UNIVERSITY OF PÉCS
Doctoral School of Chemistry

Homogeneous catalytic functionalization of the steroidal framework

Ph.D. Thesis

by
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Abstract

Using palladium-catalyzed homogeneous aminocarbonylation as a key reaction 3,17-dicarboxamido-androst-3,5,16-triene and 3,17-dicarboxamido-androst-2,4,16-triene derivatives possessing various amide moieties were synthesized under mild reaction conditions such as atmospheric carbon monoxide pressure and 50 °C. Compounds containing 3-iodo-3,5-diene, 3-iodo-2,4-diene and 17-iodo-5,16-diene structural motifs were used in the aminocarbonylation and the *N*-nucleophiles were varied systematically. Three amines, such as *tert*-butylamine, piperidine and methyl alaninate were used as *N*-nucleophiles in the aminocarbonylation. All variations of 3,17-dicarboxamides were synthesized using this methodology.

A set of new steroid dimers linked through ring A-ring A or ring D-ring D was synthesized under relatively harsh conditions, such as high carbon monoxide pressure and 100 °C, using palladium-catalyzed homogeneous aminocarbonylation. Compounds containing 3-iodo-3,5-diene, 3-iodo-2,4-diene and 17-iodo-5,16-diene functionalities were used in the aminocarbonylation and four diamines, such as 1,2-diaminoethane, 1,4-diaminobutane, 1,4-diaminobenzene and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were used as *N*-nucleophiles.

Androst-4-ene-3,17-dion was used as a starting material for the iodoalkene derivatives above. The synthetic strategy of the multistep synthesis was based on the consecutive use of three types of reactions: (i) the protection/deprotection of one of the keto functionalities (3-one or 17-one) as ethylene ketals, (ii) the transformation of the other keto group to iodoalkene functionality *via* its hydrazone, and (iii) palladium-catalyzed aminocarbonylation of the iodoalkene functionality.

Kivonat

Palládium-katalizált homogénkatalitikus kulcsreakció felhasználásával, enyhe reakciókörülményeket (atmoszférikus szén-monoxid nyomás, 50 °C) alkalmazva különböző amid szerkezeti részlettel rendelkező androszta-3,5,16-trién-3,17-dikarbonsavamidokat és androszta-2,4,16-trién-3,17-dikarbonsavamidokat állítottam elő.

A 3-jód-3,5-dién, a 3-jód-2,4-dién és a 17-jód-5,16-dién szerkezeti részlettel rendelkező származékok aminokarbonilezését különféle *N*-nukleofilek (*terc*-butil-amin, piperidin, alanin-metil-észter) jelenlétében végeztem; a módszer alkalmazásával előállítottam az összes lehetséges 3,17-dikarbonsavamidot.

Palládium-katalizált homogénkatalitikus aminokarbonilezési reakció alkalmazásával, erélyes reakciókörülmények között (40 bar szén-monoxid nyomás, 100 °C) egy sor új, A-gyűrűkön vagy D-gyűrűkön keresztül kapcsolt szteroid dimert állítottam elő 3-jód-3,5-dién, 3-jód-2,4-dién és 17-jód-5,16-dién szerkezeti részletet tartalmazó származékokból, *N*-nukleofilként 1,2-diaminoetánt, 1,4-diaminobutánt, 1,4-diaminobenzolt és (1*S*,2*S*)-(+)-1,2-diaminociklohexánt felhasználva.

A fenti jódalkének előállításához kiindulási anyagként androszta-4-én-3,17-diont használtam. A többlépéses szintézis szintetikus stratégiáját háromféle egymást követő reakció alkalmazására alapoztam: (i) a keto funkciós csoport (3-on vagy 17-on) védése/védőcsoport eltávolítása, (ii) a keto-csoport átalakítása hidrazon származékon keresztül jódalkénné, és (iii) a jódalkén funkciós csoport palládium-katalizált aminokarbonilezési reakcióban történő átalakítása.

Graphical abstract

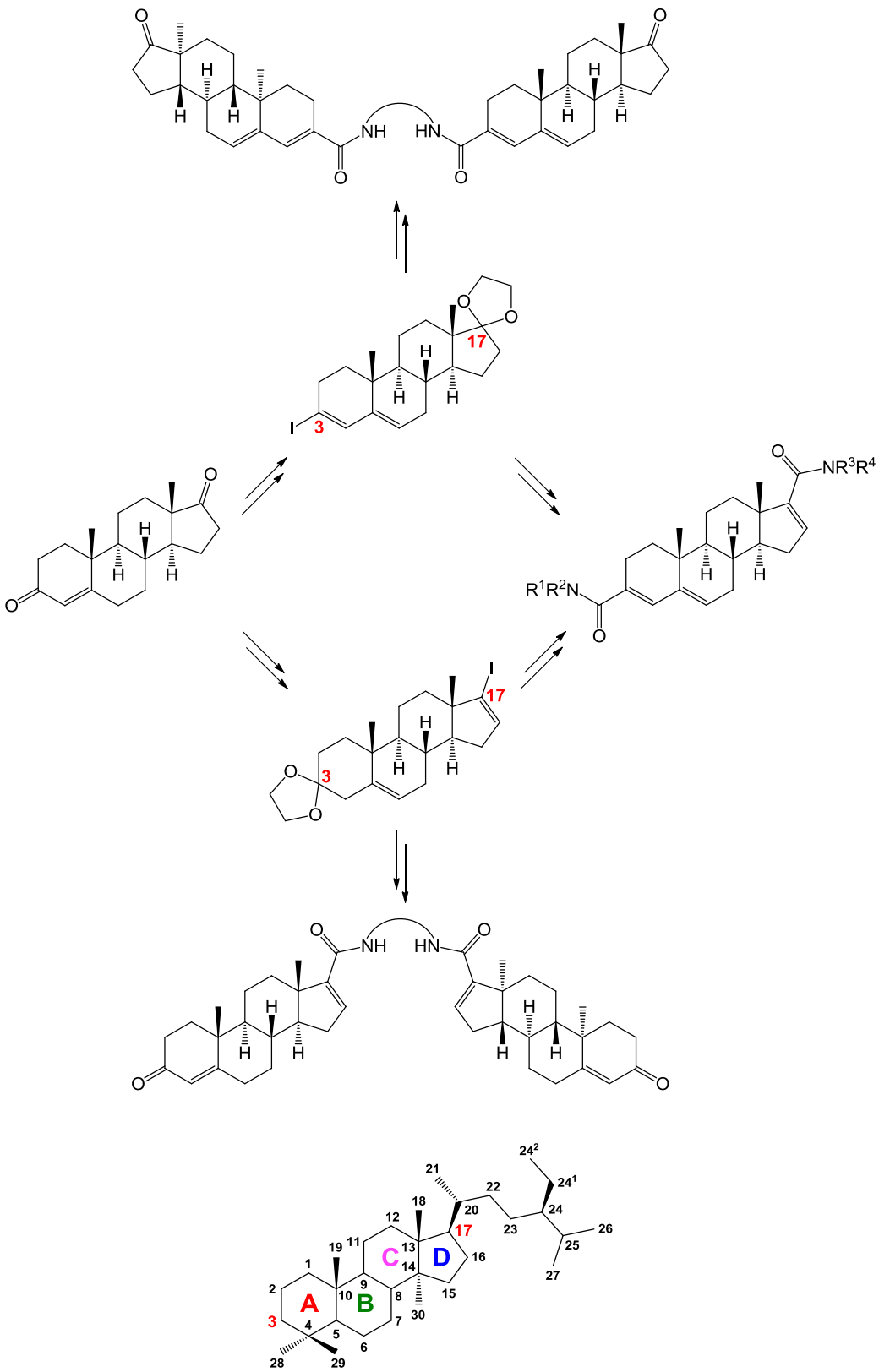

Figure 1. Numbering of the steroidal skeleton.[1]

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1. List of abbreviations

Ac	acetyl
Ad	adamantyl
AlaOMe	*L*-alanine methyl ester
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	1,1’-bi(2-naphthol)
[BMIM][BF_4]	1-butyl-3-methylimidazolium tetrafluoroborate
Bn	benzyl
^{t}Bu	tertiary butyl
$BuPAd_2$	butyl-diadamantylphosphine or CataCXium A
$C_2B_{10}H_{10}$	dicarba-dodecaborane or carboranyl
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
CNT	carbon nanotube
CYTOP®292	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DHT	dihydrotestosterone
DMF	*N*,*N*-dimethylformamide
dppf	1,1’-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
DTBB	4,4-di-*tert*-butylbiphenyl
dtbpx	bis(di-*tert*-butylphosphino)-*o*-xylene
Et_3N	triethylamine
Fc	ferrocenyl
GlyOMe	*L*-glycine methyl ester
HMDS	hexamethyldisilazane
Im	imidazolyl
IRA900	a sort of quaternary ammonium ion exchange resin
MPR	Mn(III) 5,10,15-tris(tolyl)-20-(4-hydroxyphenyl) porphyrin covalently attached to *M*errifield’s *p*eptide *r*esin
MW	microwave irradiation

NADPH	reduced form of *n*icotinamide *a*denine *d*inucleotide *p*hosphate
nbd	norbornadiene
NiNPs	nickel(0) nanoparticles
$PdCl_2$(phen)@Y	Y-zeolite encaged palladium-1,10-phenanthroline complex
PdNPs	palladium(0) nanoparticles
$Pd(OAc)_2$	palladium(II) acetate
Ph	phenyl
phen	1,10-phenanthroline
PEI	polyethyleneimine
Piv	pivaloyl
$P(OPh^*)_3$	tris(*o*-*tert*-butylphenyl)phosphite
PPh_3	triphenylphosphine
ProOMe	*L*-proline methyl ester
PS-Pd-NHC	polymer supported palladium-*N*-heterocyclic carbene complex
Ses	trimethylsilylethanesulfonyl
SILP-Pd-1	a silica supported palladium catalyst
TBAB	tetrabutyl ammonium bromide
TBS	*tert*-butyldimethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TPPMS	(3-sulfonatophenyl)(diphenyl)phosphine monosodium salt
Ts	tosyl
*p*TsOH	*p*-toluenesulphonic acid
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

2. Introduction

In the second half of the twentieth century the chemistry of transition metal complexes expanded significantly. The central metal atom of these complexes is capable of, in their coordination area, binding different 'small' molecules as ligands such as dihydrogen, carbon monoxide, carbon dioxide, *etc*. In the beginning, the major aim was either transforming compounds with simple skeletons in large volume using primarily cobalt- and rhodium-containing catalytic systems, or preparing more complex starting materials with practical (*e.g*., biological, pharmacological) importance using homogenous catalytic reactions catalyzed by rhodium, ruthenium, copper, palladium, platinum complexes. In the latter cases, several new compounds with special properties have been synthesized.

One of the significant breakthroughs in synthetic organic chemistry was the application of homogenous catalytic reactions using transition metal catalysts. In these reactions the starting material and the catalyst are most often in the same solvent and therefore, every atom of the transition metal could act as active center during the catalysis.

Beyond the synthesis of compounds containing transition metal-carbon bonds, the understanding of the structure as well as binding modes is of fundamental importance. Furthermore, the better understanding of the basics of the elementary reactions occurring in the coordination sphere of the transition metal, the latter being the basic steps of the catalytic reactions, could lead to synthetic reactions of practical importance.

The industrial application of homogenous catalytic synthesis is expanding rapidly. In the process of developing new technologies for creating compounds, the aim of producing the least amount of side material along with the process being economical became a standard requirement. All these can be met by using selective reactions for which the most modern solutions are the homogenous catalytic reactions. In this way, only small amounts of transition metal complexes with catalytic activity leading to the transformation of substrates have been applied. Yields of practical importance have been obtained using reactions with excellent chemo-, regio- and enantioselectivities.

Nowadays, researchers in synthetic organic chemistry more and more often use transition metal complexes, organometallic reagents in the synthesis of several compounds which cannot be obtained using standard methods. In some cases, the

conventional synthetic approaches might be resulted in especially low yields when new functional groups were introduced into the given positions of a well-known skeleton.

The view that completely new reactions can mostly be expected from the field of organometallic catalysis is widely accepted.[2] The increase of the practical importance of transition metal organic chemistry is proved by Nobel Prize in chemistry being awarded in 2001 to B. Sharpless,[3] W. S. Knowles,[4] and R. Noyori[5] for the development of enantioselective homogeneous catalytic reactions.[6-8] Furthermore, development of the metathesis method in organic synthesis[9] resulted in the Nobel Prize in chemistry in 2005 awarded to Y. Chauvin,[10] R. H. Grubbs,[11] and R. R. Schrock.[12] The 2010 Nobel Prize in chemistry was awarded to R. F. Heck,[13] E. Negishi,[14,15] and A. Suzuki[16-18] for the development of palladium-catalyzed cross-coupling reactions in organic synthesis.[19,20]

In addition to the synthesis of simple building blocks, homogeneous catalytic reactions have been widely used for the functionalization of various skeletons, among them biologically important backbones.[6,7,21] There is an increasing interest in developing new strategies to introduce functional groups into specific positions (especially into 3-, 11- and 17-positions) of the steroidal framework in order to improve their pharmacological efficacy. Starting from the 1970s, various transition metal catalyzed reactions have been used for the selective modification of the steroidal backbone.[22] (A more detailed discussion of these results will be given in the 'review of the literature' part.)

Among the functional groups of pharmacological importance, the amido functionality plays an important role due to its presence in steroids with 5α-reductase inhibitor properties. The synthesis of steroidal carboxamides, possessing the amide functionality either at the A- or the D-ring at the distinguished position-3 and -17, respectively,[23-28] was accomplished in facile palladium-catalyzed aminocarbonylation reactions. The highly reactive palladium-steroidal acyl intermediate, a key intermediate in aminocarbonylation reaction, makes this reaction important from the point of view of industrial applications as well.[29,30]

Recently, aminocarbonylation of steroidal iodoalkenes was successfully carried out in our group even at the sterically more hindered 12- and 11-positions of the C-ring in the presence of *in situ* formed palladium catalysts.[31,32,33]

In general, the literature published after 2003 have been mainly used in my dissertation. Some comprehensive reviews on the approaches published before 2003 have been embedded as well, in case their citation is supporting the better understanding of the preliminaries of my study.[22,34]

The aim of my dissertation is to explore the possibility of applying palladium-catalyzed aminocarbonylation reactions in a special field of synthetic organic chemistry. I will present some homogenous catalytic functionalization reactions of the steroidal framework. In most cases, the products of potential practical importance cannot be synthesized using standard ('conventional') synthetic methods. Some of my results, obtained with the widely available keto steroids which can be transformed to steroidal compounds with iodoalkene moieties, are summarized here. The androstane-based steroids possessing iodoalkene functionality were systematically investigated in palladium-catalyzed aminocarbonylation as key-reaction.

In my doctoral dissertation, I will report also on the palladium-catalyzed syntheses of novel androstene-based 'mixed dicarboxamides' (*i.e.*, with different carboxamide functionalities) and 'dimeric' steroids containing dicarboxamide spacers either at the position-3 and/or -17.

3. Review of the literature

3.1. Hydrogenation of steroids

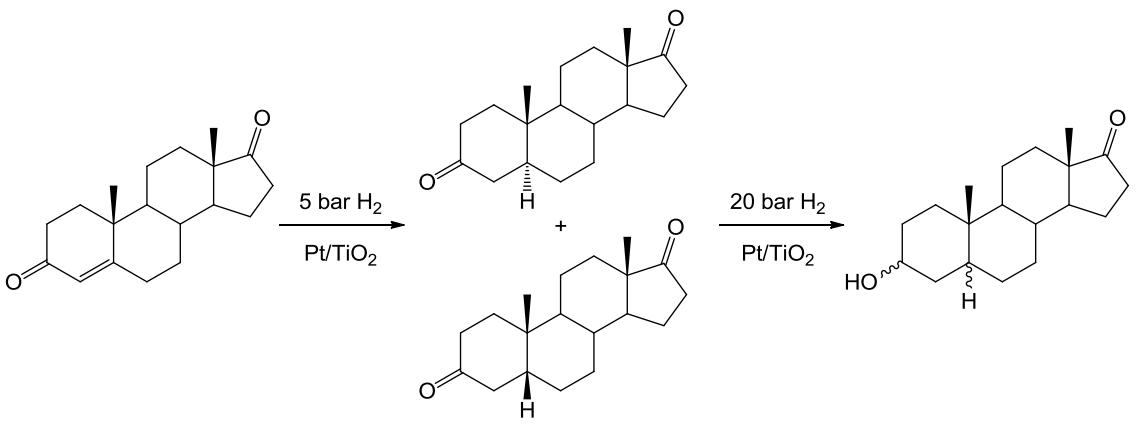
Hydrogenation reactions were among the first ones utilized for the synthesis of steroids in homogeneous catalytic reactions applying transition metal catalysts.[22] Using various transition metal catalysts as iron,[35] rhodium,[36-38] nickel,[39-41] palladium,[40,42-47] platinum,[48,49] copper,[35,50] cerium,[43,51] samarium,[51] in homogenous[37,38,41,46] or heterogeneous[49] catalytic reactions led to the hydrogenation of the carbon−carbon double bonds[35,37-40,42-44,49,50] and the reduction of carbonyl group in ketones.[37,41,43,48-50]

The homogeneous catalysts could be rather efficient for the hydrogenation of steroidal carbon–carbon double bonds, in spite of the fact, that heterogeneous catalysts (exemplified by palladium on charcoal) were extensively studied in these reactions.[52] As for the stereochemistry of hydrogenation, both enantioselective and diastereoselective hydrogenations have been used in heterogeneous catalytic reactions.[48]

One of the most important advantages of using these hydrogenations is that the reactions are chemo-,[37,38,46,49] stereo-,[37,38,40-43,48-51] enantio-,[48] or regioselective.[39,50] The other important feature is that reusable catalysts may be applied.[38,49]

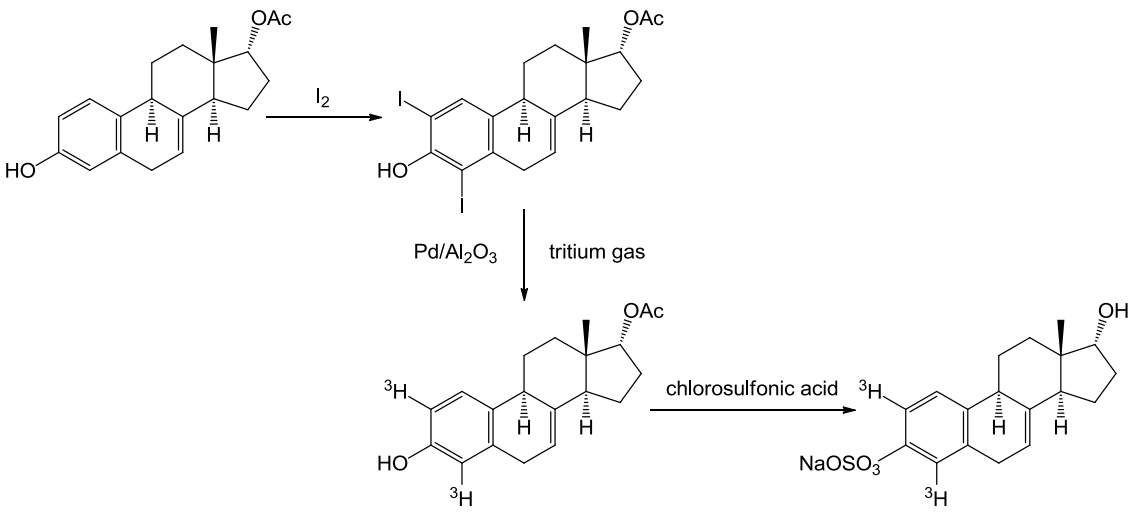
3.1.1. Recent hydrogenations using heterogeneous catalysts

Recyclable TiO_2 supported platinum nanoparticles were applied on heterogeneous hydrogenation of α,β-unsaturated oxosteroids (Scheme 1).[49]



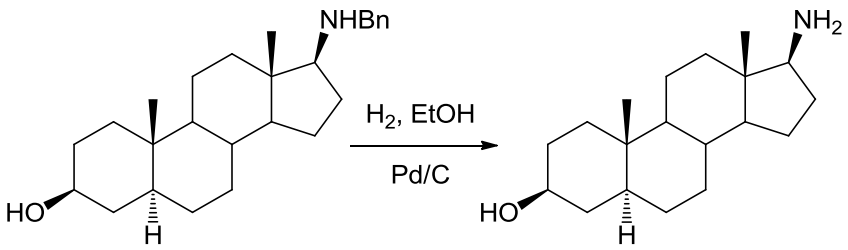
Scheme 1. Heterogeneous hydrogenation of the 4-androstene-3,17-dione *via* platinum onto TiO_2 surface.

The iodination followed by the catalytic tritium dehalogenation were applied in the synthesis of tritiated equilin, a metabolite, and several tritiated sulfate conjugates (Scheme 2).[47]



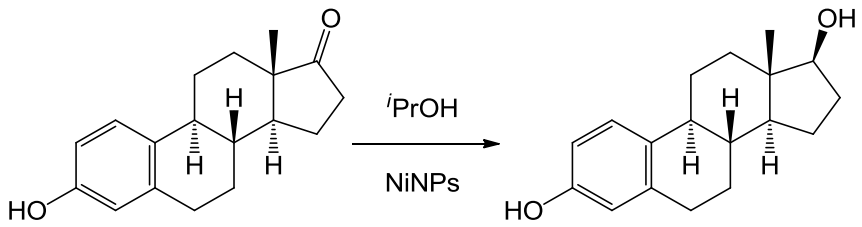
Scheme 2. Synthesis of the tritium-labeled equine derivatives using palladium on alumina catalyst.

Utilizing palladium on carbon catalyst, the hydrogenolysis of 17β-benzylamino derivatives were carried out (Scheme 3).[45]



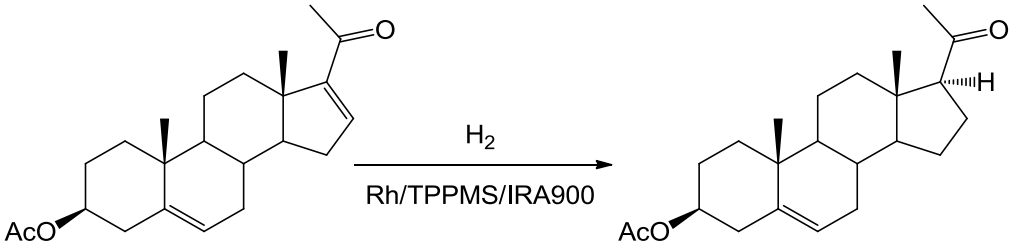
Scheme 3. Formation of the 17β-amino-5α-androstan-3β-ol *via* palladium on carbon catalyst.

The reduction of various ketones and aldehydes was investigated by transfer hydrogenation using isopropyl alcohol as hydrogen donor, and nickel(0) nanoparticles (NiNPs) as catalyst, generated from nickel(II) chloride, lithium powder, and a catalytic amount of 4,4-di-*tert*-butylbiphenyl (DTBB) in tetrahydrofuran (THF), in a homogeneous catalytic hydrogenation (Scheme 4).[41]



Scheme 4. Transfer hydrogenation of the estrone with nickel(0) nanoparticles as catalyst.

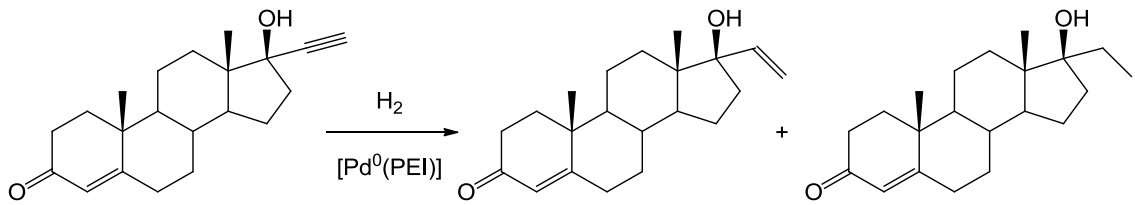
Immobilized and recyclable homogeneous rhodium catalysts were prepared and used in the α-diastereoselective hydrogenation of unsaturated oxosteroids (conjugated 16-ene-20-one systems) (Scheme 5).[38]



Scheme 5. Diastereoselective hydrogenation of the 3β-acetoxyandrost-5,16-dien-20-one by an immobilized rhodium catalyst.

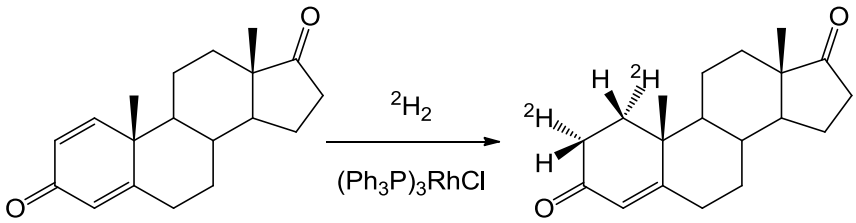
3.1.2. Recent hydrogenations using homogeneous catalysts

Various alkynes were selectively hydrogenated to the corresponding alkenes applying palladium–polyethyleneimine ([Pd^0PEI]) complex as the catalyst (Scheme 6).[46]



Scheme 6. Palladium–polyethyleneimine catalyzed partial hydrogenation of ethisterone.

Under deuterium atmosphere, [1α,2α-$^2H_2$]androst-4-ene-3,17-dione was synthesized by selective reduction of the 1,2-double bond of 1,4-diene-3-one derivative with chlorotris(triphenylphosphine)rhodium(I) as catalyst (Scheme 7).[36]

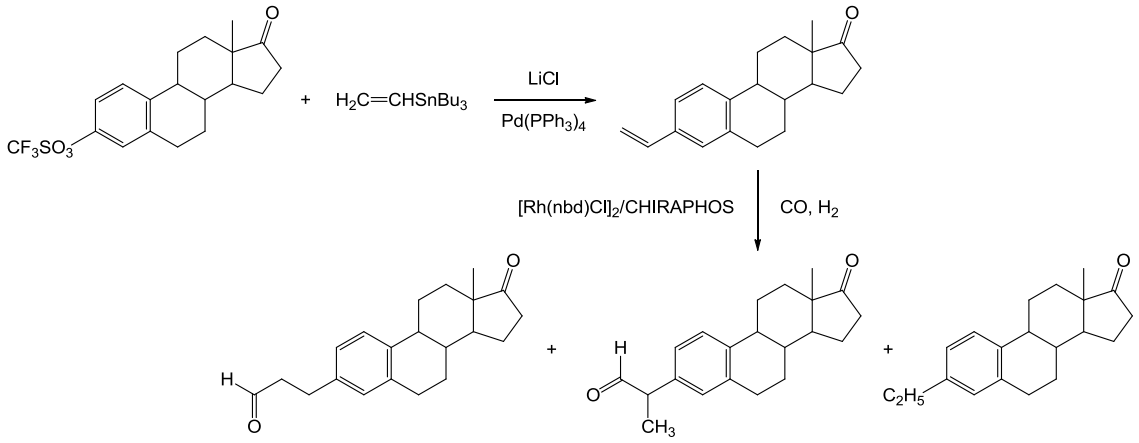


Scheme 7. Synthesis of a deuterium-labeled androstene derivative *via* rhodium-catalyzed reaction.

3.2. Hydroformylation

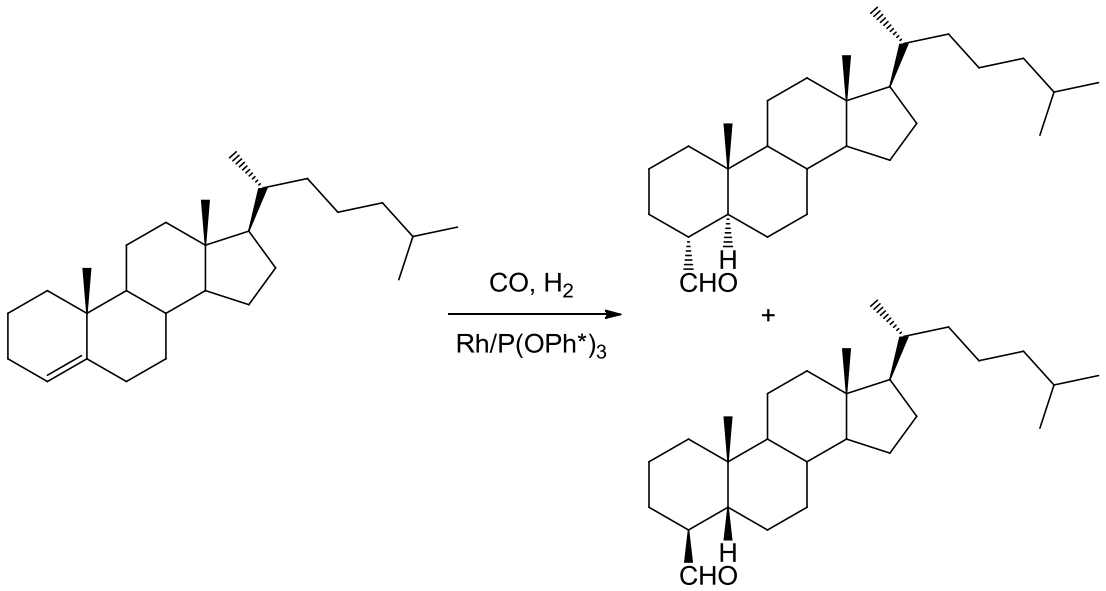
In spite of unceasingly interest in the hydroformylation of various substrates, this reaction has been only occasionally described for unsaturated steroids, though the first papers were published in the 1950s, there are only a few contributions in this area.[22]

Applying vinyltributyltin, the estrone triflate was vinylated *via* palladium-catalyzed reaction. The rhodium- or platinum-catalyzed hydroformylation of the vinylated estrone resulted in the formyl-products; the hydrogenated product was the 3-ethylestrone (Scheme 8).[53]



Scheme 8. Homogeneous catalytic coupling and hydroformylation reactions of the estrone framework.

The hydroformylation of Δ^4- and Δ^5-steroids was investigated applying rhodium catalysts modified with *P*-donor ligands containing electron withdrawing substituents, such as tris(*o*-*tert*-butylphenyl)phosphite, $P(OPh^*)_3$; tris(*o*-trifluoromethylphenyl)phosphine, $P(o\text{-}CF_3\text{-}C_6H_4)_3$; and tris(*p*-trifluoromethylphenyl)phosphine, $P(p\text{-}CF_3\text{-}C_6H_4)_3$ (Scheme 9).[54]

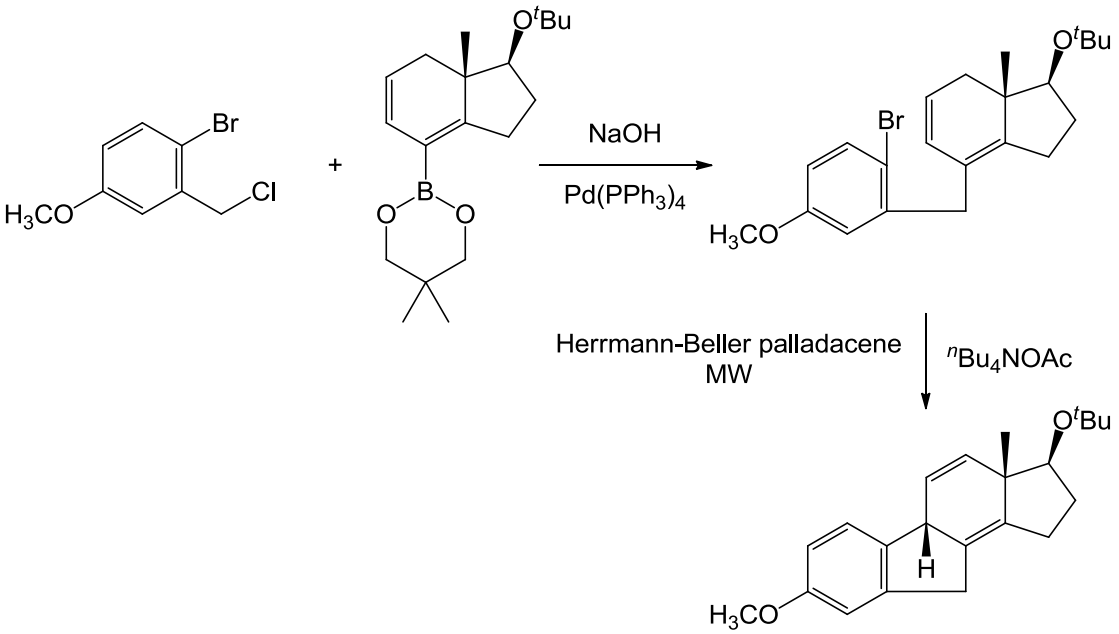


Scheme 9. Hydroformylation of cholest-4-ene catalyzed by rhodium catalyst modified with *P*-donor ligands.

3.3. Carbon−carbon bond-forming reactions – coupling reactions (excluding carbonylation reactions)

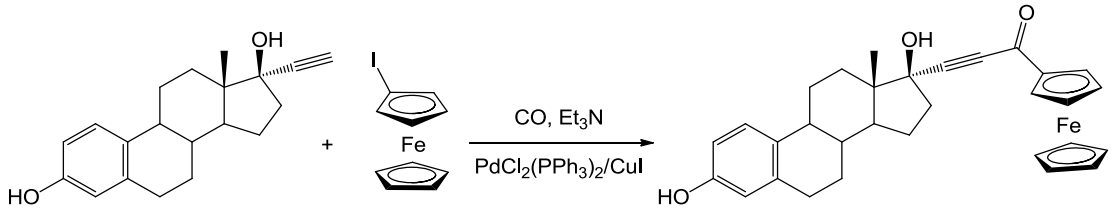
For the creation of new carbon-carbon bonds, the palladium-catalyzed coupling reactions have become one of the most important homogeneous catalytic reactions,[55-61] which are widely applied both for the functionalization of the steroidal skeleton and for the formation of the steroid framework.[22] In the literature, we can find several important applications of the transition metal catalysts such as iron,[62] ruthenium (2nd generation Grubbs catalyst),[63] copper[57,64] or silver[56] resulting new steroidal compounds such as carbon–carbon bonded steroidal homodimers,[63] D-ring unsaturated 17-alkynylsteroids,[56] steroidal BINOLs,[62] diastereomeric biaryl diols,[64] *etc*.

Applying two subsequent palladium-catalyzed reactions such as a Suzuki-coupling of the benzylchloride and the boronic ester followed by an intramolecular Heck reaction was resulted in the synthesis of the novel B-nor-estradiol analogue (Scheme 10).[55]



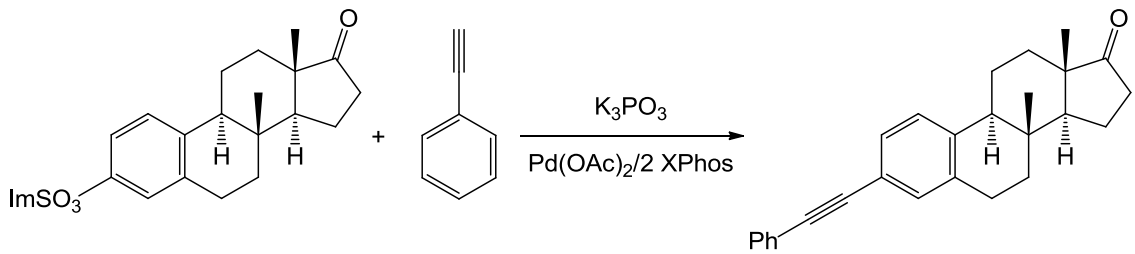
Scheme 10. Synthesis of an enantiopure B-nor-steroid *via* multiple palladium-catalyzed transformations.

The synthesis of ferrocene-labeled steroids were carried out using carbonylative Sonogashira coupling (Scheme 11) and copper-catalyzed azide-alkyne cycloaddition.[58]



Scheme 11. Synthesis of a ferrocene-labeled steroid derivative by palladium-catalyzed carbonylative Sonogashira coupling.

Steroidal phenylacetylene derivatives were synthesized from estron-3-yl imidazylate *via* palladium-catalyzed Sonogashira cross-coupling reaction (Im = imidazolyl), (Scheme 12).[60]



Scheme 12. Sonogashira cross-coupling reaction of estrone imidazylate and phenylacetylene.

3.4. Carbonylation reactions

3.4.1. Alkoxycarbonylation reactions

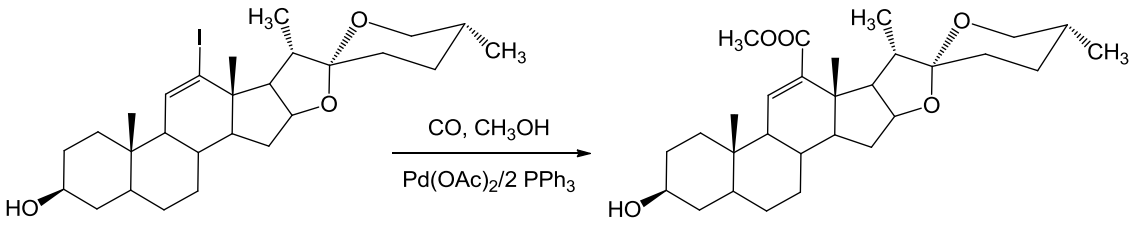
Arylpalladium(II) or alkenylpalladium(II) complexes can be formed using aryl or alkenyl triflates/halides. The substrate could be oxidatively added to Pd(0) precursors resulting in aryl/alkenyl-palladium(II) species. The appropriate acylpalladium(II) complexes are formed with carbon monoxide in insertion reaction, and could act as acylating agents and result in different carboxylic acid derivatives. A successful method of integrating carboxylic acid, ester, or amide functionalities into the steroidal framework is achieved using a base resulting in the conversion of Pd(0) species converted from hydrido-palladium(II) complexes *via* reductive elimination in the product-forming step.[22]

5α-Reductase inhibitors may be formed efficiently using carbonylaton reactions as shown by a number of patents and publications. The enzyme 5α-reductase is accountable for the conversion of testosterone, depending on NADPH, to dihydrotestosterone (DHT). High DHT levels are found to cause benign prostatic hyperplasia, prostatic carcinoma, male pattern baldness, and other endocrine diseases. The steroid 5α-reductase inhibiting may decrease the presence of DHT in the tissues; consequently 5α-reductase inhibitors such as finasteride, epristeride, are used in pharmacological therapy.

The syntheses of steroidal 3-carboxylic acid compounds by the vinyl/aryl triflate–carboxylic acid ester–carboxylic acid reaction sequence were presented by Holt and co-workers.[29,30,65-68] Using methanol in the palladium-catalyzed carbonylation of vinyl or aryl triflates was followed by the conversion of methyl esters to carboxylic acids by hydrolysis.

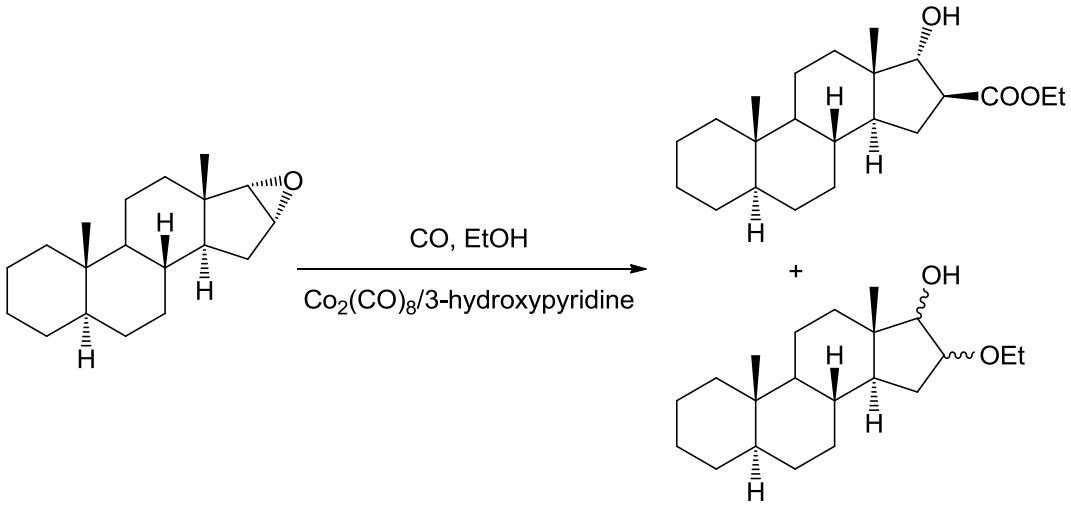
In our research group, palladium-catalyzed homogeneous alkoxycarbonylation reactions were carried out using triphenylphosphine as ligand.[31,69-71]

In palladium-catalyzed alkoxycarbonylation reactions 12-alkoxycarbonyl-11-spirostenes were synthesized from 12-iodo-11-ene derivative, which tolerated the 3-hydroxy substituent and the spiroacetal moiety (Scheme 13).[31]



Scheme 13. Synthesis of a 12-substituted spirostane in alkoxycarbonylation reaction of the 12-iodo-11-ene derivative.

In high chemo- and regioselective reactions, using $Co_2(CO)_8$/3-hydroxypyridine catalytic system, epoxy-steroids were transformed to the corresponding esters in ring-opening alkoxycarbonylation (Scheme 14).[72]



Scheme 14. Alkoxycarbonylation of a 16α,17α-epoxy steroid derivative.

3.4.2. Aminocarbonylation reactions

3.4.2.1. Aminocarbonylation reactions (excluding steroids)

In the presence of amines as *N*-nucleophiles, the carbonylation of enol/aryl triflates or alkenyl halides results in the production of carboxamides or 2-ketocarboxamides.

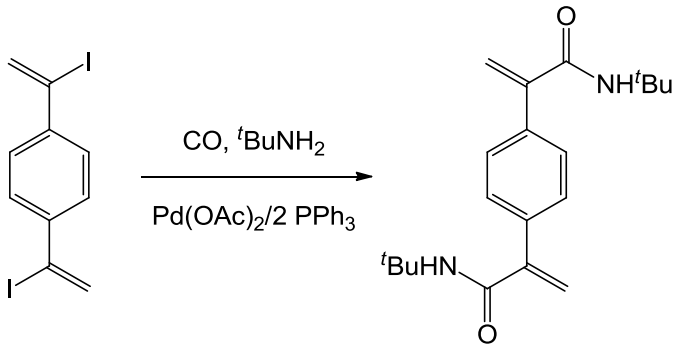
In our research group the homogeneous aminocarbonylation reactions were accomplished by $Pd(OAc)_2$/2 PPh_3 catalyst system in the presence of various primary or secondary amines as *N*-nucleophiles using iodoalkene or aryl iodide derivatives.[73-85]

At first in several cases, the corresponding iodoalkene or aryl iodide substrates used in the aminocarbonylation were synthesized utilizing Barton's methodology modified accordingly.[86,87] The standard ketone–hydrazone–iodoalkene route was

followed.[73,76-78,84] The corresponding keto derivatives were converted to the appropriate hydrazones using barium oxide or triethylamine. Hydrazone compounds were reacted with iodine in the presence of a base (*N,N,N',N'*-tetramethylguanidine) resulting in the corresponding iodoalkene derivatives. The last iodoalkene product-forming step was carried out under argon providing strictly moisture- and oxygen-free conditions.

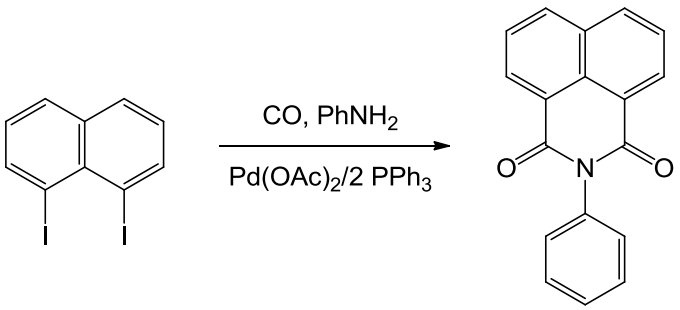
Since the present doctoral research work is mainly devoted to the synthesis of carboxamides *via* palladium-catalyzed aminocarbonylation, this reaction is presented in a wider context.

In high-yielding palladium-catalyzed aminocarbonylation reactions, α-iodostyrene and α,α'-diiodo-1,4-divinylbenzene were prepared and used as substrates (Scheme 15).[73]



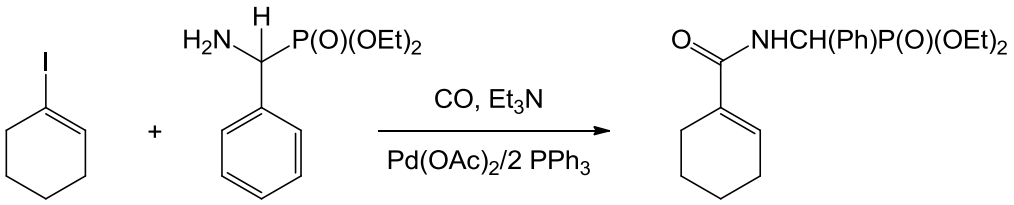
Scheme 15. A transformation of α,α'-diiodo-1,4-divinylbenzene.

Dicarboxamides and *N*-substituted naphtalimides were synthesized using 1,8-diiodo-naphthalene and various primary and secondary amines in the presence of Pd(OAc)$_2$/2 PPh$_3$ catalytic system (Scheme 16).[74]



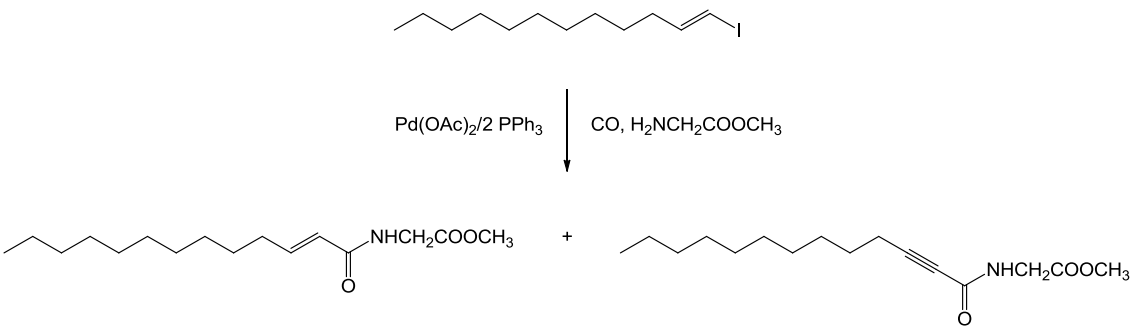
Scheme 16. Formation of an *N*-substituted 1,8-naphthalimide.

A set of new *N*-acyl phosphonates with unprecedented structure were synthesized by palladium-catalyzed aminocarbonylation of iodoalkene derivatives such as 1-iodo-cyclohexene (or 1-iodo-4-*tert*-butyl-cyclohexene, 1-iodo-2-methyl-cyclohexene, α-iodostyrene) under mild reaction conditions (1-60 bar carbon monoxide pressure, 50 °C), (Scheme 17).[75]



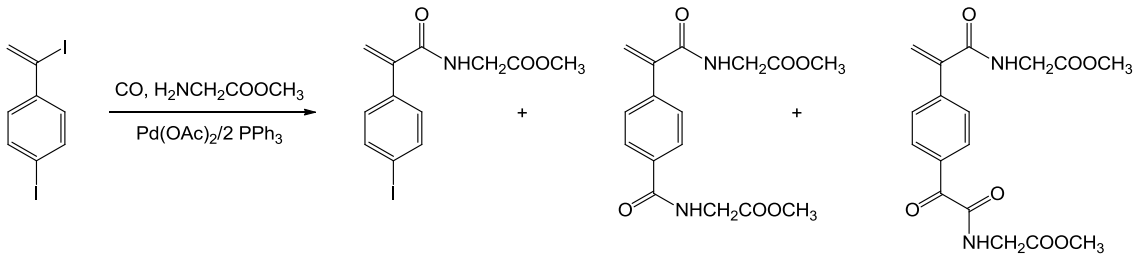
Scheme 17. Aminocarbonylation reaction of the 1-iodocyclohexene using diethyl α-aminobenzyl-phosphonate as *N*-nucleophile.

(*E*)- and (*Z*)-1-iodo-1-dodecene substrates were synthesized from 1-dodecanal by their hydrazones. The resulted iodoalkenes were aminocarbonylated using various amine nucleophiles including glycine methyl ester resulted in the corresponding odd-number carboxamides (Scheme 18).[76]



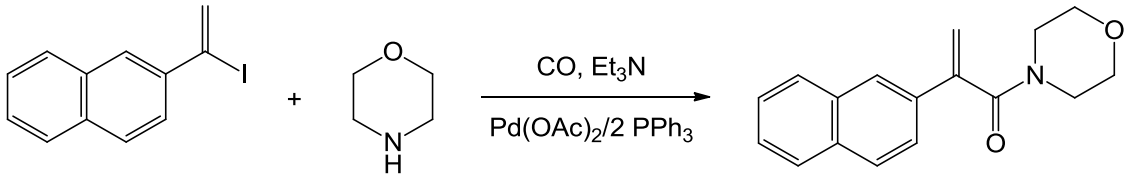
Scheme 18. Synthesis of odd-number carboxamides using palladium catalyst.

In palladium-catalyzed aminocarbonylation, 1',4-diiodostyrene was synthesized and transformed to the corresponding dicarboxamides and amide–ketocarboxamides. Using atmospheric carbon monoxide pressure, 4-iodophenylacrylamides were selectively prepared due to the different reactivity of the two iodo-functionalities (Scheme 19).[77]



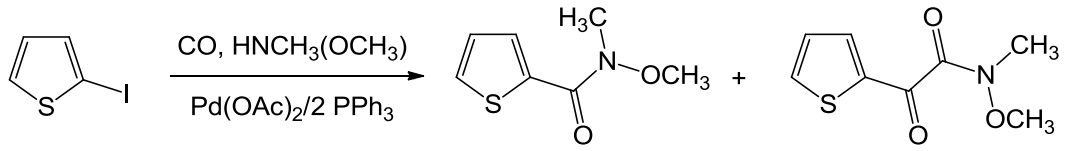
Scheme 19. A palladium-catalyzed aminocarbonylation of 1',4-diiodostyrene.

The extremely reactive 1-iodo-1-(2-naphthyl)ethene and 1-iodo-1-(1-naphthyl)ethene were synthesized from the corresponding acetonaphthone isomers *via* their hydrazones and transformed to the corresponding amides in palladium-catalyzed aminocarbonylations (Scheme 20).[78]



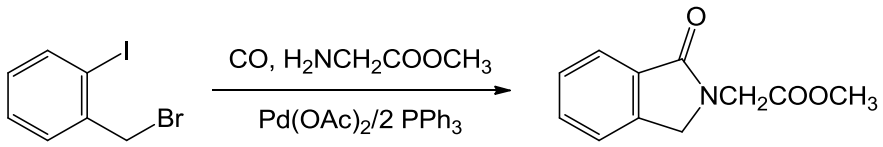
Scheme 20. A carbonylation reaction of 1-iodo-1-(2-naphthyl)ethene.

High-yielding synthesis of Weinreb amides were carried out using iodoarenes (iodobenzene and 2-iodothiophene) and iodoalkenes (1-iodocyclohexene, 1-iodo-4-*tert*-butylcyclohexene, 1-iodo-2-methylcyclohexene and 1-iodo-1-(1-naphthyl)ethene) as substrates with *N*,*O*-dimethylhydroxylamine (Scheme 21).[79]



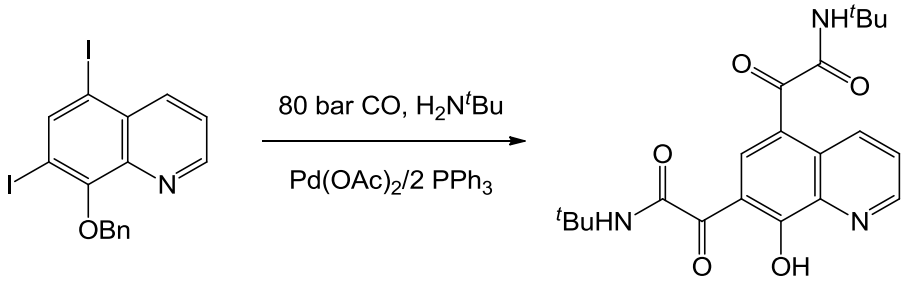
Scheme 21. Palladium-catalyzed aminocarbonylation of 2-iodothiophene with *N*,*O*-dimethylhydroxylamine.

Bifunctional substrates such as 2-iodobenzyl bromide and 2-iodobenzylamine were transformed to 1-isoindolinone derivatives. *N*-Substituted 1-isoindolinones were accomplished using primary amines (Scheme 22), while secondary amines react both with the benzyl bromide and iodoarene moieties producing the corresponding *ortho*-(*N*-piperidino/morpholinomethyl)-benzamides.[80]



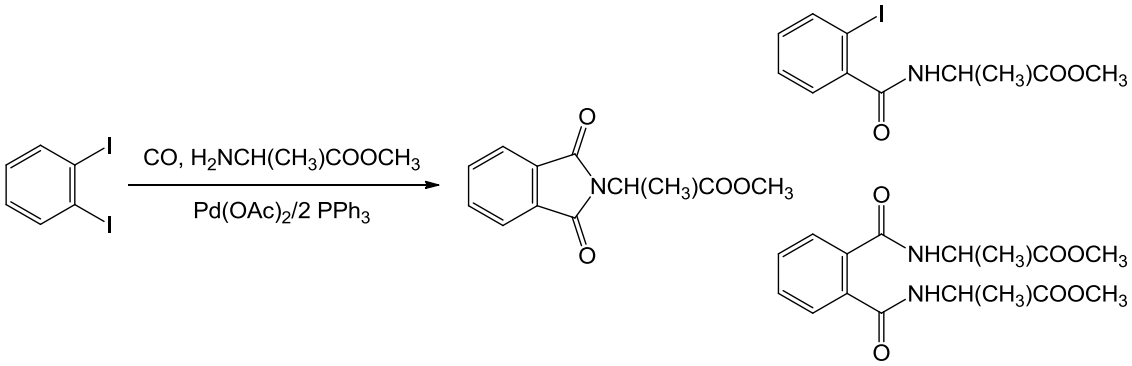
Scheme 22. Cycloaminocarbonylation of 2-iodobenzyl bromide in the presence of palladium catalyst.

The transformation of 5,7-diiodo-8-benzyloxyquinoline were accomplished to 5-carboxamido-7-iodo-8-benzyloxyquinoline derivatives. Interestingly, using *tert*-butylamine as *N*-nucleophile, 5,7-bis(*N*-*tert*-butyl-glyoxylamido)-8-hydroxyquinoline was achieved under high carbon monoxide pressure (Scheme 23).[81]



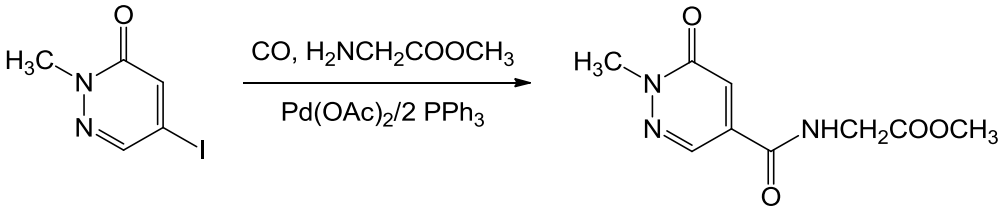
Scheme 23. An aminocarbonylation reaction of 5,7-diiodo-8-benzyloxyquinoline.

The use of primary amines in the aminocarbonylation of 1,2-diiodobenzene, the major products were *N*-substituted phthalimides in double carbonylation, while secondary amines react with one of the iodoarene functionalities resulting the corresponding 2-iodobenzamides. The formation of the possible 2-ketocarboxamide-carboxamide or bis-2-ketocarboxamide derivatives depends strongly on the reaction conditions (Scheme 24).[82]



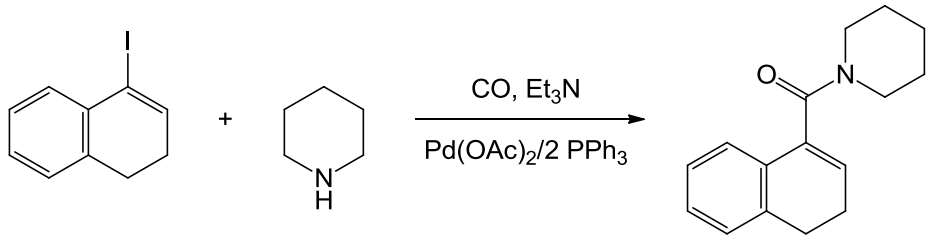
Scheme 24. An aminocarbonylation of 1,2-diiodobenzene using *L*-alanine methyl ester.

In the presence of various amines including amino acid methyl esters, 5-iodo- and 4,5-dibromo-2-methylpyridazin-3(2H)-ones were carbonylated (Scheme 25).[83]



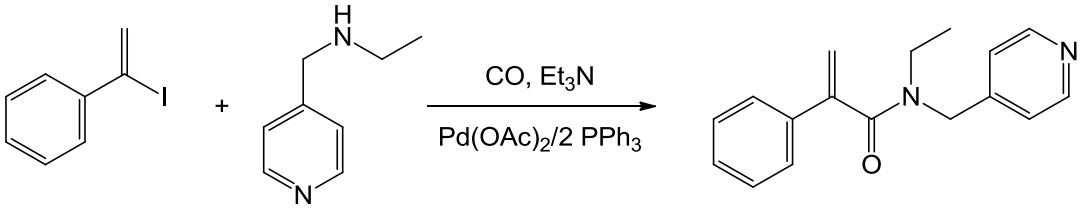
Scheme 25. The synthesis of a 5-carboxamido-2-methylpyridazin-3(2H)-one derivative.

In the presence of palladium-phosphine precatalyst ($Pd(OAc)_2$/2 PPh_3), 1-iodo-3,4-dihydronaphthalene, acquired from α-tetralon, was carbonylated (Scheme 26).[84]



Scheme 26. An aminocarbonylation reaction of 1-iodo-3,4-dihydronaphthalene.

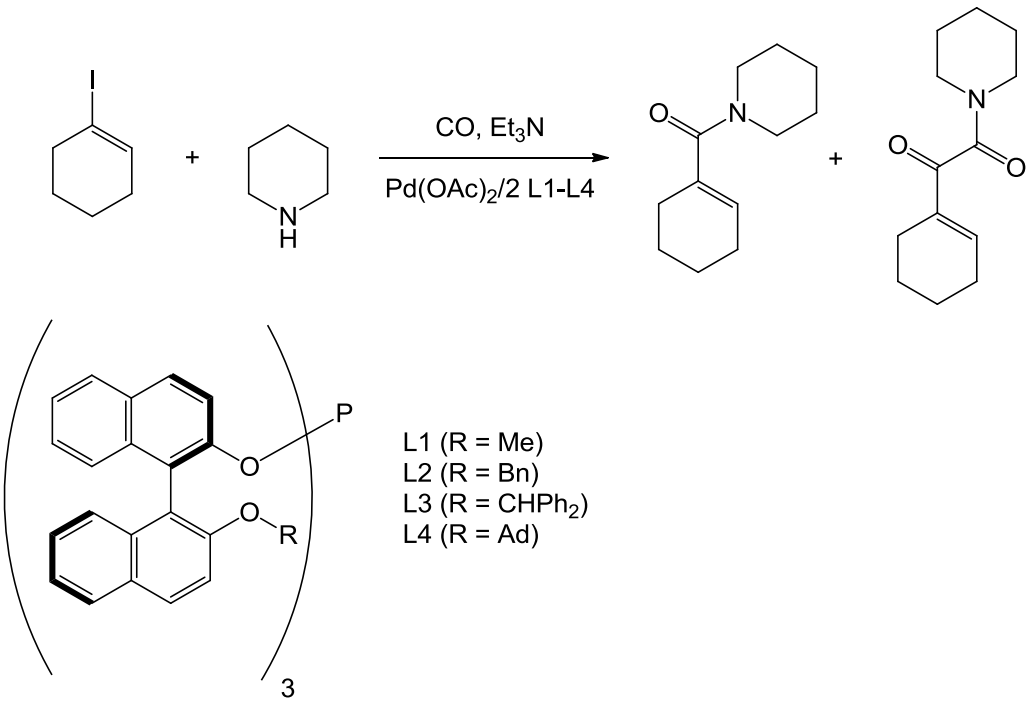
The aminocarbonylation of iodobenzene, 1-iodocyclohexene and 1'-iodostyrene in the presence of *N*-nucleophiles including pyridyl moieties (2-, 3- and 4-picolylamine, *N*-ethyl-4-picolylamine, di-(2-picolyl)amine) was accomplished resulting in the intermediates of pharmacologically important compounds (Scheme 27).[85]



Scheme 27. An aminocarbonylation reaction of 1'-iodostyrene in the presence of 4-(ethylaminomethyl)pyridine.

Although the aminocarbonylation of iodoalkenes is highly chemoselective towards carboxamides, it was shown that in the presence of palladium-phosphite precatalysts the 1-iodocyclohexene model substrate was doubly carbonylated. In this reaction,

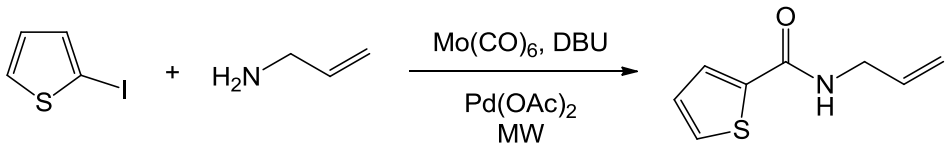
arylphosphite heterobidentate *P,O*-ligands with π-acceptor abilities possessing binaphthyl skeleton were applied as ligands in palladium catalysts (Scheme 28).[88]



Scheme 28. An aminocarbonylation of 1-iodocyclohexene by palladium-phosphite precatalyst.

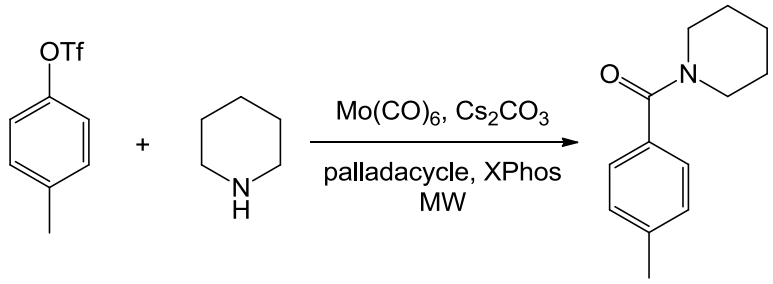
Using solid CO sources such as $Mo(CO)_6$[89-96] or $Co_2(CO)_8$[97] under high-density microwave irradiation (MW)[89-93,97] or under conventional conditions[94-96] expanded the application of transition metal-mediated aminocarbonylation protocols.

Various (hetero)aryl iodides, bromides and chlorides were aminocarbonylated with allylamine using $Mo(CO)_6$ as a solid CO source and microwave-enhanced conditions (Scheme 29).[89]



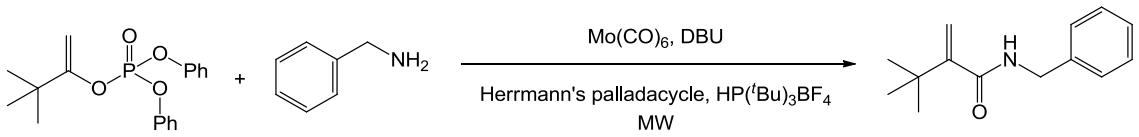
Scheme 29. An aminocarbonylation reaction in the presence of a solid CO source.

Palladium-catalyzed carbonylations of aryl triflates with various nucleophiles using $Mo(CO)_6$ as a solid CO source were carried out *via* microwave irradiation (Scheme 30).[90]



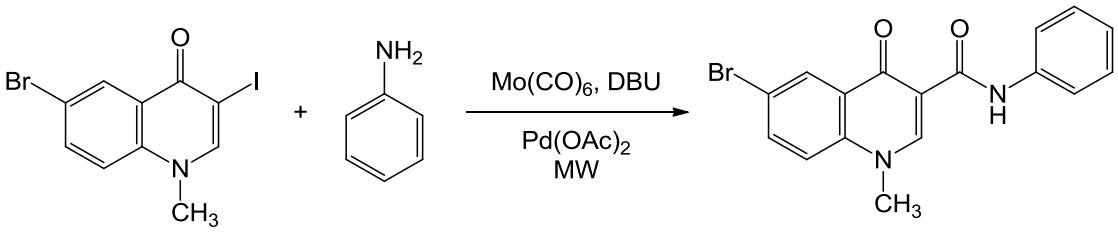
Scheme 30. Aminocarbonylation of *p*-tolyl triflate with piperidine in the presence of a solid CO source.

Using $Mo(CO)_6$ as a solid carbon monoxide source, alkenyl chlorides, bromides, triflates, and surprisingly alkenyl phosphates were aminocarbonylated in palladium-catalyzed reactions by microwave irradiation (Scheme 31).[91]



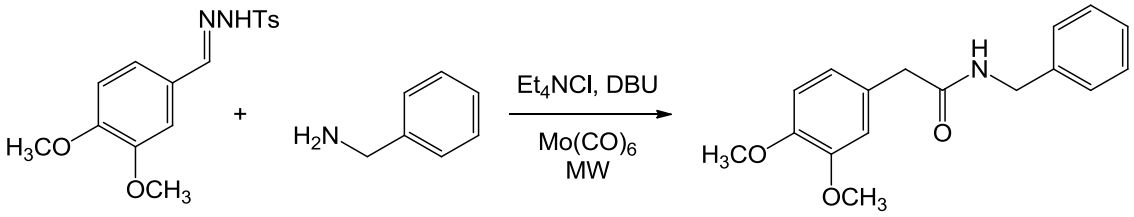
Scheme 31. Synthesis of an acrylamide from an alkenyl phosphate as a coupling partner.

Under microwave irradiation, 1,3,6-trisubstituted quinolin-4(1H)-ones were synthesized from 1-alkyl-6-bromo-3-iodoquinolin-4(1H)-one in palladium-catalyzed reactions (Scheme 32).[92]



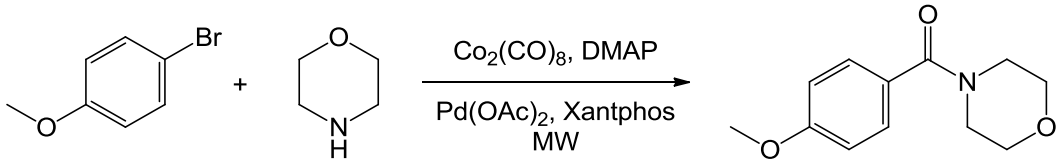
Scheme 32. An aminocarbonylation reaction of 6-bromo-3-iodoquinolin-4(1H)-one.

A palladium-free microwave assisted aminocarbonylation of *N*-tosylhydrazones were accomplished from aromatic aldehydes and ketones mediated by molybdenum hexacarbonyl as carbon monoxide source and catalyst (Scheme 33).[93]



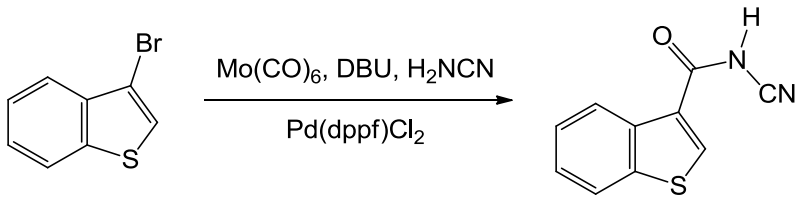
Scheme 33. A Pd-free aminocarbonylation of an *N*-tosylhydrazone derivative.

Using solid $Co_2(CO)_8$ as a convenient CO source, aryl halides were transformed directly to benzamides under microwave irradiation (Scheme 34).[97]



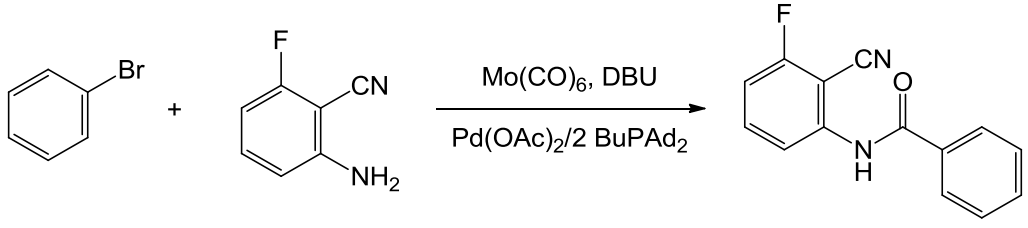
Scheme 34. An aminocarbonylation reaction of 4-bromoanisole in the presence of morpholine.

Utilizing $Mo(CO)_6$ as CO source or CO gas in the palladium-catalyzed aminocarbonylation, a set of new 3-(*N*-cyanocarboxamido)-benzo[b]thiophenes were synthesized from aryl halides and cyanamide (Scheme 35).[94]



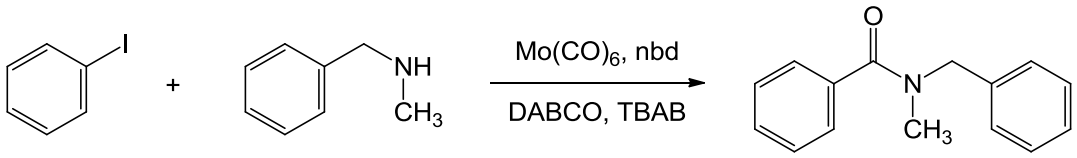
Scheme 35. Synthesis of an *N*-cyanocarboxamido derivative using $Mo(CO)_6$ as CO source.

Using $Mo(CO)_6$ as CO source, the synthesis of *N*-(2-cyanoaryl)benzamides were carried out in the presence of aryl bromides and 2-aminobenzonitriles as substrates (Scheme 36).[95]



Scheme 36. Synthesis of an *N*-(2-cyanoaryl)benzamide derivative with $Mo(CO)_6$ as CO source.

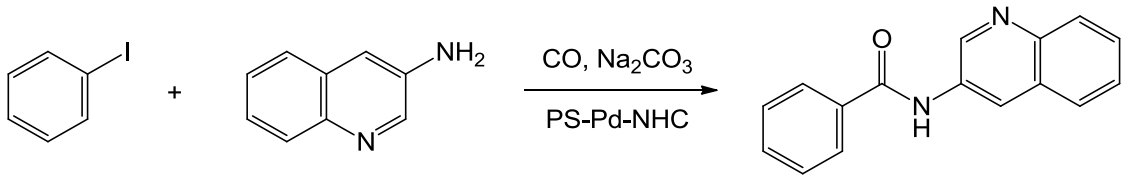
Using *in situ* generated molybdenum tetracarbonyl norbornadiene [$Mo(CO)_4$(nbd)] complex as a carbon monoxide source, the efficient aminocarbonylation of aryl, benzyl, and styryl iodides and bromides was carried out (Scheme 37).[96]



Scheme 37. A carbonylation of iodobenzene by *in situ* generated molybdenum tetracarbonyl norbornadiene complex.

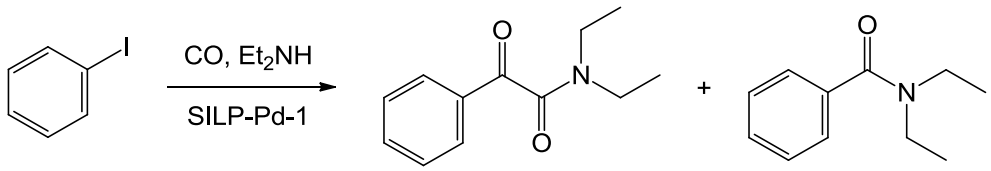
Several transition metal catalytic systems have a number of limitations like necessity of air and moisture-sensitive phosphine-containing ligands, limited substrate compatibility, high carbon monoxide pressure, higher catalyst loading, or the use of organic solvents.[98] Consequently, developing carbon monoxide-free,[89-97,99] palladium-free,[93] reusable,[98-102] heterogeneous,[98-100] or phosphine-free[98,102] catalytic system in aminocarbonylations might be advantageous.

Polymer supported palladium-*N*-heterocyclic carbene complex (PS-Pd-NHC) can be used as an efficient heterogeneous, reusable catalyst in the carbonylation of aryl iodides with various aliphatic and aromatic primary and secondary amines. The important advantages of these reactions are the phosphine-free protocol in aqueous environment and a catalyst recycled four times which did not lose its selectivity and activity (Scheme 38).[98]



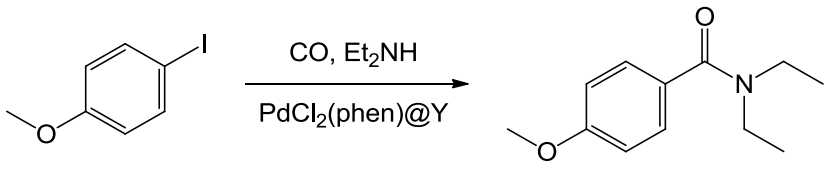
Scheme 38. An aminocarbonylation reaction in aqueous medium.

Various phosphine-free, recyclable, silica supported palladium catalysts (SILP-Pd-1–SILP-Pd-4) were prepared and examined in the formation of α-ketoamides (Scheme 39).[102]



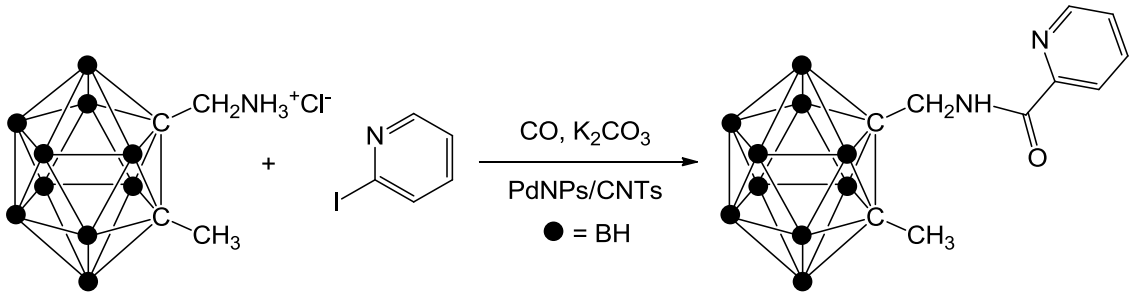
Scheme 39. A phosphine-free aminocarbonylation reaction of iodobenzene.

Using an Y-zeolite encaged palladium-1,10-phenanthroline complex in the aminocarbonylation reactions of various aryl iodides is an encouraging strategy for the catalytic synthesis. This heterogeneous catalyst is immensely reusable, the 16 times reused catalyst accomplished an appropriate yield, and the reactions necessitate low palladium loadings (Scheme 40).[100]



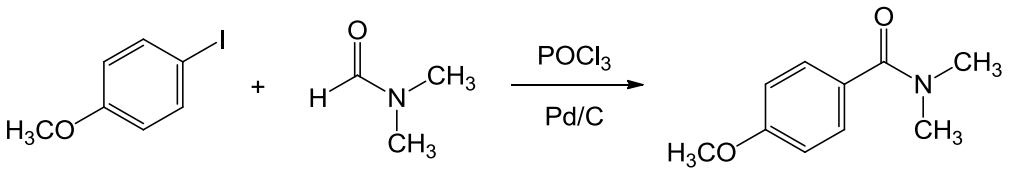
Scheme 40. Transformation of an aryl iodides using heterogeneous palladium catalyst.

A set of carboranyl amides, 1-R-2-[$CH_2NHC(=O)Ar$]-1,2-$C_2B_{10}H_{10}$ (R = H, Me; Ar = C_6H_5, 4-Me-C_6H_4, 4-MeO-C_6H_4 and 2-C_5NH_4), were synthesized and the reactions were catalyzed by a three times recyclable palladium(0) nanoparticles (PdNPs) supported on carbon nanotubes (CNTs) (Scheme 41).[101]



Scheme 41. A transformation of a carboranyl ammonium salt.

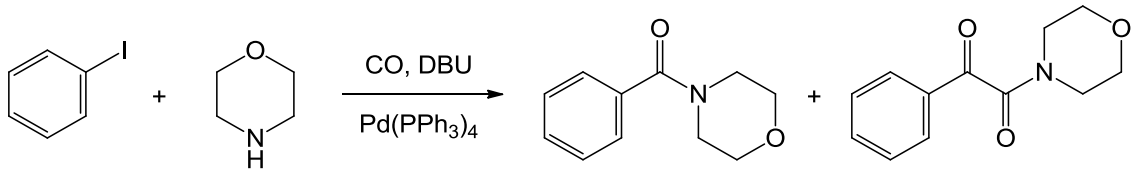
Applying Pd/C as a heterogeneous and three times recyclable catalyst in the carbon monoxide-free aminocarbonylation, coupling reactions of *N*,*N*-dimethylformamide (DMF) with aryl iodides were accomplished (Scheme 42).[99]



Scheme 42. A Pd/C catalyzed aminocarbonylation by *N*,*N*-dimethylformamide.

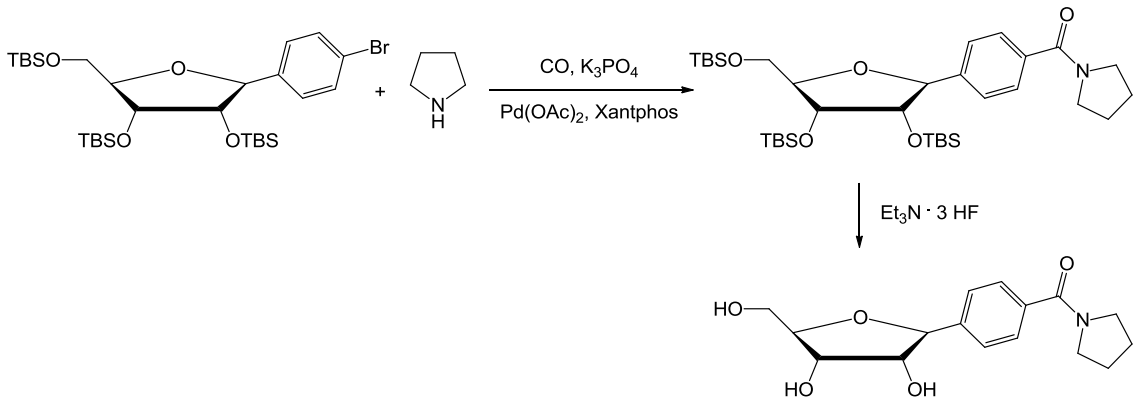
In most cases, double aminocarbonylation reactions require high pressure conditions;[81,88,103] however there are some examples in the literature for the use of atmospheric carbon monoxide pressure[77,82,102] to form ketocarboxamides.

In a microfluidics-based high throughput flow reactor (X-Cube^{TM}),[104-106] double aminocarbonylation of iodobenzene was accomplished efficiently using immobilized $Pd(PPh_3)_4$ catalyst (Scheme 43).[103]



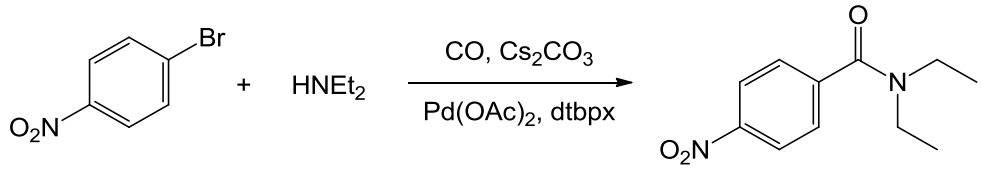
Scheme 43. A formation of an α-ketoamide using X-Cube^{TM} flow reactor.

Using various primary and secondary amines or NH_4Cl, *tert*-butyldimethylsilyl (TBS) protected 3- and 4-bromophenyl-*C*-ribonucleosides were transformed to *p*- and *m*-substituted benzamide-*C*-ribonucleosides. Free *C*-ribonucleosides were produced *via* deprotection by $Et_3N \cdot 3$ HF or trifluoroacetic acid (TFA), (Scheme 44).[107]



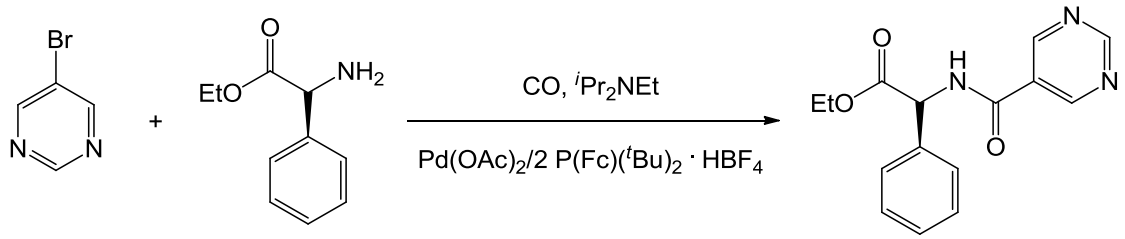
Scheme 44. A carbonylation reaction of 4-bromophenyl-*C*-ribonucleoside.

The application of bis(di-*tert*-butylphosphino)-*o*-xylene (dtbpx) as ligand in palladium-catalyzed carbonylative reactions was reported (Scheme 45).[108]



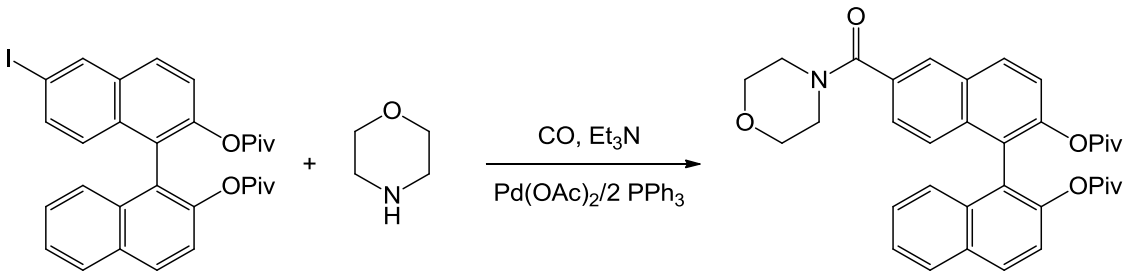
Scheme 45. Aminocarbonylation of bromoarene substrate using bis(di-*tert*-butylphosphino)-*o*-xylene as ligand.

Using di-*tert*-butylphosphinoferrocene monodentate ligand as tetrafluoroborate salt, heteroaryl halides were aminocarbonylated in palladium-catalyzed reactions (Scheme 46).[109]



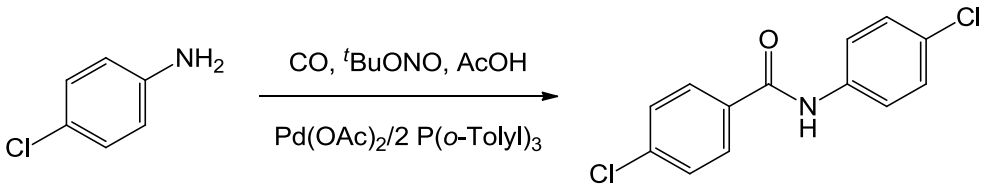
Scheme 46. Synthesis of (*R*)-ethyl-2-phenyl-2-(pyrimidine-5-carboxamido)-acetate.

By palladium-catalyzed reactions of 6-halogeno-binaphthyl derivatives, 6-substituted binaphthyl compounds were achieved, which were synthesized from 2,2'-dihydroxy-1,1'-binaphthyl (Scheme 47).[110]



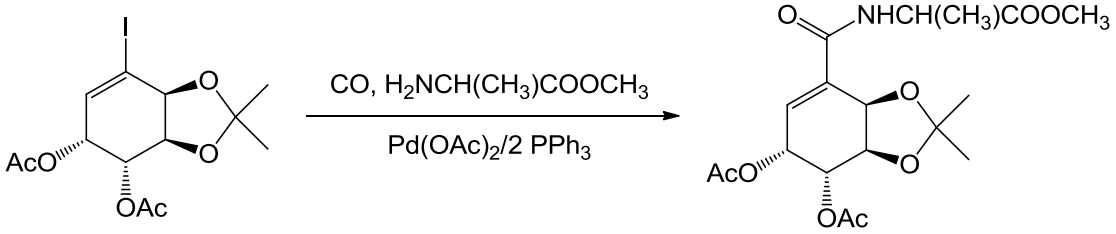
Scheme 47. A palladium-catalyzed reaction of a 6-iodo-1,1'-binaphthyl derivative.

Without base at low temperature, *N*-arylbenzamides were synthesized from aniline derivatives in diazotization/aminocarbonylation reactions (Scheme 48).[111]



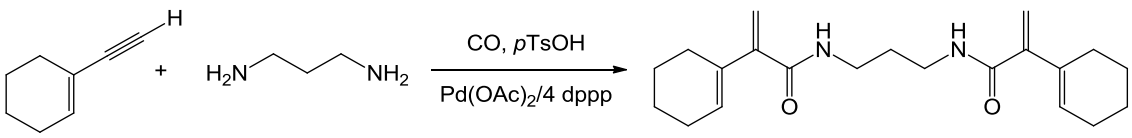
Scheme 48. Synthesis of an *N*-arylbenzamide derivative.

An iodo-cyclohexenetetraol derivative was carbonylated using amino acid methyl ethers as *N*-nucleophiles. The aminocarbonylation methodology was applied to the transformation of diastereoisomeric bromocyclohexenetetraols, which were previously prepared through biotransformation of bromobenzene by mutant strains of *Pseudomonas putida* F39/D (Scheme 49).[112]



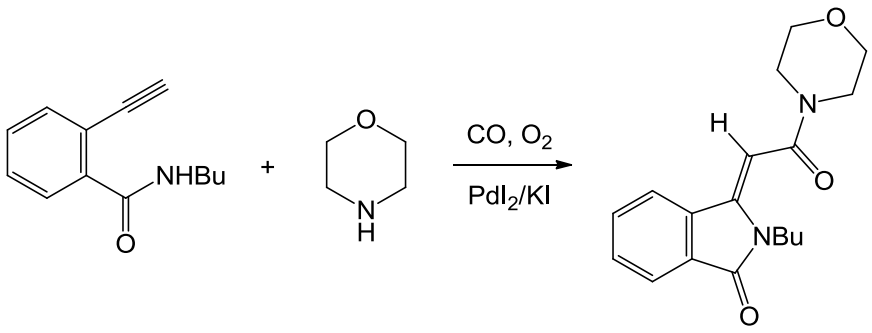
Scheme 49. An aminocarbonylation of iodo-cyclohexenetetraol derivative using *L*-alanine methyl ester as *N*-nucleophile.

In the presence of various amines, diaminoalkanes, and aminoalcohols, the palladium-catalyzed aminocarbonylation of enynes were resulted in novel conjugated dienamides (Scheme 50). The products were used as substrates and transformed to ω-amidoesters using $Pd(PPh_3)_2Cl_2$ as catalyst and methanol as nucleophile in alkoxycarbonylation reactions.[113]



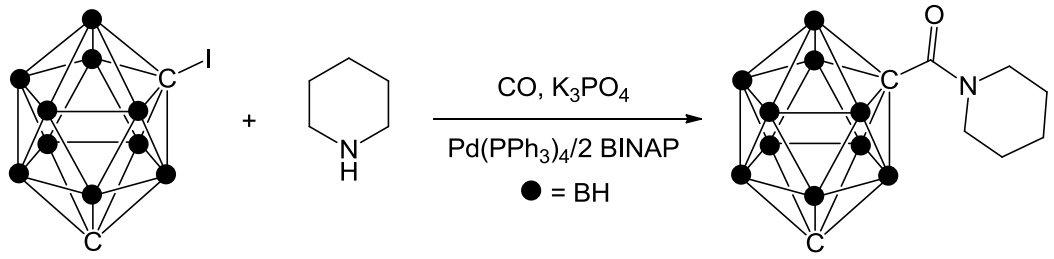
Scheme 50. Aminocarbonylation of an enyne using a diamine.

In a cascade process, secondary 2-ethynylbenzamides were monoaminocarbonylated oxidatively, followed by intramolecular conjugate addition of the arylamido group to the alkynylamido group of the intermediate alkynylamides, resulting in functionalized isoindolinone derivatives (Scheme 51).[114]



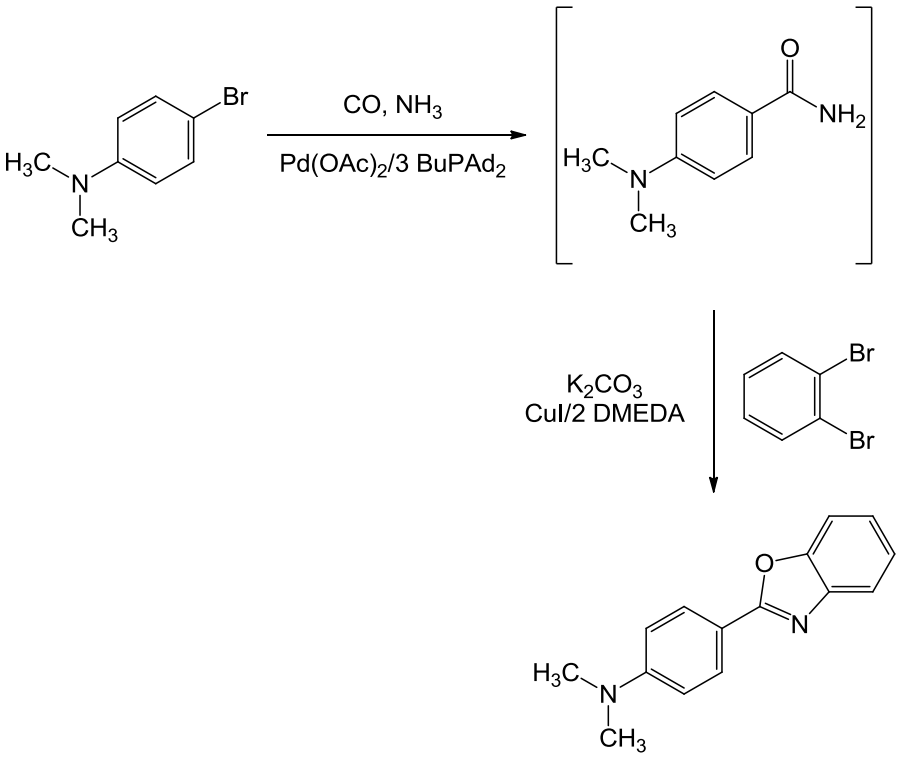
Scheme 51. Synthesis of a 3-[(dialkylcarbamoyl)methylene]isoindolin-1-one derivative *via* oxidative carbonylation.

1-Iodo-1,7-dicarba-*closo*-dodecaborane, 1-I-1,7-$C_2B_{10}H_{10}$, was transformed to *m*-carboranyl amides by the one-pot one-step aminocarbonylation (Scheme 52).[115]



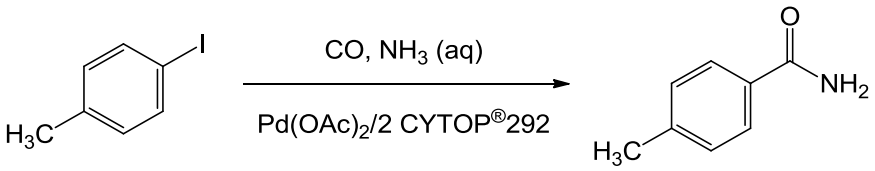
Scheme 52. An aminocarbonylation reaction of 1-iodo-1,7-dicarba-*closo*-dodecaborane.

2-Aryl-substituted benzoxazoles were produced from aryl bromides and 1,2-dihalobenzenes in palladium-catalyzed aminocarbonylation and subsequent copper-catalyzed coupling reaction (Scheme 53).[116]



Scheme 53. Synthesis of a 2-arylbenzoxazole derivative in a one-pot process.

Using aqueous ammonia in aminocarbonylation reactions, various primary aromatic amides were synthesized in the presence of $Pd(OAc)_2$/2 CYTOP®292[117,118] catalyst system (Scheme 54).[119]

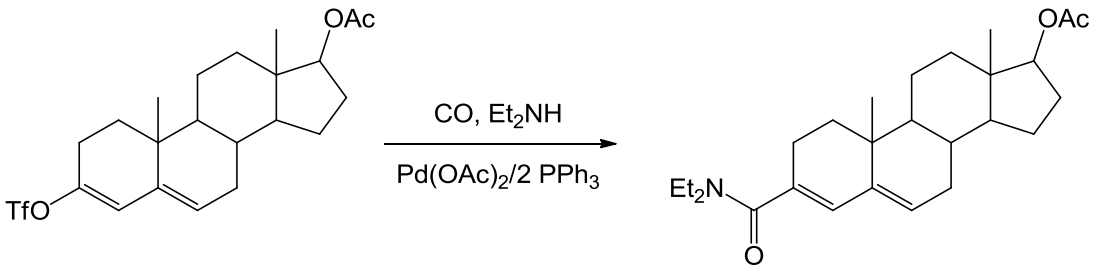


Scheme 54. An aminocarbonylation of an aryl iodide derivative using aqueous ammonia.

3.4.2.2. Aminocarbonylation reactions of steroidal compounds

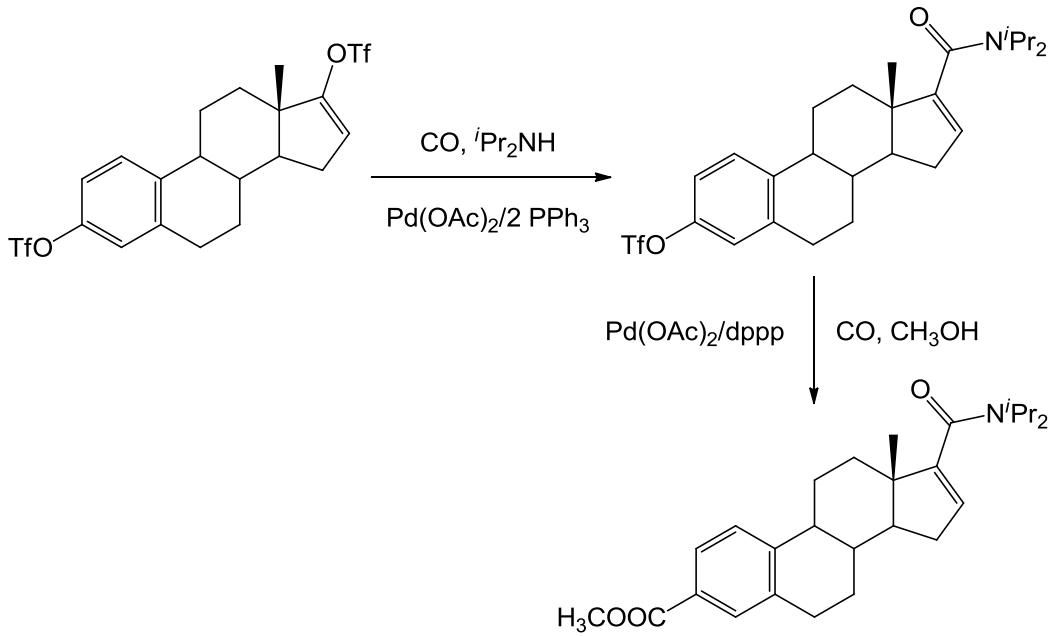
The transformation of steroidal enol/aryl triflates or alkenyl halides in the presence of amines as *N*-nucleophiles leads to the corresponding carboxamides. Several analogous compounds available in aminocarbonylation reactions possess significant practical use in the pharmacological industry.

The carbonylation of steroidal enol triflates in the presence of $Pd(OAc)_2$/2 PPh_3 catalysts at room temperature and atmospheric CO pressure leads to good yields (Scheme 55).[120]



Scheme 55. Palladium-catalyzed aminocarbonylation with diethylamine as *N*-nucleophile.

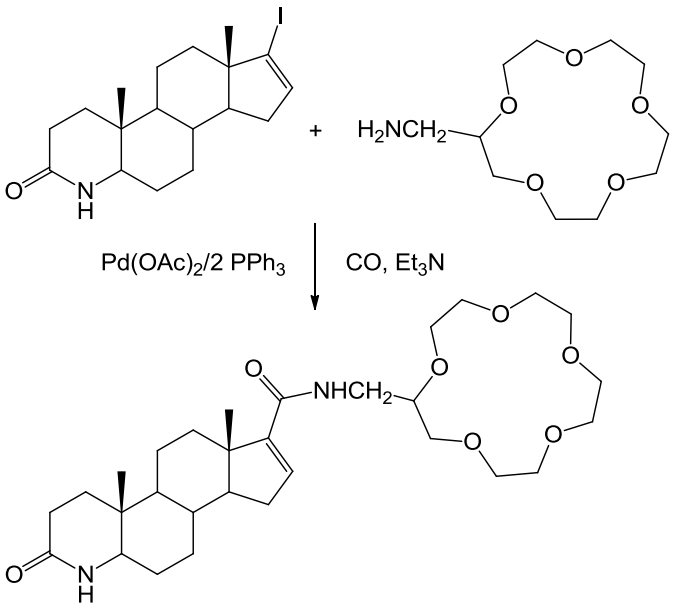
The production of 5α-reductase inhibitors was achieved by introducing 17-carboxamido moiety to the steroidal framework by Holt and co-workers (Scheme 56).[29,30,65,66,121-126]



Scheme 56. The transformation of the 3,17-bis-triflyloxy-estra-1,3,5(10),16-tetraene.

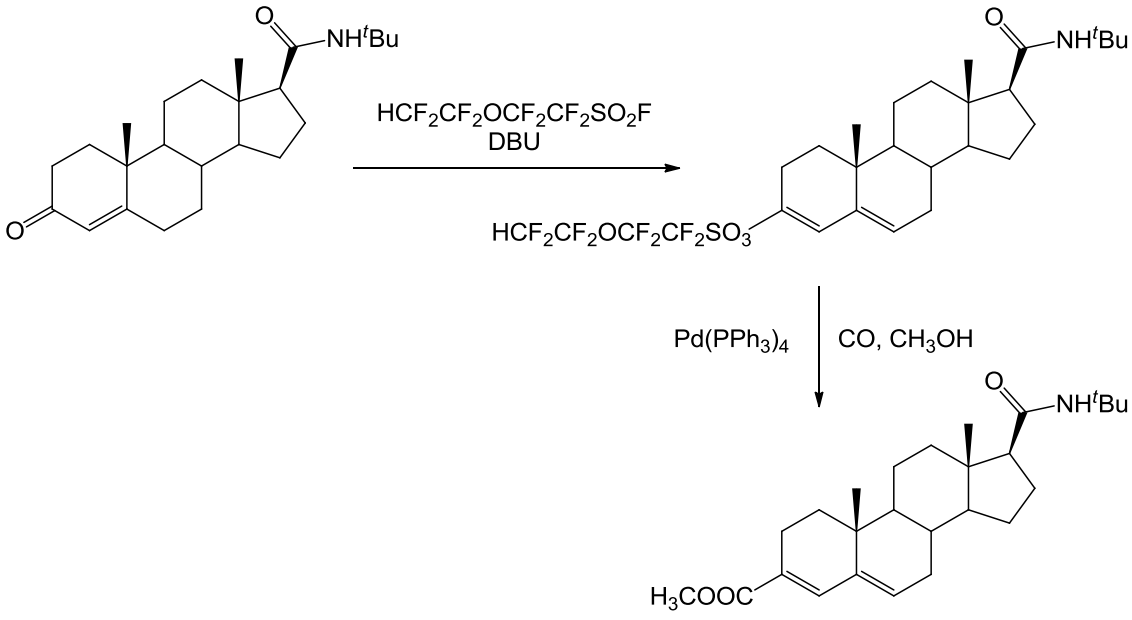
The conversion of the 3,17-bis-triflyloxy-estra-1,3,5(10),16-tetraene can be carried out in two steps resulting in 3,17-heterosubstituted derivatives. The chemoselective introduction of the D-ring carboxamide in the presence of the $PdCl_2(PPh_3)_2$ catalyst was allowed by the preferential oxidative addition of the vinyl triflate over the aryl triflate on palladium(0). The more active $Pd(OAc)_2$(dppp) catalyst was used at higher temperature in the A-ring methoxycarbonylation.[29,30,65]

In carbonylation reactions, 17-iodoandrost-16-ene derivatives were transformed to 17-carboxamido-androstanes using amino crown ethers (Scheme 57).[28]



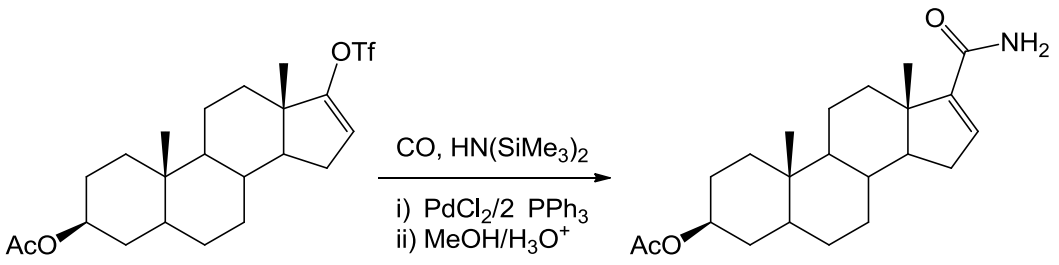
Scheme 57. Synthesis of steroidal crown ethers.

Steroidal enol sulfonates as substrates were introduced to the alkoxycarbonylation reactions resulting in a compound with both ester and amide functionalities. These derivatives exhibited high 5α-reductase inhibitor activity *in vitro* assay (Scheme 58).[127,128]



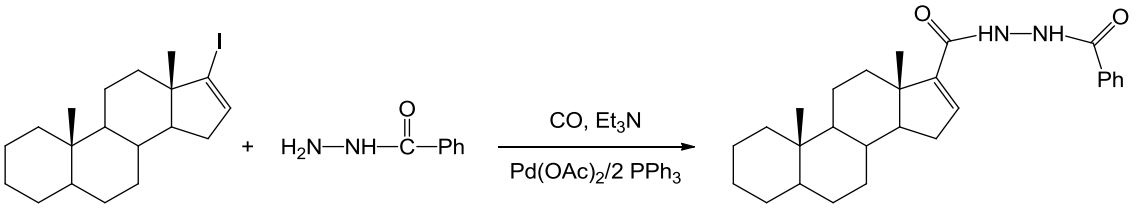
Scheme 58. A practical synthesis of 3-substituted $\Delta^{3,5}$-steroid derivatives.

Primary amides were synthesized in the presence of $PdCl_2$/2 PPh_3 or $PdCl_2$/2 dppp using carbonylation reactions of enol and aryl triflates with hexamethyldisilazane as *N*-nucleophile (Scheme 59).[129]



Scheme 59. A palladium-catalyzed carbonylative route to a primary amide.

To the synthesis of steroidal hydrazides[130,131] and hydroxamic acids[132,133] *N*- or *O*-substituted hydroxylamines as nucleophiles can be used (Scheme 60). These reactions can also be considered as the acylation of the nucleophiles. The iodovinyl derivatives are activated *via* oxidative addition followed by carbon monoxide insertion which resulted in acylpalladium complex. Following the conventional thought of synthetic chemistry, this intermediate can be considered as acylation agent in the carboxamides-forming reaction. The acylation takes place either at the nitrogen bearing methyl substituent (in case of methylhydrazine) or at the unsubstituted nitrogen (in case of acetyl- or phenylhydrazine), *i.e.*, at the more basic nitrogen of the corresponding hydrazine derivative.



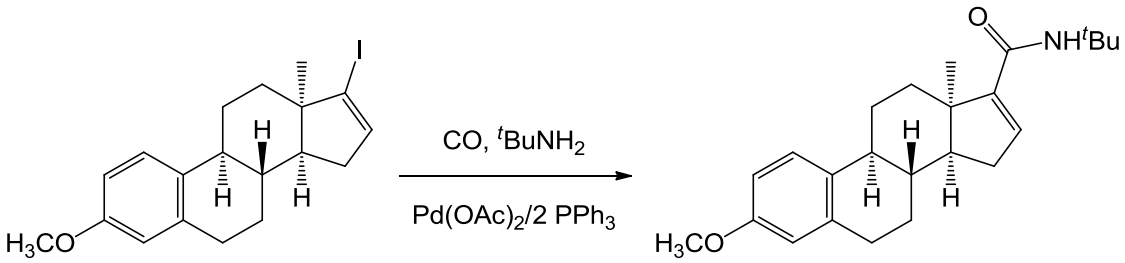
Scheme 60. Hydrazinocarbonylation of a 17-iodo-16-ene derivative with benzoylhydrazide.

O-Acylated products were formed in an excellent yield by using *N*-*tert*-butylhydroxylamine or *N*-acetylhydroxylamine. It has to be underlined that the reaction conditions (solvent, substrate structure, temperature) influenced the site of acylation regarding the *N*-methylhydroxylamine.

In the following syntheses, similar methods were developed with the aim of producing new compounds and with that of shedding some more light on structure–reactivity relations using palladium-catalyzed aminocarbonylation reactions.

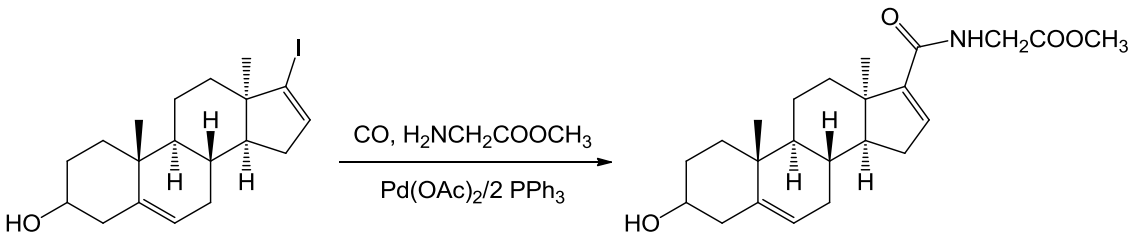
In several cases, 17-iodo-16-ene moiety was involved in the procedure as a substrate. The synthesis of iodoalkene moieties were based on the transformation of the corresponding keto derivatives to hydrazones, which were treated with iodine in the presence of 1,1,3,3-tetramethylguanidine as a base.[31,32,69-71,87,134]

In a palladium-catalyzed aminocarbonylation, 17-iodo-13α-estra-1,3,5(10),16-tetraene derivatives were transformed to 17-carboxamido-13α-estra-1,3,5(10),16-tetraenes (Scheme 61).[69]



Scheme 61. Synthesis of a 17-carboxamido-13α-estra-1,3,5(10),16-tetraene.

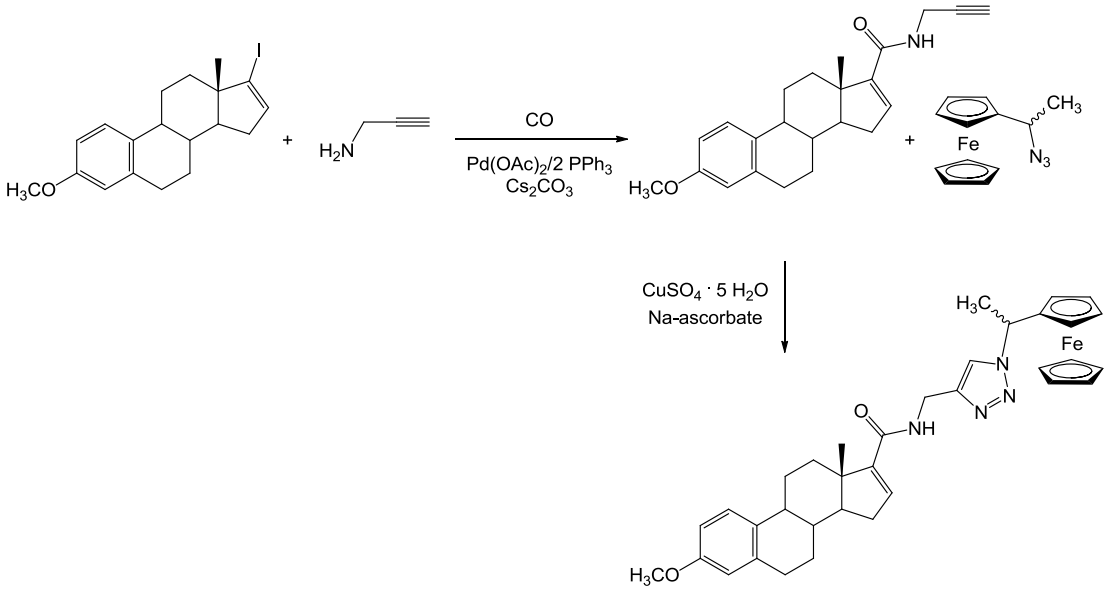
A similar protocol was applied in the androstane series: 17-carboxamido-3β-hydroxy-13α-androst-5,16-diene derivatives were obtained by the use of 3β-hydroxy-17-iodo-13α-androst-5,16-diene and amines, including amino acid esters, as *N*-nucleophiles in a high-yielding and chemoselective reaction (Scheme 62).[70]



Scheme 62. Synthesis of a 17-carboxamido-3β-hydroxy-13α-androst-5,16-diene.

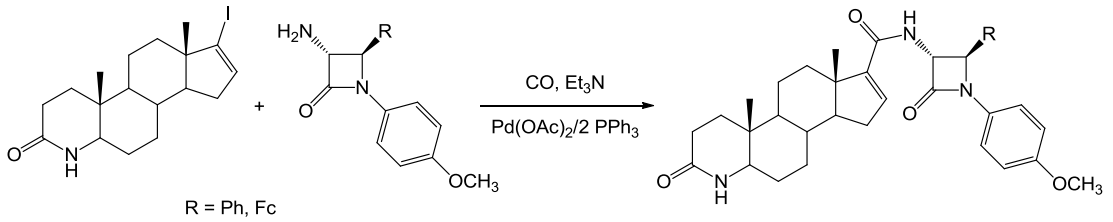
Ferrocene-labeled steroidal 17-carboxamides were synthesized *via* 17-iodo-16-ene derivatives. Firstly, the palladium-catalyzed aminocarbonylation of the alkenyl iodides with prop-2-yn-1-amine in the presence of the $Pd(OAc)_2$/2 PPh_3 catalyst system was carried out. Secondly, the steroid–ferrocene conjugates were synthesized *via* facile

azide–alkyne cycloaddition with ferrocenyl azides of the product *N*-(prop-2-ynyl)-carboxamides using $CuSO_4$/sodium ascorbate catalyst (Scheme 63).[135]



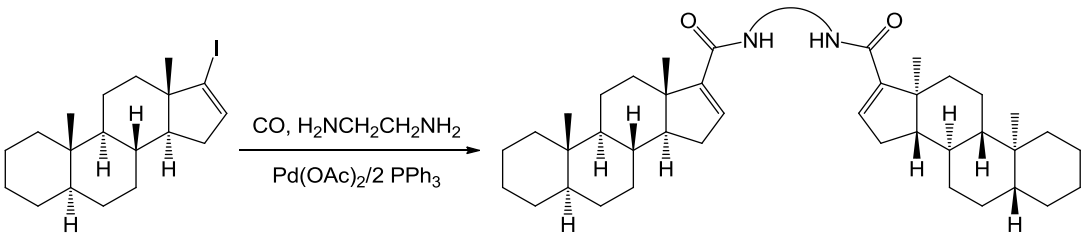
Scheme 63. Synthesis of a ferrocene-labeled steroidal 17-carboxamide.

Steroid-β-lactam and steroid-β-lactam-ferrocenyl derivatives were synthesized *via* 17-iodo-16-ene derivatives using 3-amino-azetidin-2-ones (Scheme 64).[136]



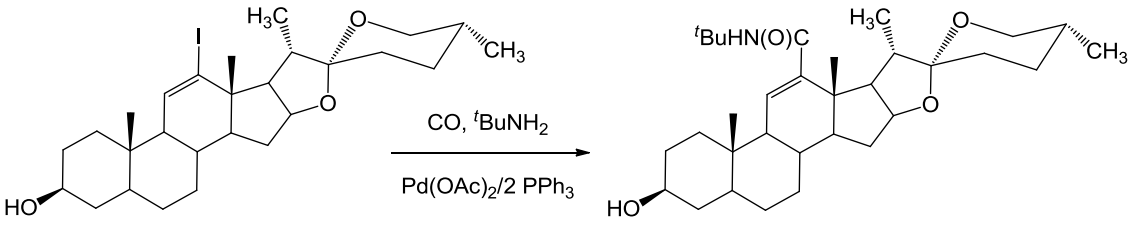
Scheme 64. Synthesis of steroid-β-lactam conjugates.

In a highly chemoselective reaction, 17-iodo-5α-androst-16-ene was transformed to steroid dimers containing 17,17'-dicarboxamide spacers by diaminocarbonylation using aliphatic or aromatic diamines as *N*-nucleophiles (Scheme 65).[137]



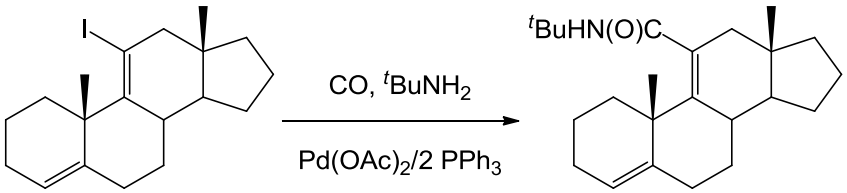
Scheme 65. Synthesis of a steroid dimer containing dicarboxamide spacer.

The efficiency of aminocarbonylation was also shown in those cases where the introduction of any kind of functionalities is rather difficult. The high-yielding synthesis of 12-carboxamido-11-spirostenes was carried out *via* the aminocarbonylation of a sterically highly congested 12-iodo-11-ene functionality. A further interesting feature of this reaction is that it can tolerate the 3-hydroxy substituent and the spiroacetal moiety (Scheme 66).[31]



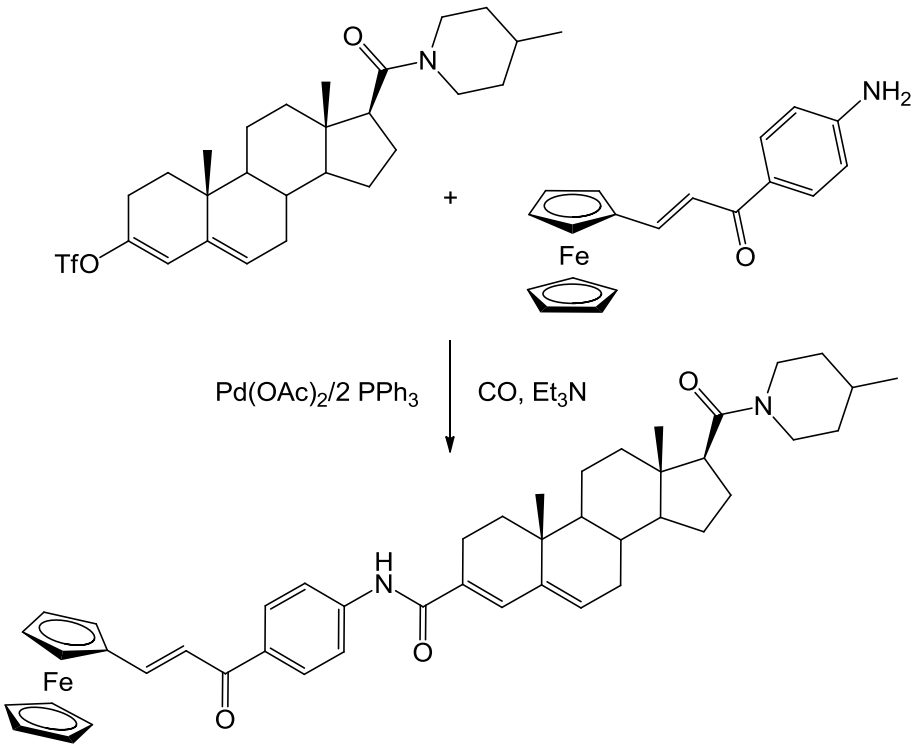
Scheme 66. Synthesis of a 12-substituted spirostene derivative *via* carbonylation reaction.

At one of the most hindered position, 11-carboxamido-androst-4,9(11)-dienes were synthesized using 11-iodoandrost-4,9(11)-diene and simple alkyl/arylamines or amino acid methyl esters as *N*-nucleophiles under mild reaction conditions (atmospheric carbon monoxide pressure, 50 °C) (Scheme 67).[32]



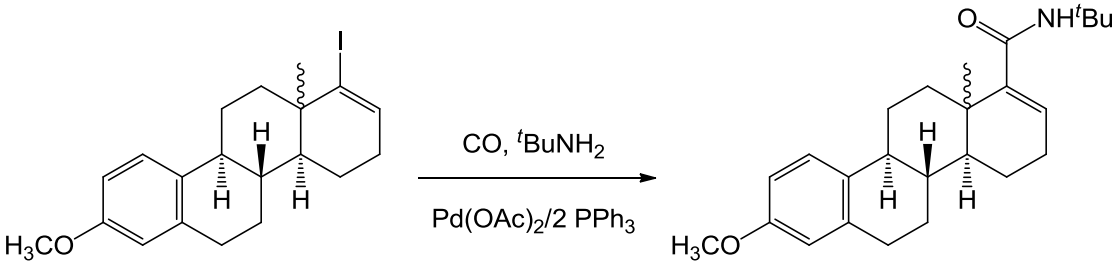
Scheme 67. Synthesis of an 11-substituted androstane.

The *N*-(4'-((2-ferrocenyl-ethenyl)-carbonyl)-phenyl)-carbamoyl derivatives were produced using some representative steroidal substrates such as alkenyl iodides or enol triflates in the presence of (*E*)-1-(4'-aminophenyl)-3-ferrocenyl-prop-2-en-1-one as the nucleophile (Scheme 68).[138]



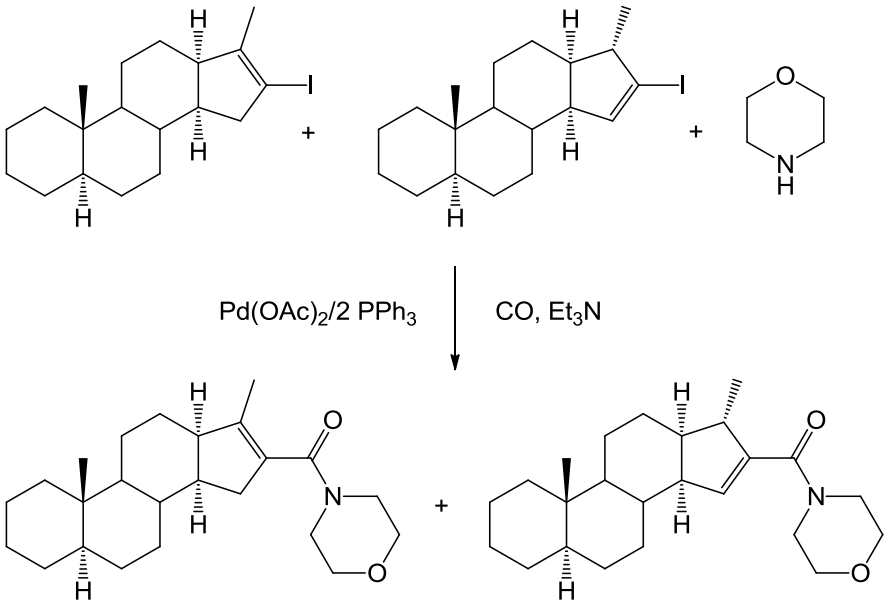
Scheme 68. A palladium-catalyzed carbonylation reaction in the presence of a ferrocenyl chalcone derivative.

In a completely chemoselective reaction, 17a-methoxycarbonyl- and 17a-carboxamido-D-homoestra-1,3,5(10),17-tetraene compounds were synthesized *via* 17a-iodo-D-homoestra-1,3,5(10),17-tetraene derivatives using methanol and various amines as *O*- and *N*-nucleophiles, respectively. The high-yielding synthesis of 13β-epimer of the 17a-iodo-17-ene functionalities was carried out under mild conditions (1 or 40 bar carbon monoxide pressure, 50 °C). However, high carbon monoxide pressure was necessary to achieve excellent yields in the 13α series (Scheme 69).[71]



Scheme 69. Synthesis of novel 13β- and 13α-D-homo steroids.

In a high-yielding reaction, 13α-18-nor-16-carboxamido steroids were synthesized *via* 16-iodo-16-ene and 16-iodo-15-ene derivatives which were obtained by Barton's methodology (Scheme 70).[86,87] The 'unnatural' starting material (13α-16-keto steroid) was obtained by a Wagner–Meerwein rearrangement of a 16α,17α-epoxide in the presence of ionic liquid [BMIM][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate).[134]



Scheme 70. Synthesis of 13α-18-nor-16-carboxamido derivatives.

3.5. Other homogeneous catalytic transformations of the steroidal compounds

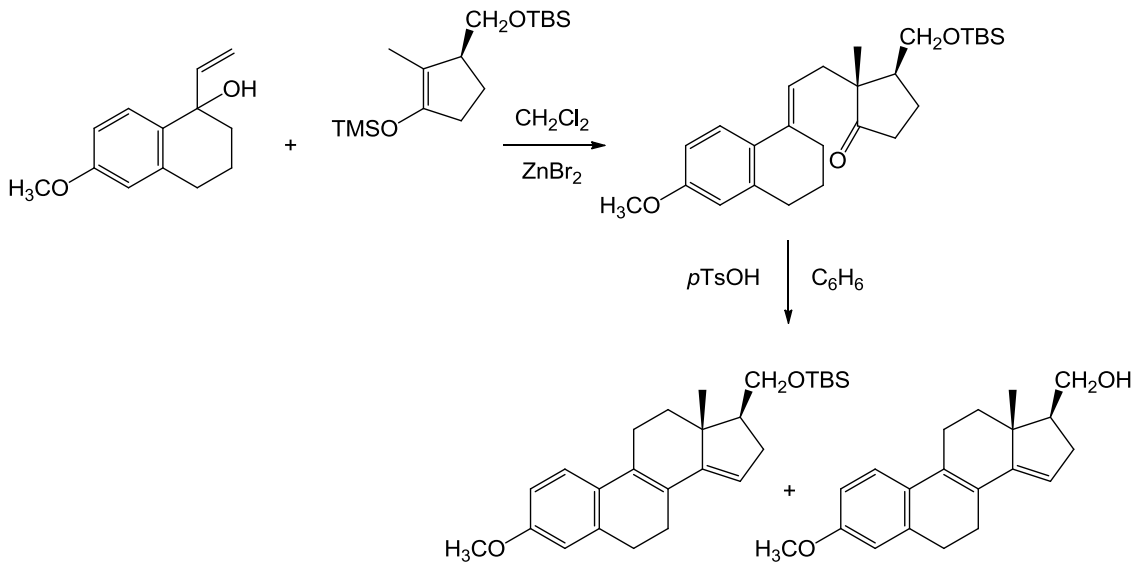
3.5.1. Cyclization reactions

3.5.1.1. Formation of the basic steroidal skeleton via cyclization reactions

Functionalization reactions of various positions of steroids or partial synthesis are the most examined subject of the publications; however there are a number of transition metal-catalyzed approaches for the building of the steroid nucleus, including the cyclization of polyenes or polyynes, coupling, and ring-expansion reactions.[22]

Using cyclization reactions, the formation of the basic steroidal skeleton was carried out applying various transition metal catalysts[139] such as copper,[140] zinc,[141] or palladium.[142]

A chiral C17 functionalized steroid framework was synthesized from a steroid ring D precursor silyl enol ether using the addition of a carbocation, generated with $ZnBr_2$ from a Torgov reagent, followed by cyclization of the adduct (Scheme 71).[141]

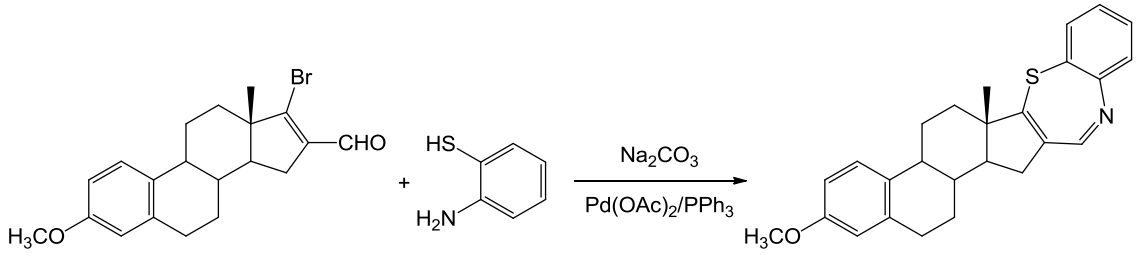


Scheme 71. The reaction of the Torgov reagent with the silyl enol ether.

3.5.1.2. Synthesis of cyclic systems attached to the basic 4-ring steroidal skeleton

Various five-,[139,143,144] six-,[139,145-147] or seven-membered[148,149] rings were attached to the 4-ring framework. These reactions involve coupling reactions followed by cyclization;[22] ring closing metathesis;[145,148,149] Grubbs metathesis reaction;[143] or catalytic cycloaluminations using transition metal catalysts such as zirconium;[144,147] 1st generation[145,150] or 2nd generation[143,148] Grubbs catalyst containing ruthenium; or palladium.[22,146,149]

Steroidal benzo[*b*][1,4]thiazepine derivatives were synthesized from palladium-catalyzed reaction of steroidal β-halovinyl aldehydes and 2-aminothiophenols (Scheme 72).[149]

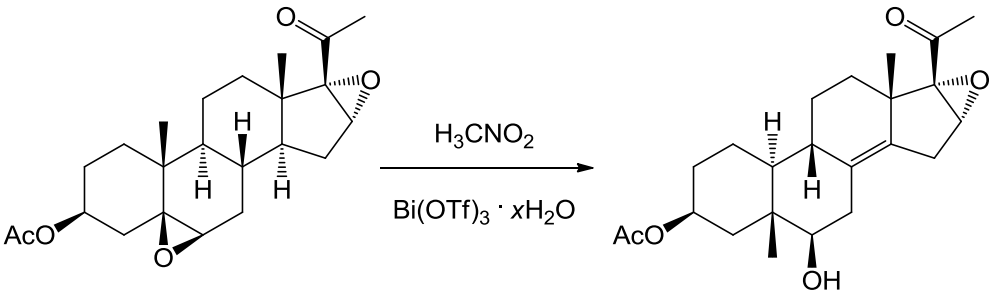


Scheme 72. Synthesis of a steroidal benzo[*b*][1,4]thiazepine derivative.

3.5.2. Catalytic rearrangements

Rearrangement reactions of the steroidal skeleton have been intensively studied, due to the variety of new frameworks obtained by single-step reactions.[22,151,152]

The use of 'ecofriendly' $Bi(OTf)_3 \cdot xH_2O$ catalyst, Wagner–Meerwein-type rearrangements were accomplished starting from 16α,17α-epoxy-20-oxosteroids (Scheme 73).[152]

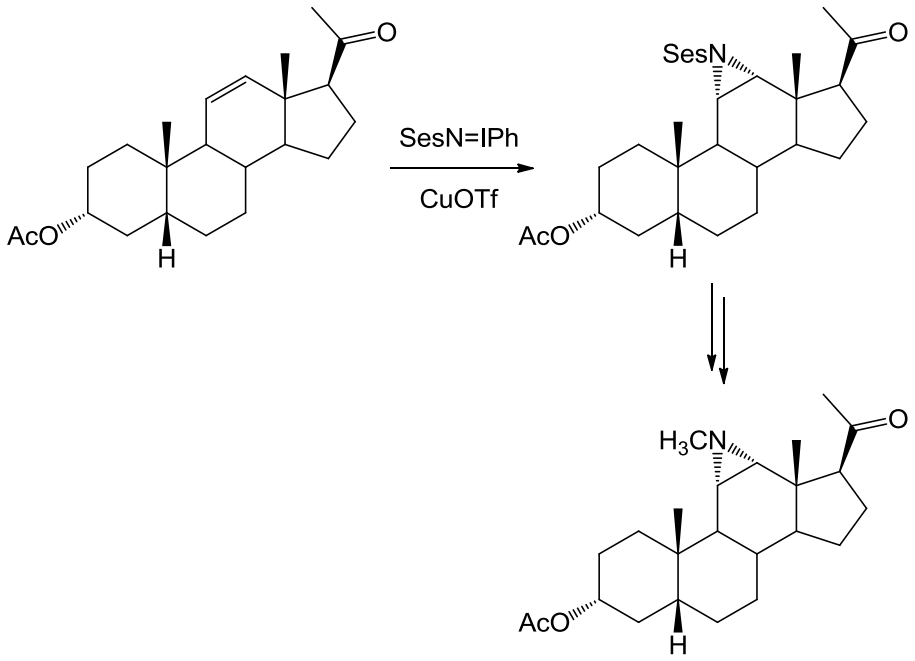


Scheme 73. Bi(III)-catalyzed 'backbone' rearrangement of a 5β,6β;16α,17α-diepoxysteroid.

3.5.3. Aziridination

Steroidal aziridine derivatives may serve as inhibitors of various enzymes or reactive intermediates, which lead to amino steroids after nucleophilic ring opening.[22]

In the presence of copper(I) triflate, α,α-11,12-aziridino steroids were synthesized starting from 11-pregnene-3,20-dione or 3α-acetoxy-11-pregnen-20-one with trimethylsilylethanesulfonyl (Ses) iminoiodinane (Scheme 74).[153]



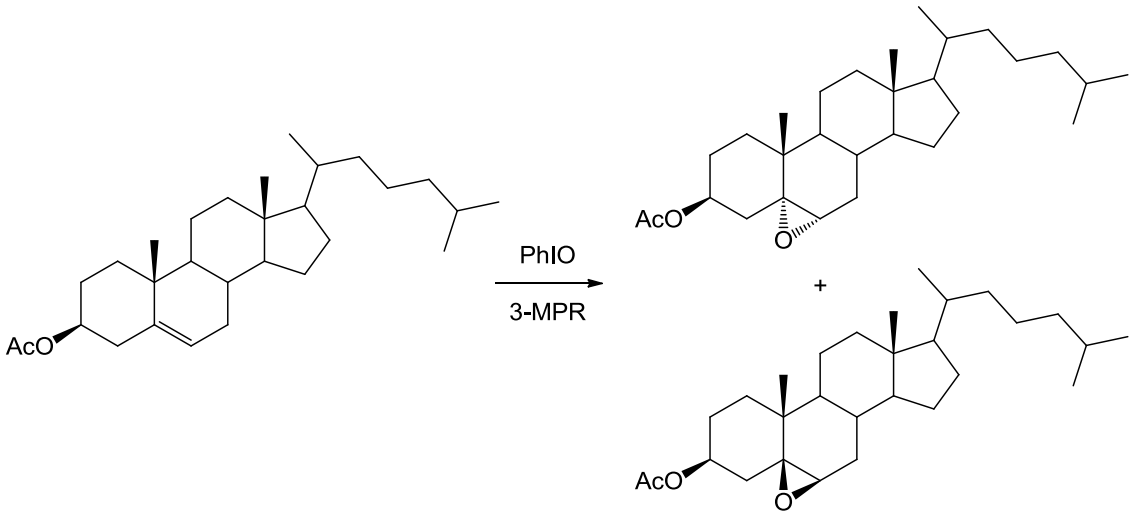
Scheme 74. Synthesis of an 11,12-aziridino derivative as a neuroactive steroid analogue.

3.5.4. Epoxidation

Epoxides have a great practical importance, due to their simple ring opening, which allows the introduction of the new substituents into unsaturated steroids using stereoselective epoxidation.[22]

Using environmentally benign methods,[154,155] a set of new epoxidation reactions were carried out by various recoverable,[155] or recyclable[154,155] transition metal catalysts as titanium,[156] manganese,[154] or cobalt[155] resulting in regio-,[155] and stereoselective reactions.[154-156]

Utilizing manganese(III) 5,10,15-tris(tolyl)-20-(4-hydroxyphenyl) porphyrin covalently attached to Merrifield's peptide resin (MPR) as catalyst, the epoxidation of cholest-5-ene derivatives was accomplished with iodosylbenzene (Scheme 75).[154]

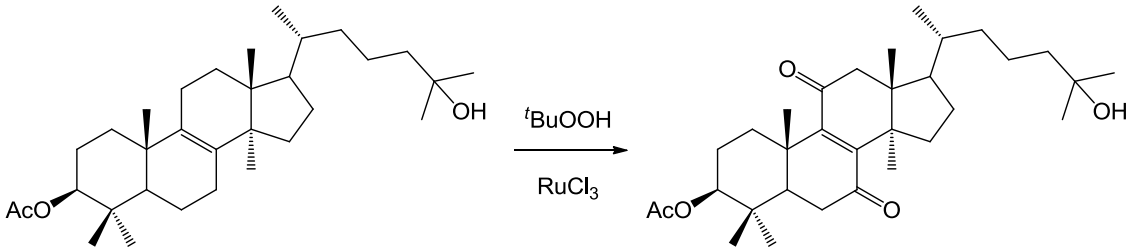


Scheme 75. Synthesis of an epoxidal α-and β-stereoisomer from a Δ^5-steroid.

3.5.5. Oxidation

In regio-,[157,158] chemo-,[159] and stereoselective reactions,[157,159] using transition metal catalyst such as manganese,[158] iron,[159] cobalt,[160] copper,[161-163] ruthenium[164,165] or rhenium,[157] oxidation reaction were accomplished *via* air exposure,[161] allylic oxidation,[160,162] H_2O_2,[157,159] or methyl(trifluoromethyl)dioxirane.[158]

In the presence of ruthenium chloride catalyst, various $\Delta^{8(9)}$-lanosterol derivatives were transformed into 7,11-dienones using *tert*-butyl hydroperoxide (Scheme 76).[165]

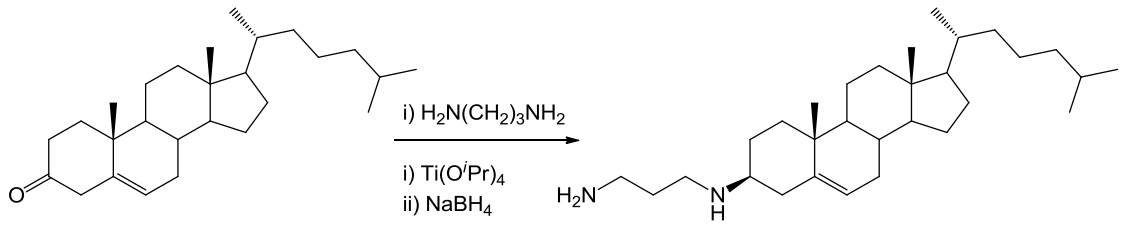


Scheme 76. Allylic oxidation of the 3β-acetoxylanost-8-en-25-ol.

3.5.6. Amination

Steroidal aryl triflates,[166] aryl chlorides,[167] or ketones[168,169] were used as starting material for the synthesis of steroidal amines *via* transition metal-catalyzed amination. Various catalysts such as titanium,[168,169] rhodium[170] or palladium[166-169] were applied for C-N coupling or remote C–H amination.

As an example, a new stereoselective reductive amination should be mentioned where a series of 3-amino and polyaminosterol analogues of squalamine and trodusquemine with antimicrobial activities were produced in a titanium mediated reaction (Scheme 77).[169]



Scheme 77. Titanium(IV) reductive amination of 5-cholesten-3-one using 1,3-diaminopropane.

4. Results

4.1. Purposes

The aim of my doctoral dissertation was a systematic investigation of the homogeneous catalytic aminocarbonylation reactions of androstane based compounds containing iodoalkene moiety using various monoamines and diamines as *N*-nucleophiles. Based on the previous studies of our research group, compounds containing iodoalkene moiety have been used instead of the enol-triflates because *i)* facile isolation of the target compounds in a 'clean' reaction can be accomplished, *ii)* less expensive reagents for the synthesis of iodoalkenes are necessary and *iii)* the iodoalkene-based synthesis can considered more environmentally friendly related to the corresponding triflates.

The following goals were aimed at during my research:

- The synthesis of new steroidal carboxamides with possible practical and pharmacological importance *via* palladium-catalyzed aminocarbonylation.
- The investigation of the effect of the reaction conditions such as carbon monoxide pressure, reaction time, *N*-nucleophile on the chemoselectivity of aminocarbonylation of a steroidal skeleton. Furthermore, to explore the structure-reactivity relations were also aimed at.
- The synthesis of novel steroidal dicarboxamides (containing various linkers) showing the efficiency of the aminocarbonylation reaction.

4.2. Synthesis of various homo-3,17-dicarboxamides

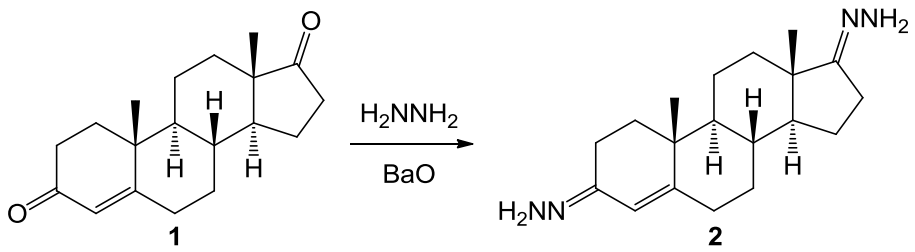
The most important characteristics, which make the homogeneous catalytic reactions desirable both for the stereoselective synthesis of the steroidal skeleton and for the functionalization of the androstane framework, are the enhanced selectivities, the investigation of the reaction mechanism, the finely tuneable attributes of the catalysts and also the applicability of standard techniques.

In order to improve the pharmacological efficiency of the steroidal framework, there is an expanding enquiry in developing new procedures to introduce functional groups especially into position-3 and -17 either at the A- or the D-ring, respectively. As has

been shown in the literature survey above, the amido functionality in steroids possesses 5α-reductase inhibitor properties as a pharmacological importance.[22,29,30,171-174]

Based on the previous studies of our research group, androst-4-en-3,17-dione (**1**) was used as a parent compound and transformed to 3,17-diiodo derivatives (**3** and **3'**) as key-intermediates.

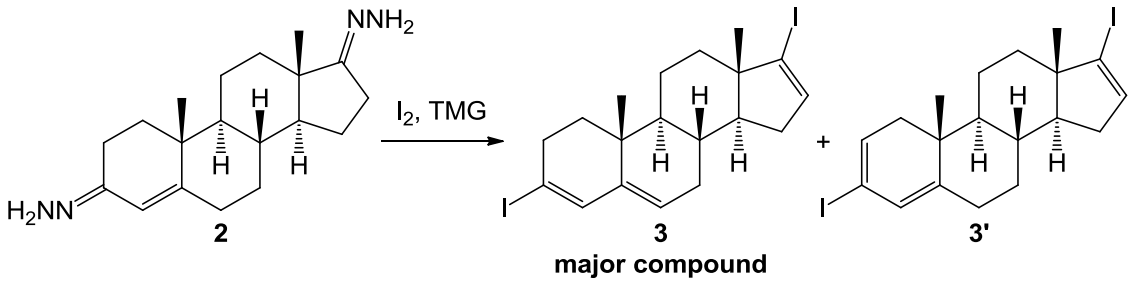
Androst-4-en-3,17-dione (**1**), freshly distilled hydrazine hydrate and barium oxide were heated for 2 days at 160 °C in 2-methoxy-ethanol. After the work-up procedure, the 3,17-dihydrazone product (**2**) was used in the next step without further purification (Scheme 78).



Scheme 78. Synthesis of 3,17-dihydrazone-androst-4-ene.

To a stirred solution of iodine in dichloromethane, 1,1,3,3-tetramethylguanidine then the solution of 3,17-dihydrazone derivative (**2**) in dichloromethane was added drop-wise. The mixture was stirred for an hour then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 hours.

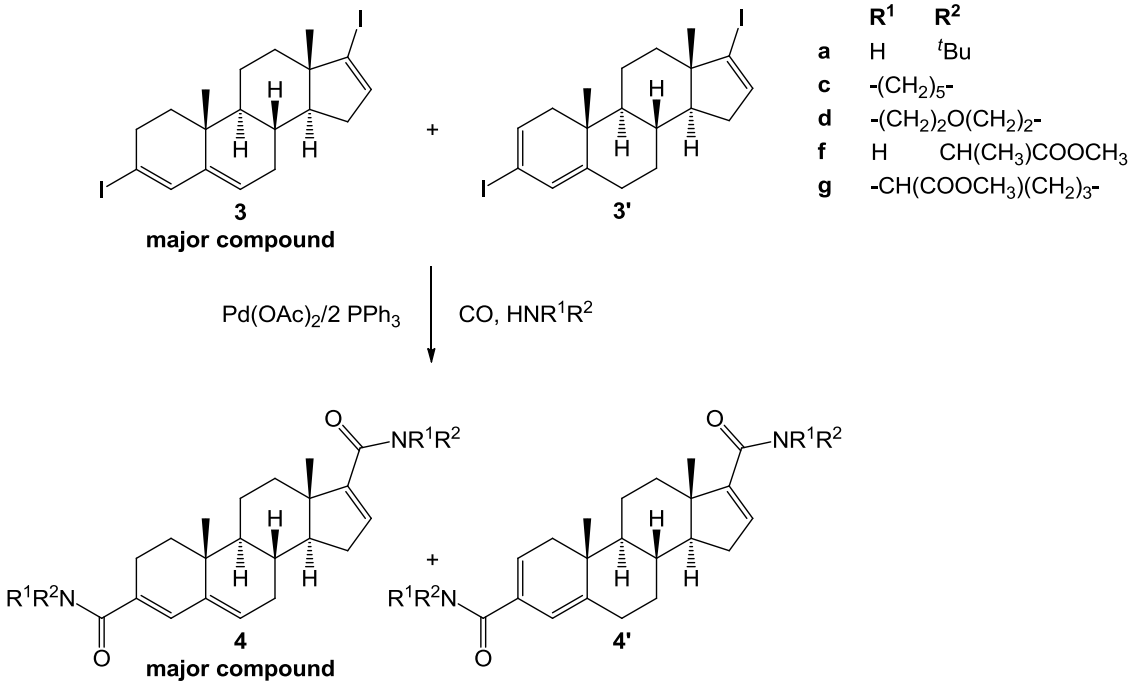
After the work-up procedure, the column chromatography resulted the mixture of 3,17-diiodo derivatives (**3** and **3'**), where the iodoalkene functionalities served for the introduction of the carboxamide groups (Scheme 79).



Scheme 79. Synthesis of 3,17-diiodo-androstene derivatives.

A mixture of 3,17-diiodo derivatives (**3** and **3'**) were aminocarbonylated in the presence of various primary or secondary amines as *tert*-butylamine (**a**), piperidine (**c**), morpholine (**d**), *L*-alanine methyl ester (**f**), *L*-proline methyl ester (**g**) at atmospheric carbon monoxide pressure in 2-butanone in moderate to high yields depending on the structure of the amine. *In situ* formed palladium(0) catalyst obtained from palladium(II) acetate and triphenylphosphine precursors was used (Scheme 80).

The *in situ* formation of highly active coordinatively unsaturated palladium(0) catalysts with mono- and bidentate phosphines was discussed before.[175] I would like to emphasize that the aminocarbonylation of monoiodo derivatives was carried out *via* the same catalytic system (*vide infra*).



Scheme 80. Synthesis of the 3,17-dicarboxamido-androstene derivatives *via* aminocarbonylation.

Using 3,17-diiodo-3,5,16-triene derivative (**3**) as a substrate, the corresponding dicarboxamides (**4a**, **4c**, **4d**, **4f** and **4g**) were isolated in high yields. The secondary amines (**c**, **d** and **g**) were shown decreased reactivity, *i.e.*, longer reaction times were required to accomplish high yields (Table 1).

Table 1. Synthesis of androstane-based homo-3,17-dicarboxamides *via* palladium-catalyzed aminocarbonylation of **3**.[a)]

Entry	Amine	Amine:substr. ratio	Reaction time [h]	Conversion [%][b)]	Isolated yield (amide) [%]
1	^{t}BuNH$_2$ (**a**)	3	20	>98	78 (**4a**)
2	piperidine (**c**)	1.5	90	>98	80 (**4c**)
3	morpholine (**d**)	1.5	200	>98	77 (**4d**)
4	morpholine (**d**)	1.5	90	>95	74 (**4d**)
5	AlaOMe (**f**)	1.1	20	>98	66 (**4f**)
6	ProOMe (**g**)	1.1	200	>98	75 (**4g**)

a) Reaction conditions: 0.025 mmol Pd(OAc)$_2$; 0.05 mmol PPh$_3$, 1 mmol substrate (**3**); 10 mL 2-butanone; reaction temperature: 50 °C; *p*(CO) = 1 bar.
b) Based on the iodoalkene substrate; determined by ^{1}H NMR.

When the 3/1 mixture of the 3,17-diiodo-3,5,16-triene and 3,17-diiodo-2,4,16-triene derivatives (**3** and **3'**) was utilized, an entire conversion towards dicarboxamides was achieved (Scheme 80). Two of them, **4a** and **4c** were isolated as pure compounds with acceptable yields by column chromatography, however, **4d** and **4g** were accomplished in slightly lower yields. The isolation of 2,4-diene isomers (**4'a**, **4'c**, **4'd**, **4'f** and **4'g**) as pure compound was not efficient from the reaction mixture. It is worth noting that during the aminocarbonylation the partial isomerization of the 2,4-diene functionality to 3,5-diene was noticed, *i.e.*, the initial 2,4-diene/3,5-diene ratio of 3-iodo derivatives were shifted towards the 3,5-diene structure of 3-carboxamides. The ratio of **4**/**4'** isomers was found between 10/1 and 12/1. This might be due to the oxidative addition of the 3-iodo-2,4-diene (**3'**) to palladium(0) forming a palladium(II)-2,4-dienyl intermediate which underwent isomerization to palladium(II)-3,5-dienyl derivative. Its aminocarbonylation resulted in the formation carboxamides **4**.

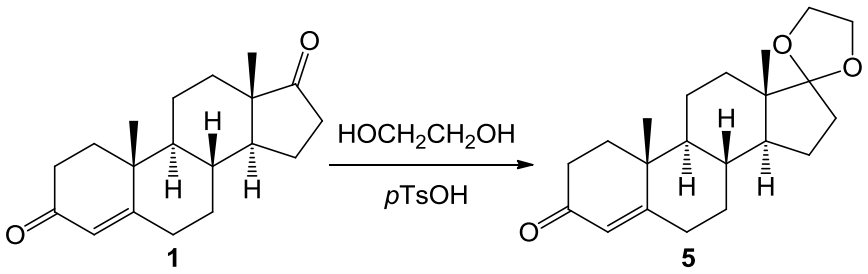
*To sum up of the results of this topic, 3,17-dicarboxamido-androst-3,5,16-triene derivatives (**4** and **4'**) were synthesized from the corresponding 3,17-diiodo-androst-3,5,16-trienes (**3** and **3'**) in a highly chemoselective palladium-catalyzed homogeneous aminocarbonylation under mild reaction conditions (Scheme 80). The ketone—hydrazone—iodoalkene reaction sequence was utilized for the preparation of the 3,17-diiodoalkene key-intermediate (Scheme 78-79).*

4.3. Synthesis of various ‘mixed dicarboxamides’ (hetero-3,17-dicarboxamides) using 3-iodo-17-ethylene ketal derivative as a key-intermediate

In order to retain the 3-keto or 17-keto (see the next chapter) functionality of **1**, one of them was protected as ethylene ketal following conventional synthetic strategies.

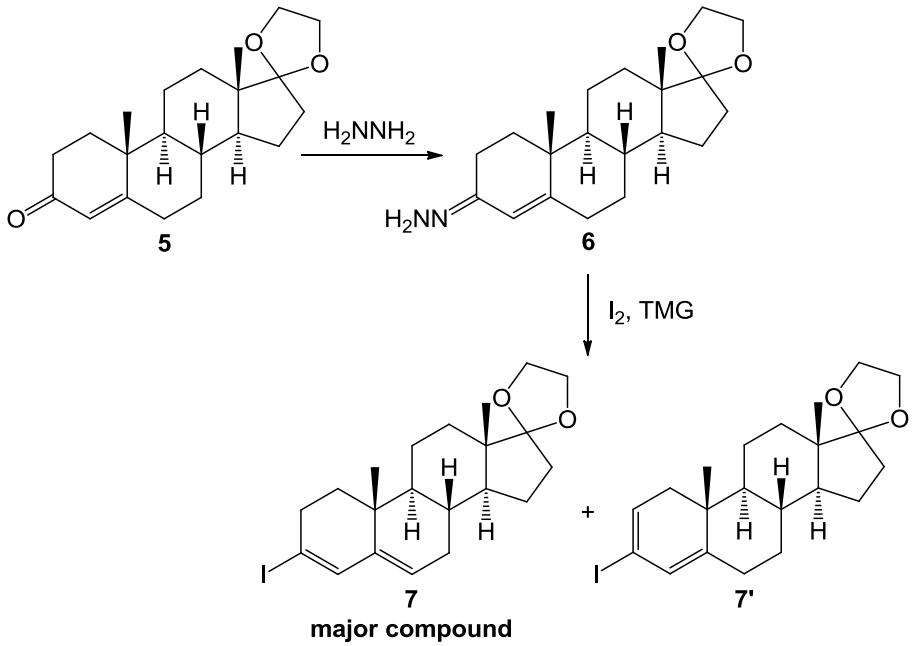
Androst-4-ene-3-one-17-ethylene ketal (**5**) was synthesized starting from androst-4-ene-3,17-dione (**1**) in chloroform and ethylene glycol containing *p*-toluenesulfonic acid catalyst. The reaction mixture was stirred under reflux for a day in a Dean–Stark water separator (Scheme 81).

After the work-up procedure, the product (**5**) was purified by column chromatography (the exact details are given in the Experimental chapter).



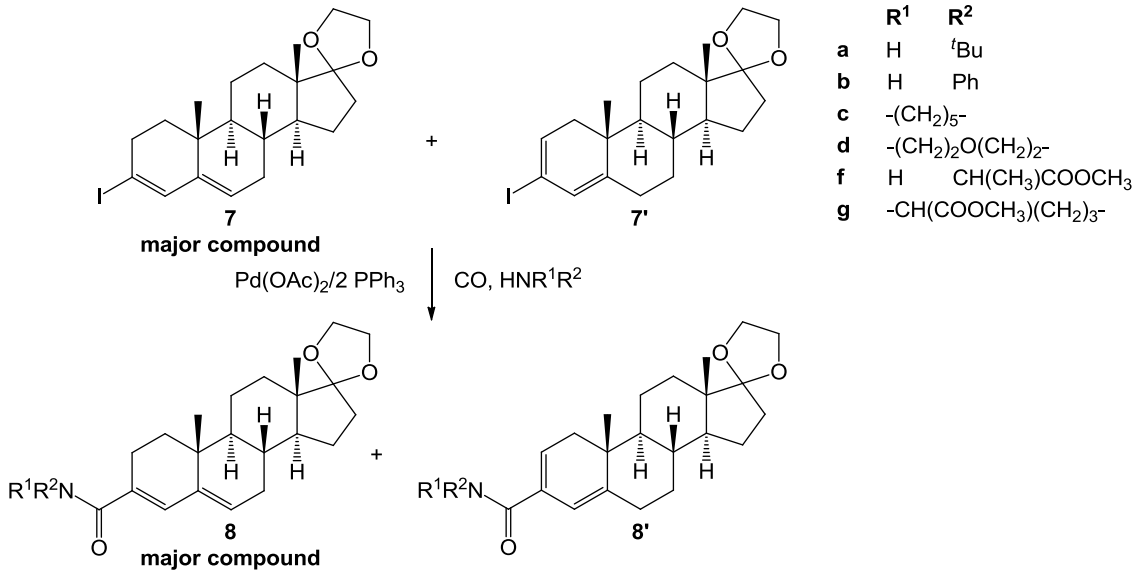
Scheme 81. Synthesis of the androst-4-ene-3-one-17-ethylene ketal.

The 3-keto-17-ethylene ketal derivative (**5**) was transformed to the corresponding 3-iododiene derivatives (**7** and **7’**) *via* 3-hydrazone (**6**) according to the procedure described above (Scheme 82).



Scheme 82. Synthesis of the 3-iodo-androst-3,5-diene-17-ethylene ketal (and the corresponding 2,4-diene) derivatives.

Using palladium(II) acetate and triphenylphosphine precatalysts, 3-iodo-androstadiene-17-ethylene ketal derivatives (**7** and **7'**) were carbonylated in the presence of various primary or secondary amines as *tert*-butylamine (**a**), aniline (**b**), piperidine (**c**), morpholine (**d**), *L*-alanine methyl ester (**f**) and *L*-proline methyl ester (**g**) at atmospheric carbon monoxide pressure (Scheme 83).



Scheme 83. Synthesis of 3-carboxamido-androst-3,5-diene-17-ethylene ketal (and the corresponding 2,4-diene) derivatives.

Using secondary amines (**c**, **d** and **g**) in the aminocarbonylation of 3-iodo-3,5-diene derivative (**7**), the conversions were 55, 35, and 30%, respectively. Longer reaction times had to be utilized to obtain higher conversion and higher isolated yields (Table 2).

Table 2. Synthesis of androstane-based 3-carboxamides *via* palladium-catalyzed aminocarbonylation of **7**.[a)]

Entry	Amine	Amine:substr. ratio	Reaction time [h]	Conversion [%][b)]	Isolated yield (amide) [%]
1	^{t}BuNH$_2$ (**a**)	3	96	>98	70 (**8a**)
2	aniline (**b**)	2	90	>98	80 (**8b**)
3	piperidine (**c**)	1.5	200	>98	80 (**8c**)
4	piperidine (**c**)	1.5	48	55	n.d.[c)]
5	morpholine (**d**)	1.5	48	35	30 (**8d**)
6	AlaOMe (**f**)	1.1	68	>98	63 (**8f**)
7	ProOMe (**g**)	1.1	48	30	22 (**8g**)

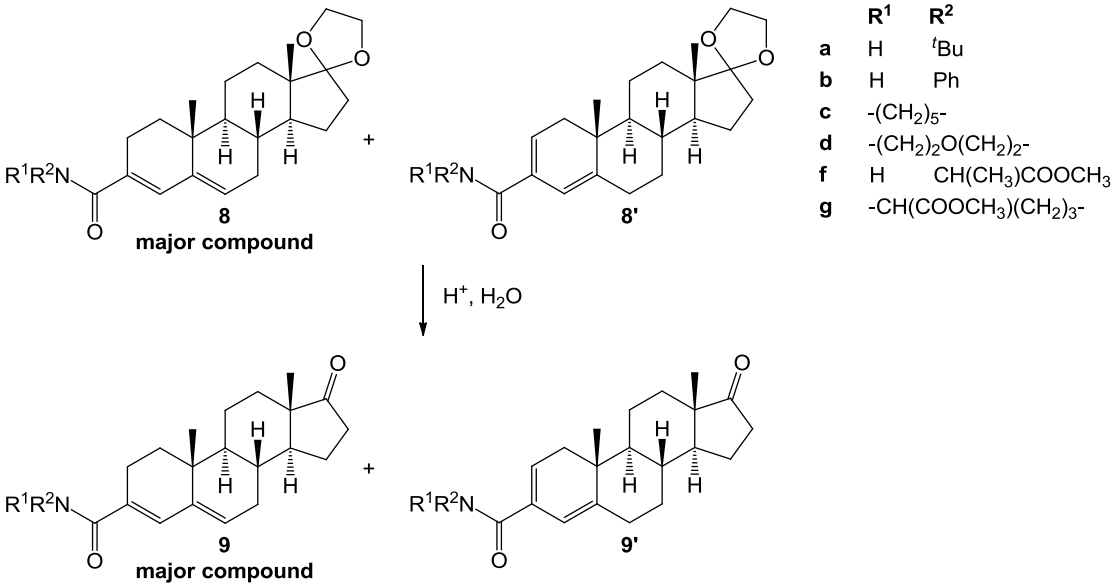
a) Reaction conditions: 0.025 mmol Pd(OAc)$_2$; 0.05 mmol PPh$_3$, 1 mmol substrate (**7**); 10 mL 2-butanone; reaction temperature: 50 °C; *p*(CO) = 1 bar.

b) Based on the iodoalkene substrate; determined by GC.

c) Not determined.

The *ca.* 3/1 mixture of the 3-iododiene derivatives (**7** and **7'**) were totally converted to the corresponding 3-carboxamido-17-ethylene ketals (**8c**, **8d** and **8g**) (Scheme 83). As discussed above, during palladium-catalyzed carbonylation reaction the isomerization of the conjugated double bond system from 2,4- to 3,5-positions occurred, allowing the isolation of 3-carboxamido-3,5-dienes in good yields.

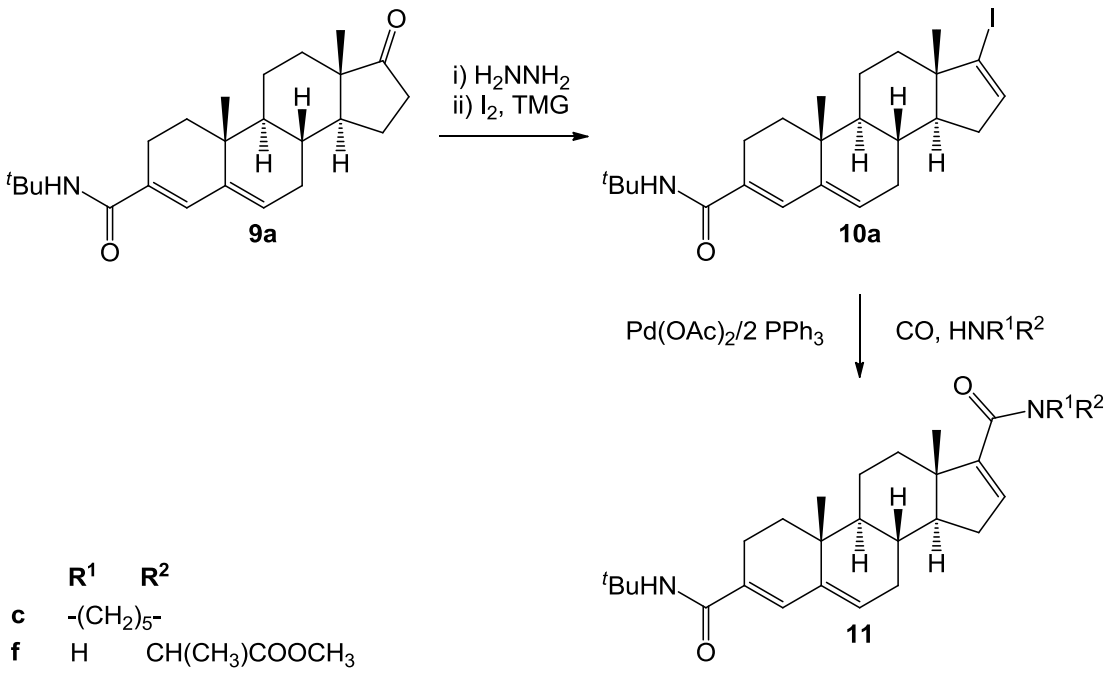
To a solution of *N*-substituted 3-carboxamido-androstadiene-17-ethylene ketal derivatives in acetone, water and 1 M aqueous HCl was added and stirred overnight at room temperature. After the purification procedures, *N*-substituted 3-carboxamido-androstadiene-17-one derivatives were obtained (Scheme 84).



Scheme 84. Synthesis of 3-carboxamido-androst-3,5-diene-17-ones (and the corresponding androst-2,4-diene-17-ones).

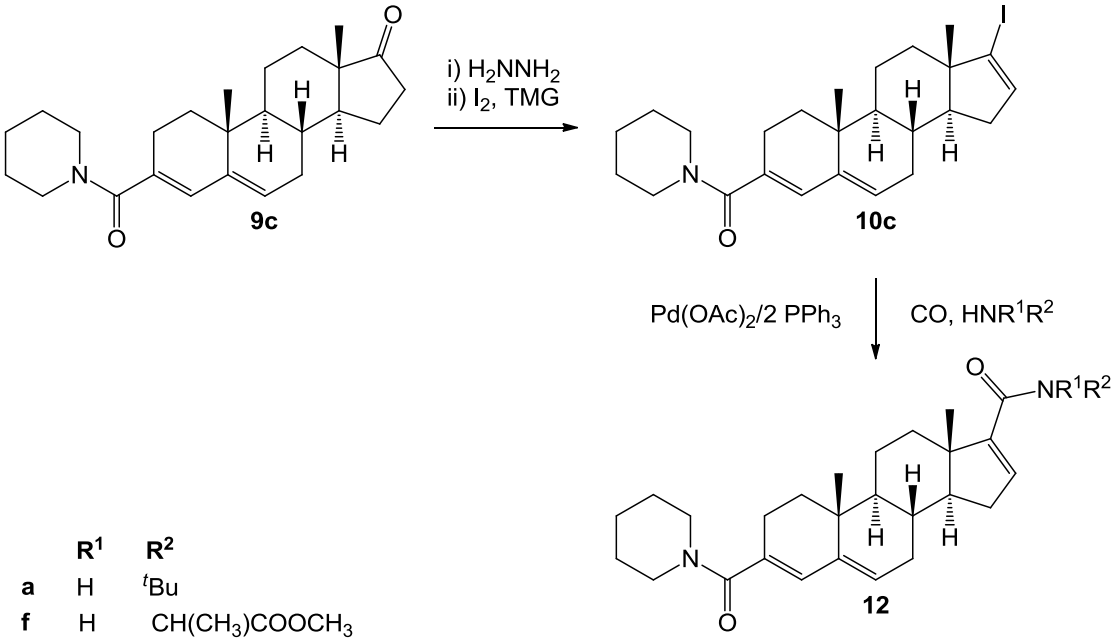
The corresponding 3-carboxamido-17-keto derivatives (**9c**, **9d** and **9g**) were synthesized *via* deprotection at the position-17 in excellent yields. The isolation of **8'** and **9'** as pure compounds was failed, however the characterization of 2,4-diene-17-ethylene ketals (**8'**) and 17-ketones (**9'**) was successful in two-component mixtures.

The ketone–hydrazone–iodoalkene reaction sequence was utilized for the preparation of the 17-iodo-3-carboxamide substrates as key-intermediates, which were transformed to the appropriate 'mixed diamides' with different carboxamido functionalities (Schemes 85-87).



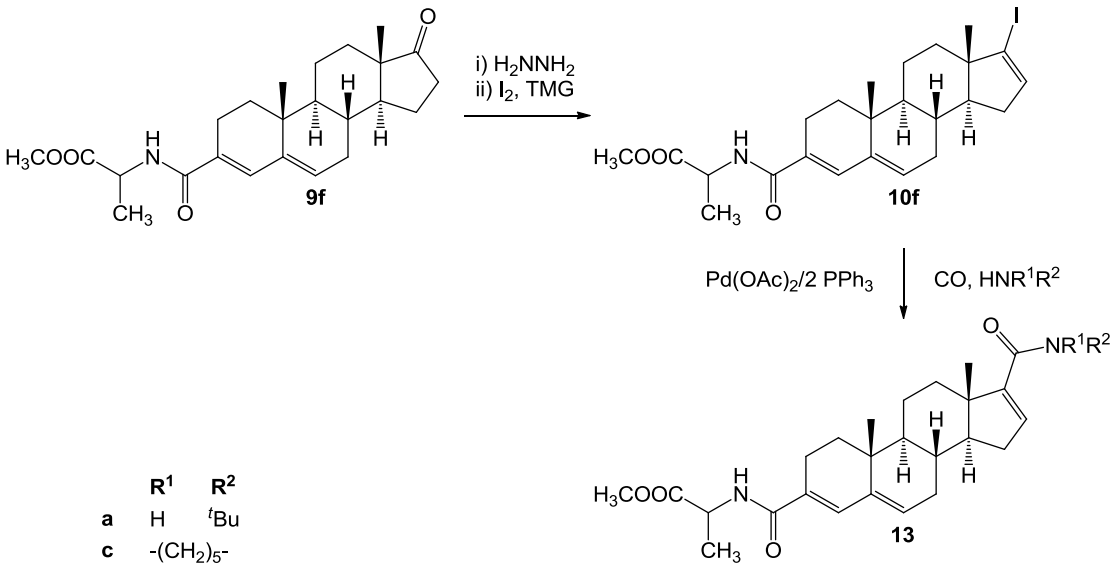
	R^1	R^2
c	-$(CH_2)_5$-	
f	H	$CH(CH_3)COOCH_3$

Scheme 85. Transformation of the 3-(*N*-*tert*-butylcarboxamido)-17-one derivative.



	R^1	R^2
a	H	^{t}Bu
f	H	$CH(CH_3)COOCH_3$

Scheme 86. Transformation of the 3-(*N*,*N*-pentan-1,5-diylcarboxamido)-17-one derivative.



Scheme 87. Transformation of the 3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-17-one derivative.

*In summary, in case of the synthesis of 'mixed bis-carboxamides', we followed a different procedure from that used for the synthesis of **4a**, **4c**, **4d**, **4f**, and **4g**. At first, the 17-keto functionality was protected as ethylene ketal, while the 3-iodo-3,5-diene moiety was formed (**7**). The corresponding 3-carboxamides (**8a-d** and **8f-g**) were synthesized via aminocarbonylation reactions in position-3 with full conversion and good isolated yields using various primary and secondary amines as N-nucleophiles.*

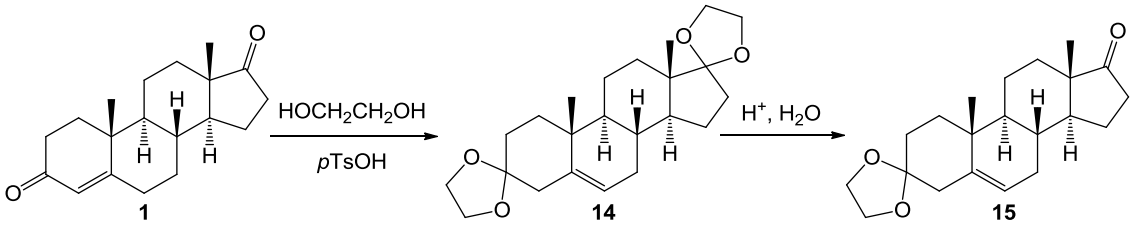
In the subsequent step, using hydrolysis, position-17 was deprotected to keto functionality which was transferred to the corresponding 17-hydrazone and subsequently, to the 17-iodoalkene derivatives. Finally, the target 'mixed dicarboxamides' were synthesized in aminocarbonylation reactions of the corresponding 3-carboxamido-17-iodo-16-ene derivatives through various amines different from those in position-3.

4.4. Synthesis of various 'mixed dicarboxamides' (hetero-3,17-dicarboxamides) using 17-iodo-3-ethylene ketal derivative as a key-intermediate

Further 'mixed dicarboxamides' (those ones missing from the above synthetic procedure) can be synthesized by introducing 17-carboxamide functionality first, and then the substitution pattern in position-3 can be varied. In order to carry out this

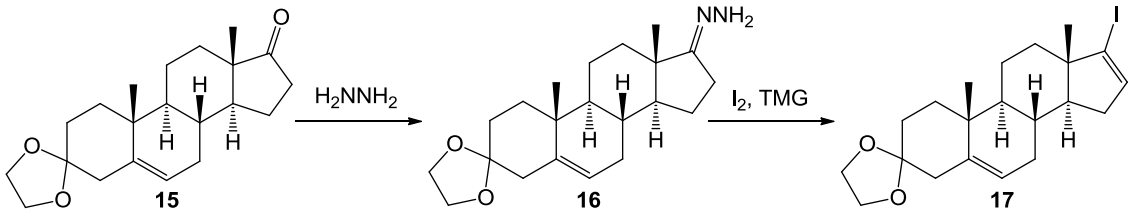
reaction sequence, the substrate containing 17-iodo-5,16-diene moiety had to be synthesized, while the 3-keto functionality was protected as ethylene ketal.

The 17-keto-3-ethylene ketal derivative (**15**) was formed in two steps, due to the reactivity difference between the position-3 and -17 (Scheme 88).



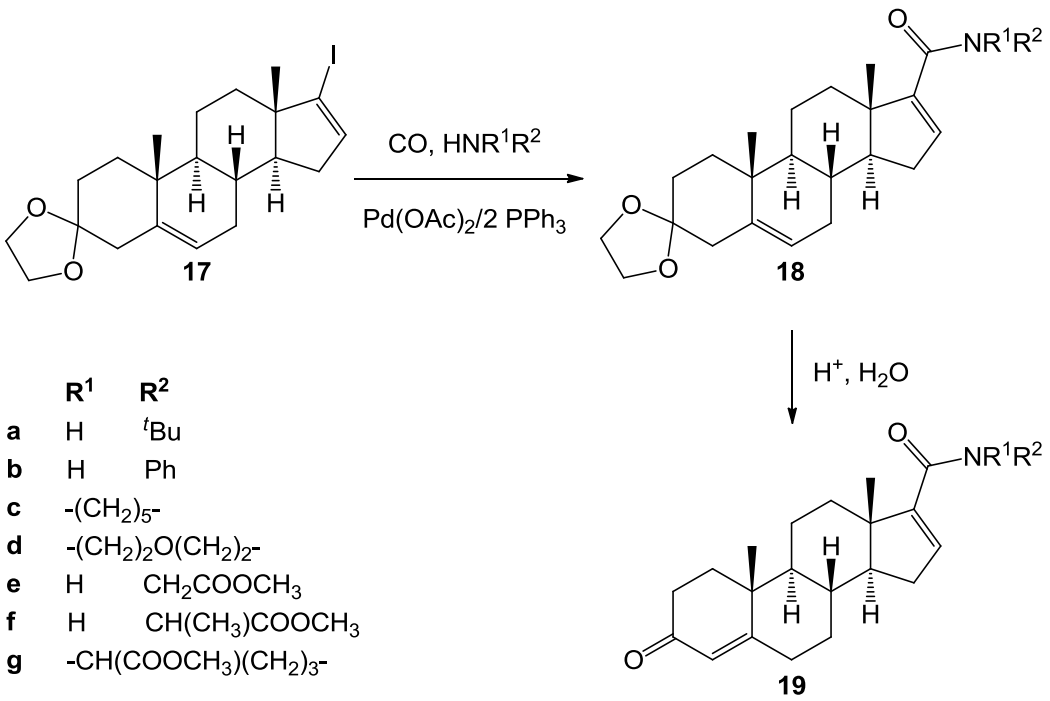
Scheme 88. Synthesis of androst-5-ene-17-one-3-ethylene ketal.

The 17-keto-3-ethylene ketal derivative (**15**) was transformed to the corresponding 17-iodo-5,16-diene derivative (**17**) *via* 17-hydrazone (**16**) according to the procedure described above (Scheme 89).



Scheme 89. Synthesis of 17-iodo-androst-5,16-diene-3-ethylene ketal.

The highly reactive 17-iodo-androst-5,16-diene-3-ethylene ketal (**17**) was aminocarbonylated in the presence of various primary or secondary amines such as *tert*-butylamine (**a**), aniline (**b**), piperidine (**c**), morpholine (**d**), *L*-glycine methyl ester (**e**), *L*-alanine methyl ester (**f**) and *L*-proline methyl ester (**g**) at atmospheric pressure *via* $Pd(OAc)_2$/2 PPh_3 catalyst system in a high-yielding synthesis. The highest isolated yield was achieved with *tert*-butyl-amine, while the lowest with secondary amines (Table 3). Then the position-3 was deprotected to keto functionality by hydrolysis resulting in the appropriate 17-carboxamido-3-ones (**19a-g**) in high yields, which were potential intermediates for further functionalization reactions (Scheme 90).



Scheme 90. Synthesis of 17-carboxamido-androst-4,16-dien-3-ones.

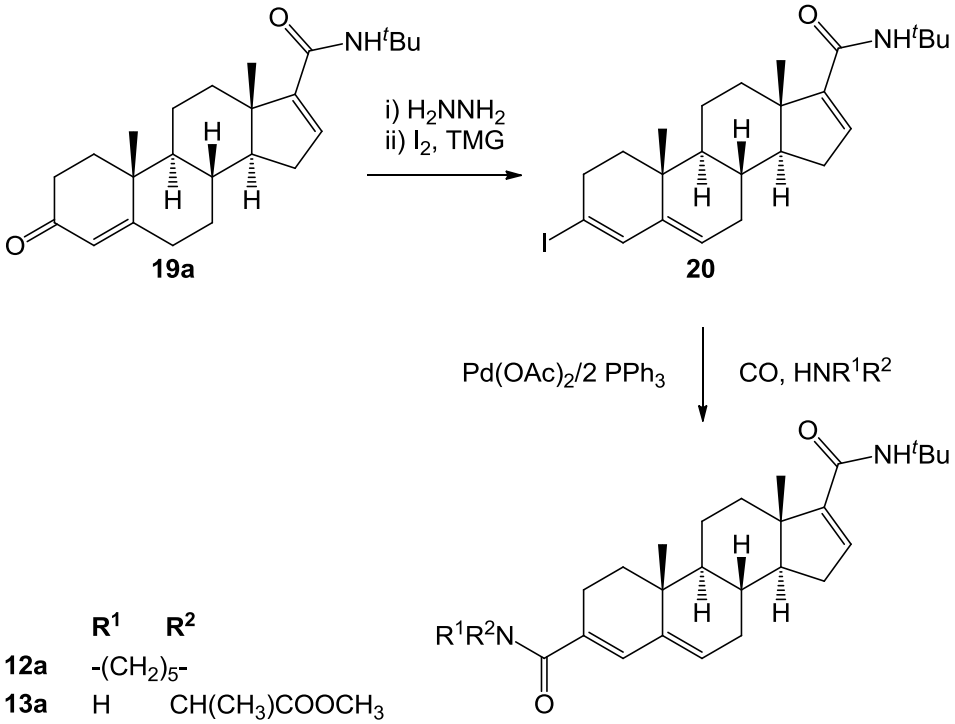
Table 3. Synthesis of androstane-based 17-carboxamides *via* palladium-catalyzed aminocarbonylation of **17**.[a)]

Entry	Amine	Amine:substr. ratio	Reaction time [h]	Conversion [%][b)]	Isolated yield (amide) [%]
1	^{t}BuNH$_2$ (**a**)	3	20	>98	82 (**18a**)
2	aniline (**b**)	2	20	>98	80 (**18b**)
3	piperidine (**c**)	1.5	20	60	41 (**18c**)
4	morpholine (**d**)	1.5	20	40	30 (**18d**)
5	GlyOMe (**e**)	1.1	20	>98	81 (**18e**)
6	AlaOMe (**f**)	1.1	20	>98	78 (**18f**)
7	ProOMe (**g**)	1.1	60	>98	77 (**18g**)

a) Reaction conditions: 0.025 mmol Pd(OAc)$_2$; 0.05 mmol PPh$_3$, 1 mmol substrate (**17**); 10 mL 2-butanone; reaction temperature: 50 °C; *p*(CO) = 1 bar.

b) Based on the iodoalkene substrate; determined by GC.

The 17-(*N*-*tert*-butylcarboxamido)-3-one derivative (**19a**) was transformed to dicarboxamides through 3-iodo-3,5-diene functionality, in order to show that the synthesis of 'mixed carboxamides' **12**–**13** could be accomplished in a way different from that described above (Scheme 91).



	R^1	R^2
12a	-$(CH_2)_5$-	
13a	H	$CH(CH_3)COOCH_3$

Scheme 91. Synthesis of 3,17-dicarboxamido-androst-3,5,16-triene derivatives through 17-*N*-*tert*-butylcarboxamido-3-iodoandrost-3,5,16-triene as key-intermediate.

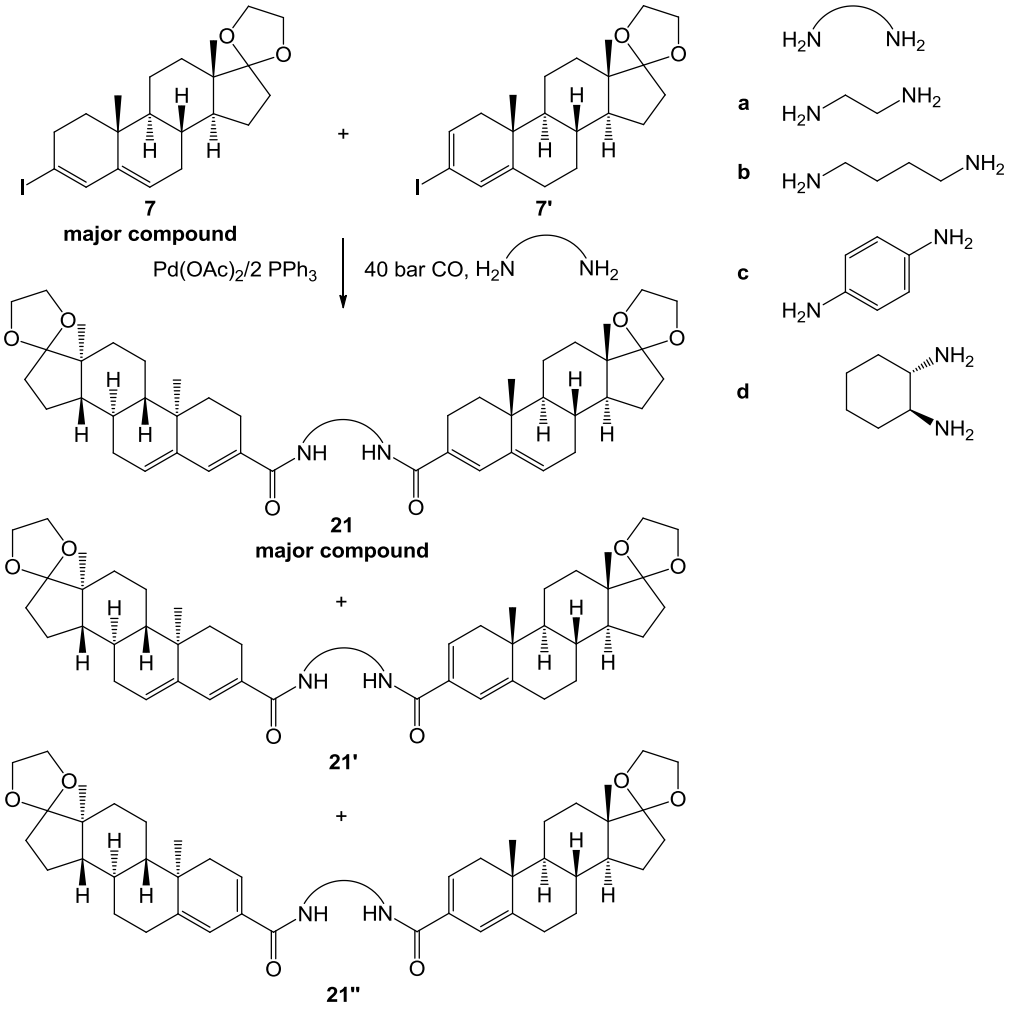
To ensure whether the formation of 'mixed dicarboxamides' may be achieved in another way, we also produced the 17-carboxamido-3-keto derivatives (**19a-g**) (Scheme 90). Firstly, 17-iodo-16-ene moiety was aminocarbonylated, while position-3 was protected as ethylene ketal (Scheme 90). Following the deprotection of the 3-ethylene ketal moiety, the 3-keto-4-ene functionality was transformed to 3-iodo-diene moiety *via* its 3-hydrazone (Scheme 91). At last, the 17-carboxamido-3-iodo-triene derivative (**20**) was aminocarbonylated using different amines resulting in the target 'mixed carboxamides' (**12a** and **13a**) (Scheme 91) with slightly lower yields than those obtained in the 3-carboxamide-17-one–3-carboxamide-17-iodo-16-ene–3,17-dicarboxamide reaction pathway (Schemes 85-87).

It can be stated, that iodoalkene functionalities in all positions (3,17-diiodo-triene, 3-iodo-3,5-diene, 3-iodo-2,4-diene, 17-iodo-16-ene) reacted quantitatively under mild reaction conditions (atmospheric carbon monoxide pressure, 50 °C) using monoamines as N-nucleophiles. In this way, 3,17-dicarboxamido-3,5,16-triene derivatives, 3-carboxamido-3,5-diene derivatives and 17-carboxamido-16-ene derivatives were synthesized in moderate to high yields depending on the structure of the amine.

4.5. Synthesis of new steroid dimers containing dicarboxamide-spacers

In general, ‘dimeric’ steroids constitute a class of compounds with pharmaceutical importance,[176-183] with micellular detergent activity,[184] may act as ligands for proteins,[185-187] and some of them show liquid–crystal behavior[188] and play a key role in the rate enhancement from hydrophobic binding.[189]

In order to synthesize 3,3’-dicarboxamido (‘dimeric’) structures with various linkers, the mixture of 3-iodo-17-ethylene ketals (**7** and **7’**) was aminocarbonylated in the presence of various diamines such as 1,2-diaminoethane (**a**), 1,4-diaminobutane (**b**), 1,4-diaminobenzene (**c**) or (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (**d**) at 40 bar carbon monoxide pressure by *in situ* formed palladium(0) catalyst from palladium(II) acetate and triphenylphosphine precursors in DMF (Scheme 92).

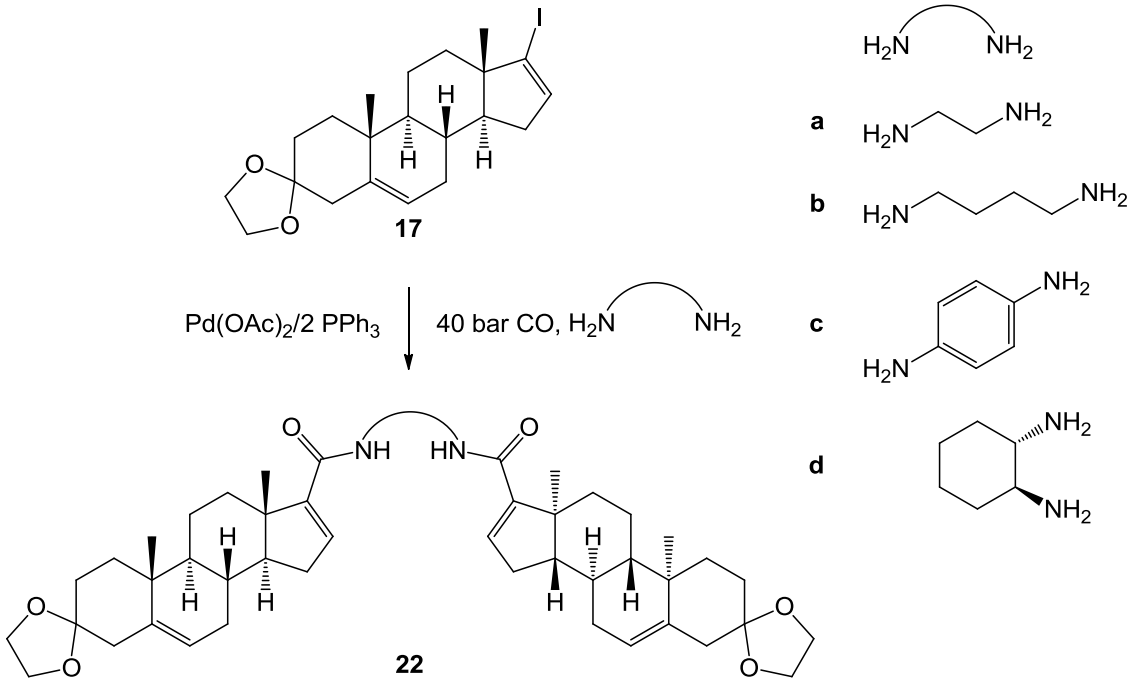


Scheme 92. Synthesis of various ‘dimeric’ steroids containing 3,3’-dicarboxamide spacers.

The *ca*. 4/1 mixture of the 3-iododiene compounds (**7** and **7'**) was used, a complete conversion towards 'dimeric' steroids was achieved (Scheme 92). Based on the NMR spectra, the main product was a steroid dimer containing 3,5-diene moiety in both androstene framework (**21a-d**). It should be mentioned that the target compounds (**21a-d**) still contained some isomers with 3,5-diene and 2,4-diene moiety (**21'a-d**) or 2,4-diene moiety in both androstane skeleton (**21''a-d**).

It should be mentioned that the partial isomerization of the 2,4-diene moiety to 3,5-diene was observed during the aminocarbonylation in this case. As a consequence of that, **21'a-d** and **21''a-d** products were present in the target compounds in trace amounts only.

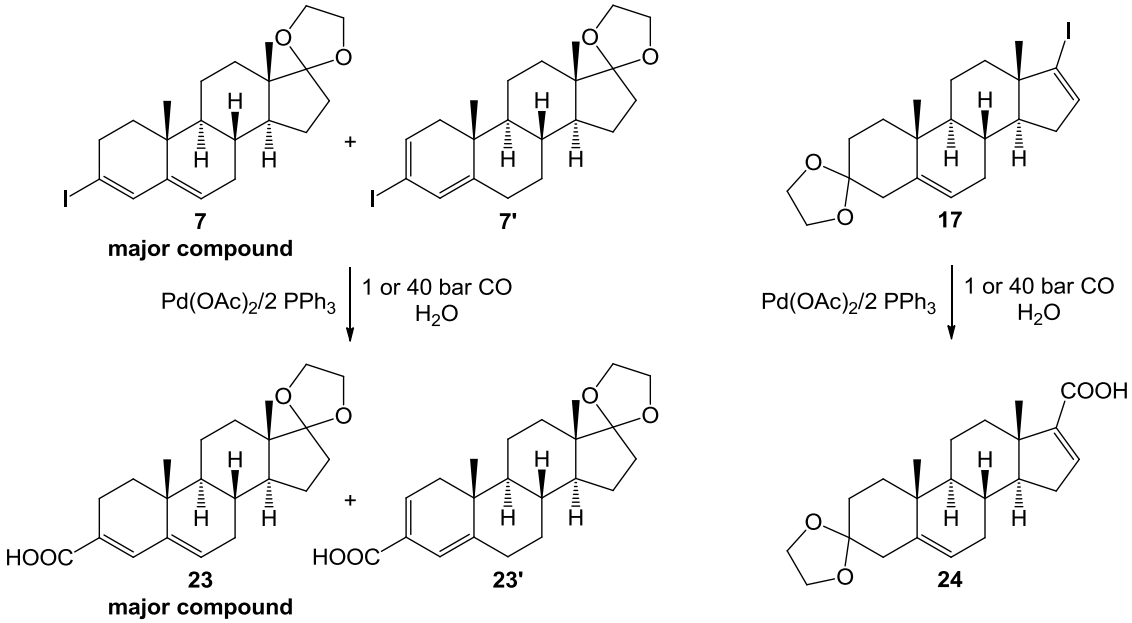
A more convenient isolation of 17,17'-dicarboxamides can be achieved due to the facile transformation of the 17-keto functionality to the corresponding 17-iodo-16-ene intermediate. The use of pure 17-iodo-3-ethylene ketal substrate (**17**) resulted in the formation of pure 'dimeric' steroids containing 17,17'-spacers in the diaminocarbonylation reactions (Scheme 93).



Scheme 93. Synthesis of various 'dimeric' steroids containing 17,17'-dicarboxamide spacers.

It is worth noting that the use of 2-butanone instead of DMF in the presence of **a**, **b**, **c** and **d** as *N*-nucleophiles (both at atmospheric or high carbon monoxide pressure) resulted in carboxylic acids (**23**, **23'** and **24**). That is, both types of subrates

(3-iododiene (**7** and **7'**) or 17-iodo-16-ene (**17**)) underwent hydroxycarbonylation reaction as a side reaction (Scheme 94).

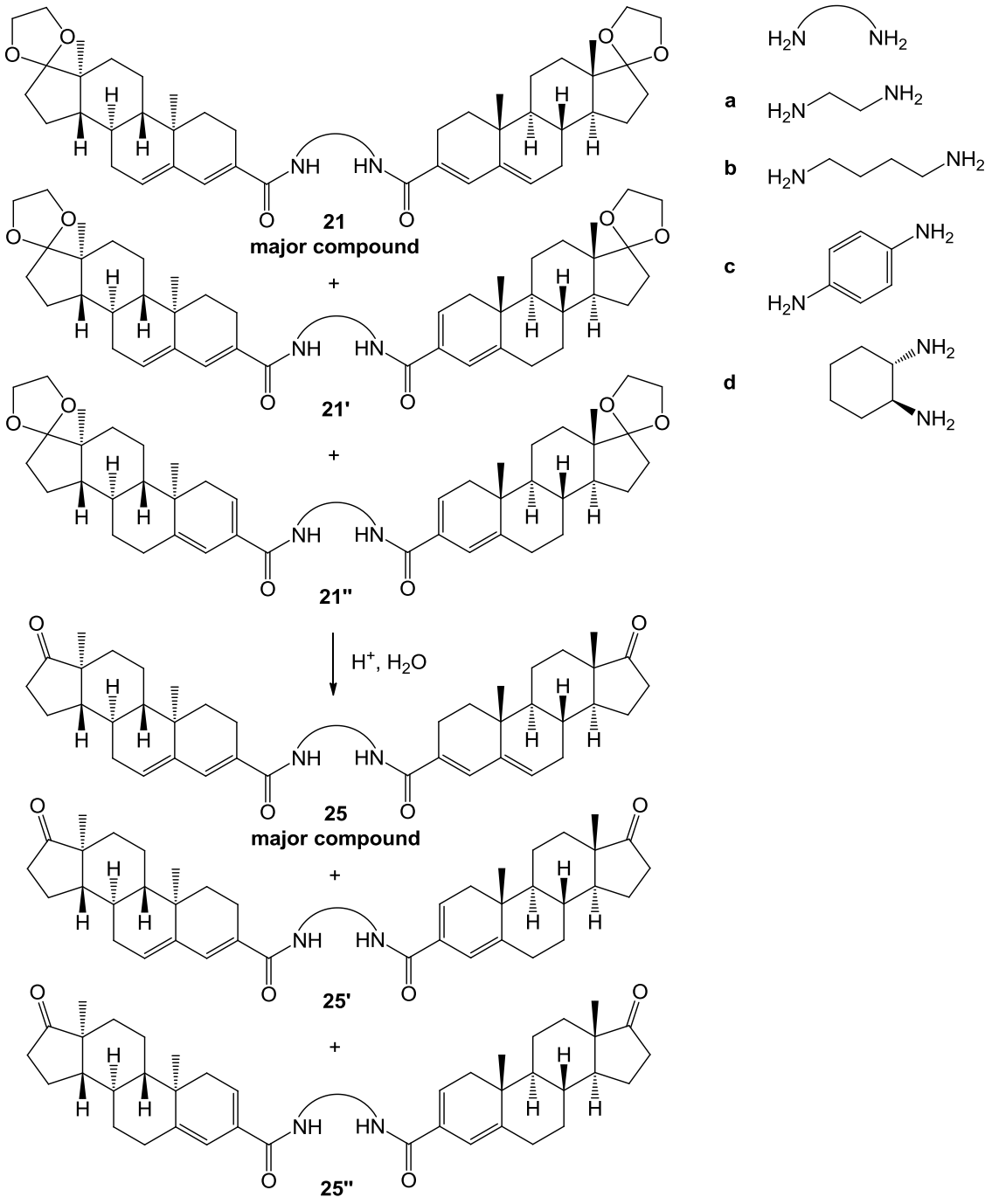


Scheme 94. Synthesis of carboxylic acid derivatives *via* hydroxycarbonylation side-reaction in the presence of water.

It may be explained by the water content of the solvent. That is, the hydroxycarbonylation side-reaction has been promoted in place of the aminocarbonylation resulting in the appropriate carboxylic acid derivatives (**23**, **23'** and **24**).

A similar result has been found using 17-iodo-5α-androst-16-ene as a substrate in the absence of *N*-nucleophiles.[190]

In the next step, position-17 or -3 was deprotected to keto functionality using hydrolysis resulting in the various steroidal dicarboxamido-ketone derivatives (**26**, **26'**, **26''** and **27**) (Scheme 95-96).



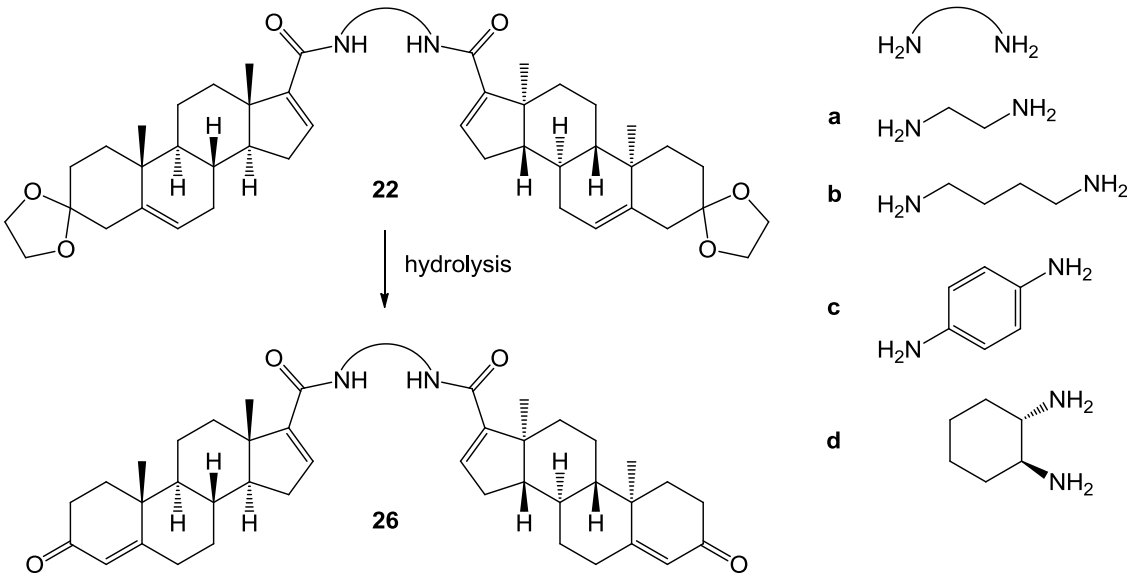
Scheme 95. Synthesis of various steroidal 3,3'-dicarboxamido-diketone derivatives.

In case of the 3,3'-dicarboxamido-17-ethylene ketal derivatives (**21**, **21'** and **21''**), the hydrolysis was carried out by using the mixture of chloroform and acetone, water and 1 M aqueous HCl at mild reflux temperature for a day. Using room temperature instead of mild reflux temperature, the ethylene ketal substrates did not transform to the appropriate ketones (**25**, **25'** and **25''**) (Scheme 95). It may be explained that the

iodoalkene substrates have lower reactivity towards diamines, due to the use of higher temperature was essential.

In case of the synthesis of 17-(*N,N'*-(butane-1,4-diyl)-carboxamido)-3-ethylene ketal (**26b**) compound, the same strategy was followed as the formation of the **25**, **25'** and **25''**.

However there are some other hydrolysis strategies which have to be used to produce dicarboxamido-ketone derivatives. The synthesis of 17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-3-one derivative (**26a**) was carried out using 1,4-dioxane as a solvent and 1 M HCl at mild reflux temperature. This modification was necessary because **22a** did not dissolve in acetone and THF neither at elevated temperature. The 17-(*N,N'*-(1,4-phenylene)-carboxamido)-3-ethylene ketal derivative (**22c**) was transformed to the corresponding ketone (**26c**) utilizing THF as a solvent and *p*-toluenesulfonic acid in acetone at mild reflux temperature. As above, **22c** substrate did not dissolve in acetone, and the hydrolysis did not occurred in room temperature. Surprisingly, the 17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-3-ethylene ketal derivative (**22d**) was easily transformed to the appropriate ketone (**26d**) in acetone without chloroform at room temperature using 1 M HCl (Scheme 96).



Scheme 96. Synthesis of various steroidal 17,17'-dicarboxamido-diketone derivatives.

In summary, conjugated unsaturated steroidal 3,17-dicarboxamides possessing different carboxamide functionalities and unsaturated 'dimeric' steroids with various dicarboxamide linkers can be synthesized in a multistep synthesis starting from

androst-4-ene-3,17-dione. The ketone functionalities were protected as ethylene ketal or transformed to iodoalkene functionality via its hydrazone. The 3-iodo-3,5-diene, 3-iodo-2,4-diene and the 17-iodo-16-ene moieties were aminocarbonylated in palladium-catalyzed reaction.

5. Experimental

5.1. The applied chemicals, solvents, gases and other materials

Triphenylphosphine was purchased from Fluka and the 1,1,3,3-tetramethylguanidine (TMG) from Aldrich. The palladium(II) acetate was a generous gift of Johnson Matthey.

Androst-4-ene-3,17-dione (**1**), a well-known starting compound for the production of several pharmaceutically active steroids, was produced by bioconversion of fitosterols in Gedeon Richter Plc.

Commercial Et_3N, primary and secondary amines, as well as diamines (Aldrich) were used without further purification. Dimethylformamide and 2-butanone (Aldrich) were dried according to the standard procedures.

The solvents for the work-up and purification procedures (chloroform, dichloromethane, ethyl acetate, petroleum ether (40-70 °C), methanol, ethanol, and acetone) were purchased from Aldrich, Fluka, Merck, VWR and Molar Chemicals Ltd.

TLC analyses were carried out by using Merck TLC sheets (Silica gel 60 F_{254}) and chloroform/ethyl acetate, ethyl acetate/chloroform, dichloromethane/ethyl acetate and petroleum ether (40-70 °C)/ethyl acetate mixtures were used as appropriate eluents. (The exact ratios are given at the corresponding synthetic procedures.)

The purifications by column chromatograph were achieved by utilizing Silica gel 60 (0.035-0.070 mm and 0.063-0.200 mm) from Fluka and Merck.

The argon gas was dried through potassium hydroxide, silica gel and phosphorus pentoxide in an inert system. The argon and carbon monoxide gases were purchased from Linde.

The steroidal monoketals (**5** and **15**) were synthesized according to modified conventional synthetic procedures[191] using the corresponding keto derivatives as starting materials. The transformation of the keto functionality to iodoalkene moiety was carried out by the modification of the Barton's methodology.[86,87]

5.2. Instrumentation used for product characterization

The ^{1}H- and ^{13}C-NMR spectra were recorded in a Varian Inova 400 spectrometer (at 400 and 100.58 MHz, respectively) and in a Bruker Avance III 500 spectrometer

(at 500 and 125.7 MHz, respectively). The chemical shifts are given as δ values (ppm) and referenced to tetramethylsilane.

Mass-spectrometry data have been obtained by using a GC-MS system consisting of a Perkin Elmer AutoSystem XL gas-chromatograph and Perkin Elmer TurboMass mass spectrometer.

MALDI-TOF spectra were obtained on an Autoflex II TOF/TOF spectrometer (Bruker Daltonics) in positive ion modes, using a 337 nm pulsed nitrogen laser (accelerating voltage: 20.0 kV, matrix: 2,5-dihydroxybenzoic acid).

The infrared spectrometry data have been acquired by utilizing SPECORD IR-75 system purchased from Carl Zeiss and using potassium bromide pellets.

The elemental analyses were carried out *via* Carlo Elba 1108 Elemental Analyzer.

5.3. General procedures and syntheses

5.3.1. Synthesis of androst-4-ene-3-one-17-ethylene ketal (5)

A solution of androst-4-ene-3,17-dione (**1**) (5.98 g, 20.9 mmol) in chloroform (100 mL) and 1.40 mL (1.56 g, 25.1 mmol) of ethylene glycol containing *p*-toluenesulfonic acid (40 mg) was stirred under reflux for a day in a Dean–Stark water separator. The reaction mixture was cooled, neutralized and washed with 5% aqueous NaOH and water. It was dried on sodium sulfate, evaporated and purified by column chromatography (silica gel 0.035-0.070 mm, petroleum ether (40–70 °C)/EtOAc = 7/3). Pure **5** as a white solid material was obtained. Yield: 3.12 g (45%).

5.3.2. Synthesis of androst-5-ene-17-one-3-ethylene ketal (15)

A solution of androst-4-ene-3,17-dione (**1**) (10 g, 35.0 mmol) in chloroform (150 mL) and 4.70 mL (5.24 g, 84.4 mmol) of ethylene glycol containing *p*-toluenesulfonic acid (150 mg) was stirred under reflux for four days in a Dean–Stark water separator. The reaction mixture was cooled, neutralized and washed with 5% aqueous NaOH and water. It was dried on sodium sulfate, evaporated and purified by column chromatography (silica gel 0.035-0.070 mm, petroleum ether (40–70 °C)/EtOAc = 75/25). Pure 3,17-diketal (**14**) as a white solid material was obtained. Yield: 8.50 g (65%).

To a solution of **14** (5 g, 13.4 mmol) in acetone (500 mL) and water (50 mL), 1 M aqueous HCl (10 mL) was added and stirred at room temperature for 1.5 h. After addition of saturated $NaHCO_3$ (200 mL), the mixture was concentrated under reduced pressure. The residue was dissolved in chloroform (150 mL), washed with water and brine, dried on sodium sulfate and evaporated. Purification by column chromatography (silica gel 0.035-0.070 mm, petroleum ether (40–70 °C)/EtOAc = 75/25) gave pure **15** as a white solid material. Yield: 1.76 g (40%).

5.3.3. A general procedure for the preparation of steroidal iodoalkenes

A mixture of the corresponding steroidal ketone (**5**, **9a**, **9c**, **9f** or **15**) (2 mmol), freshly distilled hydrazine hydrate (98%, 300 mg, 6 mmol) and barium oxide (8 mg) in 2-methoxy-ethanol (15 mL) were heated for 2 days at 160 °C. After completion of the reaction the mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with water, and brine. It was dried over sodium sulfate and evaporated to give the 3- or 17-hydrazone derivative. The product was used in the next step without further purification.

To a stirred solution of iodine (1.12 g, 4.4 mmol) in dichloromethane (20 mL) 1,1,3,3-tetramethylguanidine (TMG, 2.07 g, 18 mmol) was added slowly and cooled by iced water bath during the addition. The solution of the 3- or 17-hydrazone derivative, (2 mmol) in dichloromethane (15 mL) was added drop-wise at room temperature. After the addition was completed, the mixture was stirred for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with dichloromethane. The combined organic layer was washed with 1 M aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. The iodoalkene products (**7**, **7'**, **10a**, **10c**, **10f** and **17**) were used in the next step without further purification.

5.3.4. A general procedure for aminocarbonylation of the steroidal iodoalkenes at atmospheric pressure

A mixture of the iodoalkene derivative (**7**, **7'**, **10a**, **10c**, **10f** or **17**) (1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were dissolved in 20 mL 2-butanone under argon. Et_3N (0.5 mL) and *tert*-butylamine (**a**)

(0.30 mL, 3 mmol) (or another *N*-nucleophile such as piperidine (**c**) (0.15 mL, 1.5 mmol)) were added. The *L*-alanine methyl ester (**f**) was used as hydrochloride salt (1.1 mmol) and was added together with the catalyst. The atmosphere was changed to CO (1 bar), and the reaction was conducted at 50 °C for 96 h. The composition of the reaction mixture was checked by GC. The solvent was evaporated, and the residue was dissolved in 20 mL of CH_2Cl_2. It was washed in turn with 3 × 20 mL of water. The organic layer was separated, dried over Na_2SO_4 and evaporated. Column chromatography (silica gel 0.063-0.200 mm, $CHCl_3$/EtOAc = 99/1, 9/1, 8/2, 85/15; the exact ratios are given below) resulted in the target carboxamides (**8a**, **8c**, **8f**, **11c**, **11f**, **12a**, **12f**, **13a**, **13c**). In more cases, the products obtained by column chromatography were subjected to re-crystallization (solvents used are given below).

5.3.5. A general procedure for the deprotection of 3-carboxamido-17-ethylene ketal derivatives

To a solution of the *N*-substituted 3-carboxamido-17-ethylene ketal derivative (**8a**, **8c** or **8f**) (2.5 mmol) in acetone (100 mL) and water (10 mL), 1 M aqueous HCl (5 mL) was added and stirred overnight at room temperature. After addition of saturated $NaHCO_3$ (100 mL), the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (100 mL), washed with water and brine, dried on sodium sulfate and evaporated. Purification by column chromatography (silica gel 0.063-0.200 mm, CH_2Cl_2 or $CHCl_3$/EtOAc = 9/1, 8/2, 85/15; exact ratios are given in the Characterization) gave the pure *N*-substituted 3-carboxamido-17-one or 17-carboxamido-3-one derivatives (**9a**, **9c** and **9f**). (Isolated yield and full characterization of a compound is given in the Characterization).

5.3.6. A general procedure for aminocarbonylation of steroidal iodoalkenes at high pressure

A mixture of 3-iodo-17-ethylene ketal (**7** and **7'**) or 17-iodo-3-ethylene ketal derivative (**17**) (1 mmol), palladium(II) acetate (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were dissolved in 15 mL dimethylformamide under argon. Et_3N (0.5 mL) and ethylenediamine (33.5 μL, 0.5 mmol) (or another *N*-nucleophile) were added. (The 1,4-diaminobutane was used as hydrochloride salt (0.55 mmol) and was added together with the catalyst.) The atmosphere was changed to CO (40 bar), and the

reaction was conducted in a 100 mL stainless steel (Cr/Mo/Ni = 18/8/8) autoclave at 100 °C for 48 h (in case of the carbonylation of 17-iodo-3-ethylene ketal derivative (**17**)) or for 72 h (in case of the carbonylation of 3-iodo-17-ethylene ketal derivative (**7** and **7'**)). The composition of the reaction mixture was checked by TLC. The solvent was evaporated, and the residue was dissolved in 20 mL of $CHCl_3$ and washed with 20 mL of water. The aqueous phase was washed with 2 × 15 mL of $CHCl_3$. The combined organic layer was washed in turn with 3 × 50 mL of water than with 50 mL brine, dried over Na_2SO_4 and evaporated. Column chromatography (silica gel 0.063-0.200 mm, EtOAc/$CHCl_3$ = 7/3, 6/4, 5/5, 4/6, 3/7; the exact ratios are given below) resulted in the target carboxamides (**21a-d** and **22a-d**).

5.3.7. Synthesis of steroidal dicarboxamido-diketone ('dicarboxamide dimers') derivatives

To a solution of 3,3'-dicarboxamido-17,17'-ethylene ketal derivative (**21a-d**) or 17-(*N,N'*-(butane-1,4-diyl)-carboxamido)-3-ethylene ketal (**22b**) (0.1 mmol) in $CHCl_3$ (4 mL) and acetone (40 mL), water (4 mL), 1 M aqueous HCl (2 mL) were added and stirred at 70 °C for 24 h. After the reaction was completed, the mixture was cooled, than saturated $NaHCO_3$ (6 mL) was added. The mixture was shaken with 20 mL $CHCl_3$ and 40 mL water. The aqueous phase was washed with 20 + 2 × 10 mL of $CHCl_3$. The combined organic layer was washed in turn with 3 × 100 mL of water than with 50 mL brine, dried over Na_2SO_4 and evaporated. Purification by column chromatography (silica gel 0.063-0.200 mm, EtOAc/$CHCl_3$ = 8/2, 7/3, 4/6, 2/8; exact ratios are given below) gave pure 3,3'-dicarboxamido-17,17'-dione derivative (**25a-d**) or 17-(*N,N'*-(butane-1,4-diyl)-carboxamido)-3-one (**26d**).

5.3.8. Synthesis of the 17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-3-one derivative (26a)

To a solution of 17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-3-ethylene ketal derivative (**22a**) (0.2 mmol) in 1,4-dioxane (120 mL) and 1 M aqueous HCl (2.5 mL) were added and stirred at 60 °C for 72 h. After the reaction was completed, the mixture was cooled, than saturated $NaHCO_3$ (10 mL) was added. The mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (25 mL), washed with water (40 mL). The aqueous phase was washed with 25 + 15 mL of $CHCl_3$. The combined

organic layer was washed in turn with 3 × 60 mL of water than with 50 mL brine, dried over Na_2SO_4 and evaporated. Purification by column chromatography (silica gel 0.063-0.200 mm, EtOAc/$CHCl_3$ = 8/2) gave pure 17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-3-one derivative (**26a**).

5.3.9. Synthesis of the 17-(*N,N'*-(1,4-phenylene)-carboxamido)-3-one derivative (26c)

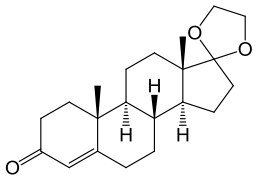
To a solution of 17-(*N,N'*-(1,4-phenylene)-carboxamido)-3-ethylene ketal derivative (**22c**) (0.1 mmol) in tetrahydrofuran (48 mL) and *p*-toluenesulfonic acid (50 mg) in acetone (2 mL) were added and stirred at 85 °C for 24 h. After the reaction was completed, the mixture was cooled, than saturated $NaHCO_3$ (5 mL) was added. The mixture was shaken with $CHCl_3$ (25 mL) and water (75 mL). The aqueous phase was washed with 25 + 15 + 10 mL of $CHCl_3$. The combined organic layer was washed in turn with 3 × 100 mL of water than with 50 mL brine, dried over Na_2SO_4 and evaporated. Purification by column chromatography (silica gel 0.063-0.200 mm, $CHCl_3$/EtOAc = 6/4) gave pure 17-(*N,N'*-(1,4-phenylene)-carboxamido)-3-one derivative (**26c**).

5.3.10. Synthesis of the 17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-3-one derivative (26d)

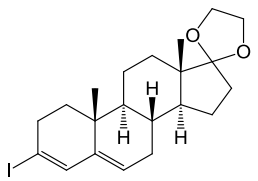
To a solution of 17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-3-ethylene ketal derivative (**22d**) (0.26 mmol) in acetone (40 mL), and water (4 mL), 1 M aqueous HCl (2 mL) were added and stirred at room temperature for 24 h. After addition of saturated $NaHCO_3$ (9 mL), the mixture was shaken with 40 mL CH_2Cl_2 and 40 mL water. The aqueous phase was washed with 25 + 15 mL of CH_2Cl_2. The combined organic layer was washed in turn with 3 × 100 mL of water than with 50 mL brine, dried over Na_2SO_4 and evaporated. Purification by column chromatography (silica gel 0.063-0.200 mm, $CHCl_3$/EtOAc = 6/4) gave pure 17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-3-one derivative (**26d**).

6. Analytical and spectroscopic data of compounds

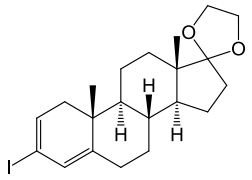
Androst-4-ene-3-one-17-ethylene ketal (**5**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.68 (br s, 1H, 4-CH); 3.79–3.91 (m, 4H, $O(CH_2)_2O$); 0.88–2.42 (m, 19H, skeleton protons); 1.16 (s, 3H, 19-CH_3); 0.85 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 199.3; 171.1; 123.8; 119.0; 65.2; 64.5; 53.6; 49.7; 45.7; 38.6; 35.8; 35.7; 34.0; 33.9; 32.7; 31.3; 30.3; 22.6; 20.4; 17.4; 14.2. MS (*m*/z/rel.int.): 330/34 (M^+), 285/4, 266/9, 99/100. IR (KBr, (cm^{-1})): 1672 (C=O), 1619 (C=C). Analysis calculated for $C_{21}H_{30}O_3$ (M=330.47): C, 76.33; H, 9.15; Found: C, 76.21; H, 9.01. R_f = 0.73 (petroleum ether (40–70 °C)/EtOAc = 7/3). Mp. 168–170 °C. White powder-like material (as obtained after column chromatography). Yield: 3.2 g (45%).



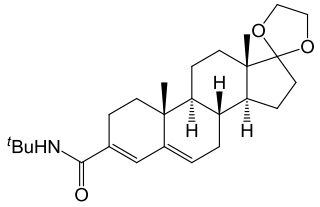
3-Iodo-androst-3,5-diene-17-ethylene ketal (**7**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.51 (br s, 1H, 4-CH); 5.32 (br s, 1H, 6-CH); 3.78–3.93 (m, 4H, $O(CH_2)_2O$); 2.55–2.63 (m, 2H, 7-CH_2); 0.80–2.24 (m, 15H, skeleton protons); 0.90 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 142.3; 139.3; 124.4; 119.3; 94.8; 65.2; 64.5; 50.7; 47.9; 45.8; 37.3; 36.3; 34.3; 34.2; 31.9; 30.9; 30.5; 22.6; 20.4; 18.9; 14.3. MS (*m*/z/rel.int.): 440/41 (M^+), 378/100, 352/66, 337/17, 99/68. IR (KBr, (cm^{-1})): 1620, 1603 (C=C). Analysis calculated for $C_{21}H_{29}O_2I$ (M=440.36): C, 57.28; H, 6.64; Found: C, 57.12; H, 6.82. R_f = 0.83 (petroleum ether (40–70 °C)/EtOAc = 7/3).Mp.144–147 °C. Pale yellow crystalline material. Yield: 1.59 g (31%).



3-Iodo-androst-2,4-diene-17-ethylene ketal (**7'**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.17 (br s, 1H, 2-CH); 5.68 (br s, 1H, 4-CH); 3.80–3.94 (m, 4H, $-O(CH_2)_2O-$); 2.53–2.62 (m, 2H, 1-CH_2); 0.80–2.24 (m, 15H, skeleton protons); 0.90 (s, 3H, 19-CH_3); 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 148.7; 131.4; 125.0; 119.2; 88.3; 65.2; 64.5; 54.3; 49.7; 45.8; 36.5; 36.4; 34.2; 34.1; 30.8; 30.5; 30.4; 22.7; 20.9; 17.0; 14.2. MS (*m*/*z*/rel.int.): 440/92 (M^+), 325/12, 395/7, 99/100. Analysis calculated for $C_{21}H_{29}O_2I$ (M=440.36): C, 57.28; H, 6.64; Found: C, 57.07; H, 6.85. R_f = 0.79 (petroleum ether (40–70 °C)/EtOAc = 7/3). Yellow viscous material (as obtained after column chromatography). Yield: 123 mg (19%).

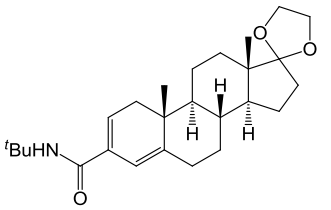


3-(*N*-*tert*-butylcarboxamido)-androst-3,5-diene-17-ethylene ketal (**8a**): ^{1}H NMR (400 MHz, $CDCl_3$): 5.61 (br s, 1H, 4-CH); 5.43 (br s, 1H, 6-CH); 3.98–4.03 (m, 1H, NH); 3.70–3.82 (m, 4H, $O(CH_2)_2O$); 0.70–2.28 (m, 17H, skeleton protons); 1.31 (s, 9H, ^{t}Bu); 1.27 (s, 3H, 18-CH_3); 1.17 (s, 3H, 19-CH_3). ^{13}C NMR (100.58 MHz, $CDCl_3$): 167.8; 140.7; 132.6; 129.4; 119.2; 65.0; 64.3; 62.7; 51.0; 50.0; 49.3; 47.8; 45.7; 34.6; 34.0; 33.9; 31.8; 31.4; 29.5; 22.5; 20.4; 18.8; 14.0. MS (*m*/*z*/rel.int.): 413/100 (M^+); 351/60; 325/37; 99/83; 57/19. Analysis calculated for $C_{26}H_{39}O_3N$ (M=413.60): C, 75.50; H, 9.50; N, 3.39; Found: C, 75.35; H, 9.67; N, 3.21. R_f = 0.59 ($CHCl_3$/EtOAc = 9/1). Mp. 83–84 °C. Pale-yellow solid material (crystallized from ethyl acetate). Yield: 289 mg (70%).

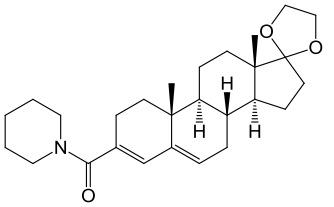


3-(*N*-*tert*-butylcarboxamido)-androst-2,4-diene-17-ethylene ketal (**8'a**) (identified as minor component in a two-component mixture with **8**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.23 (br s, 1H, 2-CH); 5.82 (br s, 1H, 4-CH); 4.05–4.15 (m, 1H, NH); 3.78–3.92 (m, 4H, $O(CH_2)_2O$); 1.31 (s, 9H, ^{t}Bu); 0.80–2.39 (m, 17H, skeleton protons); 1.16 (s, 3H, 18-CH_3); 0.82 (s, 3H, 19-CH_3). ^{13}C NMR (100.58 MHz, $CDCl_3$): 166.7; 147.5; 139.7;

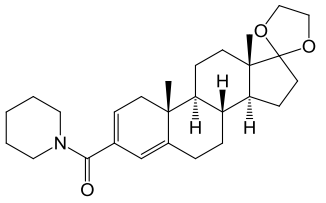
133.5; 129.3; 119.1; 61.9; 60.2; 51.1; 49.7; 49.6; 45.6; 36.4; 36.0; 33.4; 33.3; 29.8; 28.4; 27.6; 23.5; 21.9; 21.2; 20.9; 16.2. MS (*m*/*z*/rel.int.): 413/55 (M^+); 386/3; 368/21; 295/20; 99/100. R_f = 0.59 (CH_2Cl_2/EtOAc = 92/8). Yellow viscous material (as obtained after column chromatography). Yield: 93 mg (21%).



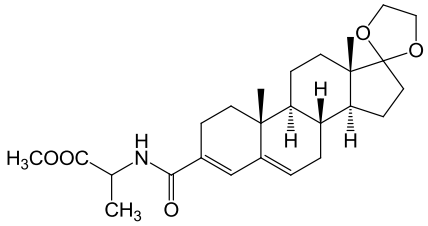
3-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-3,5-diene-17-ethylene ketal (**8c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.89 (br s, 1H, 4-CH); 5.41 (br s, 1H, 6-CH); 3.73–3.90 (m, 4H, $O(CH_2)_2O$); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.30 (m, 23H, skeleton protons + $(CH_2)_3$); 0.89 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.3; 140.2; 130.7; 128.6; 119.3; 116.1; 65.1; 64.5; 54.6; 50.7; 49.8; 48.0; 45.8; 37.2; 36.5; 34.7; 34.1; 33.4; 32.0; 31.3; 30.6; 24.7; 23.8; 22.7; 20.4; 19.1; 14.2. MS (*m*/*z*/rel.int.): 425/100 (M^+), 363/14; 324/15; 99/38. IR (KBr, (cm^{-1})): 1633 (CON). Analysis calculated for $C_{27}H_{39}O_3N$ (M=425.61): C, 76.20; H, 9.24; N, 3.29; Found: C, 76.00; H, 9.41; N, 3.11. R_f = 0.58 ($CHCl_3$/EtOAc = 8/2). Yellow highly viscous material. Yield: 216 mg (80%).



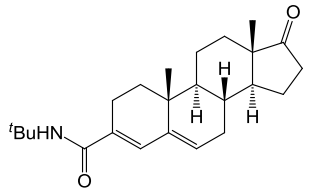
3-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-2,4-diene-17-ethylene ketal (**8'c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.70 (br s, 1H, 2-CH); 5.47 (br s, 1H, 4-CH); 3.75-3.90 (m, 4H, $O(CH_2)_2O$); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.30 (m, 23H, skeleton protons + $(CH_2)_3$); 0.89 (s, 3H, 18-CH_3); 0.79 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 170.0; 147.0; 131.9; 126.5; 122.8; 119.2; 65.1; 64.4; 54.6; 50.7; 49.8; 48.0; 45.8; 37.8; 36.5; 34.7; 34.1; 33.4; 32.0; 31.2; 30.5; 24.6; 23.8; 22.6; 21.1; 19.1; 14.2. MS (*m*/*z*/rel.int.): 425/80 (M^+), 424/100; 380/53; 362/13; 99/71. IR (KBr, (cm^{-1})): 1633 (CON). (Identified in the 15/85 mixture of **8'c**/**8c**). Yield: 79 mg (17%).



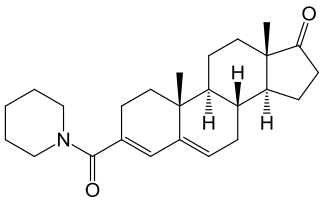
3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-androst-3,5-diene-17-ethylene ketal (**8f**): ^{1}H NMR (400 MHz, $CDCl_3$): 6.32 (br s, 1H, NH); 5.86 (brs, 1H, 4-CH); 5.75 (br s, 1H, 6-CH); 4.68 (qi, 7.2 Hz, 1H, $CHCH_3$); 3.80–3.92 (m, 4H, $O(CH_2)_2O$); 1.42 (d, 7.2 Hz, 1H, $CHCH_3$); 0.77–2.28 (m, 17H, skeleton protons); 0.97 (s, 3H, 18-CH_3); 0.93 (s, 3H, 19-CH_3). ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.9; 167.6; 140.7; 134.2; 130.3; 119.2; 65.1; 64.5; 52.3; 50.6; 49.8; 48.1; 47.9; 45.8; 45.7; 34.7; 34.1; 33.4; 31.9; 31.7; 30.4; 22.5; 20.5; 18.9; 18.5; 14.2. MS (*m*/*z*/rel.int.): 443/77 (M^+); 381/85; 341/52; 207/35; 171/19; 99/100; 73/25. Analysis calculated for $C_{26}H_{37}O_5N$ (M=443.68): C, 70.40; H, 8.41; N, 3.16; Found: C, 70.25; H, 8.27; N, 3.01. R_f = 0.35 ($CHCl_3$/EtOAc = 99/1). Mp. 82–84 °C. White crystalline material (re-crystallized from ethyl acetate). Yield: 279 mg (63%).



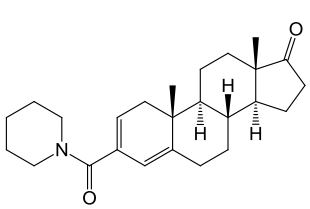
3-(*N*-*tert*-butylcarboxamido)-androst-3,5-diene-17-one (**9a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.70 (br s, 1H, 4-CH); 5.72 (br s, 1H, 6-CH); 5.51 (br s, 1H, NH); 5.55 (br s, 1H, 16-CH); 0.70–2.54 (m, 17H, skeleton protons); 1.34 (s, 9H, ^{t}Bu); 0.91 (s, 3H, 18-CH_3); 0.88 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.5; 167.4; 140.8; 132.4; 129.6; 128.4; 51.6; 50.9; 49.7; 48.0; 47.5; 35.6; 34.7; 33.3; 31.2 (double intensity); 30.8; 28.7; 28.8 (double intensity); 21.6; 20.2; 18.7; 13.5. MS (*m*/*z*/rel.int.): 369/100 (M^+); 313/52; 297/35; 269/12; 207/6; 91/13. IR (KBr, (cm^{-1})):3355 (NH), 1739 (C=O), 1637 (CON). Analysis calculated for $C_{24}H_{35}O_2N$ (M=369.55): C, 78.00; H, 9.55; N, 3.79; Found: C, 77.85; H, 9.64; N, 3.70. R_f = 0.62 (CH_2Cl_2/EtOAc = 85/15). Mp. 193–194 °C. White crystalline material (re-crystallized from abs. ethanol). Yield: 738 mg (80%).



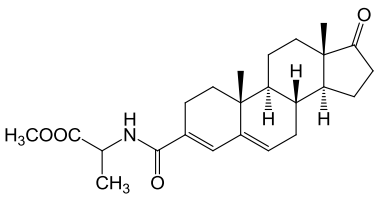
3-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-3,5-diene-17-one (**9c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.89 (brs, 1H, 4-CH); 5.42 (br s, 1H, 6-CH); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.41 (m, 23H, skeleton protons + $(CH_2)_3$); 0.90 (s, 3H, 18-CH_3); 0.81 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.6; 171.2; 140.3; 131.0; 128.3; 125.8; 54.7; 51.7; 50.8; 48.2; 47.5; 37.7; 35.7; 34.7; 33.3; 31.3; 30.7; 26.1; 24.6; 23.7; 21.7; 20.2; 19.0; 17.2; 13.6. MS (*m*/*z*/rel.int.): 381/100 (M^+), 366/15; 297/22. IR (KBr, (cm^{-1})): 1736 (C=O); 1633 (CON); 1608 C=C). Analysis calculated for $C_{25}H_{35}O_2N$ (M=381.56): C, 78.70; H, 9.25; N, 3.67; Found: C, 78.55; H, 9.43; N, 3.44. R_f = 0.49 ($CHCl_3$/EtOAc = 8/2). Mp. 102–103 °C. Yellow crystalline material. Yield: 638 mg (75%).



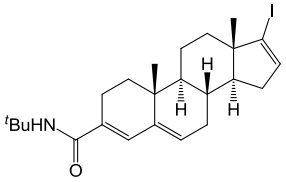
3-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-2,4-diene-17-one (**9'c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.70 (br s, 1H, 2-CH); 5.48 (br s, 1H, 4-CH); 3.40 (br s, 4H, $N(CH_2)_2$); 0.80–2.41 (m, 23H, skeleton protons + $(CH_2)_3$); 0.90 (s, 3H, 18-CH_3); 0.80 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.6; 169.8; 146.3; 131.8; 122.8; 116.4; 51.7; 50.8; 47.8; 47.5; 37.2; 35.7; 34.7; 33.3; 31.4; 31.0; 30.0; 26.1; 24.6; 23.7; 21.7; 20.8; 19.0; 17.2; 13.8. MS (*m*/*z*/rel.int.): 381/77 (M^+), 380/100; 365/40; 281/49; 207/65. (Identified in the 20/80 mixture of **9'c**/**9c**). Yield: 105 mg (20%).



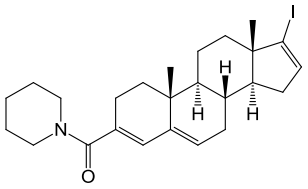
3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-androst-3,5-diene-17-one (**9f**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.80 (br s, 1H, 4-CH); 6.38 (br s, 1H, 6-CH); 6.35 (br s, 1H, NH); 5.75 (br s, 1H, 16-CH); 4.65 (qi, 7.2 Hz, 1H, NCH); 3.75 (br s, 3H, OCH_3); 1.42 (d, 7.2 Hz, 3H, $CHCH_3$); 0.65–2.60 (m, 17H, skeleton protons); 0.90 (s, 3H, 18-CH_3); 0.87 (s, 3H, 19-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 220.5, 173.9; 167.4; 140.9; 134.0; 129.6; 127.9; 52.5; 51.8; 48.1 (triple intensity); 47.7; 35.8; 34.9; 33.4; 31.3 (double intensity); 31.1; 21.8; 20.4; 19.0; 18.6; 13.7. MS (*m*/*z*/rel.int.): 399/63 (M^+); 296/100; 253/7; 147/10; 119/10; 91/18. IR (KBr, (cm^{-1})): 3384 (NH), 1748 (COO), 1739 (C=O), 1649 (CON). Analysis calculated for $C_{24}H_{33}O_4N$ (M=399.53): C, 72.15; H, 8.33; N, 3.51; Found: C, 72.01; H, 8.45; N, 3.31. R_f = 0.60 ($CHCl_3$/EtOAc = 9/1). Mp. 119–121 °C. White crystalline material (re-crystallized from abs. ethanol). Yield: 698 mg (70%).



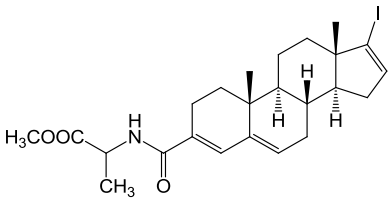
3-(*N*-*tert*-butylcarboxamido)-17-iodoandrost-3,5,16-triene (**10a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.38 (br s, 1H, 4-CH); 6.12 (br s, 1H, 6-CH); 5.71 (br s, 1H, NH); 5.57 (br s, 1H, 16-CH); 0.66–2.50 (m, 15H, skeleton protons); 1.37 (s, 9H, ^{t}Bu); 0.95 (s, 3H, 18-CH_3); 0.74 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 167.6; 141.3; 137.4; 132.4; 129.9; 128.8; 112.6; 54.8; 53.4; 51.1; 50.0; 48.4; 36.2; 36.1; 35.0; 33.6; 33.5; 31.5; 31.0; 28.9; 22.0; 20.9; 18.9; 15.2. MS (*m*/*z*/rel.int.): 479/100 (M^+); 423/32; 219/5; 145/11; 91/23. IR (KBr, (cm^{-1})): 1655 (C=O). Analysis calculated for $C_{24}H_{34}ONI$ (M=479.44): C, 60.12; H, 7.15; N, 2.92; Found: C, 60.05; H, 7.41; N, 2.70. R_f = 0.64 ($CHCl_3$/EtOAc = 99/1). Mp. 166–167 °C. Pale-brown crystalline material (crystallized from ethyl acetate). Yield: 383 mg (40%).



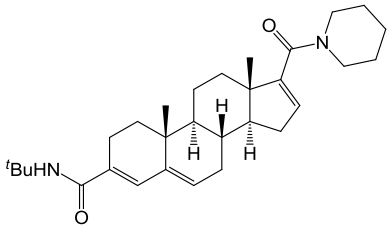
17-Iodo-3-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-3,5,16-triene (**10c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.17 (br s, 1H, 4-CH); 5.97 (br s, 1H, 6-CH); 5.52 (br s, 1H, 16-CH); 3.49 (br s, 4H, $N(CH_2)_2$); 0.71–2.49 (m, 21H, skeleton protons + $(CH_2)_3$ (piperidine); 1.00 (s, 3H, 18-CH_3); 0.78 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.3; 140.7; 137.4; 131.1; 128.4; 126.1; 112.6; 54.9; 50.0; 48.5; ca. 45 (v br, double intensity); 36.1; 35.0; 33.6; 33.4; 31.3; 30.9; 26.2 (br, double intensity); 24.7; 23.8; 20.8; 19.0; 15.2. MS (*m*/*z*/rel.int.): 491/100 (M^+); 407/13; 207/4; 117/7; 91/13. IR (KBr, (cm^{-1})): 1631 (C=O). Analysis calculated for $C_{25}H_{34}ONI$ (M=491.46): C, 61.10; H, 6.97; N, 2.85; Found: C, 61.01; H, 6.85; N, 2.67. R_f = 0.66 ($CHCl_3$/EtOAc = 9/1). Mp. 67–68 °C. Brown crystalline material (crystallized from ethyl acetate). Yield: 374 mg (38%).



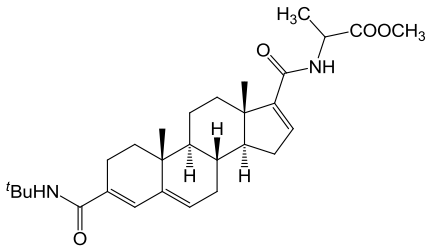
3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-17-iodoandrost-3,5,16-triene (**10f**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.65 (br s, 1H, 4-CH); 6.35 (br s, 1H, 6-CH); 6.17 (br s, 1H, NH); 5.77 (br s, 1H, 16-CH); 4.72 (qi, 7.2 Hz, 1H, NCH); 3.40 (br s, 3H, OCH_3); 1.48 (d, 7.2 Hz, 3H, $CHCH_3$); 0.70–2.65 (m, 15H, skeleton protons); 1.00 (s, 3H, 18-CH_3); 0.96 (s, 3H, 19-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 173.5; 167.5; 167.1; 141.0, 137.4; 134.2; 129.9; 112.5, 59.0; 54.8, 50.0; 48.2; 44.2; 40.2; 34.9; 33.8, 33.4; 31.5; 31.2; 25.6; 21.8; 19.0; 16.7; 15.2. IR (KBr, (cm^{-1})): 1742 (C=O), 1652 (C=O). Analysis calculated for $C_{24}H_{32}ONI$ (M=477.42): C, 60.38; H, 6.76; N, 2.93; Found: C, 60.25; H, 6.70; N, 2.75. R_f = 0.66 ($CHCl_3$/EtOAc = 9/1). Mp. 148–149 °C. Pale brown crystalline material (re-crystallized from ethyl acetate). Yield: 315 mg (33%).



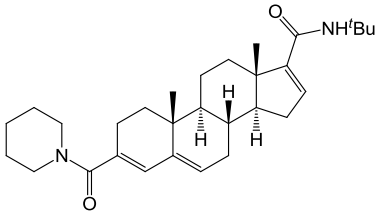
3-(*N*-*tert*-butylcarboxamido)-17-(*N*,*N*-pentan-1,5-diylcarboxamido)-androst-3,5,16-triene (**11c**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.65 (br s, 1H, 4-CH); 5.68 (br s, 2H, 6-CH + NH); 5.54 (br s, 1H, 16-CH); 3.50 (br s, 4H, $N(CH_2)_2$); 0.70–2.40 (m, 21H, skeleton protons + $(CH_2)_3$); 1.34 (s, 9H, ^{t}Bu); 1.06 (s, 3H, 18-CH_3); 0.91 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 167.8; 167.6; 149.0; 141.2; 132.5; 129.7; 129.3; 128.9; 56.8; 51.0; 48.6 (double intensity); 48 (br s); 43 (br s); 34.9; 34.1; 33.5; 32.0; 31.9; 30.1; 28.8 (triple intensity); 26.0 (br s, double intensity); 24.7; 22.0; 20.7; 18.8; 16.7. MS (*m*/*z*/rel.int.): 464/100 (M^+); 393/17; 281/11; 207/19; 112/11; 73/14. IR (KBr, (cm^{-1})): 3352 (NH), 1653 (CON), 1647 (CON). Analysis calculated for $C_{30}H_{44}O_2N_2$ (M=464.64): C, 77.54; H, 9.54; N, 6.03; Found: C, 77.39; H, 9.66; N, 5.91. R_f = 0.28 ($CHCl_3$/EtOAc = 9/1). Mp. 138–139 °C. White crystalline material (re-crystallized from abs. ethanol). Yield: 278 mg (60%).



3-(*N*-*tert*-butylcarboxamido)-17-(*N*-(1-methoxycarbonyl)ethyl-carboxamido)-androst-3,5,16-triene (**11f**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.68 (br s, 1H, 4-CH); 6.37 (br s, 1H, 6-CH); 6.30 (d, 1H, NH); 5.70 (br s, 1H, 16-CH); 5.54 (br s, 1H, NH); 4.62 (qi, 7.2 Hz, 1H, $CHCH_3$); 3.72 (br s, 3H, OCH_3); 0.80–2.43 (m, 15H, skeleton protons); 1.41 (d, 7.2 Hz, 3H, $CHCH_3$); 1.34 (s, 9H, ^{t}Bu); 1.03 (s, 3H, 18-CH_3); 0.91 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.8; 167.7; 165.2; 150.1; 141.3; 136.3; 132.5; 129.8; 128.8; 56.7; 52.4; 51.1; 48.4; 47.7; 46.5; 34.9; 34.6; 33.5; 31.7; 31.6; 30.1; 28.9 (triple intensity); 22.0; 20.8; 18.8; 18.6; 16.4. MS (*m*/z/rel.int.): 482/100 (M^+); 410/20; 281/22; 207/43; 154/30; 73/16. IR (KBr, (cm^{-1})): 3340 (NH), 1766 (COO), 1647 (CON). Analysis calculated for $C_{29}H_{42}O_4N_2$ (M=482.66): C, 72.17; H, 8.77; N, 5.80; Found: C, 72.03; H, 8.91; N, 5.66. R_f = 0.27 ($CHCl_3$/EtOAc = 9/1). Mp. 105–106 °C. White crystalline material (re-crystallized from abs. ethanol). Yield: 347 mg (72%).

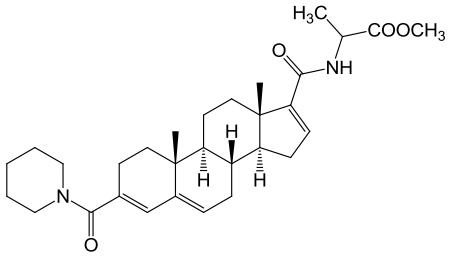


3-(*N*,*N*-pentan-1,5-diylcarboxamido)-17-(*N*-*tert*-butylcarboxamido)androst-3,5,16-triene (**12a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.20 (br s, 1H, 4-CH); 5.97 (br s, 1H, 6-CH); 5.51 (br s, 1H, NH); 5.46 (br s, 1H, 16-CH); 3.50 (br s, 4H, $N(CH_2)_2$); 0.77–2.43 (m, 21H, skeleton protons + $(CH_2)_3$); 1.40 (s, 9H, ^{t}Bu); 1.03 (s, 3H, 18-CH_3); 1.00 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 171.4; 165.6; 151.8; 140.7; 134.0; 131.0; 128.4; 126.1; 56.9; 51.1; 48.5; 46.5; ca. 45 (v br, double intensity); 34.9; 34.7; 33.3; 31.5; 31.4; 30.1; 28.9 (triple intensity); 26.2 (br, double intensity); 24.7; 23.8; 20.7; 19.0; 16.4. MS (*m*/*z*/rel.int.): 464/25 (M^+); 341/37; 281/60; 207/100; 73/46. Analysis calculated for $C_{30}H_{44}O_2N_2$ (M=464.69): C, 77.54; H, 9.54; N, 6.03; Found: C, 77.47; H, 9.67; N, 5.91. R_f = 0.59 ($CHCl_3$/EtOAc = 9/1). Mp. 108–110 °C. White crystalline material (re-crystallized from abs. ethanol). Yield: 335 mg (72%).

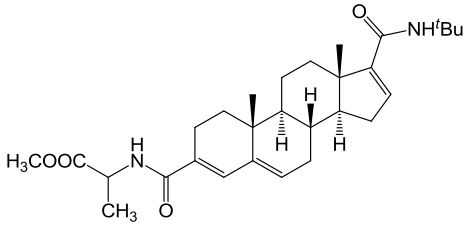


3-(*N*,*N*-pentan-1,5-diylcarboxamido)-17-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-androst-3,5,16-triene (**12f**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.38 (br s, 1H, 16-CH); 6.31 (br d, 1H, NH); 5.49 (br s, 1H, 6-CH); 4.63 (qi, 7.2 Hz, 1H, NCH); 3.72 (br s, 3H, OCH_3); 3.48 (br s, 4H, $N(CH_2)_2$); 1.40 (d, 7.2 Hz, 3H, $CHCH_3$); 0.75–2.40 (m, 21H, skeleton protons + $(CH_2)_3$) (piperidine); 1.03 (s, 3H, 18-CH_3); 0.95 (s, 3H, 19-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.8; 171.3; 165.2; 149.9; 140.6; 136.4; 131.9; 128.5; 126.1; 56.7; 52.4; 48.4; 47.7; 46.4; ca. 43 (v br); 41.1; 34.8; 34.5; 33.3; 31.6; 31.4; 30.0; 26.1 (br, double intensity); 24.6; 23.7; 20.6; 19.0; 18.5; 16.3. IR (KBr, (cm^{-1})): 3419 (NH), 1743 (COO), 1665 (CON). Analysis calculated for $C_{30}H_{42}O_4N_2$ (M=494.67): C, 72.84; H, 8.56; N, 5.66; Found: C, 72.65;

H, 8.63; N, 5.51. R_f = 0.67 ($CHCl_3$/EtOAc = 85/15). Mp. 177–179 °C. White crystalline material (re-crystallized from ethyl acetate). Yield: 345 mg (70%).

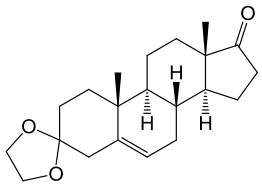


3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-17-(*N*-*tert*-butyl-carboxamido)-androst-3,5,16-triene (**13a**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.78 (br s, 1H, NH); 6.35 (br s, 1H, NH); 6.17 (br s, 1H, 16-CH); 5.70 (br s, 1H, 6-CH); 5.47 (br s, 1H, 4-CH); 4.62 (q, 7.2 Hz; 1H, $CHCH_3$); 3.72 (s, 3H, OCH_3); 1.41 (d, 7.2 Hz; 3H, $CHCH_3$); 0.85–2.42 (m, 15H, skeleton protons); 1.30 (s, 9H, ^{t}Bu); 0.99 (s, 3H, 19-CH_3); 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 173.8; 167.3; 165.5; 151.6; 141.0; 134.1; 131.9; 129.9; 127.6; 56.6; 52.4; 51.0; 48.2; 48.0; 46.4; 34.8; 34.5; 33.2; 31.7; 31.3; 29.9; 28.8 (triple intensity); 21.6; 20.6; 18.8; 18.4; 16.3. MS (*m*/z/rel.int.): 482/75 (M^+), 410/10, 364/100. IR (KBr, (cm^{-1})): 3393 (NH), 1745 (COO), 1664 (CON). Analysis calculated for $C_{29}H_{44}O_4N_2$ (M=482.66): C, 72.17; H, 8.77; N, 5.80; Found: C, 72.05; H, 8.89; N, 5.61. R_f = 0.54 ($CHCl_3$/EtOAc = 9/1). Mp. 137–139 °C. White crystalline material (re-crystallized from ethyl acetate). Yield: 337 mg (70%).

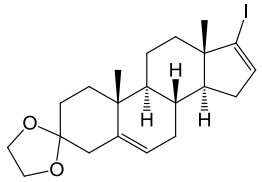


Androst-5-ene-17-one-3-ethylene ketal (**15**): ^{1}H NMR ($CDCl_3$, 400 MHz): 5.35 (br s, 1H, 6-CH); 3.85–3.95 (m, 4H, $O(CH_2)_2O$); 0.98–2.56 (m, 19H, skeleton protons); 1.02 (s, 3H, 19-CH_3); 0.85 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 220.9; 140.4; 121.3; 109.3; 64.4; 64.2; 51.8; 49.9; 47.5; 41.8; 36.8; 36.3; 35.8; 31.5; 31.4; 31.0; 30.7; 21.9; 20.3; 18.9; 13.5. MS (*m*/z/rel.int.): 330/3 (M^+), 99/100. IR (KBr, (cm^{-1})): 1738 (C=O). Analysis calculated for $C_{21}H_{30}O_3$ (M=330.47): C, 76.33; H, 9.15; Found: C, 76.42; H, 9.41. R_f = 0.79 (petroleum ether (40–70 °C)/EtOAc = 75/25).

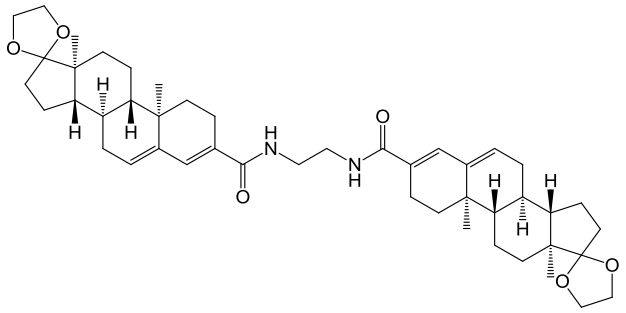
Mp. 195–197 °C. White powder-like material (as obtained after column chromatography). Yield: 1.76 g (40%).



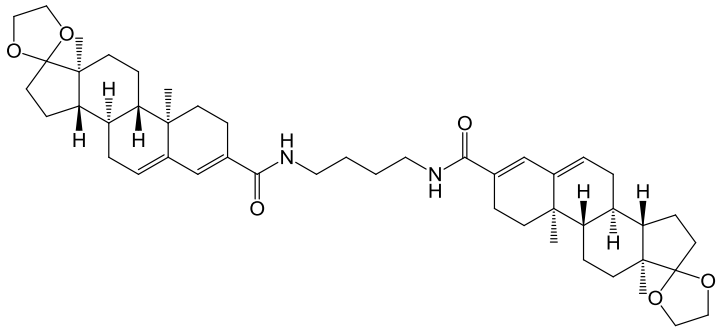
17-Iodo-androst-5,16-diene-3-ethylene ketal (**17**): ^{1}H NMR ($CDCl_3$, 400 MHz): 6.12 (br s, 1H, 16-CH); 5.35 (br s, 1H, 6-CH); 3.88–3.97 (m, 4H, $O(CH_2)_2O$); 2.53–2.60 (m, 2H, 4-CH_2); 0.80–2.18 (m, 15H, skeleton protons); 1.05 (s, 3H, 19-CH_3); 0.75 (s, 3H, 18-CH_3); ^{13}C NMR (100.58 MHz, $CDCl_3$): 140.6; 137.5; 121.6; 112.7; 109.4; 64.4; 64.2; 54.8; 50.1; 49.9; 41.8; 36.9; 36.2; 36.1; 33.7; 31.1; 31.0 (double intensity); 20.8; 18.8; 15.1. MS (*m*/z/rel.int.): 440/5 (M^+), 99/100, 55/8. IR (KBr, (cm^{-1})): 1577 (C=C). Analysis calculated for $C_{21}H_{29}O_2I$ (M=440.36): C, 57.28; H, 6.64; Found: C, 57.01; H, 6.80. Mp. 183–186 °C. Pale yellow crystalline material. Yield: 1.54 g (35%).



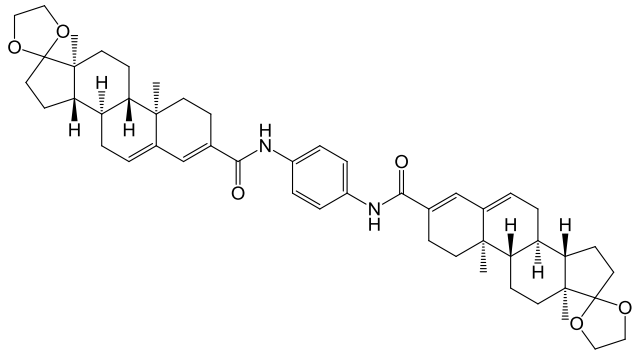
3-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-diandrost-3,5-diene-17-ethylene ketal (**21a**): ^{1}H NMR ($CDCl_3$, 500 MHz): 7.01 (br s, 2H, NH); 6.79 (br s, 2H, 4-CH); 5.71 (br s, 2H, 6-CH); 3.75-3.98 (m, 8H, OCH_2CH_2O); 3.49 (br s, 4H, NCH_aH_b); 0.76-2.52 (m, 34H, skeleton protons); 0.87 (s, 6H, 19-CH_3); 0.85 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 169.5; 140.9; 134.3; 130.2; 127.7; 119.3; 65.2; 64.5; 50.7; 47.9; 45.9; 40.4; 34.7; 34.2; 33.5; 32.0; 31.6; 30.5; 22.6; 21.8; 20.5; 18.9; 14.3. IR (KBr, (cm^{-1})): 3373 (v br, NH); 1724 (CON); 1682 (C=C). MS (*m*/z/rel.int.): 741.846 $[M+H]^+$. R_f = 0.27 (EtOAc/$CHCl_3$ = 7/3). Mp. 158-160 °C. Brown crystalline material. Yield: 156 mg (42%).



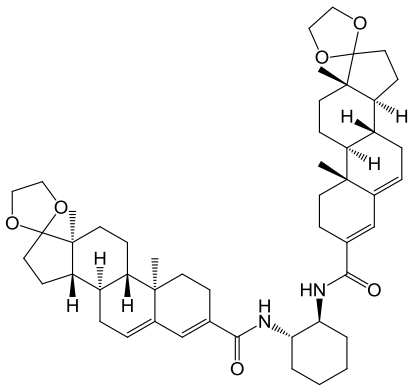
3-(*N,N'*-(butane-1,4-diyl)-carboxamido)-diandrost-3,5-diene-17-ethylene ketal (**21b**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.78 (br s, 2H, 4-CH); 6.20 (br s, 2H, NH); 5.73 (br s, 2H, 6-CH); 3.75-4.02 (m, 8H, OCH_2CH_2O); 3.36 (br s, 4H, $NCH_2CH_2CH_2CH_2N$); 0.54-2.69 (m, 38H, skeleton protons + $NCH_2CH_2CH_2CH_2N$); 0.90 (s, 6H, 19-CH_3); 0.89 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 168.6; 140.1; 132.5; 129.3; 125.0; 119.3; 65.2; 64.5; 50.7; 47.9; 45.9; 39.2; 34.8; 34.2; 33.4; 32.0; 31.6; 30.5; 27.0; 22.6; 21.9; 20.5; 18.9; 14.2. IR (KBr, (cm^{-1})): 3387 (v br, NH); 1738 (CON); 1641 (C=C). MS (*m*/*z*/rel.int.): 769.745 $[M+H]^+$. R_f = 0.32 (EtOAc/$CHCl_3$ = 7/3). Mp. 106-108 °C. Yellow crystalline material. Yield: 60 mg (16%).



3-(*N,N'*-(1,4-phenylene)-carboxamido)-diandrost-3,5-diene-17-ethylene ketal (**21c**): ^{1}H NMR ($CDCl_3$, 500 MHz): 7.53 (br s, 4H, aromatic H); 7.51 (br s, 2H, NH); 6.88 (br s, 2H, 4-CH); 5.81 (br s, 2H, 6-CH); 3.78-4.01 (m, 8H, OCH_2CH_2O); 0.68-2.61 (m, 34H, skeleton protons); 0.96 (s, 6H, 19-CH_3); 0.92 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 166.3; 148.4; 140.8; 134.3; 130.8; 120.7 (double intensity); 119.3; 114.4; 65.2; 64.6; 50.7; 47.9; 45.9; 37.4; 34.8; 34.2; 33.5; 32.0; 30.5; 22.7; 22.0; 20.6; 19.0; 14.3. IR (KBr, (cm^{-1})): 3346 (v br, NH); 1662 (CON); 1612 (C=C). MS (*m*/*z*/rel.int.): 789.814 $[M+H]^+$. R_f = 0.79 (EtOAc/$CHCl_3$ = 6/4). Mp. 245-247 °C. Off-white crystalline material. Yield: 119 mg (20%).

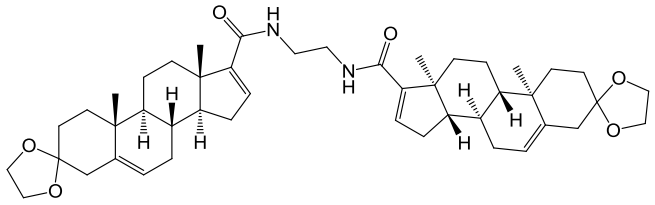


3-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-diandrost-3,5-diene-17-ethylene ketal (**21d**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.71 (br s, 2H, 4-CH); 6.35 (br s, 2H, NH); 5.69 (br s, 2H, 6-CH); 3.84-4.05 (m, 8H, OCH_2CH_2O); 3.80 (br s, 2H, NCH); 0.64-2.52 (m, 42H, skeleton protons + NCHCH_aH_bCH_2CH_2CH_aH_bCHN); 0.87 (s, 6H, 19-CH_3); 0.84 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 168.9; 140.8; 133.9; 129.9; 128.1; 119.4; 65.2; 64.6; 54.7; 54.1; 50.7; 49.8; 47.9; 45.9; 37.3; 34.7; 34.2; 32.0; 31.6; 30.5; 24.9; 22.6; 20.5; 18.8; 14.3. IR (KBr, (cm^{-1})): 3346 (v br, NH); 1660 (CON); 1533 (C=C). MS (*m*/*z*/rel.int.): 795.856 $[M+H]^+$. R_f = 0.69 (EtOAc/$CHCl_3$ = 6/4). Mp. 159-161 °C. Light brown crystalline material. Yield: 158 mg (40%).

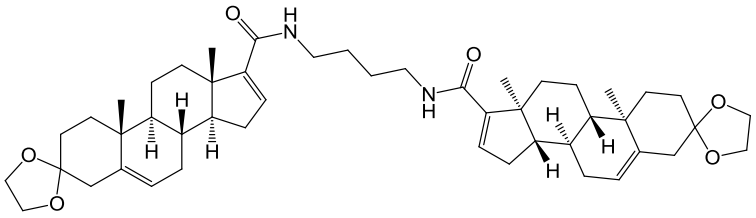


17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-diandrost-5,16-diene-3-ethylene ketal (**22a**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.50 (br s, 2H, NH); 6.33 (br s, 2H, 16-CH); 5.37 (br s, 2H, 6-CH); 3.89-4.01 (m, 8H, OCH_2CH_2O); 3.40-3.55 (d, 4H, NCH_aH_b); 0.80-2.63 (m, 34H, skeleton protons); 1.07 (s, 6H, 19-CH_3); 1.00 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 167.2; 150.1; 140.6; 136.2; 121.6; 109.4; 64.4; 64.2; 56.7; 50.1; 46.4; 41.8; 39.8; 36.8; 36.3; 34.7; 31.8; 31.3; 31.0; 30.2; 20.7; 18.8; 16.3. IR (KBr, (cm^{-1})): 3333 (v br, NH); 1645 (CON); 1594 (C=C). MS (*m*/*z*/rel.int.): 741.872 $[M+H]^+$.

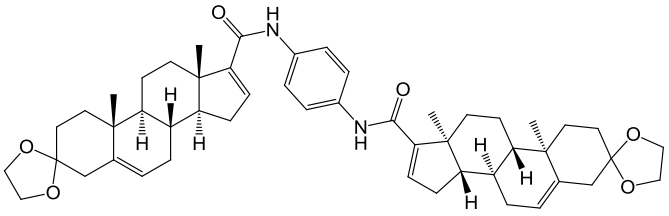
R_f = 0.23 (EtOAc/$CHCl_3$ = 6/4). Mp. 245-247 °C. Beige crystalline material. Yield: 182 mg (49%).



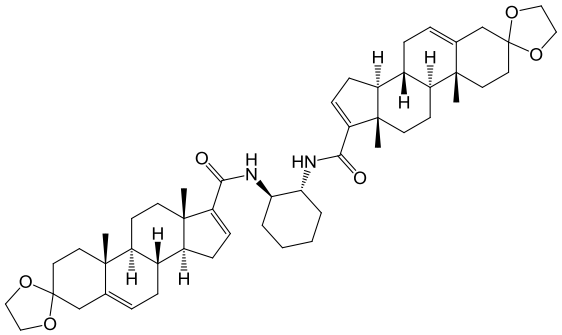
17-(*N,N'*-(butane-1,4-diyl)-carboxamido)-diandrost-5,16-diene-3-ethylene ketal (**22b**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.33 (br s, 2H, 16-CH); 5.91 (br s, 2H, NH); 5.38 (br s, 2H, 6-CH); 3.89-4.03 (m, 8H, OCH_2CH_2O); 3.35 (br s, 4H, $NCH_2CH_2CH_2CH_2N$); 0.80-2.65 (m, 38H, skeleton protons + $NCH_2CH_2CH_2CH_2N$); 1.09 (s, 6H, 19-CH_3); 1.04 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 166.3; 150.6; 140.6; 135.3; 121.6; 109.4; 64.4; 64.2; 56.7; 50.1; 46.4; 41.8; 38.6; 36.8; 36.2; 34.7; 31.7; 31.3; 31.0; 30.2; 26.7; 20.7; 18.8; 16.3. IR (KBr, (cm^{-1})): 3312 (v br, NH); 1646 (CON); 1598 (C=C). MS (*m*/*z*/rel.int.): 769.768 $[M+H]^+$. R_f = 0.28 ($CHCl_3$/EtOAc = 1/1). Mp. 178-180 °C. Off-white crystalline material. Yield: 245 mg (32%).



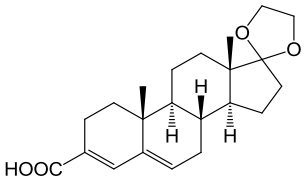
17-(*N,N'*-(1,4-phenylene)-carboxamido)-diandrost-5,16-diene-3-ethylene ketal (**22c**): ^{1}H NMR ($CDCl_3$, 500 MHz): 7.51 (br s, 4H, aromatic H); 7.47 (br s, 2H, NH); 6.46 (br s, 2H, 16-CH); 5.39 (br s, 2H, 6-CH); 3.91-4.03 (m, 8H, OCH_2CH_2O); 0.85-2.64 (m, 34H, skeleton protons); 1.10 (s, 6H, 19-CH_3); 1.09 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 163.9; 151.1; 140.7; 136.3; 134.2; 121.6; 120.3 (double intensity); 109.4; 64.4; 64.2; 56.7; 50.1; 46.8; 41.8; 36.8; 36.2; 34.7; 32.0; 31.3; 31.0; 30.2; 20.7; 18.8; 16.4. IR (KBr, (cm^{-1})): 3418 (v br, NH); 1664 (CON); 1595 (C=C). MS (*m*/*z*/rel.int.): 789.676 $[M+H]^+$. R_f = 0.63 ($CHCl_3$/EtOAc = 7/3). Mp. >260 °C. Light brown crystalline material. Yield: 103 mg (26%).



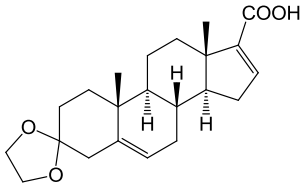
17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-diandrost-5,16-diene-3-ethylene ketal (**22d**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.18 (br s, 2H, 16-CH); 6.13 (br s, 2H, NH); 5.32 (br s, 2H, 6-CH); 3.86-3.98 (m, 8H, OCH_2CH_2O); 3.76 (br s, 2H, NCH); 0.75-2.59 (m, 42H, skeleton protons + NCHCH_aH_bCH_2CH_2C$H_a$$H_b$CHN); 1.03 (s, 6H, 19-$CH_3$); 0.92 (s, 6H, 18-$CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$): 166.5; 150.3; 140.6; 135.5; 121.6; 109.4; 64.4; 64.2; 56.5; 53.2; 50.1; 46.5; 41.8; 36.8; 36.2; 34.4; 32.4; 31.8; 31.3; 31.0; 30.1; 24.9; 20.7; 18.8; 16.3. IR (KBr, (cm^{-1})): 3335 (v br, NH); 1641 (CON); 1590 (C=C). MS (*m*/*z*/rel.int.): 795.777 $[M+H]^+$. R_f = 0.89 ($CHCl_3$/EtOAc = 6/4). Mp. 163-165 °C. Beige crystalline material. Yield: 242 mg (61%).



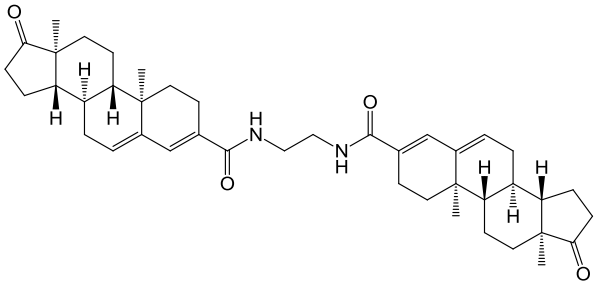
Androst-3,5-diene-17-ethylene ketal-3-carboxylic acid (**23**): ^{1}H NMR (500 MHz, $CDCl_3$): 7.21 (br s, 1H, 4-CH); 5.73 (br s, 1H, 6-CH); 3.68-3.90 (m, 4H, OCH_2CH_2O); 0.85-2.52 (m, 17H, skeleton protons); 0.91 (s, 3H, 19-CH_3); 0.86 (s, 3H, 18-CH_3), ^{13}C NMR (125.7 MHz, $CDCl_3$): 173.2; 141.2; 140.6; 132.9; 124.9; 119.1; 65.1; 64.6; 50.6; 47.8; 45.8; 34.7; 34.1; 33.3; 31.9; 31.8; 30.4; 22.6; 21.4; 20.4; 19.0; 14.3. IR (KBr (cm^{-1})): *ca*. 3200-2350 (v br, COOH (H-bonded); 1679 (C=O); 1631; 1612 (C=C). MS (*m*/z/rel.int.): 359.416 $[M+H]^+$. Analysis calculated for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; Found: C, 73.89; H, 8.74. R_f = 0.51 ($CHCl_3$/EtOAc = 7/3). Mp. 88-89 °C. White solid material. Yield: 154 mg (43%).



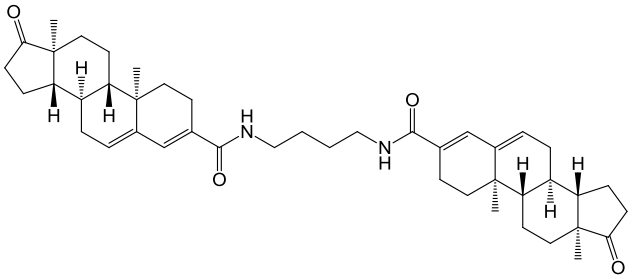
Androst-5,16-diene-3-ethylene ketal-17-carboxylic acid (**24**): ^{1}H NMR (500 MHz, $CDCl_3$): 6.93 (br s, 1H, 16-CH); 5.39 (br s, 1H, 6-CH); 3.91-4.03 (m, 4H, OCH_2CH_2O); 0.75-2.65 (m, 17H, skeleton protons); 1.09 (s, 3H, 19-CH_3); 0.98 (s, 3H, 18-CH_3), ^{13}C NMR (125.7 MHz, $CDCl_3$): 146.3; 140.7; 132.1; 128.5; 121.6; 109.4; 64.4; 64.2; 56.6; 50.1; 45.6; 41.8; 36.8; 36.2; 34.6; 32.2; 31.3; 31.0; 30.3; 20.6; 18.8; 15.8. IR (KBr (cm^{-1})): *ca*. 3350-3000 (v br, COOH (H-bonded); 1715 (C=O); 1643; 1605 (C=C). MS (*m*/*z*/rel.int.): 359.295 $[M+H]^+$. R_f = 0.30 ($CHCl_3$/EtOAc = 9/1). Mp. >260 °C. White crystalline material. Yield: 207 mg (54%).



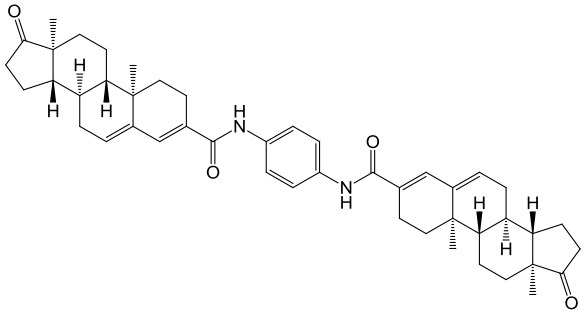
3-(*N*,*N*'-(ethane-1,2-diyl)-carboxamido)-diandrost-3,5-diene-17-one (**25a**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.86 (br s, 2H, 4-CH); 6.69 (br s, 2H, NH); 5.80 (br s, 2H, 6-CH); 3.34-3.77 (d, 4H, NCH_aH_b); 0.71-2.71 (m, 34H, skeleton protons); 0.95 (s, 6H, 19-CH_3); 0.94 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 198.7; 169.3; 141.1; 134.0; 129.4; 128.0; 53.9; 51.9; 48.2; 47.7; 40.7; 35.8; 34.9; 33.5; 31.4; 31.1; 29.7; 21.8; 20.4; 18.9; 13.7. IR (KBr, (cm^{-1})): 3397 (v br, NH); 1735 (C=O); 1653 (CON); 1539 (C=C). MS (*m*/*z*/rel.int.): 653.673 $[M+H]^+$. R_f = 0.17 (EtOAc/$CHCl_3$ = 8/2). Mp. 143-145 °C. Off-white crystalline material. Yield: 29 mg (23%).



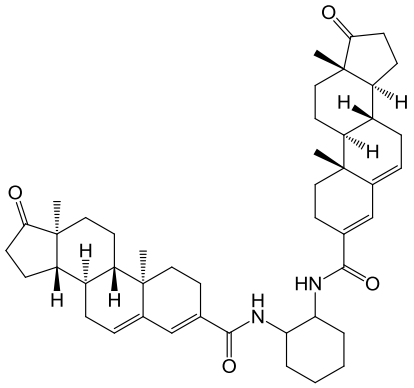
3-(*N,N'*-(butane-1,4-diyl)-carboxamido)-diandrost-3,5-diene-17-one (**25b**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.82 (br s, 2H, 4-CH); 6.16 (br s, 2H, NH); 5.79 (br s, 2H, 6-CH); 3.40 (br s, 4H, $NCH_2CH_2CH_2CH_2N$); 0.55-2.67 (m, 38H, skeleton protons + $NCH_2CH_2CH_2CH_2N$); 0.94 (s, 6H, 19-CH_3); 0.90 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 198.7; 168.4; 155.1; 147.1; 133.5; 129.2; 51.9; 48.2; 47.7; 35.8; 34.9; 31.9; 31.4; 31.1; 29.7; 27.1; 22.7; 21.8; 20.4; 19.0; 14.1; 13.7. IR (KBr, (cm^{-1})): 3412 (v br, NH); 1735 (C=O); 1654 (CON); 1628 (C=C). MS (*m*/*z*/rel.int.): 681.693 $[M+H]^+$. R_f = 0.26 (EtOAc/$CHCl_3$ = 8/2). Mp. 119-121 °C. Off-white crystalline material. Yield: 6 mg (8%).



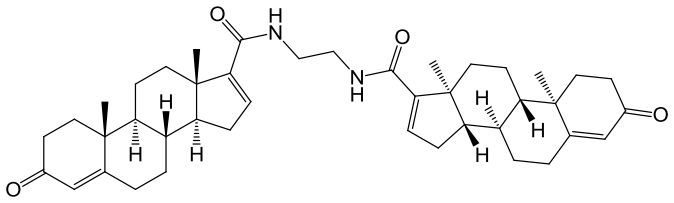
3-(*N,N'*-(1,4-phenylene)-carboxamido)-diandrost-3,5-diene-17-one (**25c**): ^{1}H NMR ($CDCl_3$, 500 MHz): 7.57 (br s, 4H, aromatic H); 7.54 (br s, 2H, NH); 6.91 (br s, 2H, 4-CH); 5.77 (br s, 2H, 6-CH); 0.65-2.65 (m, 34H, skeleton protons); 1.00 (s, 6H, 19-CH_3); 0.95 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 199.2; 166.1; 141.0; 134.4; 131.8; 124.2; 120.6 (double intensity); 114.8; 53.9; 51.8; 50.9; 48.2; 47.7; 35.8; 35.2; 33.4; 31.5; 21.8; 20.4; 19.0; 17.4; 13.7. IR (KBr, (cm^{-1})): 3447 (v br, NH); 1738 (C=O); 1637 (CON); 1608 (C=C). MS (*m*/*z*/rel.int.): 701.727 $[M+H]^+$. R_f = 0.73 ($CHCl_3$/EtOAc = 6/4). Mp. 131-133 °C. Yellow crystalline material. Yield: 30 mg (44%).



3-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-diandrost-3,5-diene-17-one (**25d**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.77 (br s, 2H, 4-CH); 6.32 (br s, 2H, NH); 5.75 (br s, 2H, 6-CH); 3.79 (br s, 2H, NCH); 0.57-2.72 (m, 42H, skeleton protons + NCHCH_aH_bCH_2CH_2CH_aH_bCHN); 0.93 (s, 6H, 19-CH_3); 0.90 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 198.7; 168.9; 141.1; 133.6; 132.0; 128.5; 53.9; 51.9; 48.2; 48.1; 45.3; 36.9; 35.8; 34.9; 31.9; 31.7; 31.1; 29.7; 29.3; 24.8; 21.8; 21.0; 13.7. IR (KBr, (cm^{-1})): 3392 (v br, NH); 1738 (C=O); 1653 (CON); 1539 (C=C). MS (*m*/*z*/rel.int.): 707.775 $[M+H]^+$. R_f = 0.45 ($CHCl_3$/EtOAc = 6/4). Mp. 129-131 °C. Yellow crystalline material. Yield: 14 mg (20%).

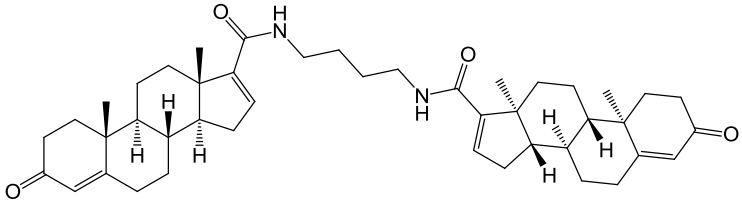


17-(*N,N'*-(ethane-1,2-diyl)-carboxamido)-diandrost-4,16-diene-3-one (**26a**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.64 (br s, 2H, NH); 6.31 (br s, 2H, 16-CH); 5.73 (br s, 2H, 4-CH); 3.35-3.58 (d, 4H, NCH_aH_b); 0.75-2.60 (m, 34H, skeleton protons); 1.21 (s, 6H, 19-CH_3); 1.00 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 199.6; 171.1; 167.0; 149.9; 135.8; 123.9; 55.9; 54.1; 46.4; 39.8; 38.7; 35.6; 34.4; 33.9; 33.8; 32.7; 31.8; 31.7; 20.8; 17.2; 16.3. IR (KBr, (cm^{-1})): 3372 (v br, NH); 1734 (C=O); 1654 (CON); 1592 (C=C). MS (*m*/*z*/rel.int.): 653.607 $[M+H]^+$. R_f = 0.24 (EtOAc/$CHCl_3$ = 8/2). Mp. 127-129 °C. Off-white crystalline material. Yield: 53 mg (43%).

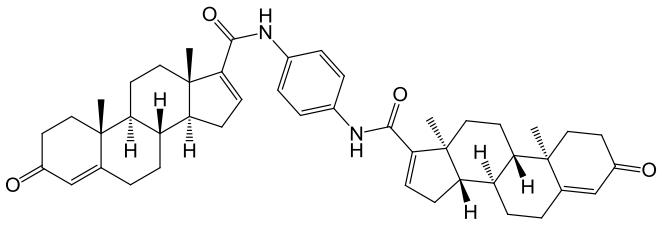


17-(*N,N'*-(butane-1,4-diyl)-carboxamido)-diandrost-4,16-diene-3-one (**26b**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.28 (br s, 2H, 16-CH); 6.12 (br s, 2H, NH); 5.72 (br s, 2H, 4-CH); 3.30 (br s, 4H, NCH_2CH_2CH_2CH_2N); 0.78-2.52 (m, 38H, skeleton protons +

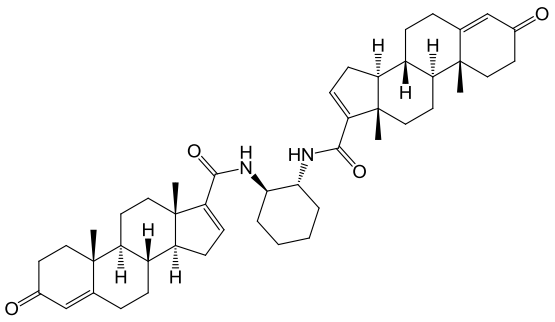
$NCH_2CH_2CH_2CH_2N$); 1.21 (s, 6H, 19-CH_3); 1.02 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 199.6; 171.1; 166.1; 150.4; 134.8; 123.9; 55.9; 54.1; 46.5; 38.7; 38.6; 35.5; 34.5; 33.9; 33.8; 32.7; 31.8; 31.6; 27.0; 20.8; 17.2; 16.4. IR (KBr, (cm^{-1})): 3356 (v br, NH); 1674 (CON); 1662 (C=O); 1591 (C=C). MS (*m*/*z*/rel.int.): 681.684 $[M+H]^+$. R_f = 0.20 (EtOAc/$CHCl_3$ = 7/3). Mp. 124-126 °C. Off-white crystalline material. Yield: 82 mg (77%).



17-(*N,N'*-(1,4-phenylene)-carboxamido)-diandrost-4,16-diene-3-one (**26c**): ^{1}H NMR ($CDCl_3$, 500 MHz): 7.54 (br s, 4H, aromatic H); 7.45 (br s, 2H, NH); 6.44 (br s, 2H, 16-CH); 5.77 (br s, 2H, 4-CH); 0.98-2.53 (m, 34H, skeleton protons); 1.25 (s, 6H, 19-CH_3); 1.13 (s, 6H, 18-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): 199.5; 170.8; 163.6; 151.0; 135.7; 134.1; 124.0; 120.3 (double intensity); 55.9; 54.1; 46.8; 38.7; 35.6; 34.4; 34.0; 33.9; 32.7; 31.9; 31.8; 20.8; 17.2; 16.4. IR (KBr, (cm^{-1})): 3353 (v br, NH); 1663 (C=O); 1614 (C=C). MS (*m*/*z*/rel.int.): 701.663 $[M+H]^+$. R_f = 0.34 ($CHCl_3$/EtOAc = 6/4). Mp. 181-183 °C. Light brown crystalline material. Yield: 48 mg (73%).



17-(*N,N'*-(cyclohexane-(1*S*,2*S*)-diyl)-carboxamido)-diandrost-4,16-diene-3-one (**26d**): ^{1}H NMR ($CDCl_3$, 500 MHz): 6.18 (br s, 2H, 16-CH); 6.17 (br s, 2H, NH); 5.59 (br s, 2H, 4-CH); 3.73 (br s, 2H, NCH); 0.87-2.44 (m, 42H, skeleton protons + $NCHCH_aH_bCH_2CH_2CH_aH_bCHN$); 1.18 (s, 6H, 19-$CH_3$); 0.94 (s, 6H, 18-$CH_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$): 199.5; 171.0; 166.3; 150.0; 135.2; 123.9; 55.7; 54.1; 53.3; 46.5; 38.7; 35.5; 34.2; 33.9; 33.8; 32.7; 32.4; 31.7; 31.6; 24.9; 20.7; 17.2; 16.3. IR (KBr, (cm^{-1})): 3334 (v br, NH); 1675 (C=O); 1643 (CON); 1616 (C=C). MS (*m*/*z*/rel.int.): 707.647 $[M+H]^+$. R_f = 0.11 ($CHCl_3$/EtOAc = 8/2). Mp. 175-177 °C. Beige crystalline material. Yield: 125 mg (68%).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7. Summary

In my doctoral studies, the systematic investigation of the formation of mono- and dicarboxamides *via* palladium-catalyzed aminocarbonylation has been carried out. Androst-4-ene-3,17-dione has been used as starting material and transformed to the carboxamides using high-yielding conventional synthetic reactions and aminocarbonylation in the presence of various nucleophiles.

The most important results are summarized below.

- Using an improved Barton's methodology, *i.e.*, the ketone–hydrazone–iodoalkene reaction sequence, steroidal iodoalkene substrates were synthesized.
- The compounds possessing 3-iodo-3,5-diene or 17-iodo-16-ene moiety were aminocarbonylated at atmospheric carbon monoxide pressure in the presence of various primary or secondary monoamines as *N*-nucleophiles using a Pd(0) catalyst formed *in situ* from palladium(II) acetate and triphenylphosphine. The systematic investigation has shown that the appropriate use of conventional and highly selective homogeneous aminocarbonylation enables the synthesis of all possible variations of homo- and mixed 3,17-diamides.
- 3-Iodo-3,5-diene-17-ethylene ketal or 17-iodo-16-ene-3-ethylene ketal derivatives were aminocarbonylated at high carbon monoxide pressure in the presence of various diamines to give 'dimeric' steroids containing dicarboxamide spacers.
- Various 'mixed dicarboxamides' and 'dimeric' steroids containing dicarboxamide spacers with possible 5α-reductase inhibitor properties were synthesized and fully characterized.
- Altogether 40 novel steroidal compounds including 3-iodo-androst-3,5-diene-17-ethylene ketal, 3-iodo-androst-2,4-diene-17-ethylene ketal, 17-iodo-androst-5,16-diene-17-ethylene ketal, 17-iodo-androst-3,5,16-triene-3-carboxamide intermediates and hetero-3,17-dicarboxamido-androst-3,5,16-triene, 3-carboxamido-diandrost-3,5-diene-17-one, 17-carboxamido-diandrost-4,16-diene-17-one target compounds were synthesized and fully characterized.

8. List of schemes

Scheme 44. A carbonylation reaction of 4-bromophenyl-*C*-ribonucleoside.

Scheme 45. Aminocarbonylation of bromoarene substrate using bis(di-*tert*-butylphosphino)-*o*-xylene as ligand.

Scheme 46. Synthesis of (*R*)-ethyl-2-phenyl-2-(pyrimidine-5-carboxamido)-acetate.

Scheme 47. A palladium-catalyzed reaction of a 6-iodo-1,1'-binaphthyl derivative.

Scheme 48. Synthesis of an *N*-arylbenzamide derivative.

Scheme 49. An aminocarbonylation of iodo-cyclohexenetetraol derivative using *L*-alanine methyl ester as *N*-nucleophile.

Scheme 50. Aminocarbonylation of an enyne using a diamine.

Scheme 51. Synthesis of a 3-[(dialkylcarbamoyl)methylene]isoindolin-1-one derivative *via* oxidative carbonylation.

Scheme 52. An aminocarbonylation reaction of 1-iodo-1,7-dicarba-*closo*-dodecaborane.

Scheme 53. Synthesis of a 2-arylbenzoxazole derivative in a one-pot process.

Scheme 54. An aminocarbonylation of an aryl iodide derivative using aqueous ammonia.

Scheme 55. Palladium-catalyzed aminocarbonylation with diethylamine as *N*-nucleophile.

Scheme 56. The transformation of the 3,17-bis-triflyloxy-estra-1,3,5(10),16-tetraene.

Scheme 57. Synthesis of steroidal crown ethers.

Scheme 58. A practical synthesis of 3-substituted $\Delta^{3,5}$-steroid derivatives.

Scheme 59. A palladium-catalyzed carbonylative route to a primary amide.

Scheme 60. Hydrazinocarbonylation of a 17-iodo-16-ene derivative with benzoylhydrazide.

Scheme 61. Synthesis of a 17-carboxamido-13α-estra-1,3,5(10),16-tetraene.

Scheme 62. Synthesis of a 17-carboxamido-3β-hydroxy-13α-androst-5,16-diene.

Scheme 63. Synthesis of a ferrocene-labeled steroidal 17-carboxamide.

Scheme 64. Synthesis of steroid-β-lactam conjugates.

Scheme 65. Synthesis of a steroid dimer containing dicarboxamide spacer.

Scheme 66. Synthesis of a 12-substituted spirostene derivative *via* carbonylation reaction.

Scheme 67. Synthesis of an 11-substituted androstane.

Scheme 68. A palladium-catalyzed carbonylation reaction in the presence of a ferrocenyl chalcone derivative.

Scheme 69. Synthesis of novel 13β- and 13α-D-homo steroids.

Scheme 70. Synthesis of 13α-18-nor-16-carboxamido derivatives.

Scheme 71. The reaction of the Torgov reagent with the silyl enol ether.

Scheme 72. Synthesis of a steroidal benzo[*b*][1,4]thiazepine derivative.

Scheme 73. Bi(III)-catalyzed 'backbone' rearrangement of a 5β,6β;16α,17α-diepoxysteroid.

Scheme 74. Synthesis of an 11,12-aziridino derivative as a neuroactive steroid analogue.

Scheme 75. Synthesis of an epoxidal α-and β-stereoisomer from a Δ^5-steroid.

Scheme 76. Allylic oxidation of the 3β-acetoxylanost-8-en-25-ol.

Scheme 77. Titanium(IV) reductive amination of 5-cholesten-3-one using 1,3-diaminopropane.

Scheme 78. Synthesis of 3,17-dihydrazone-androst-4-ene.

Scheme 79. Synthesis of 3,17-diiodo-androstene derivatives.

Scheme 80. Synthesis of the 3,17-dicarboxamido-androstene derivatives *via* aminocarbonylation.

Scheme 81. Synthesis of the androst-4-ene-3-one-17-ethylene ketal.

Scheme 82. Synthesis of the 3-iodo-androst-3,5-diene-17-ethylene ketal (and the corresponding 2,4-diene) derivatives.

Scheme 83. Synthesis of 3-carboxamido-androst-3,5-diene-17-ethylene ketal (and the corresponding 2,4-diene) derivatives.

Scheme 84. Synthesis of 3-carboxamido-androst-3,5-diene-17-ones (and the corresponding androst-2,4-diene-17-ones).

Scheme 85. Transformation of the 3-(*N*-*tert*-butylcarboxamido)-17-one derivative.

Scheme 86. Transformation of the 3-(*N*,*N*-pentan-1,5-diylcarboxamido)-17-one derivative.

Scheme 87. Transformation of the 3-(*N*-(1-methoxycarbonyl)ethylcarboxamido)-17-one derivative.

Scheme 88. Synthesis of androst-5-ene-17-one-3-ethylene ketal.

Scheme 89. Synthesis of 17-iodo-androst-5,16-diene-3-ethylene ketal.

Scheme 90. Synthesis of 17-carboxamido-androst-4,16-dien-3-ones.

Scheme 91. Synthesis of 3,17-dicarboxamido-androst-3,5,16-triene derivatives through 17-*N*-*tert*-butylcarboxamido-3-iodoandrost-3,5,16-triene as key-intermediate.

Scheme 92. Synthesis of various 'dimeric' steroids containing 3,3'-dicarboxamide spacers.

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Publications

Related to the PhD thesis:

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   A systematic approach to the synthesis of androstane-based 3,17-dicarboxamides (homo- and mixed dicarboxamides) *via* palladium-catalyzed aminocarbonylation.
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4. **Mercédesz Kiss**, Sándor Mahó, Katalin Böddi, Borbála Boros, László Kollár:
   Palladium-catalyzed diaminocarbonylation. Synthesis of androstene dimers containing 3,3'- or 17,17'-dicarboxamide spacers.
   Monatsh. Chem. **2015**, *146*, 357-364. **IF: 1.347**

5. Rui M. B. Carrilho, Ana R. Almeida, **Mercédesz Kiss**, László Kollár, Rita Skoda-Földes, Janusz M. Dąbrowski, Maria José S. M. Moreno, Mariette M. Pereira:
   One-step synthesis of dicarboxamides *via* Pd-catalysed aminocarbonylation using diamines as *N*-nucleophiles. **IF: 3.154**
   Eur. J. Org. Chem. (Accepted for publication)

6. Attila Takács, **Mercédesz Kiss**, László Kollár:
   Highly selective synthesis of carboxamides *via* transition metal catalysed aminocarbonylation.
   Curr. Green Chem. (Accepted for publication)

Conferences

List of conference presentations:

Poster:

Noémi Pálinkás, Péter Ács, Attila Takács, **Mercédesz Kiss**, Sándor Mahó, László Kollár:
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A systematic approach to the synthesis of androstane-based 3,17-dicarboxamides and steroid dimers containing 17,17'-dicarboxamide spacers *via* palladium-catalyzed aminocarbonylation
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