled advances in homogeneous catalytic reactions involving steroids as substrates. Hydrogenation, various carbonylation and coupling reactions, 1,4 additions, and cyclizations have been catalyzed by transition-metal complexes containing mainly VIIIB metals. As clearly shown, palladium complexes constitute the largest part of the accomplishments to date. The number of reaction types with steroidal substrates is steadily increasing, and a real breakthrough in the application of homogeneous catalysis has been observed in the past decade. The steroidal enol triflates and iodo alkenes readily available from the corresponding ketones have already gained direct practical applications. Several steps in a conventional multistep synthesis of a target compound might be replaced with a single selective catalytic step, resulting in a large increase in the total yield. In this way, transition-metal complexes as catalyst precursors have already become a widely used synthetic tool in the chemistry of pharmacologically important compounds.

To summarize this review, the application of chemo-, regio-, and stereoselective homogeneous catalytic reactions started showing great promise in the synthesis of steroids. Some further "miracle" organometallic reagents and reactions, considered now to be of intellectual interest only, are also expected to become powerful synthetic tools in the years to come.

14. Acknowledgments

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