Polish J. Chem., **76**, 1053–1084 (2002) **REVIEW ARTICLE**

Palladium Complexes in Carbohydrate Synthesis*

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The survey reports the results achieved in carbohydrate synthesis by application of organopalladium complexes. Most remarkable results have been noted in C-glycoside synthesis and in the chemistry of unsaturated sugars. In the majority of cases high regio- and stereoselectivity of transformations is observed. Many palladium catalysts with different organic ligands have been employed. The literature up to the end of 2001 is reviewed.

Key words: palladium(0) complexes, palladium(II) complexes, π-allylic palladium complexes, C-glycosides, annulation, Heck reaction, Stille reaction

Palladium compounds have found important applications in carbohydrate chemistry for the synthesis of C-glycosides, C-nucleosides, C- and N-substituted derivatives. Interesting bi- and tri-cyclic structures can be obtained using Pd complexes. In the majority of cases the reactions are highly stereo- and regio-selective. Simple palladium compounds are also successfully used as catalysts in many useful transformations of carbohydrates as *e.g.* substitution, oxidation, etherification. The description of the results achieved is divided into five Sections dealing with the exploitation of the Heck reaction, reactions of π-allylic systems, annulation reactions, the Stille reaction, and miscellaneous reactions. The literature up to the end of 2001 is reviewed. In recent years a number of articles dealing with the application of transition metal complexes in sugar chemistry appeared, among them texts of Frappa and Sinou [1], Du, Linhardt, and Vlahov [2], Beau and Gallagher [3], and Nicotra [4].

a. C-Substitution of unsaturated monosaccharide derivatives *via* the Heck reaction

The synthetic studies were initiated at the end of seventies by G. Doyle Daves Jr. and S. Czernecki. The Heck reaction [5] consists in addition of an organopalladium (aryl- or hetaryl-palladium) to olefins to form an addition product which – in the presence of acids or weak bases, or on heating – undergoes elimination of HPdL (L – ligand) or $Pd(OAc)_2$ to produce an aryl or hetaryl-substituted derivative. Aryl- or hetaryl-palladium can be formed by one of the three approaches: i. treatment of an iodo-arene with palladium compound in the presence of a base, ii. treatment of an

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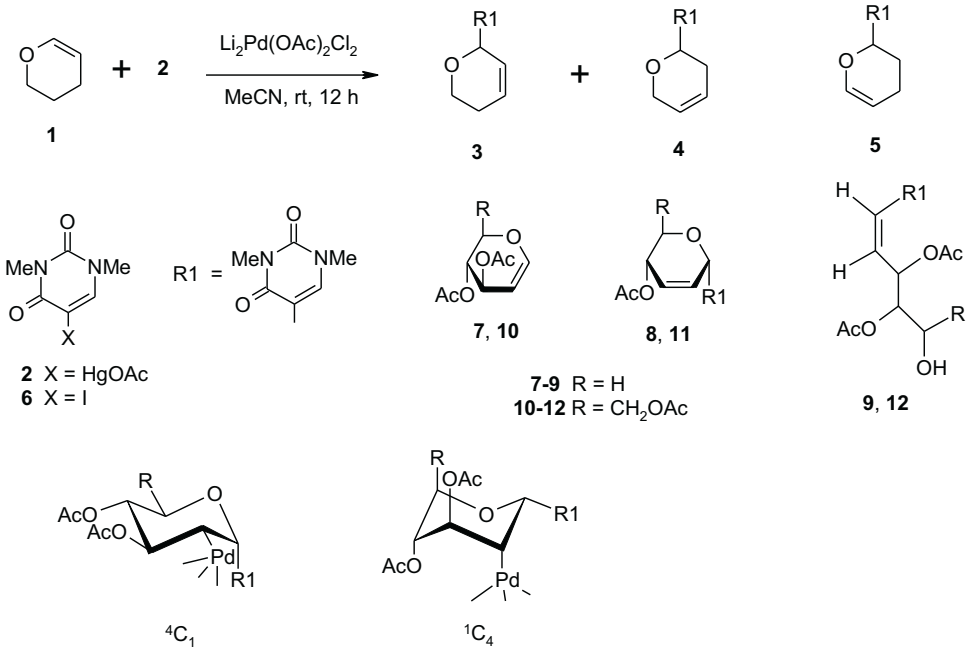
*This review is dedicated to Professor Derek Horton on the occasion of his 70th birthday in appreciation of his great contribution to carbohydrate chemistry and literature as the author of valuable monographs and as editor of *Carbohydrate Research* since its founding.

organomercury with a palladium salt, and iii. reaction of an aromatic compound with palladium acetate in the presence of acetic acid.

Scheme 1

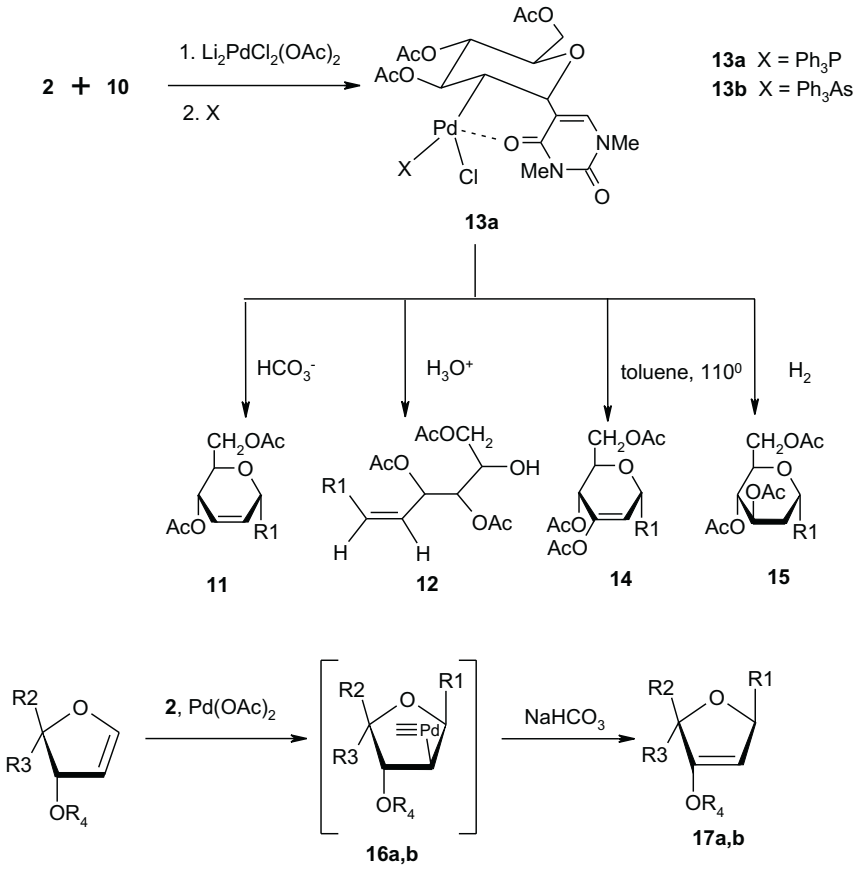


The reaction which was explored first, was a model reaction between 3,4-dihydro-2H-pyran (**1**) and (1,3-dimethyl-pyrimidine-2,4-dion-5-yl)mercury(II) acetate (**2**) in the presence of palladium acetate and lithium chloride [6,7]. Under mild reaction conditions two isomeric products (**3** and **4**) were obtained in 24 and 66% yield. Third isomer, **5**, was obtained when **1** was reacted with a reagent formed from 1,3-dimethyl-5-iodo-uracil (**6**) and catalytic amounts of diacetoxy(triphenylphosphine)palladium at 100°C.

Two peracetylated sugar derivatives, D-arabinal (**7**) and D-glucal (**10**), yielded under the same conditions 2,3-unsaturated pyranoid C-nucleosides **8** (20%) or **11** (20%), and open chain compounds **9** (32%) or **12** (73%) [7,8]. The rationalization of these results was based on *syn* addition of elements of organopalladium reagent (R1-Pd≡) to the double bond *trans* to the C3-OAc group followed by *trans*-diaxial elimination of acetoxypalladium (minor products **8** and **11**) in the $^1C_4$ (less stable) conformation or *anti* elimination of palladium-alkoxide in the preferred $^4C_1$ conformation this leading to the open-chain compounds (major products **9** and **12**) [7]. The intermediate Pd-containing products were unstable and could not be isolated. However, when a mixture of **2**, **10**, $Pd(OAc)_2$ and LiCl in acetonitrile was left at room temperature for 3 days and subsequently treated with triphenylphosphine, an addition product **13a** could be isolated by chromatography [9]. This product and the corresponding triphenylarsine analog (**13b**) were carefully characterized by ^1H, ^{13}C, ^{31}P

NMR, UV and IR spectra as well as by FAB mass spectra [10]. Decomplexation of **13a** under four different conditions: weak base, acid, by heating in toluene, or hydrogenolysis led to four different, single products **11,12,14,15** [9] (Scheme 2).

Scheme 2



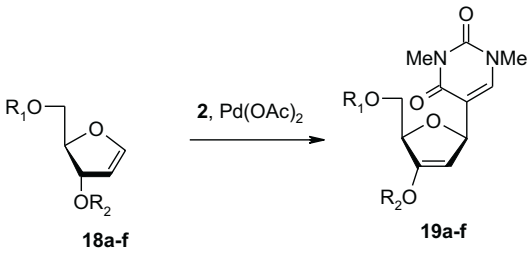
R1: cf Scheme 1 R_4 = H, OCH_2OMe, $Si(iPr)_3$

16a, 17a R2 = CH_2OCH_2Me, R3 = H. **16b, 17b** R2 = H, R3 = 2,2-dimethyl-dioxolan-4-yl

Pentose- and hexose-derived furanoid glycals, protected at O-3 and O-5, were reacted with **2** and $Pd(OAc)_2$ to form addition products **16a,b** (not isolated) which were decomplexed with $NaHCO_3$ yielding 35–90% of 2,3-unsaturated C-nucleosides **17a,b** [11,12]. These studies were further expanded to a series of variously substituted (at O-3 and O-5) furanoid glycals of D-*erythro* configuration (**18a–f**) what led to **19a–f** in good to very good yields [13], see also [14]. (For *cis*-hydroxylation of 2′,3′-unsaturated C-nucleosides [15]). Best conditions for condensation of D-*erythro* furanoid glycals **18** with pyrimidinedione **2** were found when C-3 hydroxyl group was protected with t-butyldiphenylsilyl group leaving C-5 hydroxyl free [16]. On that way syntheses of 2′-deoxypseudouridine (**20**), 2′-deoxyformycin B (**21**), and

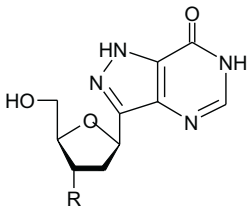
2′,3′-dideoxyformycin B (**22**) were accomplished [17] (Scheme 3). Another condensation of this type was performed by Hsieh and McLaughlin [18]. Coupling of 2-benzyloxy-5-iodo-3-methyl-2-pyridine (**23**) with furanoid glycal (**24**) in the presence of $Pd_2(dba)_3$ led to nucleoside (**25**). The use of 1,3-bis(diphenylphosphino)-propane (**26**, dppp) as a bidendate ligand in this reaction increased the yield of condensation to 90%. Deprotection and reduction of the carbonyl group in **25** yielded nucleoside **27**, expected to function as a mimic of the pyrimidine nucleoside dT [18].

Scheme 3

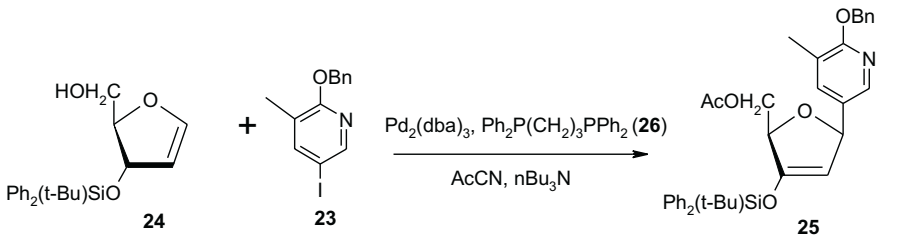


18a-f **19a-f** **20**

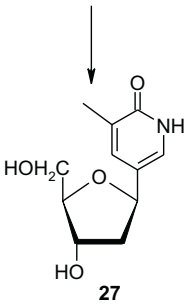
	R_1	R_2	Yield (%)
a	CH_2OMe	CH_2OMe	71
b	CH_2OMe	$Si(iPr)_3$	92
c	$Si(iPr)_3$	$Si(iPr)_3$	51
d	$SiMe_2(t\text{-}Bu)$	$Si(iPr)_3$	45
e	H	CH_2OMe	65
f	H	$CH_2OCH_2CH_2OMe$	77



21 R = OH
22 R = H



24 **23** **25**

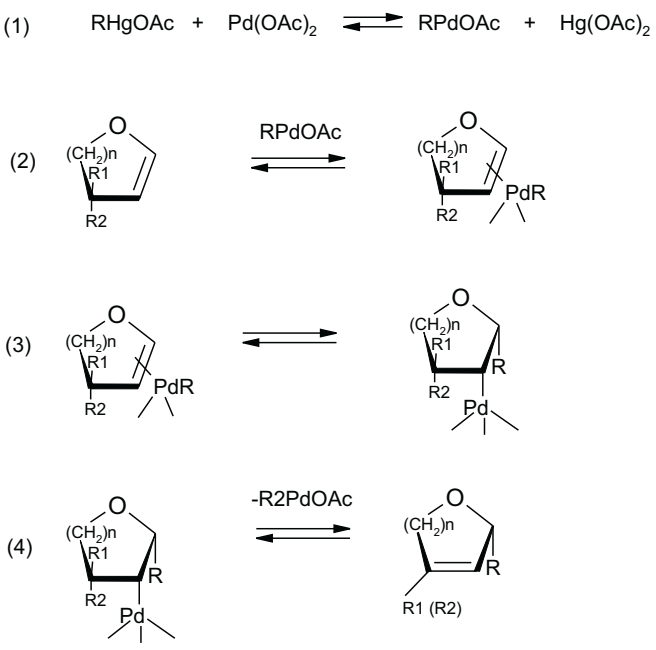


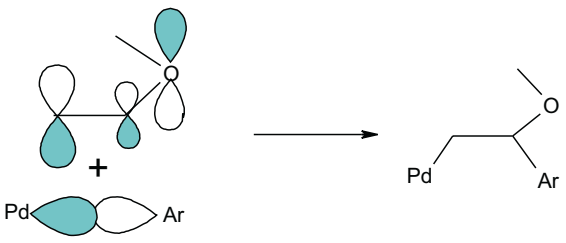
27

Studies on C-nucleoside formation were next expanded to reactions of enol ethers with **2** and three aromatic organomercurials [19]. It was found that the aromatic moiety becomes invariably bonded to the enol ether olefinic carbon atom bearing the oxygen atom. Interpretation of the formation of products having double bond in different positions (*e.g.* **3**–**5** in Scheme 1) was proposed [19,20]. An interesting analysis of transient products in the reactions of glycals with **2** or arylmercurials and $Pd(OAc)_2$ by fast atom bombardment (FAB) mass spectrometry was performed [21]. A four-step sequence of reactions was proposed [21] (Scheme 4).

Scheme 4

Steps of the palladium(II) mediated coupling of aryl or heterocyclic mercuric derivative with a glycal system

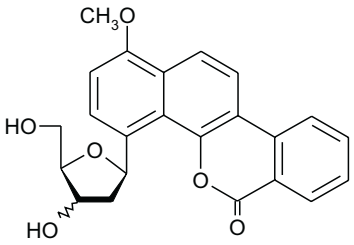




In 1987 Doyle Daves [22] performed basic studies of the arylation reaction of enol ethers. In particular, factors influencing the regiochemistry and yields of arylated products were thoroughly analysed. Arylation of non-cyclic enol ethers occurs in α or β-position. The variable parameters included halogenobenzene (PhI, PhBr), catalyst, solvent and α or β-substitution in the vinyl group. It was confirmed that 3,4-dihydro-2H-pyran is arylated exclusively at the α position [22]. The interpretation proposed by Doyle Daves is based on the assumption that the electronic factors are responsible for the collapse of the π-complex to the σ-complex (Scheme 4, step 3). Interaction of the HOMO of the enol ether with the antibonding σ* Pd(II)-aryl orbital leads in a concerted manner to a σ bond between electron-deficient Pd and electron-rich β-carbon atom of the enol ether. The relatively electron-rich aryl becomes linked to the α-carbon atom (Scheme 4). Studies of basic factors in Heck-type arylation of allylic alcohols were performed by Czernecki [23].

In another study of the Heck reaction, leading to C-nucleosides or C-glycosides, an analysis of steric and conformational factors as well as the reaction conditions on the course and yields of products was performed [24]. A comparison of arylmercuric acetates and the corresponding tributylstannanes as substrates for the palladium mediated C-arylation of glycals showed that both substrates are practically equally suitable for the reaction [25].

Scheme 5



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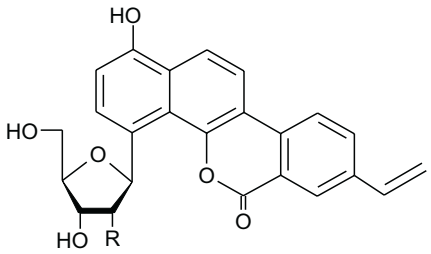
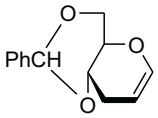


29 R = OH
30 R = H



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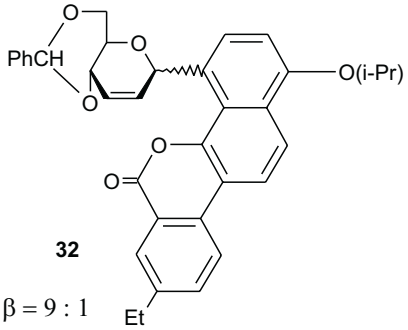


32

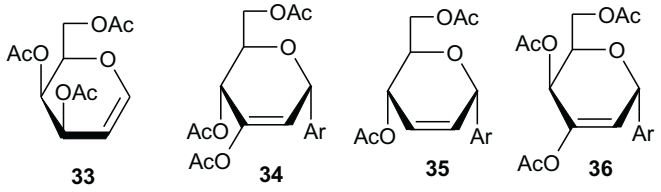
α : β = 9 : 1

A pair of C-glycosides (**28**), related to antibiotics of ravidomycin-type, having 1-methoxybenzo[d]naphto[1,2-*b*]pyran-6-one as aglycon, were synthesized by Doyle Daves [26] (Scheme 5). An extension of these works was the synthesis of C-glycosides **29** and **30** closely related to gilvocarcin-type antibiotics [27] (Scheme 5). For condensation with **2** or 8-ethyl-4-iodo-1-isopropoxybenzo[d]naphto[1,2-*b*]pyran-6-one pyranoid glycal (**31**) was employed. Both anomeric C-glycosyl derivatives (**32**) were formed with the α form prevailing [28].

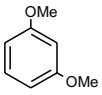
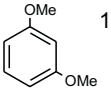
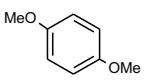
For C-glycosylation by catalytic amounts of palladium acetate iodoaglycons are suitable. Reaction conditions were determined which secured the best yields [29].

Triacetyl D-glucal (**10**) and D-galactal (**33**) were C-arylated by Czernecki [30,31], by treating with an excess of benzene or substituted benzenes in the presence of palladium acetate in acetic acid at 120°C. From **10** and benzene two products were obtained **34** („3-acetoxy-2,3-ene") and **35** („2,3-ene") in proportion depending on the

Scheme 6



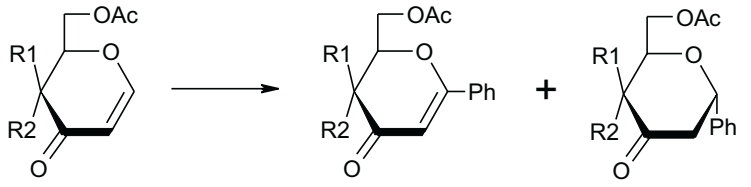
Arylation of glycals **10** and **33**

Glycal No.	Ar	Reaction cond. (°C, h)	Products
10	C_6H_6	80, 8	**34** (54), **35** (10)
10		120, 1.5	**35** (20)[a], **35** (25)[b]
33	C_6H_6	120, 2	**36** (51)
33		120, 1.5	**36** (23)[a], **36** (29)[b]
33		120, 2	**36** (43)[a]

a. Aryl substituted at C2. b. Aryl substituted at C4.

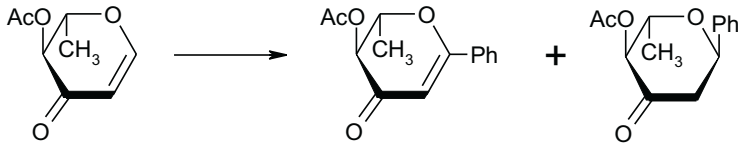
reaction conditions. With 1,3-dimethoxybenzene regioisomeric products were formed (*cf*. Scheme 6). In all investigated examples products of α configuration were obtained. The anomeric configuration was substantiated additionally by X-ray determinations performed for **35** (Ar = Ph) [32] and **36** (Ar = Ph) [33]. Considering α,β-unsaturated sugar enones as specifically suited for C-glycosylation, Czernecki condensed enones **37–39** with benzene and palladium acetate. Two products **40**,**42** (**41**,**43** and **44**,**45**, respectively) were formed in each case in proportions depending on reaction conditions.

Scheme 7



37, **38** **40**, **41** **42**, **43**

37, **40**, **42** R1 = H, R2 = OAc **38**, **41**, **43** R1 = OAc, R2 = H



39 **44** **45**

Phenylation of enones **37**-**39** with benzene and $Pd(OAc)_2$ in acetic acid

Enone	Reaction condit. (°C, h)	Yield %	Proportion of products	
37	110, 4	70	**40**:**42**	70:30
37	80, 5	45	"	68:32
38	110, 4	70	**41**:**43**	55:45
38	110, 4[a]	70	"	25:75
39	110, 4	90	**44**:**45**	70:30

a. 14% of water was added to acetic acid.

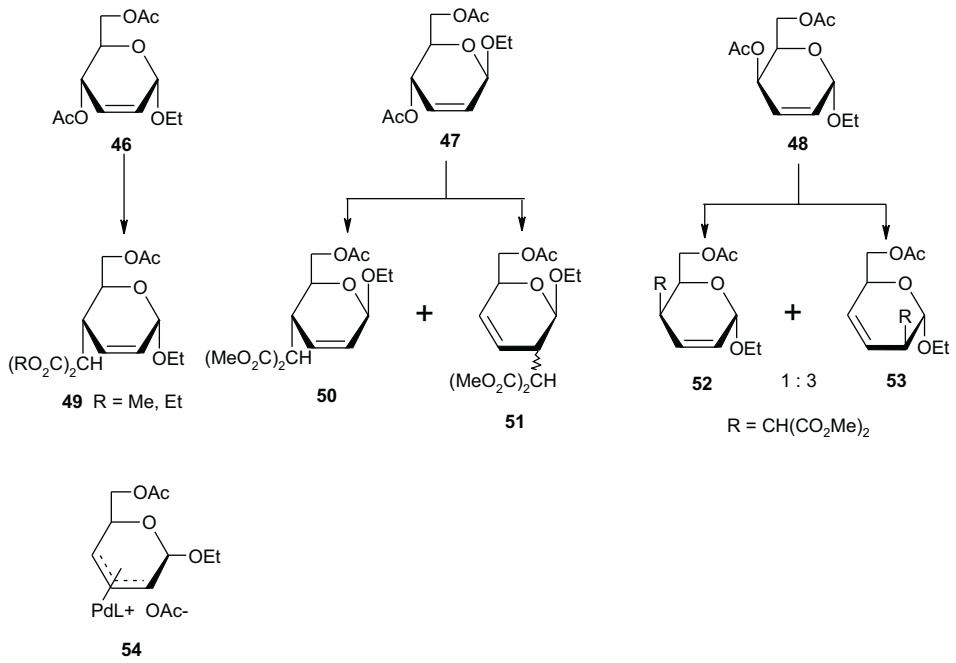
It was remarkable that addition of water to acetic acid, being the reaction medium, changed the proportion of products [34]. Doyle Daves found that palladium-mediated coupling of 2,3-dihydrofuran with nitrogen heterocycles occurred readily in the presence of water in 1:1 water-ethanol solution. Ethanol had to be added because of substrate solubility [35].

b. Substitution reactions of unsaturated monosaccharide derivatives *via* π-allylic complexes

Experiments at functionalization of unsaturated sugar derivatives *via* palladium π-allylic complexes started in 1980-ties. The reactions can be divided into three groups where C-, O-, and N-nucleophiles were employed.

b.1. C-Substitution. In a pioneering work on palladium-catalyzed substitution of carbohydrate allylic acetates Baer and Hanna [36,37] studied the reaction of ethyl 4,6-di-O-acetyl-2,3-dideoxy-D-hex-2-enopyranosides **46–48** with reactive methylene compounds like dimethyl or diethyl malonates and methyl phenylsulfonylacetate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium (0.07 mol. equiv.) and triphenylphosphine (0.7 mol. equiv.). From **46** (α-*erythro*) and dimethyl or diethyl sodiomalonates 4-C-substituted products **49** of the same configuration were obtained in high yield (83–87%). The other substrates, **47** and **48**, formed with dimethyl sodiomalonate mixtures of 4-C-substituted 2,3-unsaturated [**50** (major) and **52**] and isomeric 2-C-substituted 3,4-unsaturated [**51** (minor) and **53**] products. These results point clearly at intermediation of π-allylic cationic complex **54**. Remarkable is the high stereoselectivity of the reactions.

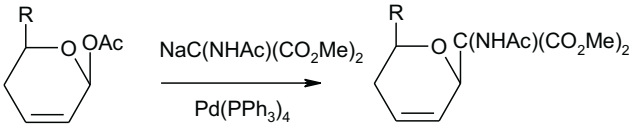
Scheme 8



In a model reaction Dunkerton [38] found that 2-acetoxy- or 2-acetoxy-6-methoxymethyl-5,6-dihydro-2H-pyrans (**55** and **56**) can react in the presence of tetrakis(triphenylphosphine)palladium with *e.g.* dimethyl acetamidomalonate to furnish in high yield the corresponding 2-C substituted products (**57** and **58**, Scheme 9). Yougai and Miwa [39] reacted a series of acetylated glycals (D-glucal, -allal, -galactal, and –xylal) with some selected β-dicarbonyl compounds in the presence of $Pd(PhCN)_2Cl_2$ and obtained 2,3-unsaturated C-glycosides (60–80%) with a distinct preference for one of the anomers. The synthesis is illustrated with the reaction of 3,4,6-tri-O-acetyl-D-allal (**59**) with acetylacetone to furnish **60** with the α anomer dominating (Scheme 9).

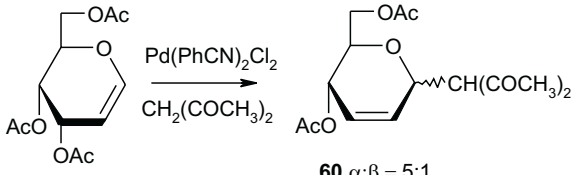
Because some other β-dicarbonyl compounds (*e.g.* cyclohexane-1,3-dione, dimethyl malonate) did not react under these conditions, RajanBabu [40] proposed a more viable solution to the reactivity problem by choosing trifluoroacetyl as the appropriate leaving group at C-3 of the glycal system and $Pd(dba)_2$ + bis(diphenylphosphino)ethane as catalyst. Thus, 4,6-O-isopropylidene-3-O-trifluoroacetyl-D-glucal (**61a**) reacted with potassium dimethyl malonate to give C-glycoside of the β configuration (**62**), whereas no reaction was observed for the analogous 3-O-acetyl derivative (**61b**) (Scheme 9).

Scheme 9

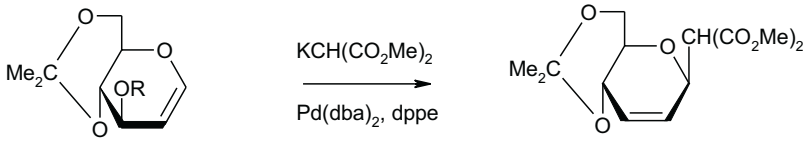


55, **56** **57** (80%), **58** (90%)

55, 57 R = H; **56**, **58** R = CH_2OMe



59 **60** α:β = 5:1



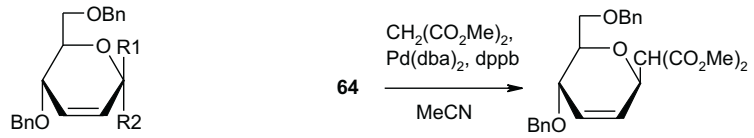
61a R = $COCF_3$
61b R = $COCH_3$

62

dppe = 1,2-bis(diphenylphosphino)ethane

In another approach to C-glycosides Sinou [41] has found that both anomers of phenyl 4,6-di-O-benzyl-2,3-dideoxy-D-hex-2-enopyranoside (**63** and **64**) readily reacted with ethyl nitroacetate in the presence of tris(dibenzylideneacetone)dipalladium(0) {$Pd(dba)_2$} and triphenylphosphine to afford stereospecifically C-glycosides **65** and **66** with retention of configuration at C-1 and in good yields [41]. Only little diastereoselectivity was found in the „aglycone" part (Scheme 10).

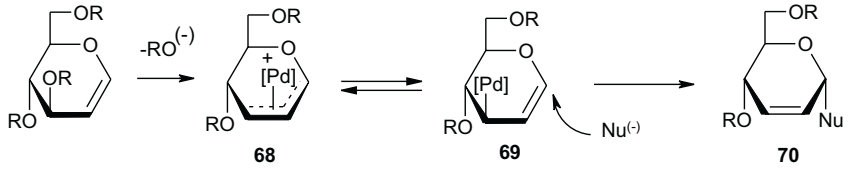
Scheme 10



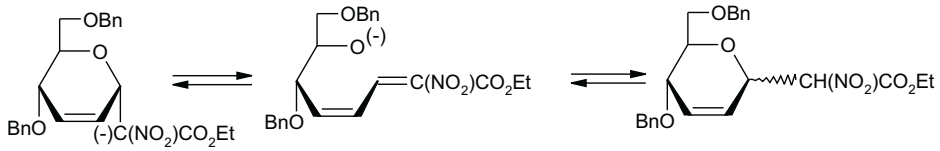
67 (84%)

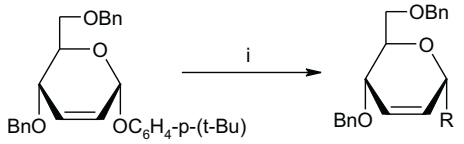
63 R1 = H, R2 = OPh
64 R1 = OPh, R2 = H
65 R1 = H, R2 = $CH(NO_2)COOEt$ (70%)
66 R1 = $CH(NO_2)COOEt$, R2 = H (50%)

Mechanism of C-glycosidation



Mechanism of anomerization (*retro*-Michael reaction)





71

72 R = Ph, p-MeC_6H_4, $PhCH_2$, 2-thienyl

i. RMgBr, palladium dichloro 1,1'-bis(diphenylphosphino)ferrocene

For alkylation of **63** and **64** other nucleophiles have been used: diethyl malonate, ethyl nitromalonate, acetylacetone, and methyl acetoacetate [42]. It was found that replacing triphenylphosphine by 1,4-bis(diphenylphosphino)butane (dppb) higher yields of C-glycosides were obtained (*e.g.* **64** → **67**, Scheme 10). In some reactions – depending on the rection conditions (time, temperature) – mixtures of both anomeric C-glycosides were obtained [42].

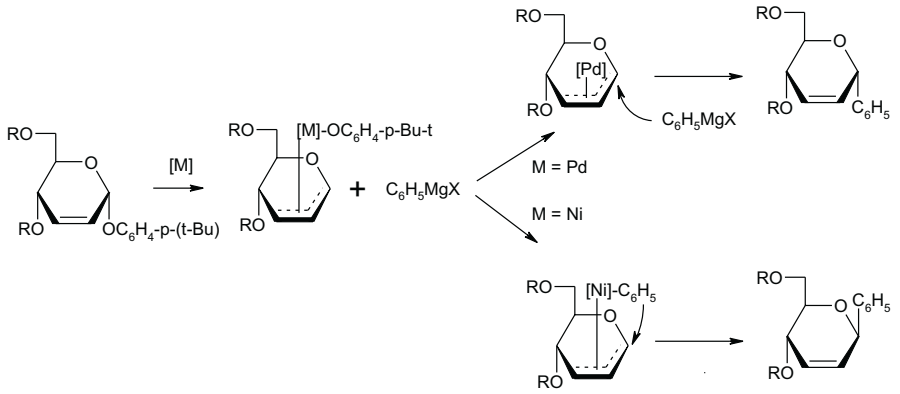
It is assumed that in all these reactions the π-allyl complex **68** formed is next transformed to the σ-complex (**69**), which is next attacked by the nucleophile followed by *cis* elimination of „hydridopalladium" to form the final product **70** [43]. The observed loss of stereoselectivity in some cases is interpreted by deprotonation at the aglycon carbon atom, retro Michael reaction, followed by Michael addition (Scheme 10). This mechanism was substantiated by retention of the anomeric configuration in C-glycosides having ternary carbon atom in the aglycon (*e.g.* nitromalonate) [43].

A new version of C-glycoside synthesis was proposed in 1995 by Sinou [44]. *P-tert*-butylphenyl 4,6-di-O-benzyl-2,3-dideoxy-α-D-hex-2-enopyranoside (**71**) underwent C-glycosidation with arylmagnesium compounds in the presence of palladium dichloro [1,1′-bis(diphenylphosphino)ferrocene] in good to very good yields. The reactions were stereospecific and yielded exclusively α anomeric C-glycosides (**72**) what indicated that the initially formed *anti* π-allyl complex was attacked „from below" (Scheme 10). No reaction was noted with $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$. It is interesting that analogous reactions with arylmagnesium reagents but with nickel dichloro 1,2-bis(diphenylphosphino)ethane as catalyst led also to C-glycosides but of β configuration. This synthesis has been expanded [45], and a full account of the results achieved, including a proposed mechanism of C-glycoside formation (Scheme 11) has been presented in 1998 [46].

A thorough study of anomeric configuration of C-glycosides was performed basing on ^1H, ^{13}C, and NOE spectrometric studies [47].

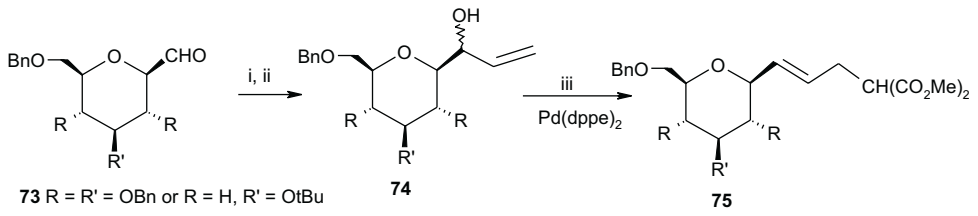
Still another approach to C-glycosides was proposed by Genet [48]. A β-C-glycosylaldehyde (**73**) [49] was reacted with trimethylsilylacetylene Grignard to form two stereoisomeric propargylic alcohols, next reduced to allylic alcohols (**74**).

Scheme 11



Stereoisomeric **74** were reacted with a number of nucleophiles (*e.g.* with dimethyl sodiomalonate) in the presence of palladium 1,2-(diphenylphosphino)ethane {$Pd(dppe)_2$} as catalyst to form C-glycosides (**75**) with *E*-double bond, suitable for further functionalization.

Scheme 12



73 R = R' = OBn or R = H, R' = OtBu **74** **75**

i. $Me_3SiCCMgBr$, -30° ii. H/Pd Lindlar cat., quinoline, iii. $NaCH(CO_2Me)_2$

A simple way to C-glycosides was recently demonstrated by Hayashi [50] by reacting D-glucal (free or acetylated, **10**) with trimethylsilyl cyanide in the presence of $Pd(OAc)_2$. 2,3-Unsaturated 1-cyanohexosides (**76**) were obtained in high (82–99%) yield, however, as mixtures of α- and β-anomers (1.5–3:1). The authors found that $Pd(PPh_3)_4$ was ineffective in this reaction.

Scheme 13

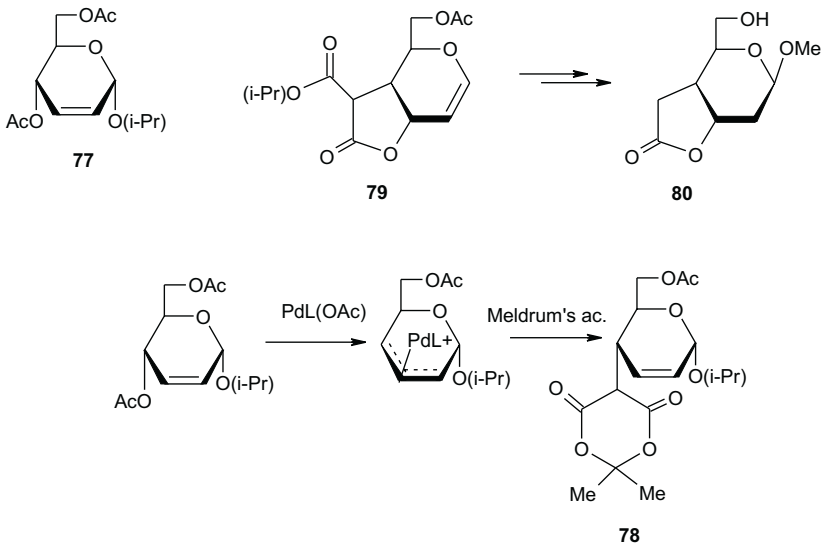
76

R = H, Ac (**10**)

Two palladium-mediated reactions, with Pd(II) and with Pd(0), performed on **10** permitted to synthesize a bicyclic precursor **80** for the synthesis of thromboxane B_2 [51] (Scheme 14). In the first reaction, a high-yield Ferrier rearrangement was realized by treatment of **10** with 0.1 molar equivalent of palladium(II) reagent {$Pd(MeCN)_2Cl_2$}, 2 molar equiv. of cupric ditriflate, and 2-propanol to furnish **77** in a quantitative yield. In the next, highly efficient step, **77** was reacted with Meldrum's acid in the presence of palladium(0) {$Pd(PPh_3)_4$} to yield bicyclic lactone **79** in 76% yield *via* a transient (not isolated) substitution product **78**. Further steps led to the desired lactone **80**.

Engelbrecht and Holzapfel [52] have shown that hex-2-enopyranosyl mixed carbonates (**81**, R = i-Bu or t-Bu) can react at room temperature with an excess of diethyl malonate (ethyl phenylsulfonylacetate, Meldrum's acid) in the presence of catalytic amounts (10% mol) of $Pd(PPh_3)_4$ and triphenylphosphine (20% mol) to form the corresponding C-glycosides (**82**) with retention of configuration (Scheme 15).

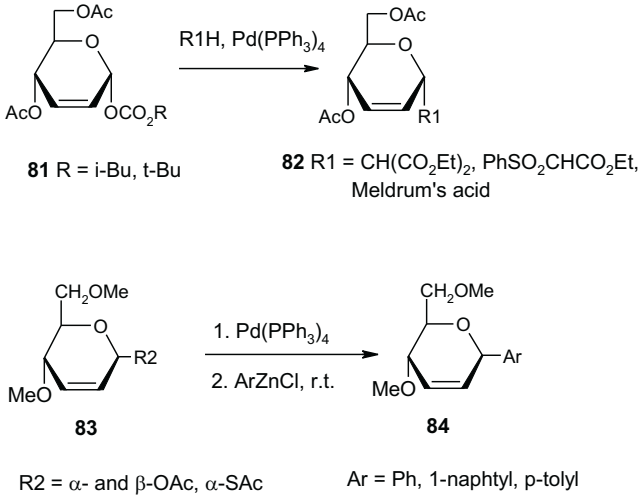
Scheme 14



The tetrakis(triphenylphosphine)palladium-activated arylation was effective also in C-glycosylation of 1-O-acetyl and 1-S-acetyl-1-thio-D-hex-2-enopyranoses (**83**) [53]. The C-glycosides **84** were formed in low yield but the reactions were apparently stereospecific with net inversion of configuration at C-1 (Scheme 15).

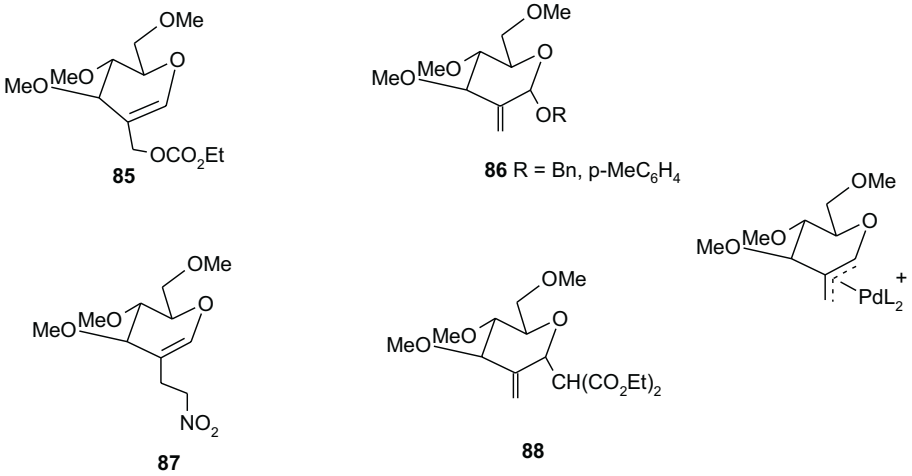
An interesting series of reactions was presented byGupta and Vancar [54]. They studied some selected reactions of 2-ethoxycarbonyloxymethyl-3,4,6-tri-*O*-methyl-D-*arabino*glycal (**85**) catalyzed by $Pd(PPh_3)_4$. Thus, reactions with alcohols, *e.g*. benzyl alcohol or *p*-cresol led to α-glycosides of 2-methylene-arabinohexopyranosides (**86**). Reaction with nitromethane under similar conditions furnished 2-β-nitroethyl-glycal (**87**). A 2-methylene *C*-glycoside (**88**) was obtained when in

Scheme 15



reaction of **85** with diethyl malonate dppe was used as a ligand mixed with $Pd(PPh_3)_4$. These transformations are intermediated by a π-allylic palladium complex reacting at C-1 with "hard" and at C-2' with "soft" nucleophiles.

Scheme 16

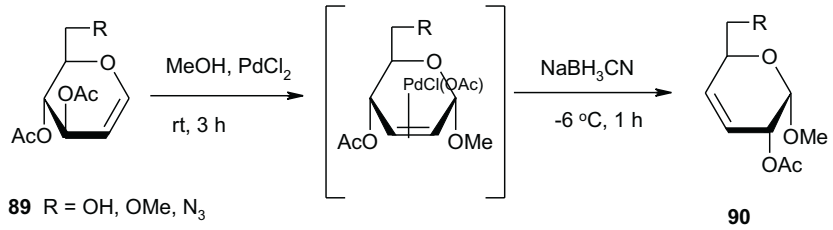


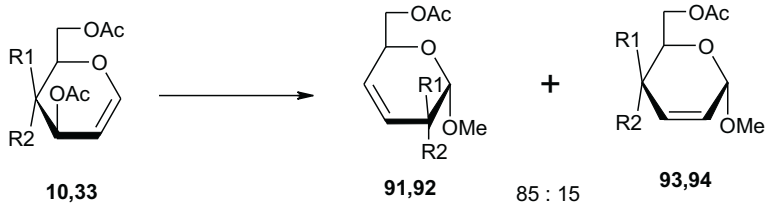
b.2. O-Substitution. In 1982 Dunkerton [55,56] reported that in the presence of $PdCl_2$ methanol {ethanol, β-(trimethylsilyl)ethanol} could be added to acetylated glycals (**89**) to form palladium π-complexes of methyl 2,3-dideoxy-hex-2-enopyranosides as intermediate products which, on addition of sodium cyanoborohydride ($NaBH_3CN$), underwent rearrangement to methyl 2-O-acetyl-3,4-dideoxy-hex-3-enopyranosides (**90**) with a *syn* acetoxy group transfer (Scheme 17). In case of 3,4,6-tri-O-acetyl-D-glucal (**10**) and -D-galactal (**33**) the respective 3,4- (rearranged) and 2,3- (unrearranged) unsaturated methyl hexenopyranosides (**91,92** and **93,94,** respectively) were formed in 85:15 proportion. The course of the reaction depended on the presence of C-6 substituents: OAc, OH, OMe, and CN groups promoted the reaction whereas no reaction was observed for SPh or NHAc groups. 3,4-Di-O-acetyl-D-xylal and –L-rhamnal formed the methyl pent- or hex-2-enopyranosides, respectively, as exclusive products.

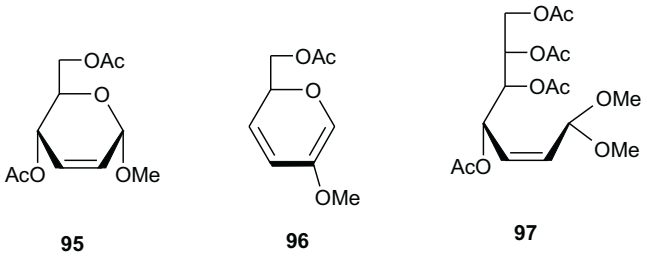
All these reactions afforded products in good to very good yields. The course of the reactions was explained by methoxypalladation *trans* to the C-3 acetoxy group followed by $NaBH_3CN$ reduction of Pd(II) to Pd(0), and palladium induced *syn* [3,3] sigmatropic rearrangement (Scheme 17).

These results were questioned by Holzapfel [57], who repeated Dunkerton's experiments with **10** and found that in all variants of the methoxypalladation reaction no **90** could be detected. Instead, three products: **95–97** were identified (Scheme 17). It was found that **95** was the main reaction product and the remaining two, **96** and **97**, originated from the follow-up, acid-catalyzed reaction of **95**. Holzapfel's observations were marked as „unpublished results" [57]. No further experiments in this field were performed, so, the controversy still remains unsolved.

Scheme 17

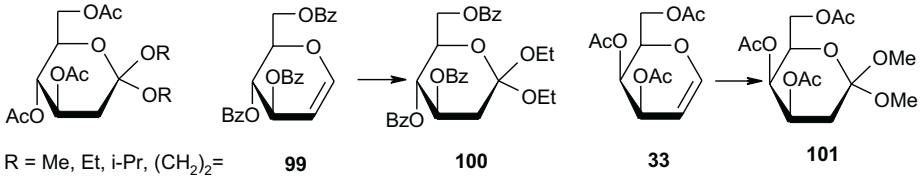






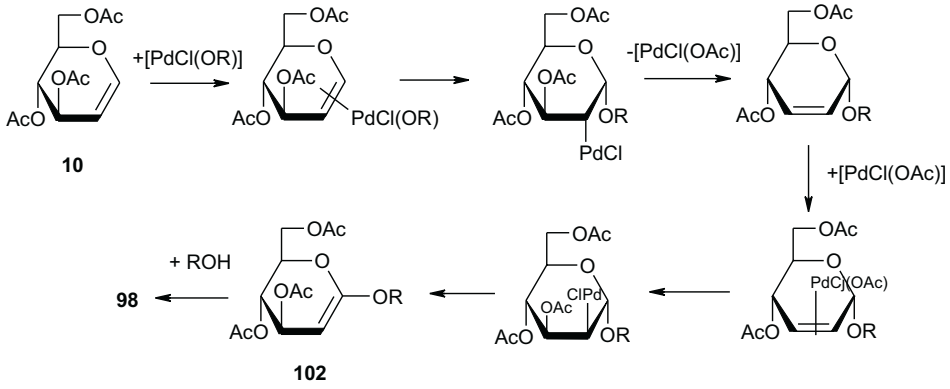
On the other hand, Holzapfel [57] found that treatment of triacetyl-D-glucal (**10**) with one molar equivalent of $PdCl_2$ and methanol followed by the addition of finely powdered sodium hydrogencarbonate afforded orthoester (**98**) as the main product. An analogous reaction was performed also with ethanol, 2-propanol and ethane-1,2-diol replacing methanol. Also, 3,4,6-tri-O-benzoyl-D-glucal (**99**) and ethanol furnished the appropriate orthoester (**100**). Triacetyl D-galactal (**33**) reacted with methanol, palladium catalyst and $NaHCO_3$ in the same way to give (**101**) in 90% yield. It was found that in the presence of $(MeCN)_2PdCl_2$ or $(BnCN)_2PdCl_2$ as catalysts the formation of orthoesters proceeded faster (Scheme 18).

Scheme 18



98 R = Me, Et, i-Pr, $(CH_2)_2$= **99** **100** **33** **101**

Sequence of reactions

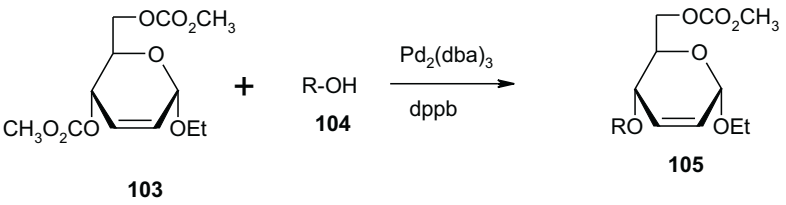


10

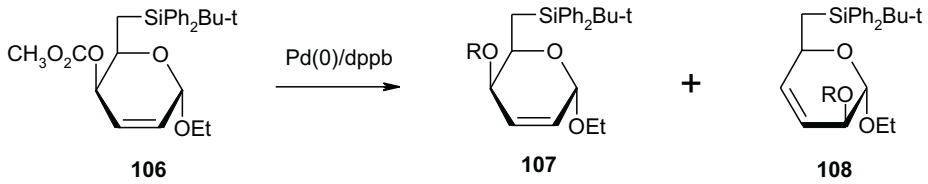
It seems that interpretation of „alkoxypalladation" of glycals can be based on i. formation of a π-complex with the double bond followed by ii. addition of OR and [PdCl] to C1 and C2, and iii. *trans* elimination of „acetoxypalladium" to hex-2-enopyranoside (*cf.* Scheme 4) iii. addition of PdCl(OAc) to the 2,3-double bond, iv. *cis*-elimination of „hydridopalladium" to enolether **102**, and v. addition of ROH to form orthoester **98**. Holzapfel [57] postulates 1,2-*trans* addition of PdCl(OMe) to the glycal double bond, *cis* and *trans* to the C3-OAc group, followed by a *cis*-elimination of „hydridopalladium" from one of the transient addition products to form **102**. However, this assumption does not seem to be justified. In all cases studied so far organopalladium reagent was added *trans* to the C3 substituent (except the case when at C3 a free hydroxyl group was present [13,16]).

Sinou [58] synthesized 1,4-disaccharides by glycosidation of ethyl 2,3-dideoxy-4,6-di-*O*-methoxycarbonyl-α-D-*erythro*-hex-2-enopyranoside (**103**) with three protected derivatives of D-mannose, D-ribose and D-glucose in the presence of $Pd_2(dba)_3$ and added ligand 1,4-(diphenylphosphino)butane (dppb). Disaccharides were obtained in moderate to good yields. The synthesis is illustrated for a derivative of ribose **104** as the alkylating agent. β-Linked disaccharide **105** was obtained in 70% as pure compound. Alkylation of the 6-*O*-*tert*-butyldiphenylsilyl analog of **103**, of the *threo* configuration **106**, led to two disaccharides: **107** (21%) and an allylic regioisomer **108** (61%).

Scheme 19



R = 2,3-O-isopropylidene-β–D-ribofuranosyl



R = 2,3:5,6-di-O-isopropylidene-α-D-mannofuranosyl

b.3. N-Substitution. Baer and Hanna in the work mentioned above [36,37] found that ethyl 4,6-di-O-acetyl-2,3-dideoxy-D-hex-2-enopyranosides (**46** and **47**) readily reacted with secondary amines in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and triphenylphosphine to form unsaturated amino sugars in 70–87%. **46** and **47** gave the corresponding 4-amino-4-deoxy-2-eno derivatives (**109** and **112,** resp.). Reacting with dibenzylamine, under similar conditions, compound **46** led to a mixture of 4-amino-4-deoxy-2-eno (**110**, minor) and 2-amino-2-deoxy-3-eno (**111**, major) derivatives.

The same methodology was subsequently used for the synthesis of 2,3-unsaturated N-glycosides: reaction of **63** with heterocyclic bases (*e.g.* adenine) in the presence of $Pd_2(dba)_3$ and dppb led in good yields and stereoselectivity to the expected products (*e.g.* **113**) [59].

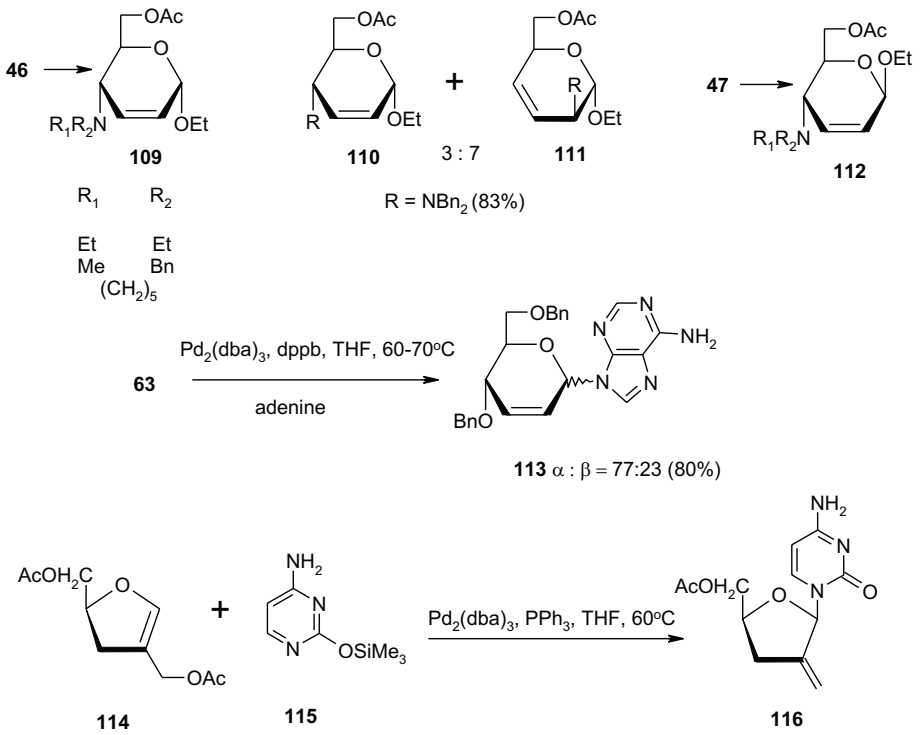
In a search for an antileukemic agent, 2-acetoxymethyl-furanoid glycal (**114**) was condensed with 2-trimethylsilyloxycytosine (**115**) in the presence of $Pd_2(dba)_3$ and triphenylphosphine. 2′-*C*-Methylidene-nucleoside (**116**) was obtained in 40%, α:β = 1:4 [60]. Deacetylated **116** did not exhibit any antitumor activity (Scheme 20).

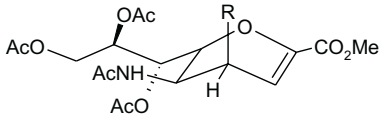
A 4-*epi*-azido-substituted sialic acid derivative **118** was synthesized from the 2,3-unsaturated compound (**117**, Neu5Ac2en) using $Pd(PPh_3)_4$ and sodium azide as the nucleophile [61]. Stereoisomer **118** was obtained as a single product. Analogously, the 6-thio derivative was synthesized from a suitable precursor [61].

c. Cyclization and annulation reactions

Reactions leading to cyclic (bi- and tricyclic) structures have been realized in three ways: i. by an intramolecular Heck reaction promoted by palladium complexes, ii. by cyclization of 1-O-substituted 2,7-dienes, and iii. by cyclization of 1,6-enynes.

Scheme 20





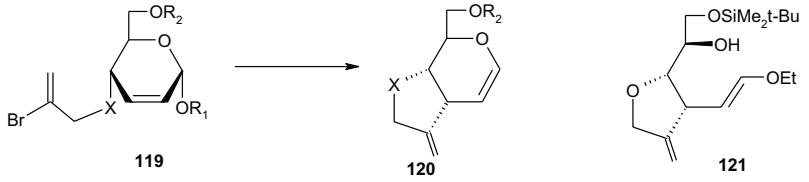
117 R = OAc
118 R = N_3

In reactions ii and iii five-membered rings are formed in the presence of transition metal complexes [62–65]. (Schemes 21, 23, and 24).

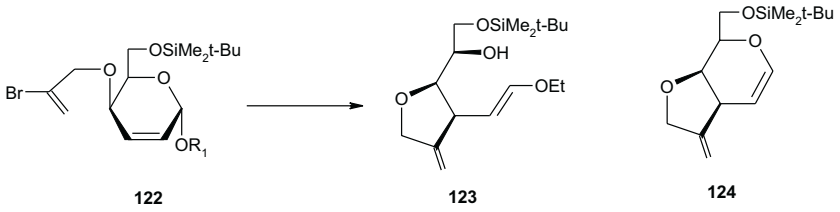
Interesting examples of intramolecular Heck reactions, leading to bicyclic products, have been presented by Sinou and his coworkers [66,67]. Glycosides of 2,3-unsaturated hexopyranosides of the *erythro* configuration (**119**, Scheme 21) having 2-bromoallyl group at O-4, underwent cyclization in the presence of $Pd(OAc)_2$ and phosphines to form bicyclic glycals **120**. However, analogous ethyl α-D-hex-2-enopyranoside (**122**) of the *threo* configuration formed a tetrahydrofuran ring but the pyranoside ring was opened to produce enolether **123**. The same product was also formed from the β anomer of ethyl hex-2-enopyranoside as substrate. This work was later expanded [68] to unsaturated hexopyranosides having different leaving groups

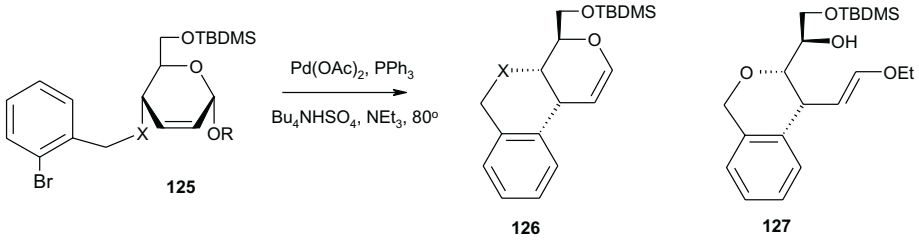
as aglycons. Thus, it was found that whereas **119** (R = 4-t-BuC_6H_4 and 4-$NO_2C_6H_4$), having good leaving groups at C-1, gives only bicyclic products **120**, ethyl glycoside **119** (R_1 = Et), reacted in DMF (instead of MeCN-H_2O) to form bicyclic product **120** (50%) and tetrahydrofuran **121** (20%). And, analogously, placement of good leaving groups at C-1 of the *threo* glycosides (**122**, R_1 = 4-t-BuC_6H_4 and 4-$NO_2C_6H_4$) facilitated the elimination and led to bicyclic structures **124**.

Scheme 21

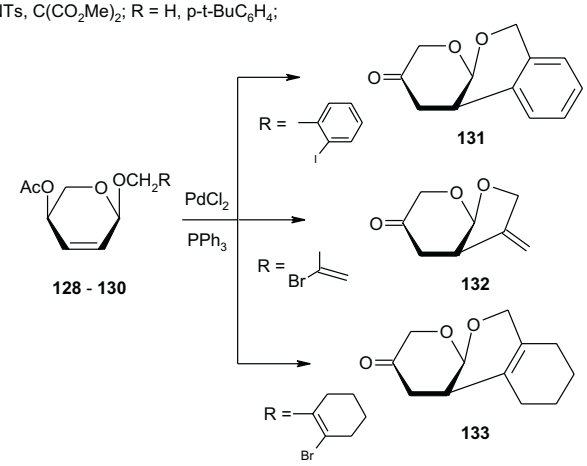


X = O, NTs, $C(CO_2Me)_2$; R_1 = Et, t-Bu, p-t-BuC_6H_4; R_2= H, TBDMS.





X = O, NTs, $C(CO_2Me)_2$; R = H, p-t-BuC_6H_4;



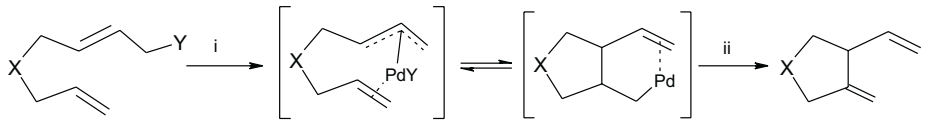
In 2000 Sinou [69] extended the synthesis of tricyclic structures by modifying the substrate **119** to 4-(*o*-bromobenzyl) group-containing 2,3-unsaturated derivatives **125**, which in reactions catalyzed by $Pd(OAc)_2$ and ligand TPP added, formed tricyclic products **126** in moderate to good yields (15–70%) accompanied by a ring-opened product **127** (13%) in case of the 4-O substrate. A number of similar reactions have been also described [69].

An alternative annulation, at positions 1 and 2 of the pyranoside skeleton, was presented by Tenaglia and Karl [70]. They found that halogeno-alkenyl or -aryl 2-enopyranosides, treated with $PdCl_2$, triphenylphosphine and triethylamine (or silver carbonate), underwent cyclization. The results are illustrated with the reactions of 2,3-dideoxy-α-L-*glycero*-pent-2-enopyranosides (**128–130**) leading to the corresponding cyclic structures **131–133** (Scheme 21).

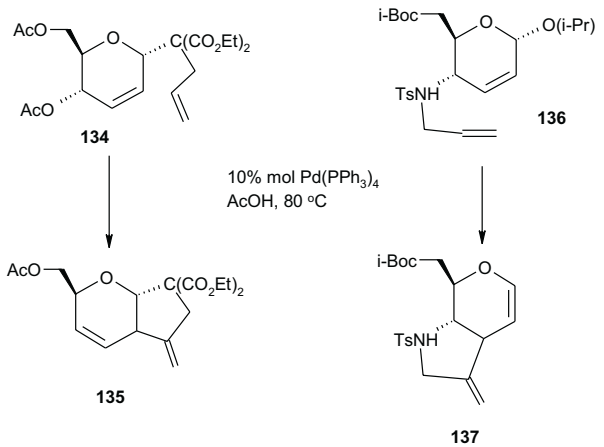
Palladium-catalyzed reaction of 1-O-substituted 2,7-diene system can be illustrated by cyclization of C-(allylmalonyl) hex-2-enopyranoside (**134**) to a bicyclic, *cis*-fused product **135** in 72% yield [71,72]. An analogous cyclization was also performed with isopropyl 4-(N-allyl)tosylamido-2,3,4-trideoxy-α-D-hex-2-enopyranoside (**136**) to yield **137** in 82%. Several other cyclization examples have been described [71, 72].

Scheme 22

Intramolecular "palladium-ene" cyclization of 1-O-substituted 2,7-dienes (Oppolzer)



X = CH_2, NR, O, $C(CO_2Me)_2$, Y = OAc, OH, OTHP i. Pd(O), AcOH ii. β-elimination



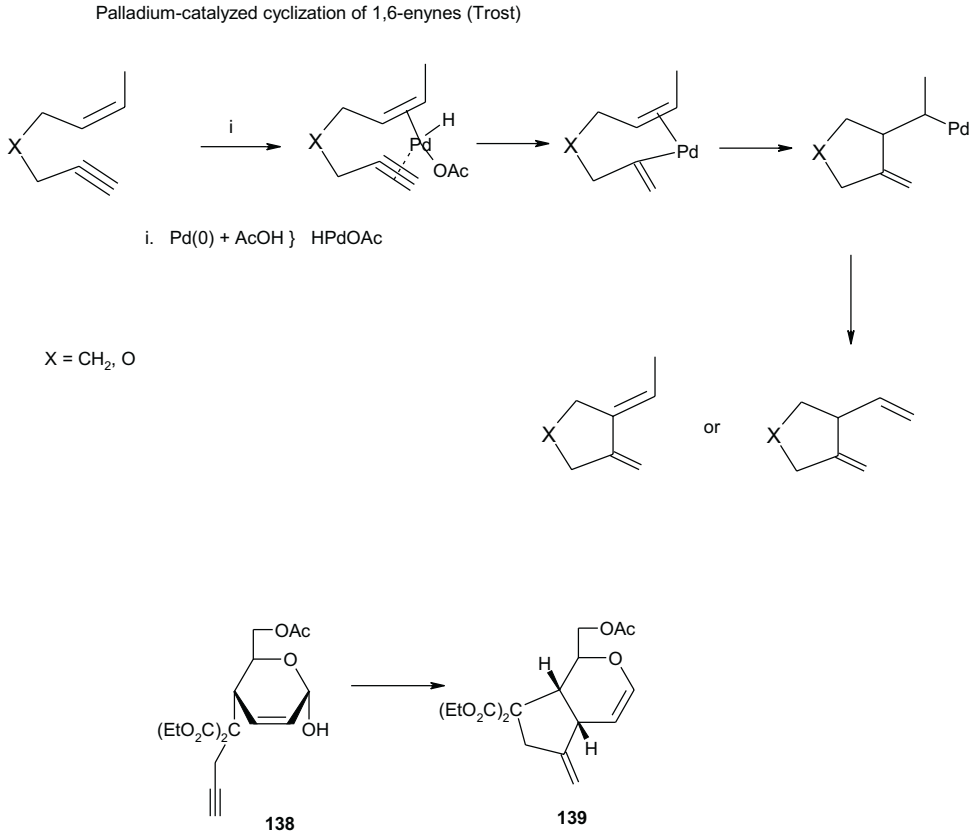
Enyne cyclization was studied on several examples [71]; the example of cyclization of 6-O-acetyl-2,3,4-trideoxy-4-C-(propargylmalonyl)-α-D-hex-2-enopyranose (**138**) is shown in Scheme 23 [72]. Treatment with $Pd_2(dba)_3 \cdot CHCl_3$, triphenylphosphine and acetic acid led to bicyclic product **139** in 81% yield.

Also „palladium-ene" cyclization/carbonylation [64,73] has been realized in the pent- (and hex-)-2-enopyranoside series. Depending on the structure of the substrate, a variety of products was obtained. As an example may serve the reaction of phenyl 2,3-dideoxy-4-O-allyl-β-D-*glycero*-pent-2-enopyranoside (**140**) with $Pd(PPh_3)_4$ and acetic acid in the atmosphere of CO. This reaction led to three products **141**–**143** [72] (Scheme 24).

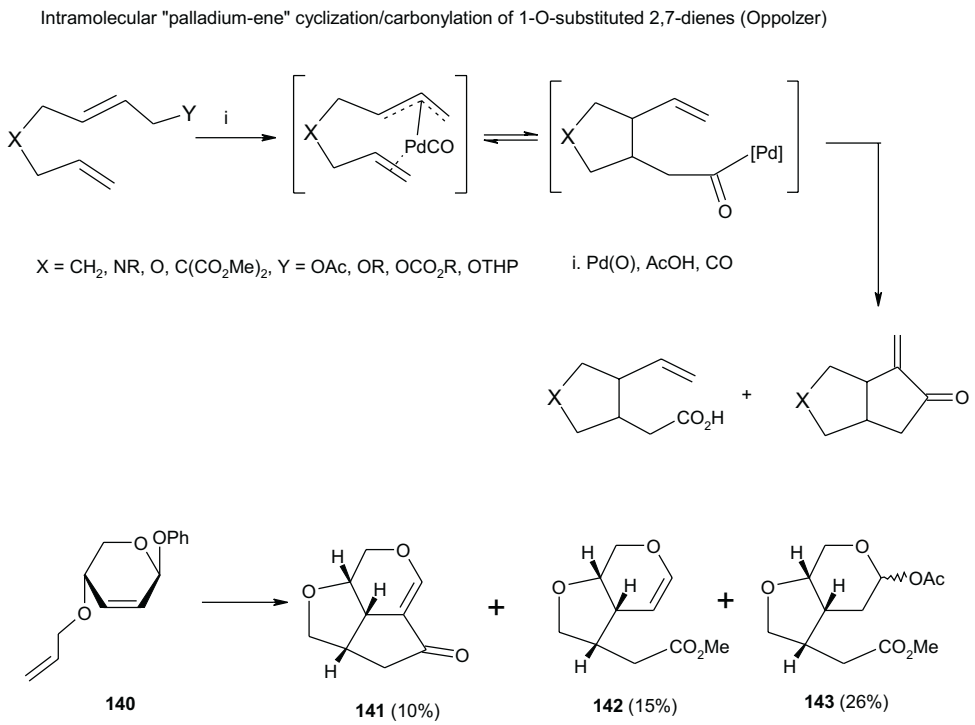
Along similar lines a cascade bis-cyclization reaction was realized, exemplified by the palladium-catalyzed conversion of **144** to **145** [74].

Syntheses of tricyclic products (**147**) starting from allyl glycosides [*e.g.* **146**, X=O, NTs, $C(CO_2Me)_2$] were described by Sinou [75] (Scheme 25). Mechanism of cyclization was discussed [76] (Scheme 26). First steps: **146** → **148** → **149** present the

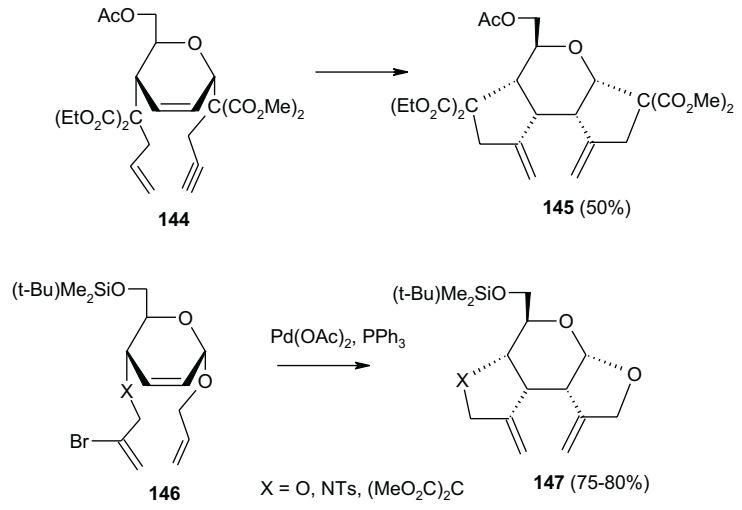
Scheme 23



Scheme 24



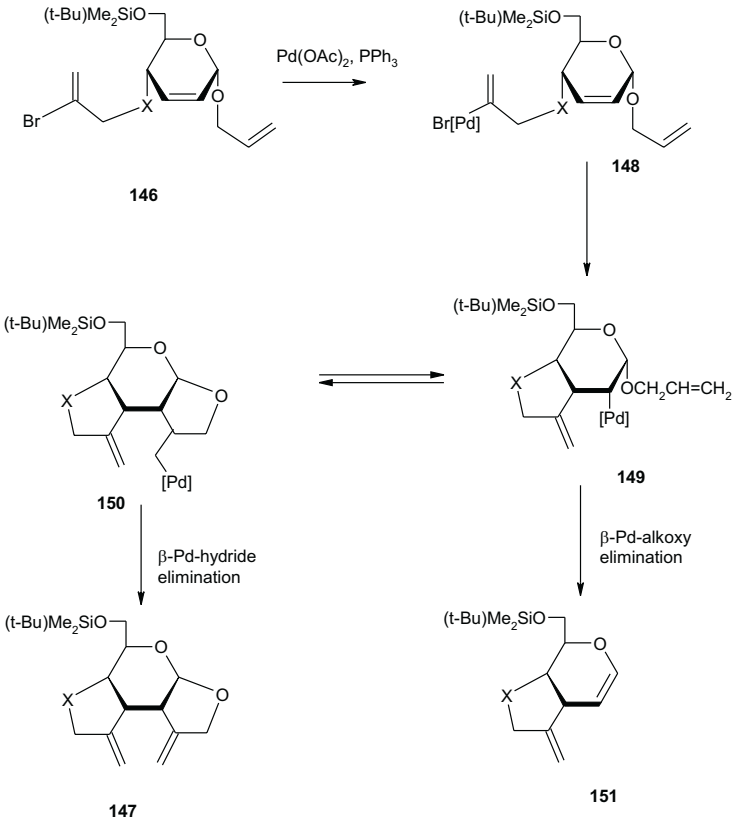
Scheme 25



intramolecular Heck reaction. From **149** *via* the β-elimination of Pd-alkoxy entity glucal **151** is formed. Transient product **149** is in equilibrium with the cyclic structure **150** which, on „hydridopalladium" elimination gives the tricyclic product **147**.

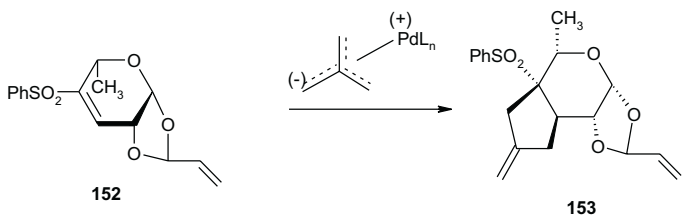
Scheme 26

Mechanism of cyclization



Another approach to bicyclic carbohydrate-based products having *exo* double bond in the five-membered ring was based on [3+2] cycloaddition [77,78]. Sulfone-activated unsaturated carbohydrate derivatives reacted readily with trimethylmethylene precursor in the presence of Pd(0) catalyst to afford single products [77]. Synthesis of compound **153**, a potential substrate for syntheses of some alkaloids, from sulfone **152** may serve as illustration. Also unsaturated nitro-sugars underwent [3+2] cycloaddition with trimethylmethylene under Pd(0) catalysis [78]. In fact, in these reactions no carbohydrate-metal bond is formed, however, because of close analogy to the reactions discussed above, inclusion of these results was regarded as justified.

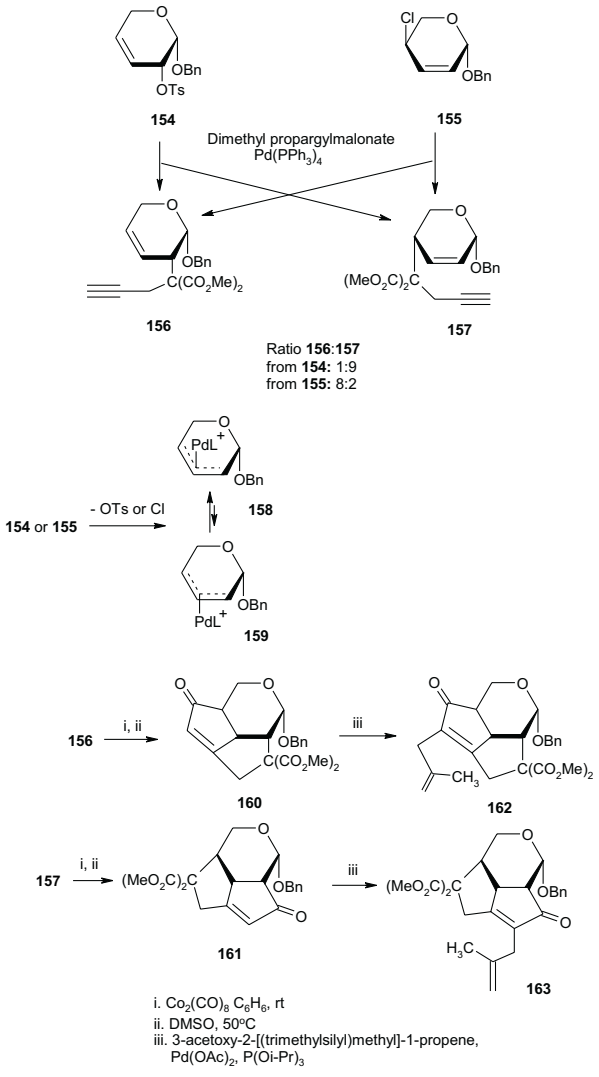
Scheme 27



An interesting work of Voelter [79] deserves to be mentioned. Tetrakis(triphenylphosphine)palladium(0)-catalyzed alkylation of unsaturated sugars **154** and **155** with dimethyl propargylmalonate led to the same mixture of alkylated derivatives **156** and **157**, however, in different proportions [79] (Scheme 28). It is rather obvious that in both cases the same palladium π-allyl complexes must be involved, with **158** dominating over **159.** Consequently, attack of the propargylmalonate anion had to occur opposite to palladium this leading to **156** and **157**.

Both alkylated sugar derivatives were next used for the Pauson-Khand, $Co_2(CO)_8$-mediated cyclization reaction [79]. The tricyclic compounds obtained, **160** (from **156**) and **161** (from **157**), were reacted with 3-acetoxy-2-[(trimethylsilyl)methyl]-1-propene (trimethylenemethane precursor) in the presence of $Pd(OAc)_2$ and triisopropyl phosphite to form alkylated products **162** and **163** (instead of the expected ring compounds) (Scheme 28).

Scheme 28

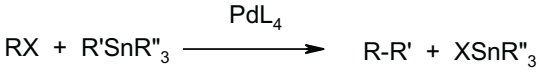


d. Stille reaction

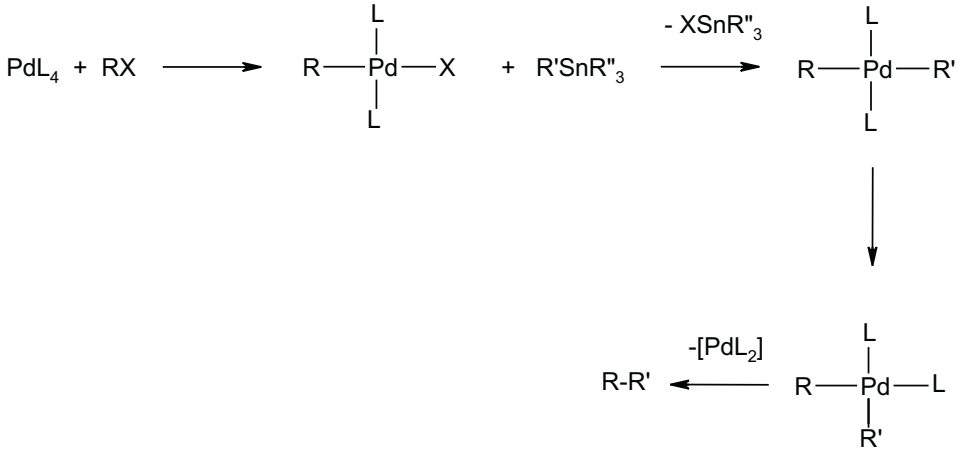
Cross-coupling reaction between organotin reagents $RSnR'_3$ and organic halides R"X, catalyzed by palladium(0) complexes, known as Stille reaction [80], leads to compounds R-R" (Scheme 29).

Scheme 29

Stille coupling



Steps:

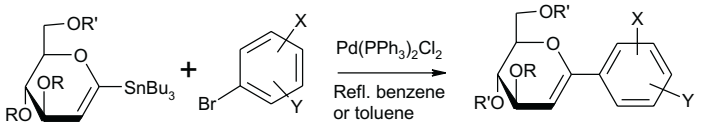


This reaction was successfully employed in sugar chemistry by Friesen and Sturino [81] and by Dubois and Beau [82] for the synthesis of C-arylated D-glucals. Both groups used essentially a very similar approach consisting in coupling of 3,4,6-tri-O-TBDMS-substituted or 3-O-TBDMS-4,6-O-benzylidene 1-tributyltin-D-glucal (**164a** and **164b**) with aryl bromide (**165**) in refluxing benzene or toluene with a catalytic amount of $Pd(PPh_3)_2Cl_2$ [or $Pd(PPh_3)_4$] to yield 40–80% of C-arylated D-glucals (**166**) (Scheme 30).

The main synthetic goal of both groups [83,84] was the preparation of a spiroketal (**167**, R = H) being the main structural fragment of antifungal antibiotics papulacandins A-D *(e.g.* papulacandin D: **167**, R" = 7-hydroxy-8,14-dimethyl-hexadeca-2E,4E,8E, 10E-tetraenoyl) and chaetiacandin. The synthesis consisted of coupling of 1-tributyl-tin-D-glucal (**164a** or **164b**) with bromo-2,4-dibenzyloxy-6-acetoxymethyl-benzene (**168**) in the presence of $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ to produce C-arylated D-glucal (**169**). This product was subsequently oxidized with dimethyldioxirane (DMDO) or with m-chloroperoxybenzoic acid, what led directly to both anomeric spiroketals **170** and **171** with the desired α product in a distinct (5:1) prevalence. Friesen and Sturino found that without separation of the anomers a simple treatment of the mixture with

pyridinium p-toluenesulfonate (PPTS) brought about the anomerization and furnished **170** as a single product in 80% yield. Deprotection of **170** gave the desired spiroketal **167** (R" = H), identical with the natural degradation product. Dubois and Beau found in their procedure that deprotection of the final mixture of both anomeric spiroketals led, similarly as in the previous case, to a single, equilibrated product of the desired configuration (Scheme 30).

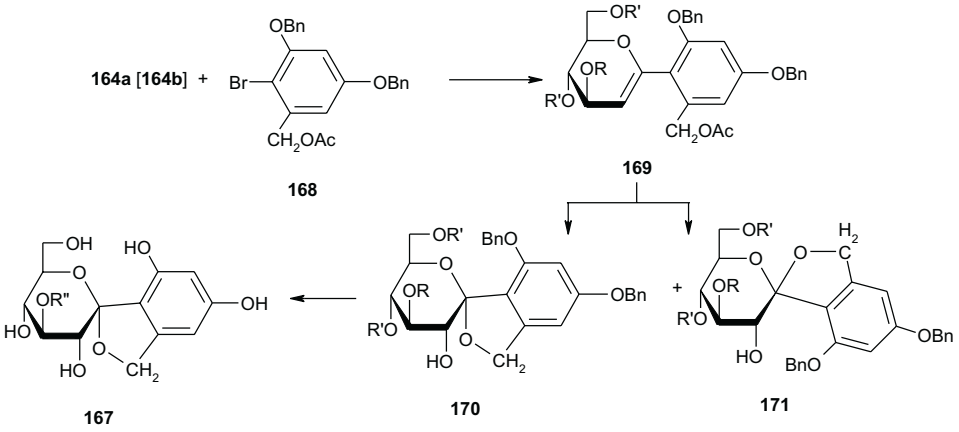
Scheme 30



166

164a R = R' = TBDMS
164b R = TBDMS, R' = PhCH= or
R = R' = Bn

165
X = 4-NO_2, 4-CN, 2-BnO, 2-MeO
Y = H, 5-MeO

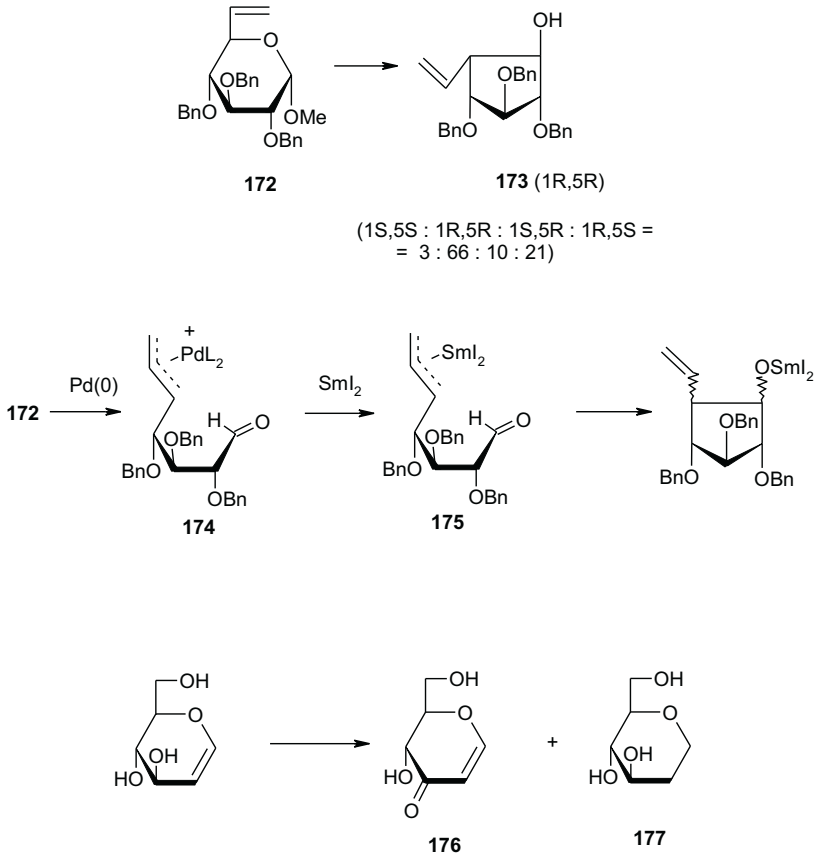


168 **167** **170** **171**

e. Miscellaneous reactions

2,3,4-Tri-O-benzyl-5-vinylcyclopenta-1,2,3,4-tetraols (**173**) can be obtained from protected methyl hexopyranosides by i. conversion to methyl 6,7-dideoxy-hept-6-enopyranosides (**172**), and ii. samarium diiodide ring contraction in the presence of catalytic amounts of $Pd(PPh_3)_4$ [85]. Vinylcyclopentatetraols **173** are obtained as mixtures of all four diastereoisomers at positions 1 and 5 with products 1,5-*trans* prevailing. However, original configuration at C-2,3,4 and 5 of starting *gluco, manno* and *galacto*pyranosides was retained in the five-membered rings. Scheme 31 exemplifies the ring contraction reaction on methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside. All stereoisomeric products were isolated and characterized.

Scheme 31



This reaction has earlier precedences, where ring contraction of methyl hexopyranosides was executed with zirconocene and boron trifluoride etherate leading to 1,5-*cis* stereoisomers as dominating products [86,87].

Interpretation of the results [85] is rationalized by assuming a Pd(0) ring opening of the heptenopyranoside what leads to a π-allylic palladium complex (**174**). Palladium is next reduced by SmI_2 to form complex **175**. Reaction of the liberated aldehyde with π-allylic samarium complex leads to the mixture of stereoisomeric vinylcyclopentantetraols hydrolyzed next to **173**.

Czernecki [88] found that Pd(II) salts display oxidizing properties. Free D-glucal treated with $PdCl_2$-NaOAc and n-Bu_3N in DMF containing 1% of water gave 1,2-en-3-one in 43–95% yield. However, when D-galactal was oxidized under these conditions, a mixture of OH-4 epimeric enones (*erythro* and *threo*) was obtained. Hayashi [89,90] extended these studies by finding that $Pd(OAc)_2$ taken in catalytic amounts in MeCN or DMF solution converted D-glucal to the corresponding 3-ulose **176** and 1,2-dihydro-D-glucal (**177**), both formed in approximately equal amounts and high overall yield. Obviously, palladium acetate (or palladium precipitate formed

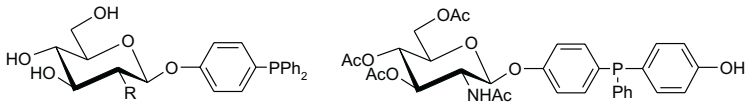
in this reaction) forms an alkoxide with the allylic OH group of D-glucal, and then an abstraction of a hydride follows. This hydride is next transferred to the double bond of the second sugar molecule. The authors performed this reaction in the presence of ethylene or, more conveniently, of vinyl acetate and found that 3-ulose was formed as the major (or exclusive – depending on reaction conditions) product in high yield. As the side product ethyl acetate was detected. Similar dehydration process was observed also for D-galactal and L-rhamnal. This oxidation means a nice improvement over the pioneering work of Czernecki.

For two-phase Suzuki, Heck and hydroformylation reactions several hydrophilic, carbohydrate-bearing phosphines (*e.g.* **178–180**, Scheme 32) have been synthesized [91]. The phosphines were mixed with palladium(II) acetate and the reactions were conducted in biphasic mixtures, *e.g.* ethanol/water/toluene 2:1:3 in the Suzuki coupling, or ethylene glycol/xylene 1:1 in the Heck reaction. These new catalysts exhibited an activity comparable to tris(*m*-sulfonatophenyl)phosphine (TPPTS)–$Pd(OAc)_2$ system, however, with distinctly higher turn-over numbers [91].

Hydrophilic TPPTS-$Pd(OAc)_2$ catalyst was used also in sucrose-butadiene telomerization performed in water [92] or isopropanol-water mixtures [93]. The reaction led to mono- and di-octadienyl ethers located at positions 1′ (major product) and 1′,4′ (minor) in the fructofuranose rest.

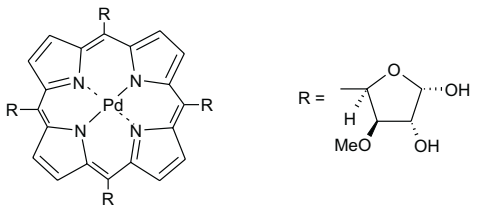
Tetra-*C*-glycosylated palladoporphyrin (**181**) [94] strictly taken, does not represent a Pd-sugar structure. However, this work is reported here as an example of modern approach to compounds playing a potential role as photoactive reagents for the cleavage of double strand DNA. The basic skeleton was obtained in low (6%) yield by BF_3 etherate-catalyzed condensation of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose with pyrrole followed by DDQ oxidation. The product obtained was next reacted with $Pd(OAc)_2$ and de-isopropylidenated with 75% aq. trifluoroacetic acid. Compound **181** was an active photocleavage reagent, whereas the corresponding Zn and Ni complexes did not show any DNA-cleaving activity [94].

Scheme 32



178 R = OH
179 R = NHAc

180



181

CONCLUSIONS

Palladium catalysts, with palladium at different oxidation stages (usually 0 or II), have demonstrated their immense synthetic potential in practically all fields of organic chemistry [5,95–99]. No wonder, therefore, that several palladium complexes have found valuable applications also in carbohydrate chemistry.

Especially valuable is the availability of Pd complexes with a variety of ligands. It has been shown many times that appropriate ligands can create an active catalyst in a given reaction. On the other hand, even the same ligands can produce completely inert catalysts in another, similar reaction. Therefore, manipulation with complex-forming compounds extends the usefulness of this metal. A thorough introduction to the existing literature by a newcomer can greatly facilitate the proper choice of a necessary palladium catalyst for the work planned.

As it is shown in this review, a plethora of useful transformations have been performed up to now. However, there is no doubt that further developments are still awaiting in the field of the popular Heck reaction, as well as in reactions intermediated by π–allylic systems, not to mention other transformations.

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