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CROSS-COUPLING REACTIONS FOR THE SYNTHESIS OF *C*-GLYCOSIDES AND RELATED COMPOUNDS

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Abstract – Cross-coupling reactions provide versatile strategies for preparing hydrolytically stable *C*-glycosides and *C*-nucleoside analogues, which are of interest in the search for new biologically active molecules. Several types of cross-coupling reactions have been studied, including Heck, Suzuki, Stille and Negishi couplings. The aim of this work is to review the state-of-the-art in that sort of reactions applied to the synthesis of *C*-glycosides and related compounds.

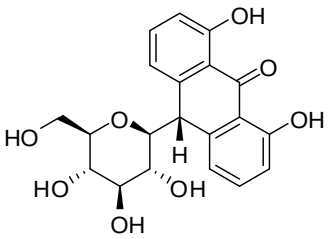
CONTENTS

This paper is dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

1. INTRODUCTION

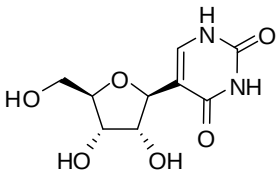
Cross-coupling reactions catalyzed by palladium and other transition metals are efficient and effective methods in the synthesis of a great variety of organic compounds. These transformations are of considerable interest due to their fundamental importance, as well as for their widespread occurrence in synthetic and catalytic processes.[1] In fact, there are a number of well-known name reactions that feature palladium as an excellent catalyst for cross-coupling reactions, including the Heck,[2] Suzuki,[3] Stille,[4] Negishi,[5] Hiyama,[6] Sonogashira,[7] Buchwald-Hartwig[8] and Heck-Matsuda[9] reactions. The importance of all these processes became evident when fundamental contributions to that topic by Ei-ichi Negishi, Akira Suzuki and Richard F. Heck were recognized with the 2010 Nobel Prize in Chemistry "*for palladium-catalyzed cross-coupling in organic synthesis*".[10] Among the myriad compounds that can be prepared by cross-coupling reactions, *C*-glycosides[11] and *C*-nucleoside analogues[12] are of particular interest because of their biological importance.

C-Glycosides are defined, by analogy with conventional *O*-glycosides, as those compounds in which the anomeric *exo*-oxygen has been replaced by a carbon atom, and they can be divided into aryl and alkyl *C*-glycosides. *C*-nucleosides are defined as those analogues to natural nucleosides in which the anomeric *exo*-nitrogen atom has also been replaced by a carbon atom. Usually, these analogues are limited to those bearing an (hetero)aromatic ring at the anomeric position. In both cases C-O and C-N bonds have been replaced by hydrolytically stable C-C bonds, which confer to the *C*-analogues particular and important biological activities.



aloin A

a C-glycoside



pseudouridine

a C-nucleoside

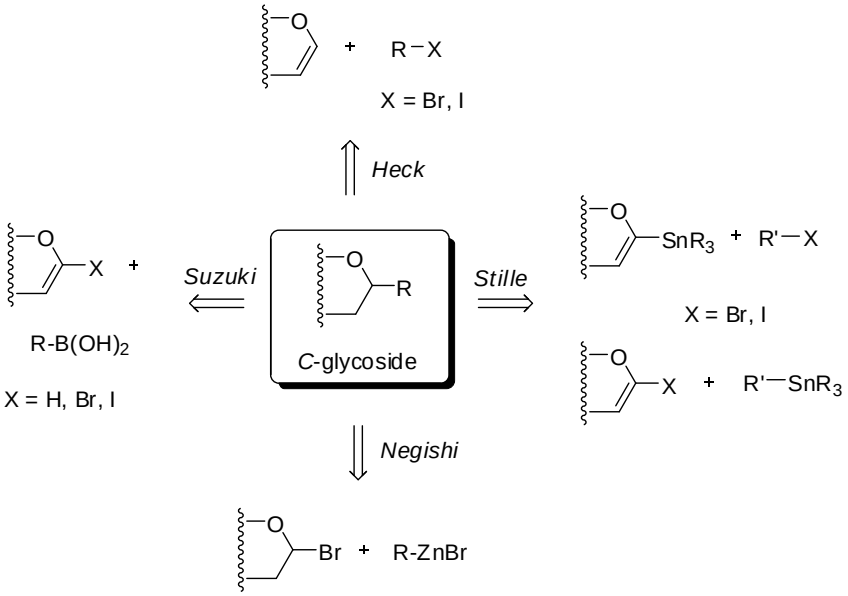
Figure 1

Even though the biological properties of *C*-glycosides and *C*-nucleosides are quite different with very diverse implication to biological processes, from a synthetic point of view they are closely related. Both types of analogues can be prepared by the direct incorporation of the alkyl, aryl or hetaryl moiety to the sugar framework. This approach is rather adequate to consider cross-coupling reactions as a suitable methodology.

Depending on the reaction different substrates are required. Glycals are suitable starting materials for incorporating the sugar unit due to their availability.[13] Glycals can be coupled with aryl halides (Heck

coupling) and boronates (Suzuki coupling). Halogenated glycals can be employed as substrates in Stille reactions with organostannanes, the opposite functionalization (stannylglycals with halides) being also possible. In addition to glycals, glycosyl bromides and iodides are also adequate starting materials for the reaction with organozinc compounds (Negishi coupling). The synthesis of *C*-glycosides and *C*-nucleosides has been reviewed elsewhere,[14] including the use of Heck reactions.[15]

In this report, the synthetic approaches outlined in Scheme 1 as well as related methodologies directed to the preparation of *C*-glycosides and related compounds will be discussed. Only approaches in which the sugar moiety is directed involved in the reaction are considered. Other syntheses where the carbohydrate is just a substituent are not considered. For the sake of clarity this review has been arranged by the type of reaction.

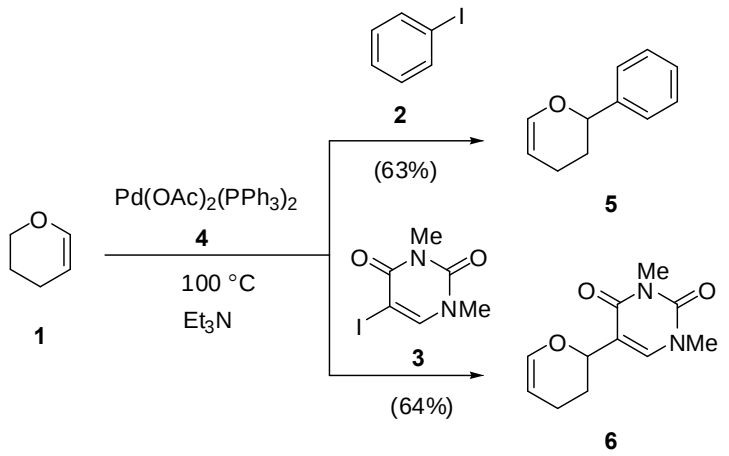


Scheme 1

2. HECK REACTIONS AND RELATED PROCESSES

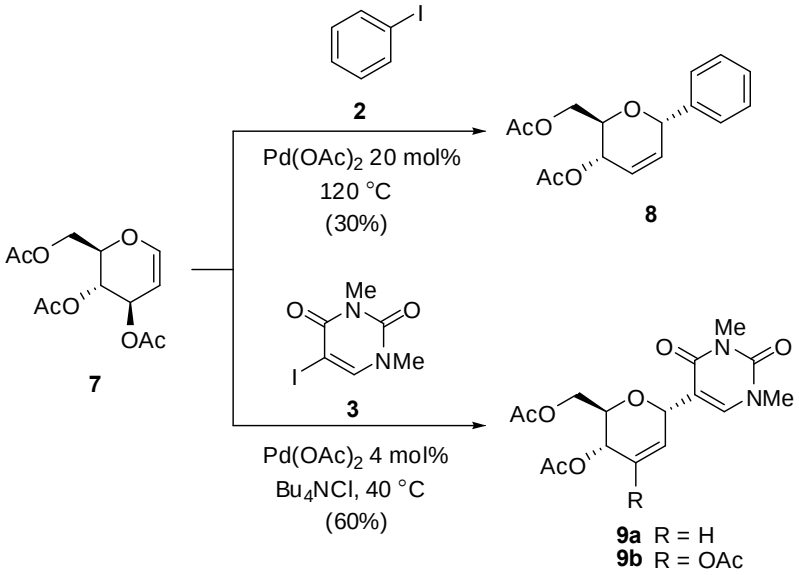
The Heck reaction involves an alkene containing at least one proton, an unsaturated halide (or triflate) and a base. It is carried out in the presence of an organopalladium catalyst.[16] Some variations in the reagents are possible and several reviews have been reported.[17] For general considerations and mechanistic discussion on Heck reaction the reader is directed to those revisions.

Coupling reactions between cyclic enol ether **1** and aryl compounds using a catalytic amount of palladium was reported for the first time by Daves and co-workers. Treatment of an excess of **1** with iodobenzene **2** and iodouracil **3** in the presence of 1 mol% of catalyst **4** afforded **5** and **6**, respectively, in good yields (Scheme 2). The addition of both iodobenzene **2**[18] and iodouracil **3** took place with migration of the double bond,[19] which was attributed to the high temperature. For the reaction with iodobenzene the yield of **5** increased to 86% when catalyst was palladium on carbon.



Scheme 2

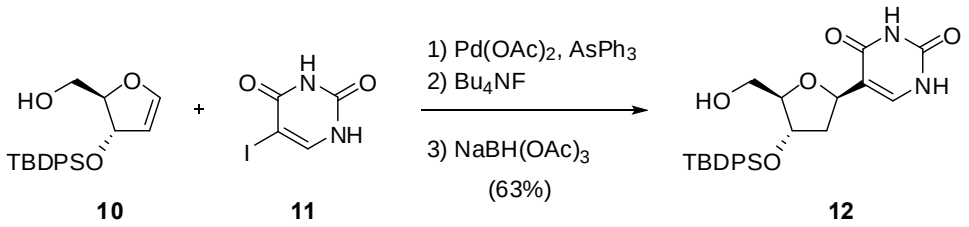
A similar reaction with glycal **7** and **2** using Pd(II) acetate as a catalyst required more temperature and the corresponding product **8**, showing migration of the double bond, was obtained in only 30% yield.[20] By carrying out the reaction with **3** at lower temperature and in the presence of additional tetrabutylammonium chloride, a 1:2 mixture of isomers **9a** and **9b** were obtained after 6 days in 60% combined yield (Scheme 3).[21] In the same paper it was also reported the efficient coupling of iododerivatives of anthracycline with furanoid and pyranoid glycals by using stoichiometric amounts of reactants, catalytic palladium(II) acetate and a tertiary amine using DMF as a solvent at room temperature.



Scheme 3

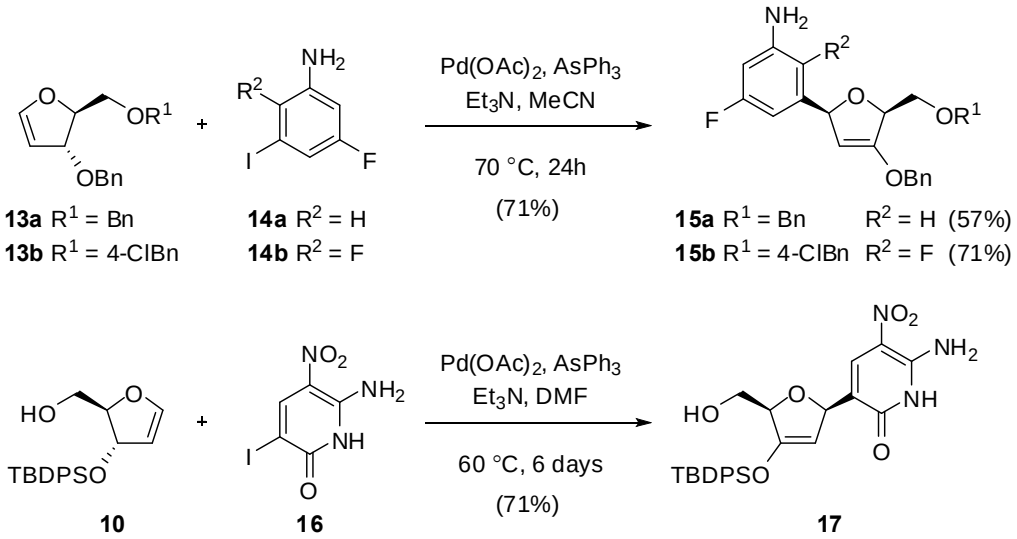
Glycal-derived enones also underwent palladium-mediated arylation to give mixtures of *C*-glycosides bearing an arylated enone and an arylated ketone.[22] Unprotected 5-iodouracil was coupled with glycal **10**

in the presence of catalytic palladium(II) acetate and triphenylarsine. The corresponding adduct was not isolated but used in a one-pot procedure to prepare 2'-deoxypseudouridine **12** as shown in Scheme 4.[23]



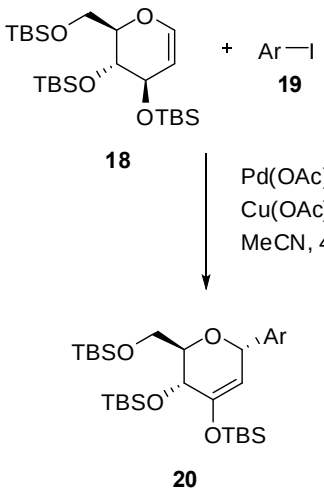
Scheme 4

Similar reactions leading to the same *C*-nucleosides have been reported by employing the mercuric acetate derivative of compound **3**.[24] Aryl iodides are excellent substrates for typical Heck reactions catalyzed by palladium(II) acetate in the presence of triphenylarsine and triethylamine. Cross-coupling reactions with furanoid derivatives provided important *C*-nucleoside analogues (Scheme 5). The reaction times can vary from 24 h[25] to several days.[26] The presence of protecting groups in the glycal should also be considered. Thus, it has also been reported a lack of reactivity for 4-hydroxymethyl furanoid glycals, bearing a bulky protecting group (i.e. *tert*-butyldimethylsilyl) at the 5'-hydroxyl group.[27]



Scheme 5

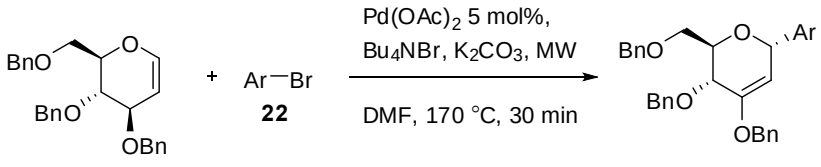
The addition of silver salts as additives contributed to increase the chemical yield of the reaction. Excellent results were obtained in the palladium-catalyzed Heck reactions between glycal **18** and several aryl iodides when the reaction was carried out in the presence of silver carbonate and copper (II) acetate. It has been proposed that silver carbonate could play a dual role by acting as a base and as a silver source to scavenge the iodide (Scheme 6).[28]



Ar	Yield (%)
2-MeC_6H_4	99
4-$MeOC_6H_4$	87
4-$NO_2C_6H_4$	59
4-$CF_3C_6H_4$	75
4-BrC_6H_4	82
4-ClC_6H_4	92
2-$MeO_2CC_6H_4$	94
1-naphthyl	95

Scheme 6

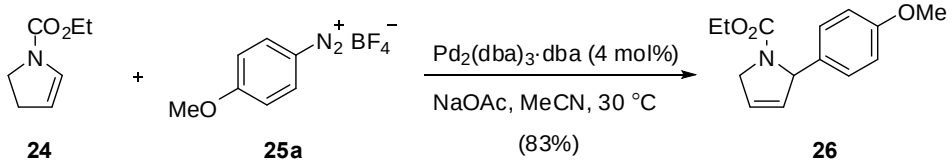
Microwave activation also provided good results for the reaction. As an example, in Scheme 7 the cross-coupling reaction between glycal **21** and several aryl bromides is illustrated. The methodology was applied to several perbenzylated glycals of different configurations and the corresponding *C*-aryl glycosides were obtained in a rapid and totally stereoselective way.[29]



R	Yield (%)
Ph	81
4-$MeOC_6H_4$	75
1-naphthyl	78

Scheme 7

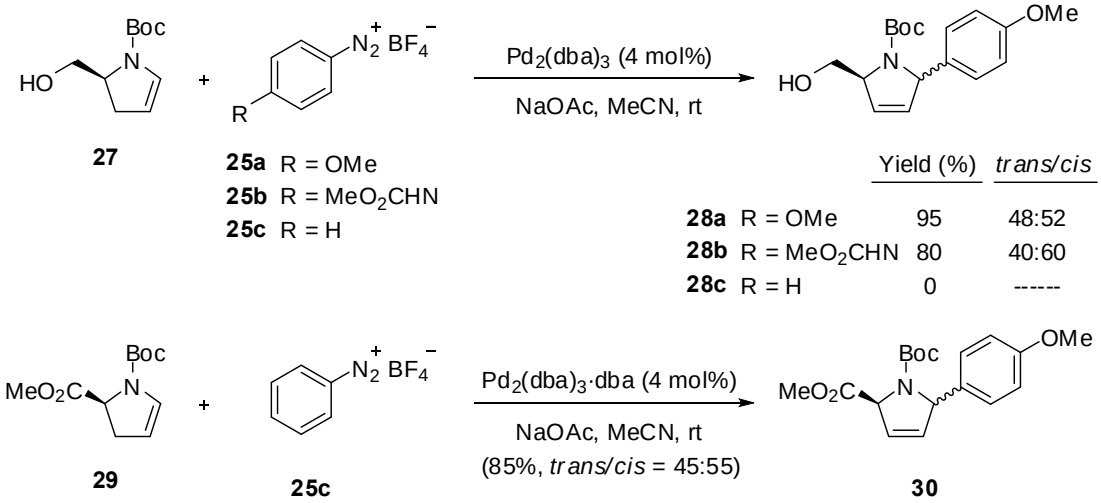
Aryldiazonium salts were used instead of aryl iodide in Heck reactions with five-membered enecarbamates en route to polyhydroxylated pyrrolidines, which can be considered iminosugar analogues. Correia and co-workers reported the Heck arylation of **24** to furnish Δ^3-pyrroline **26** (Scheme 8).[30]



Scheme 8

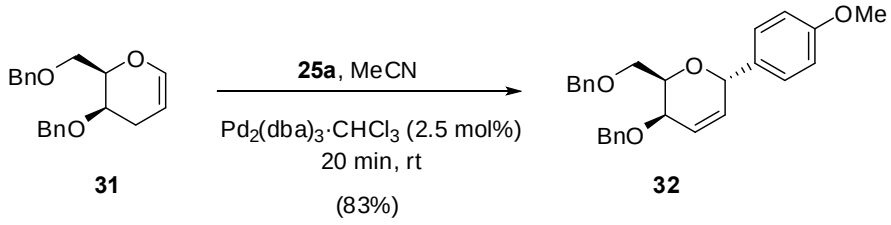
Arylation with arenediazonium salts is highly dependent on the substituents of the aromatic ring and on the nature of the group at C-5 on the enecarbamate. Whereas arylation of **27** is only feasible with salts

bearing electron-donating groups, arylation of **29** took place rapidly providing **30** as a mixture of isomers but in good yields (Scheme 9).[31] Compounds **28** and **30** were used in the synthesis of aza analogues of isoaltholactone and goniothalesdiol.



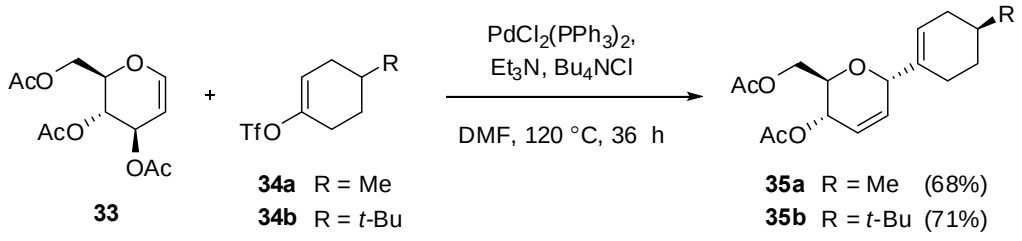
Scheme 9

Arenediazonium salts are also highly reactive with cyclic enol-ethers[32] including furanoid glycals bearing bulky protecting groups at 5'.[31] As an example, treatment of glycal **31** with **25a** in the presence of 2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ furnished *C*-aryl glycosides **32** in good yields as a single α-isomer, no undesired double bond migration being observed (Scheme 10).[33]



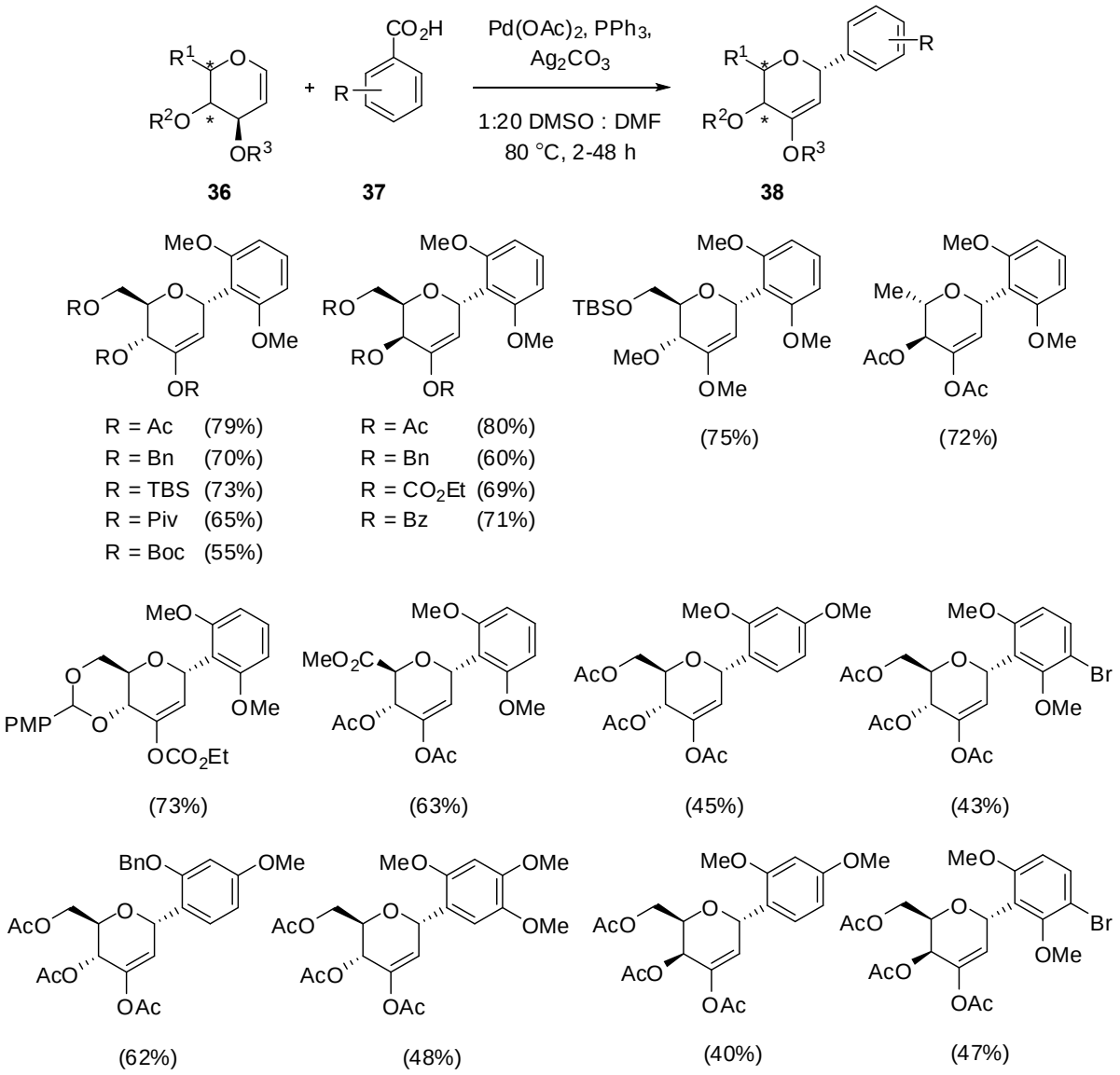
Scheme 10

Enol triflates **34** effectively reacted with glycals **35** in cross-coupling reactions that took place at the anomeric carbon providing exclusively α-isomers. The reaction presented a broad scope in both glycals and enol triflates.[34]



Scheme 11

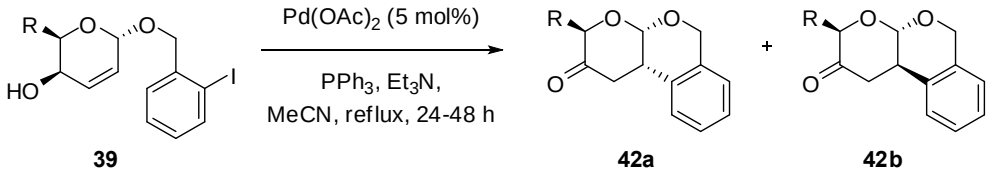
A decarboxylative Heck coupling reaction between glycals and benzoic acids has been reported by Liu and co-workers.[35] The reaction showed a broad scope and versatility affording the corresponding *C*-glycosides in moderate to good chemical yields but complete regio- and stereoselectivities (Scheme 12).



Scheme 12

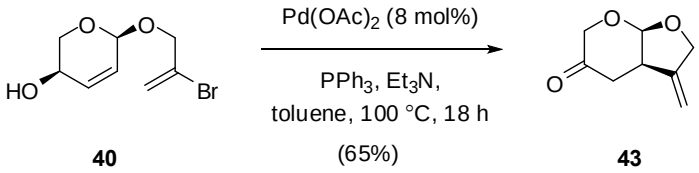
The intramolecular Heck reaction of glycosides **39-41** provided and entry to *cis*-fused bi- or tricyclic derivatives containing five- and six-membered oxa and carbocyclic rings in good yields (Scheme 13). Different reaction conditions were employed and similar results were obtained with acetonitrile and toluene as solvents. On the other hand, a mixture of isomers was obtained with **39** when triethylamine was used as a base but a complete selectivity was observed with silver carbonate. Indeed, the formation of isomeric mixtures was attributed to further epimerization after the cross-coupling reaction.[36]

The obtention of fused bicyclic compounds with exocyclic bonds like **43** was also observed with carbohydrate templates bearing the alkoxyalkenyl moiety at C-3 in a Heck reaction catalyzed by the system $Pd(OAc)_2/PPh_3$ in the presence of triethylamine and Bu_4NHSO_4.[37]

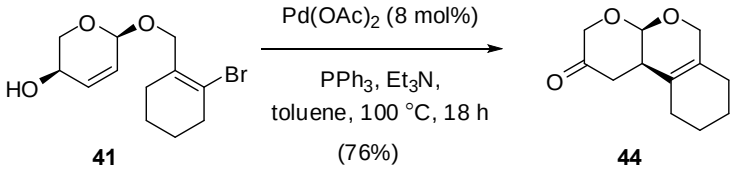


39 **42a** **42b**

R	Yield(%)	**42a** : **42b**
H	81	100:0
Me	70	100:0
CH_2OH	78	72:28
CH_2OH	54	100:0 (with Ag_2CO_3)



40 **43**



41 **44**

Scheme 13

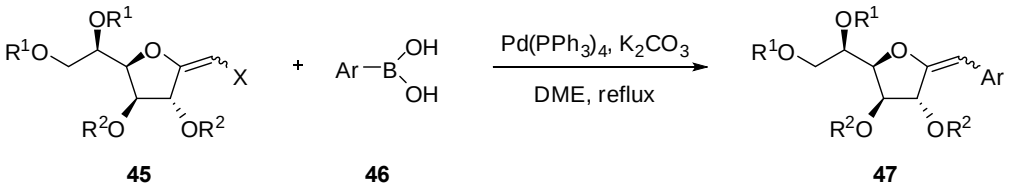
3. SUZUKI REACTIONS AND RELATED PROCESSES

The Suzuki coupling consists of the reaction between an aryl- or vinyl-boronic acid and an aryl or vinyl halide catalyzed by a palladium complex.[38] The reaction also works with triflates instead of halides and some organoboranes can be used in place of boronoic acids.

Cross coupling of halo-*exo*-glycals with boronic acids was reported by Lopez and co-workers.[39] The reaction took place in moderate to good yields upon catalysis with palladium (0). The reactivity of iodides is higher than that of bromides and alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive than those with electron-donating groups (Scheme 14). The reaction was also carried out with six-membered iodo-*exo*-glycals and both boronic acids and alkyl boranes produced good results.[40]

Dibromosubstituted *exo*-glycals underwent Suzuki coupling with aryl- and hetaryl-boronic acids but mixtures of monoarylated isomers and substrates incorporating two aryl units were obtained.[41] In the case of monosusbtituted *exo*-glycals, the remaining bromine atom was used to introduce a second aryl group through Pd-catalyzed cross-coupling. The approach can be considered highly versatile because of the

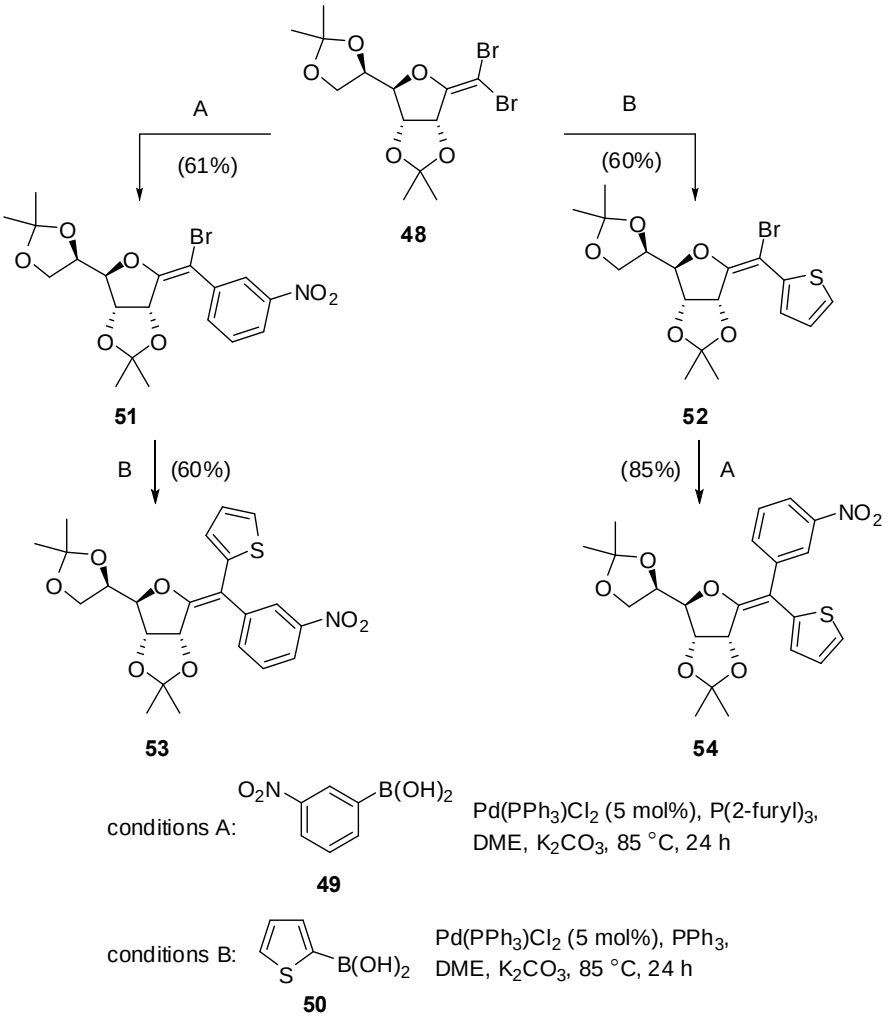
possibility of preparing any isomer in a stereochemically pure form just by exchanging the order of introduction of the aryl groups.[42] This is illustrated in Scheme 15 for compound **48**.



45 **46** **47**

R^1	R^2	Ar	X	t (h)	Yield (%)
Me_2C	H	4-$MeOC_6H_4$	Br	10	39
Me_2C	Ac	4-$MeOC_6H_4$	Br	10	58
Me_2C	Ac	Ph	Br	10	52
Me_2C	Ac	4-$HOCC_6H_4$	Br	3	68
Me_2C	Ac	4-MeC_6H_4	Br	10	48
Me_2C	Ac	2-thienyl	Br	20	53
Me_2C	Ac	4-$HOCC_6H_4$	I	1	75
Ac	Ac	4-$HOCC_6H_4$	Br	0.6	72

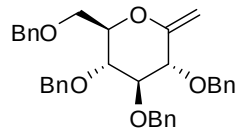
Scheme 14



48 **51** **52** **53** **54** **49** **50**

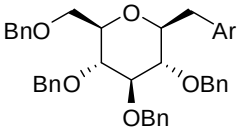
Scheme 15

Cross-coupling between organoboranes derived from *exo*-glycals and aryl halides was reported by Johnson and co-workers.[43] *Exo*-glycal **55** underwent smooth hydroboration to give the alkylborane which was coupled *in situ* with aryl halides under standard Suzuki conditions (Scheme 16).



55

1) 9-BBN, THF, reflux
2) $Pd(dppf)Cl_2$, K_3PO_4, Ar-X



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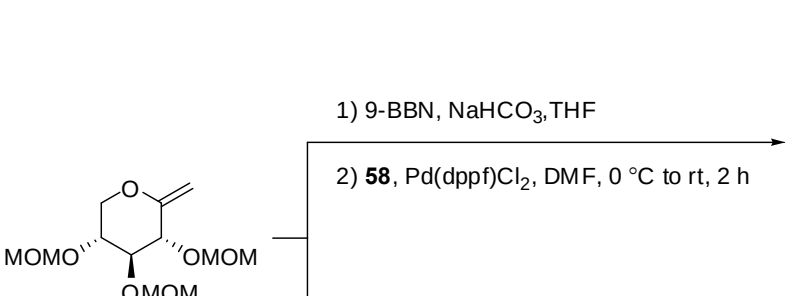
Ar	X	Yield (%)
Ph	Br	67
4-*t*-BuC_6H_4	Br	82
4-HOC_6H_4	Br	53
4-$HOCH_2C_6H_4$	I	74
4-$H_2NC_6H_4$	Br	60
4-BrC_6H_4	Br	60
4-PhC_6H_4	Br	63
2-pyridyl	Br	44
5-pyridyl	Br	21

Scheme 16

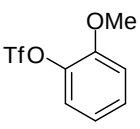
A similar approach was used for preparing *C*-glycoside analogues of phloriain, a specific inhibitor of sodium glucose co-transporter with antidiabetic properties.[44] Coupling of alkylboranes derived from glycals with aryl triflates was affected by steric hindrance of the aryl moiety. While coupling of the organoborane derived from **57** with triflate **58** took place smoothly at room temperature in 2 h, the same reaction with triflate **59** required stirring overnight at 80 ºC (Scheme 17).[45] The resulting adduct **61** was used in the preparation of the *C*-glycoside analogue of pseudopterosin A, a potent anti-inflammatory agent.[46]



57

1) 9-BBN, $NaHCO_3$,THF
2) **58**, $Pd(dppf)Cl_2$, DMF, 0 °C to rt, 2 h

1) 9-BBN, $NaHCO_3$,THF
2) **59**, $Pd(dppf)Cl_2$, DMF, 80 °C, overnight



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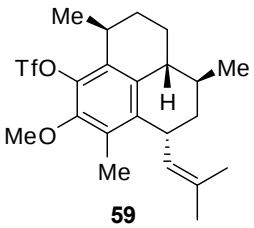

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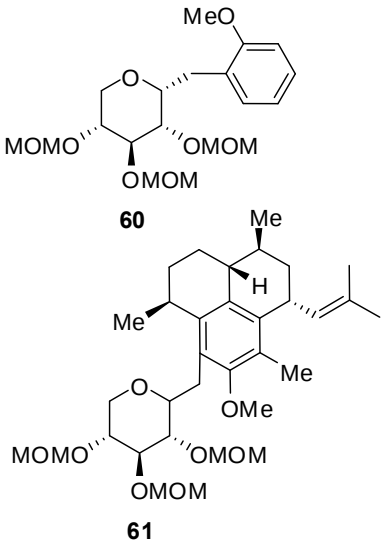
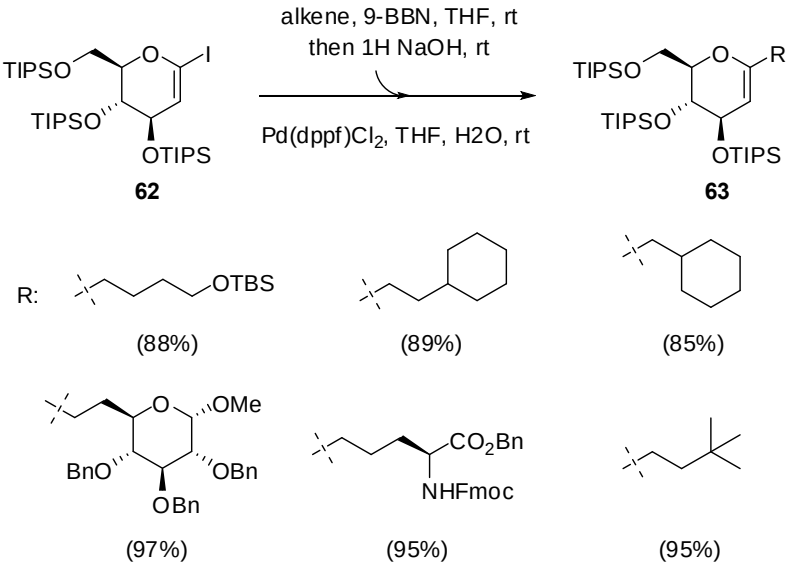


60 **61**

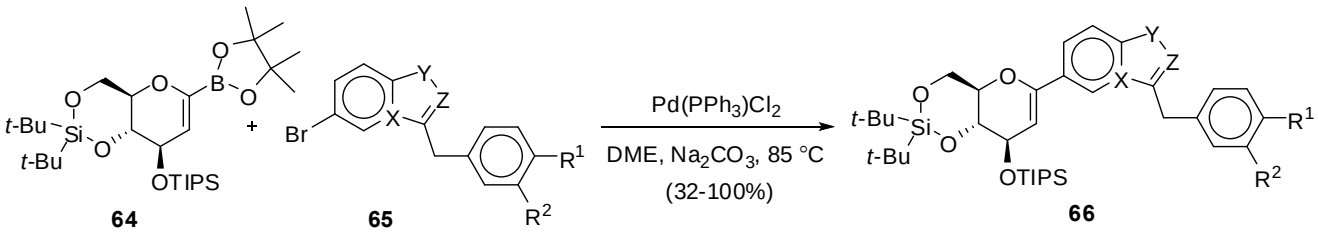
Scheme 17

Iodoglycal **62**, easily available from the parent glycal, was converted into C1-alkyl glycals by Suzuki coupling with alkylboranes prepared *in situ* from the corresponding olefins (Scheme 18).[47] 1-Iodoglycals were also coupled in a similar way with both boronic acids and boronates.[48]



Scheme 18

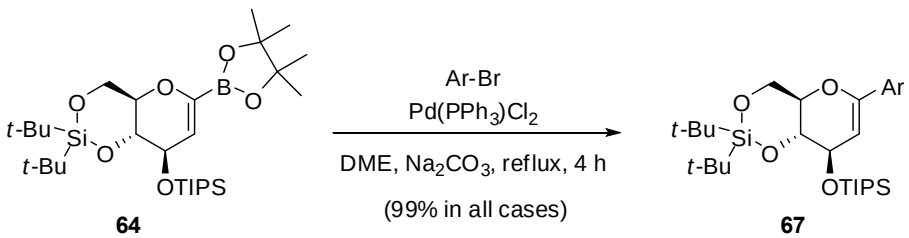
A variety of bromoheterocycles were made to react with *C*-glycosylpinacol boronate ester **64** under typical Suzuki conditions (Scheme 19).[49]



X = C, N Y = S, C, NH Z = N, C R^1 = H, Me, OMe, F, Cl, CF_3, Et, Ph, *i*-Pr, *t*-Bu, Cl R^2 = H, Me

Scheme 19

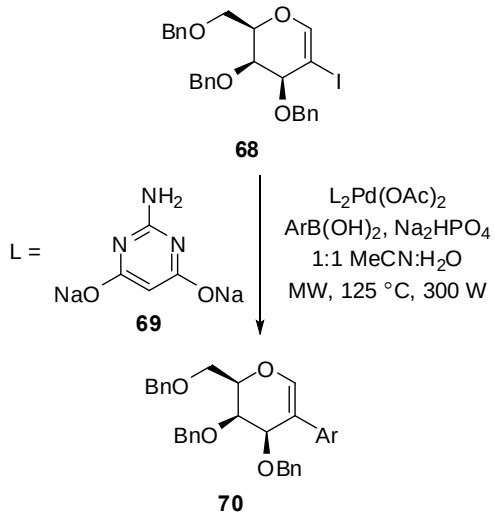
Compound **64** has also been employed for the synthesis of several 2-arylglycals through the Suzuki-coupling with aryl bromides (Scheme 20).[50] The reaction took place with excellent yields and an anti-HIV active berginin derivative was prepared to illustrate the synthetic utility of the methodology.



Ar = Ph, 4-$MeOC_6H_4$, 3-*t*-$BuO_2CC_6H_4$, 4-*t*-$BuO_2CC_6H_4$, 3-thienyl, 8-quinolyl

Scheme 20

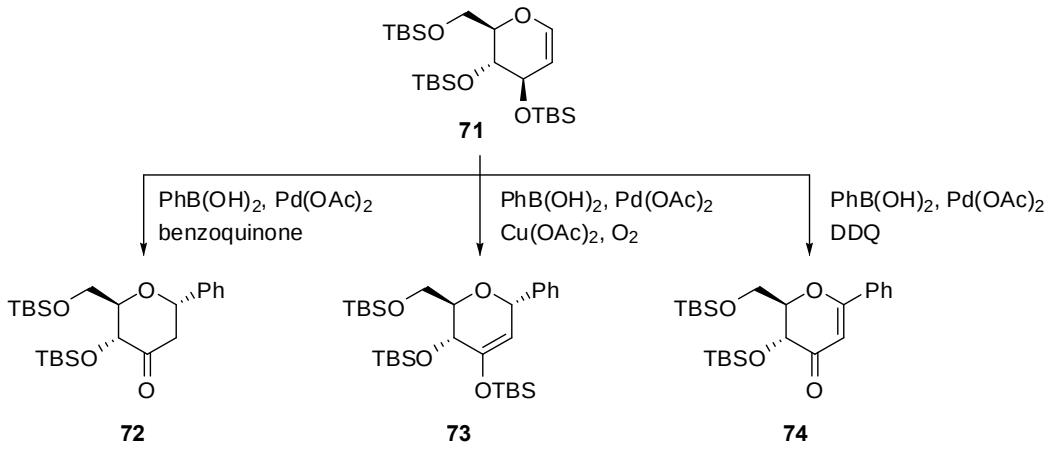
2-Arylglycals have been prepared through phosphine-free Suzuki coupling of 2-iodoglycals in aqueous media. The reaction of compound **68** with arylboronic acids in the presence of palladium catalyst was carried out under microwave activation. Under these conditions excellent yields were achieved in 5 min except in two cases that required 40 min of reaction (Scheme 21).[51] The scope of the reaction was also extended to various 2-iodoglycals differentially protected thus providing the methodology with a high versatility. Introduction of aryl groups at C-2 was also possible in iminoglycals (enecarbamates) by using phenylboronic acid and $Pd(dppf)Cl_2$ as a catalyst, in the presence of potassium phosphate.[52]



Ar	t (min)	Yield (%)
Ph	5	95
4-NCC_6H_4	5	95
4-$MeOC_6H_4$	5	95
4-FC_6H_4	5	90
2-MeC_6H_4	40	90
3-pyridyl	40	89
1-naphthyl	5	94
3,5-di$CF_3C_6H_3$	5	95

Scheme 21

The reaction of several glycals with various boronic acids using palladium(II) acetate as catalyst in the presence of various oxidants were reported by Ye and co-workers.[53] Depending on the oxidizing system different products were obtained as illustrated with glycal **71** (Scheme 22). In the presence of benzoquinone, ketone **72** was obtained; with $Cu(OAc)_2/O_2$ the enol ether **73** was the product of the reaction and with DDQ compound **74** was the only product of the reaction. All the reactions showed a broad scope in both the glycal and the arylboronic acid, proceeding in all cases with high regio- and stereoselectivities.

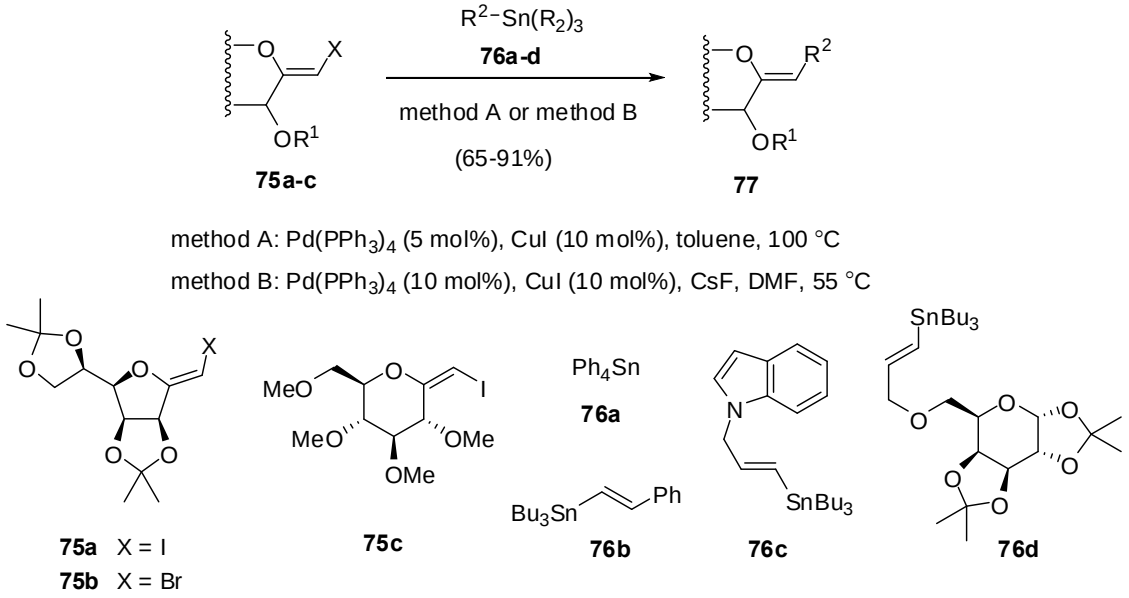


Scheme 22

4. STILLE AND HIYAMA REACTIONS AND RELATED PROCESSES

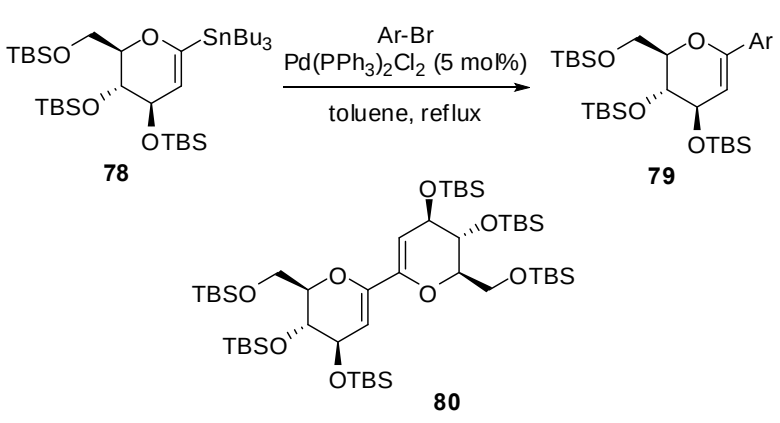
The Stille reaction is a coupling reaction between an organotin compound and a (hetero)aryl or vinyl halide, catalyzed by palladium.[54] The reaction should be carried out in an inert atmosphere and degassed solvents to avoid oxidation of the catalyst. The mechanism of the Stille reaction has been studied in detail and the reader is referred to the excellent reports published in the literature.[55]

Lopez and co-workers reported the stereocontrolled synthesis of substituted *exo*-glycals by Stille cross-coupling of (*Z*)-halo-*exo*-glycals and aryl or alkenylstannanes (Scheme 23).[56] The reaction was also applied to dibromo *exo*-glycals although mixtures of isomers were obtained.[41]



Scheme 23

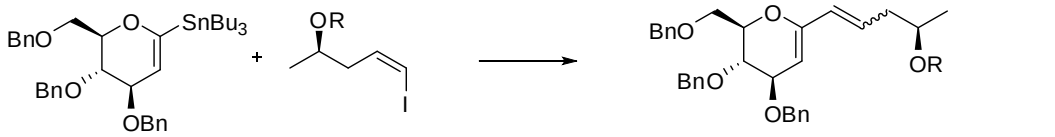
Stannylated glycals, easily available through direct metalation of glycals are excellent substrates for Stille coupling reactions with aryl and alkenyl halides. Friesen and Sturino reported the palladium-catalyzed coupling of aryl bromides and 1-(tributylstannyl)-D-glucal **78** (Scheme 24).[48,57] The reaction took place with moderate yields in most cases and minor amounts (8-15%) of dimer **80** were also obtained.



Ar	Yield (%)
Ph	41
4-$O_2NC_6H_4$	78
4-NCC_6H_4	81
4-$MeOCC_6H_4$	56
4-ClC_6H_4	49
2-MeC_6H_4	49
2-$AcOCH_2C_6H_4$	46
2-$AcOC_6H_4$	40
2-$BnOC_6H_4$	44
2,5-di-$MeOCC_6H_3$	65
1-naphthyl	59

Scheme 24

Similarly, stannyl-D-glucal **81** was coupled with alkenyl iodides **82** en route to avermectin (Scheme 25).[58] The reaction of *O*-TBS protected **82a** was catalyzed by 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ and **83a** was obtained in only 35% yield. By using unprotected alkenyl iodide **82b** and $Pd(MeCN)_2Cl_2$ as catalyst the yield of the reaction was increased to 57%.

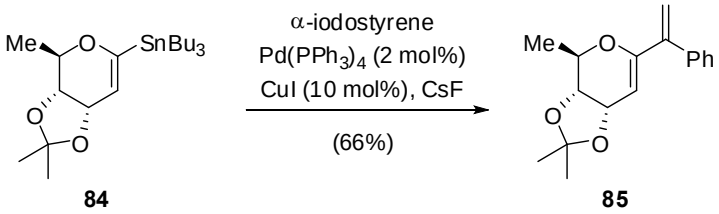


81 **82a** R = OTBS **83a** R = OTBS (35%, *Z*/*E* = 3:1 to 9:1)
82b R = H **83b** R = H (57%, *Z*/*E* = 3:1 to >16:1)

For **82a**: $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), DMF, 20 °C, 42 h
For **82b**: $Pd(MeCN)_2Cl_2$ (5 mol%), DMF, 20 °C, 42 h

Scheme 25

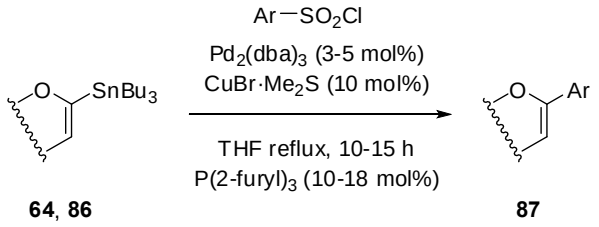
The reaction between stannyl-D-glucal **84** and α-iodostyrene using $Pd(PPh_3)_4$ as a catalyst in the presence of 10 mol% of CuI and CsF afforded adduct **85** in 66% yield (Scheme 26).[59] Compound **85** was used as an advanced intermediate for the synthesis of the antibiotic and antitumoral altromycin B.



84 **85**

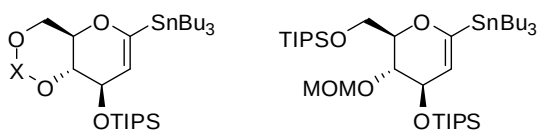
Scheme 26

A desulfurative Stille coupling between glycal **86** and aryl or benzylsulfonyl chlorides was reported by Vogel and co-workers (Scheme 27).[60]



64, **86** **87**

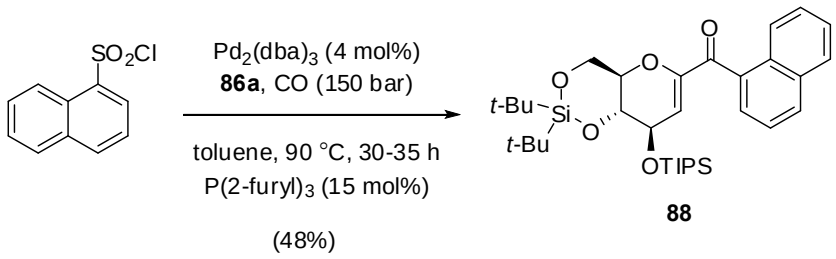
tinglycal	Ar	Yield (%)
64	1-naphthyl	58
64	4-MeC_6H_4	35
86a	1-naphthyl	69
86a	4-ClC_6H_4	54
86a	4-$O_2NC_6H_4$	50
86a	8-quinolyl	20
86a	benzyl	40
86b	benzyl	40
86b	1-naphthyl	66



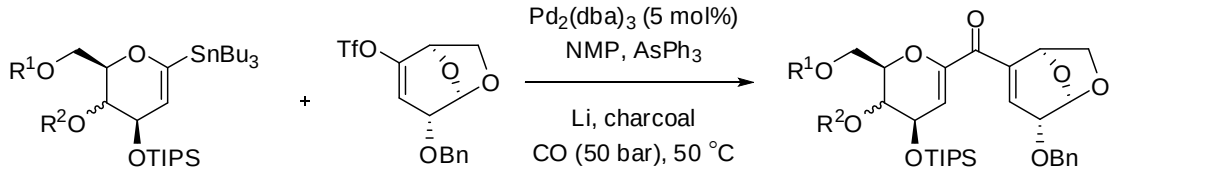
64 R = TIPS X = Si(*t*-Bu)$_2$ **86b**
86a R = TBS X = Me_2C

Scheme 27

When the reaction was carried out with **86a** and in the presence of carbon monoxide enone **88** was obtained together with some amounts (up to 15%) of an enone resulting from the homocoupling of **86a** (Scheme 28). This carbonylative Stille cross-coupling was employed by the same authors for synthesizing *C*-(1,4)-linked disaccharides.[61] The cross-coupling reaction between glycals **89** and triflate **90** afforded adducts **91** in good yields (Scheme 29). These adducts were further transformed into the target *C*-disaccharides.

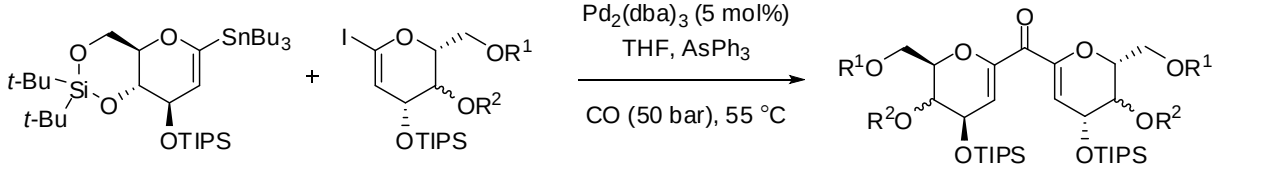


Scheme 28



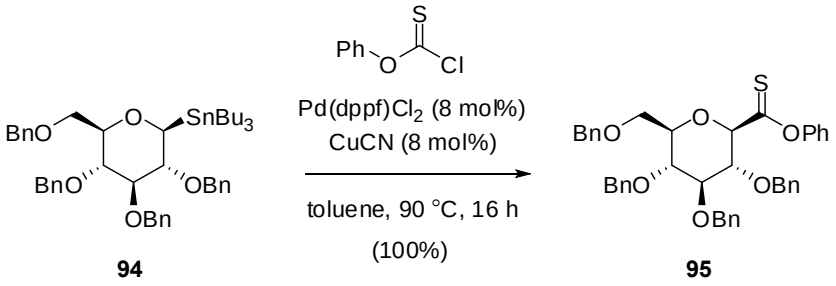
Scheme 29

The reaction showed to be sensitive to CO pressure. Indeed, no reaction took place and the starting materials decomposed below 40 bar. Also, the amount of LiCl is crucial and whereas with a Pd/LiCl ratio of 1:1 only a 23% yield is obtained, a 1:3 ratio increased the yield up to more than 70%. The reaction was also checked with iodoglycals **92** and the corresponding dienones **93** bearing two glycal units were obtained in good yields (Scheme 30).[61] In this case, using THF as a solvent led to better results than using *N*-methylpyrrolidinone (NMP).



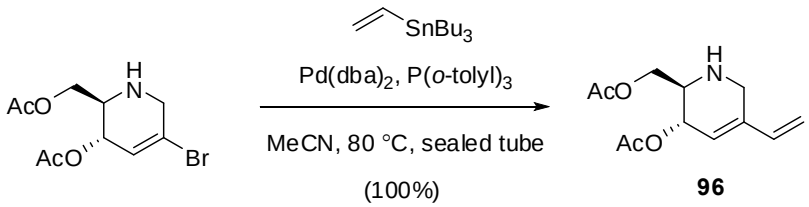
Scheme 30

Falck and co-workers described the use of stannyl glucopyranosides in cross-coupling reactions with thiono and thiochloroformates catalyzed by $PdCl_2$(dppf) and CuCN (8 mol% each) (Scheme 31).[62]



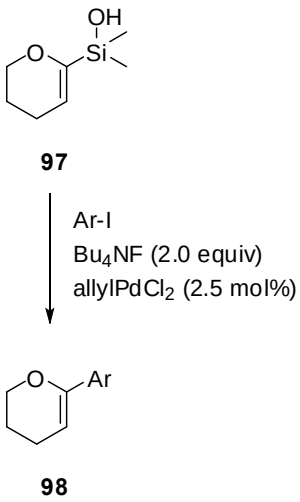
Scheme 31

Diene **96** was obtained through Stille coupling of vinyltributyltin with the corresponding imino bromo glycal (Scheme 32).[52]



Scheme 32

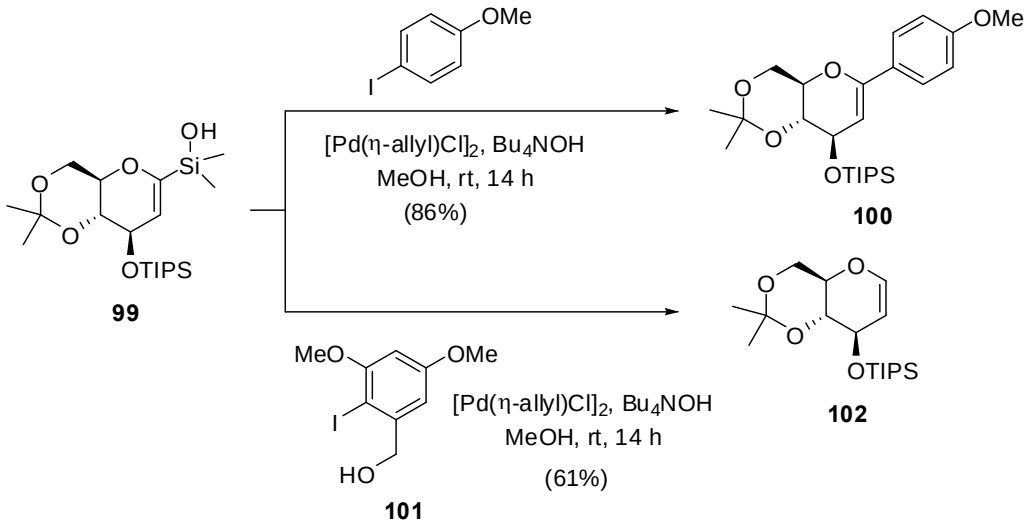
In a related process cyclic (α-alkoxyvinyl)silanol **97** was efficiently transformed into aryl vinyl ether **98** through a palladium(0)-catalyzed process. The reaction was activated by an excess of tetrabutylammonium fluoride and it took place with very good yields (Scheme 33).[63] This reactivity was employed for the preparation of an intermediate in the synthesis of the fungicide (+)-papulacandin D.[64]



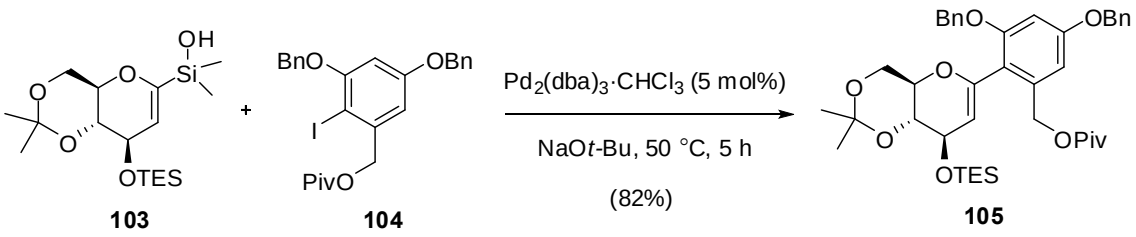
Ar	t (min)	Yield (%)
4-$EtO_2CC_6H_4$	10	84
3-$EtO_2CC_6H_4$	10	86
2-$MeO_2CC_6H_4$	240	92
2-$O_2NC_6H_4$	10	85
2-MeC_6H_4	20	80
2-$MeOC_6H_4$	10	74
2-$HOCH_2C_6H_4$	20	88
3-$AcOCH_2C_6H_4$	20	87

Scheme 33

The initial reaction showed to be rather sensitive to the iodide. Whereas cross-coupling between **99** and 4-iodoanisole took place in 81% yield, no reaction was observed with aryl iodide **101** and only desilylated glycal **102** was obtained (Scheme 34). On the other hand, after an optimization study it was found that differentially protected **103** reacted with **104**, in the presence of potassium *tert*-butoxide, to give the expected adducts in good yield (Scheme 35).[63,64]



Scheme 34



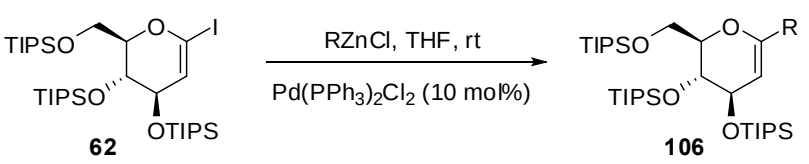
Scheme 35

5. NEGISHI REACTIONS AND RELATED PROCESSES

The Negishi coupling reaction involves an organozinc compound and an organic halide. The reaction is catalyzed by nickel or palladium catalysts, usually with phosphorous ligands.[65] Both organozinc halides and diorganozinc compounds can be used in this reaction and detailed mechanistic studies have been published on this respect.[66]

Friesen and co-workers reported the cross-coupling reaction between iodoglucal **62** and several metalated aromatics. Among them PhZnCl provided the corresponding adduct in 30 min (Scheme 36).[67] The

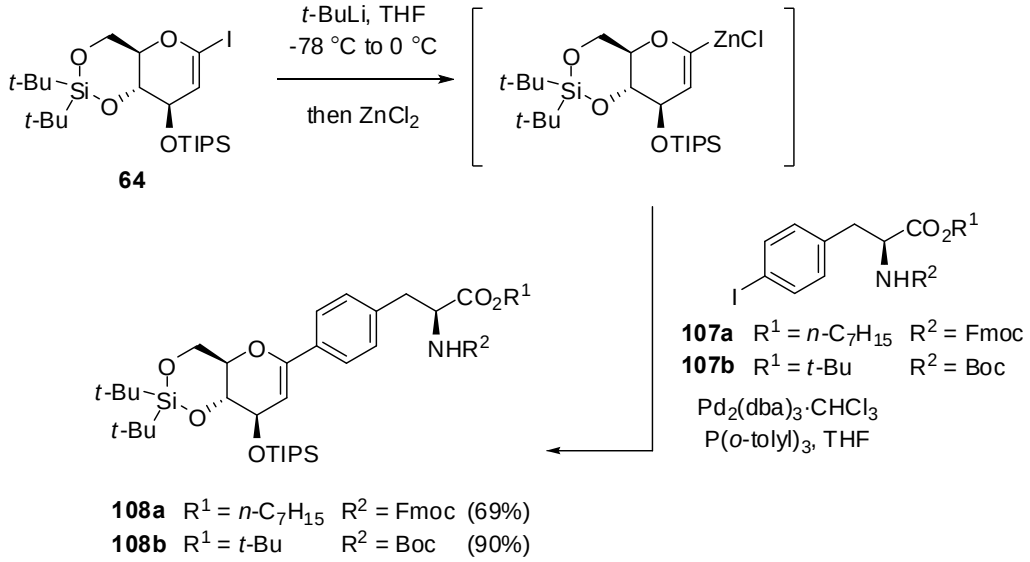
reaction required an excess of 4.0 equiv of organozinc chloride to go on completion and it can also be catalyzed by $Pd(PPh_3)_4$ although the reaction time was increased to 16 h.[48]



R	t (min)	Yield (%)
Ph	30	90
4-MeC_6H_4	15	73
2-furyl	30	79

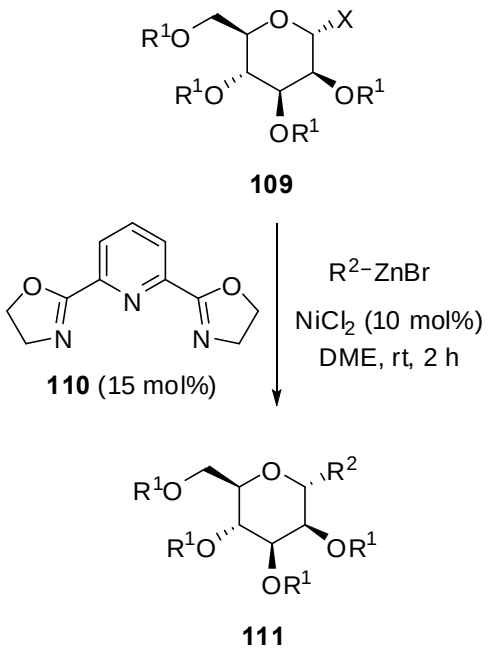
Scheme 36

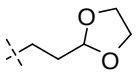
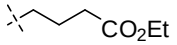
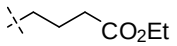
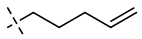
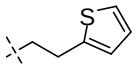
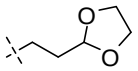
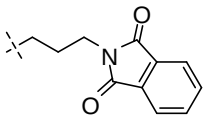
An organozinc compound was formed *in situ* from glucal **64** and made to react with iodides **107** in the presence of a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ and the bulky tris-(*o*-tolyl)phosphine (Scheme 37).[68] In the case of compound **108b** a 5% of homocoupling byproduct was also obtained.



Scheme 37

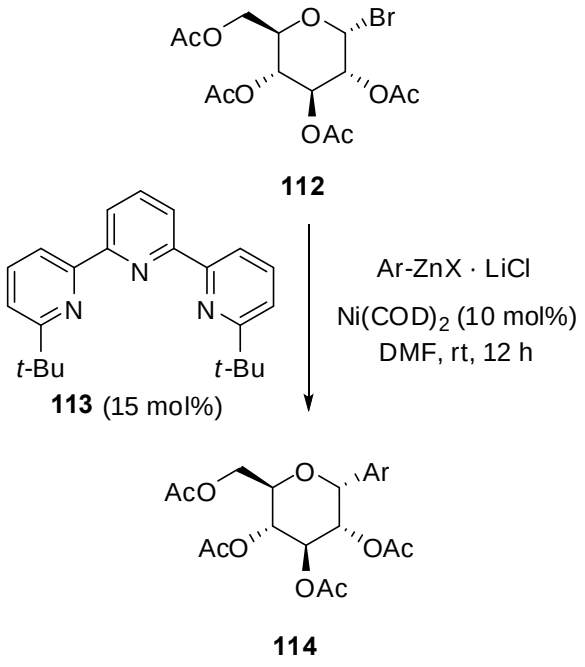
A Negishi cross-coupling between glycosyl halides and both alkyl and arylorganozinc compounds at room temperature was reported by Gagne and co-workers (Scheme 38).[69] Good yields of the corresponding *C*-glycosides were obtained by using unsubstituted Pybox ligands. The reaction showed a good selectivity particularly with mannosyl halides **109** (Scheme 38).



R^1	X	R^2	α:β	Yield (%)
Ac	Br		8:1	69
Ac	Br		8:1	70
Bn	Cl		1:0	76
Bn	Cl		1:0	40
Bn	Cl		1:0	43
Bn	Cl		1:0	65
Bn	Cl		1:0	61

Scheme 38

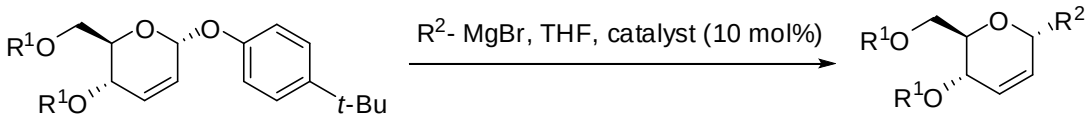
With glucosyl halides similar amounts of α- and β-anomers were obtained in the case of alkylzinc reagents. With aryl derivatives, D-glucosyl bromide **112** provided β-anomers with excellent selectivity (Scheme 39).[70] In all cases small amounts of the corresponding glycal were obtained. This technology was further applied to the total synthesis of salmochelins, a family of bacterial siderophores.[71]



Ar	X	α:β	Yield (%)
4-$MeOC_6H_4$	I	1:13	64
4-NCC_6H_4	I	1:12	79
4-$MeO_2CC_6H_4$	I	1:10	66
3-$MeO_2CC_6H_4$	I	1:14	72
3-ClC_6H_4	I	1:13	75
3-BrC_6H_4	I	1:14	77
3-IC_6H_4	I	1:10	30
2-thienyl	Br	1:16	78
3-thienyl	I	1:16	83
3-MeO-4-$MeO_2CC_6H_3$	I	1:13	82
3,4-diMeO-4-$MeO_2CC_6H_2$	I	1:11	69

Scheme 39

O-Glycosides reacted with functionalized aryl Grignard derivatives in the presence of catalytic amounts of Pd(dppf)Cl_2 to give *C*-arylglycosides having an α-configuration in excellent yields When the reaction was carried out with Ni(dppe)Cl_2 as a catalyst only the formation of α-isomers was observed. Both cross-coupling reactions proceeded under mild conditions and with complete regio- and stereoselectivities (Scheme 40).[72] The methodology was used for the synthesis of functionalized *C*-glycosides,[73] including analogues of phenylalanine.[74]



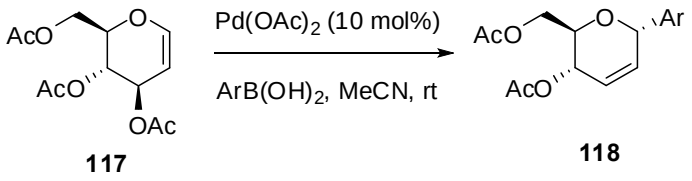
115 **116**

catalyst	R^1	R^2	T(°C)	t (h)	Yield (%)
Pd(dppf)Cl_2	Bn	Ph	25	2	95
Pd(dppf)Cl_2	TBS	Ph	25	2	80
Pd(dppf)Cl_2	Bn	4-MeC_6H_4	25	2	70
Pd(dppf)Cl_2	TBS	4-MeC_6H_4	25	2	70
Pd(dppf)Cl_2	Bn	2-MeC_6H_4	25	2	80
Pd(dppf)Cl_2	Bn	4-MeOC_6H_4	25	2	93
Pd(dppf)Cl_2	Bn	3-MeOC_6H_4	25	2	60
Pd(dppf)Cl_2	Bn	2-MeOC_6H_4	25	2	87
Pd(dppf)Cl_2	Bn	3,4-(CH_2O_2)C_6H_3	25	2	95
Pd(dppf)Cl_2	Bn	4-ClC_6H_4	25	2	76
Pd(dppf)Cl_2	Bn	4-TBSOC_6H_4	25	2	65
Pd(dppf)Cl_2	Bn	4-EtC_6H_4	25	2	72
Pd(dppf)Cl_2	Bn	2-thienyl	25	2	81
Pd(dppf)Cl_2	Bn	4-$(MeO)_2CHC_6CH_4$	25	2	65
Pd(dppf)Cl_2	Bn	2-naphthyl	0	1	78
Pd(dppf)Cl_2	Bn	2-benzyl	25	2	70
Pd(dppf)Cl_2	Bn	allyl	-10	4	72
Ni(dppe)Cl_2	Bn	Ph	-40	2	70
Ni(dppe)Cl_2	TBS	Ph	-40	2	83
Ni(dppe)Cl_2	Bn	4-MeC_6H_4	-40	2	85
Ni(dppe)Cl_2	TBS	4-MeC_6H_4	-40	2	83
Ni(dppe)Cl_2	Bn	4-MeOC_6H_4	-40	2	75
Ni(dppe)Cl_2	Bn	3-MeOC_6H_4	-40	2	60
Ni(dppe)Cl_2	Bn	2-MeOC_6H_4	-20	2	64
Ni(dppe)Cl_2	Bn	3,4-(CH_2O_2)C_6H_3	-40	2	70
Ni(dppe)Cl_2	TBS	4-ClC_6H_4	10	2	60
Ni(dppe)Cl_2	Bn	4-TBSOC_6H_4	-40	2	90
Ni(dppe)Cl_2	TBS	4-TBSOC_6H_4	-40	20	81
Ni(dppe)Cl_2	TBS	4-MOMOC_6H_4	-40	2	80

Scheme 40

6. OTHER REACTIONS

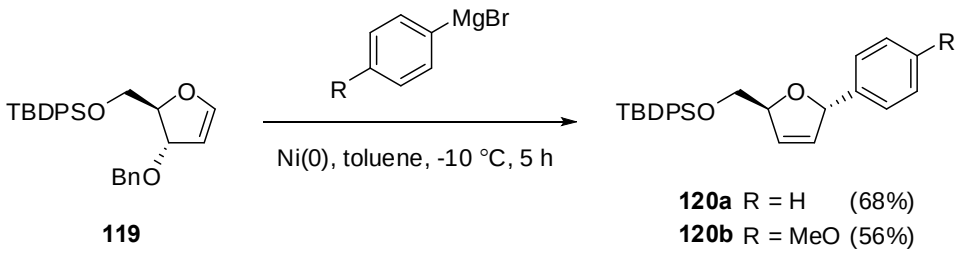
Maddaford and co-workers reported the direct coupling between peracetylated glycals and aryl boronic acid in the presence of catalytic palladium(II) acetate.[75] The reaction took place through a *syn* addition of a σ-aryl-Pd complex to the glycal double bond followed by *anti* elimination of palladium(II) acetate, which close the catalytic cycle. The final result of the reaction is the *C*-arylation and migration of the double bond with loss of the acetoxy group at C-3 showing a Ferrier-type substitution reaction (Scheme 41). In some cases, particularly with aryl derivatives substituted with an electron-donor group, an open-chain byproduct was observed.[76a] Such a byproduct was also observed with furyl-3-boronic acid.[76b]



Ar	Yield (%)
Ph	82
4-$MeOC_6H_4$	79
2-MeC_6H_4	77
4-$F_3CC_6H_4$	55
4-ClC_6H_4	57

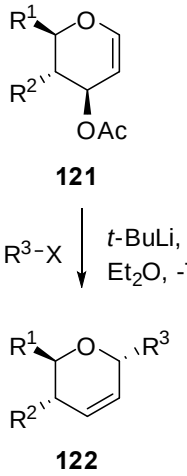
Scheme 41

The reactivity of furanoid and pyranoid glycals toward Grignard reagents in the presence of a nickel catalyst was studied by Tingoli and co-workers.[77] Only aryl Grignard reagents reacted, and with pyranoid systems open-chain adducts were obtained. On the other hand, with furanoid glycal **119** the adducts **120** were obtained in a similar reaction to that showed in Scheme 21 (Scheme 42).



Scheme 42

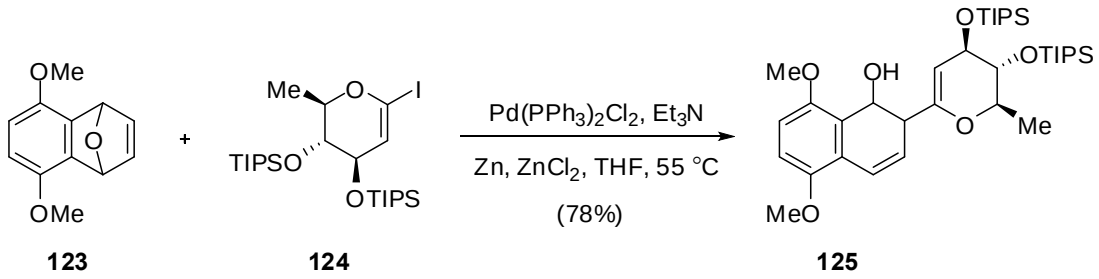
The direct addition of organozinc compounds to glycals was reported by DuBois and co-workers.[78] Both aryl and alkyl organozinc compounds led to the corresponding *C*-glycosides in good yields and stereoselectivities (Scheme 43).



R^1	R^2	R^3	X	Yield (%)
$BnOCH_2$	H	2-$TBSOC_6H_4$	Br	82
$BnOCH_2$	H	4-$MeOC_6H_4$	I	81
$BnOCH_2$	H	2-thienyl	Br	74
$PhCH_2CH_2$	H	4-$F_3CC_6H_4$	Br	78
$PhCH_2CH_2$	H	4-$MeOC_6H_4$	Br	88
$PhCH_2CH_2$	H	4-FC_6H_4	Br	85
$PhCH_2CH_2$	H	2-benzofuryl	I	66
$TBSOCH_2$	AcO	2-thienyl	Br	69
$TBSOCH_2$	AcO	2-$TBSOC_6H_4$	Br	75
$TBSOCH_2$	AcO	4-$F_3CC_6H_4$	Br	77
$PhCH_2CH_2$	H	$EtO_2CH_2CH_2$	I	72
$TBSOCH_2$	H	$EtO_2CH_2CH_2$	I	72
$PhCH_2CH_2$	H	EtO_2CH_2	I	60
$TBSOCH_2$	H	$EtO_2CH_2CH_2$	I	60
$PhCH_2CH_2$	H	$H_2C=CH(CH_2)_3$	I	63
$TBSOCH_2$	H	$H_2C=CH(CH_2)_3$	I	63
$PhCH_2CH_2$	H	$EtO_2C(CH_2)_3$	I	67
$PhCH_2CH_2$	H	*t*-$BuO_2C(CH_2)_3$	I	69

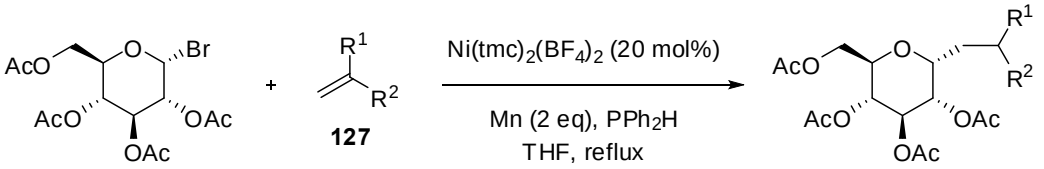
Scheme 43

The Pd-catalyzed opening of **123** with glycal **124** in the presence of Zn afforded **125**, which was further employed in the formal synthesis of galtamycinone (Scheme 44).[79]



Scheme 44

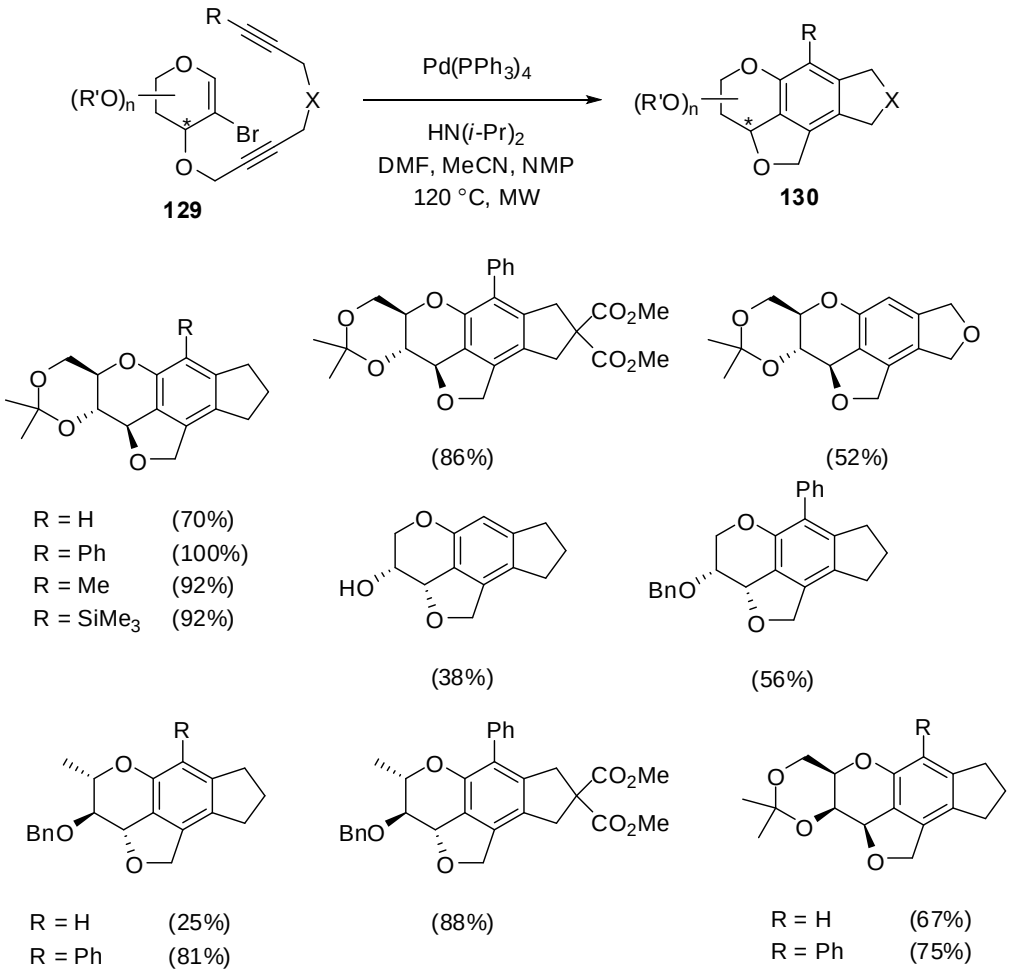
Glycosyl bromides **126** were coupled with alkenes in a radical-based reaction mediated by a readily available nickel catalyst. The reaction provided *C*-glycosides in good yields with alkenes bearing electron-deficient groups. Coupling with electron-rich alkenes was less successful. In general, the yields in the glucose series (Scheme 45) were slightly higher than those for the mannose series.[80] The reaction required 2.0 equiv of Mn and it was carried out in THF at reflux.



R^1	R^2	t (h)	Yield (%)
CO_2Me	H	5	69
CO_2Me	Me	4	98
CO_2n-Bu	H	6	6
CN	H	5	76
CO_2Me	NHZ	7	51

Scheme 45

Highly substituted chromans were prepared from carbohydrates through a domino process consisting of oxidative addition followed by two carbopalladation steps. The synthesis was completed by a cyclization to annelate the aromatic moiety (Scheme 46).[81] The corresponding isochromans were also prepared by following a similar strategy.



Scheme 46

7. CONCLUDING REMARKS

Cross-coupling reactions are one of the most efficient methods for creating carbon-carbon bonds. The past decades have witnessed remarkable developments of those reactions for preparing compounds of biological interest. Amongst these compounds, *C*-glycosides are of interest because of their stability against hydrolysis, which makes them excellent candidates for mimicking natural substrates and acting as competitive inhibitors of a variety of enzymes. With an eye toward biological relevance, cross-coupling reactions will undoubtedly continue to advance in a direction that benefits not only the organic chemical community but also biological and medicinal chemists.

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