NANYANG
TECHNOLOGICAL
UNIVERSITY

PALLADIUM CATALYZED REACTIONS ON GLYCAL SCAFFOLDS - SYNTHESES OF GLYCAL DERIVATIVES AND C-GLYCOSIDES

BAI YAGUANG

2014

PALLADIUM CATALYZED REACTIONS ON GLYCAL SCAFFOLDS - SYNTHESES OF GLYCAL DERIVATIVES AND *C*-GLYCOSIDES

BAI YAGUANG

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

2014

PALLADIUM CATALYZED REACTIONS ON GLYCAL SCAFFOLDS - SYNTHESES OF GLYCAL DERIVATIVES AND *C*-GLYCOSIDES

BAI YAGUANG

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2014

To my family

ACKNOWLEDGEMENTS

At the very first, I would like to express my greatest gratitude to my supervisor, Assoc. Prof. Dr. Liu Xue-Wei for helping me all the past 7 years from my undergraduate research to my PhD study. I would not be able to finish this thesis without his inspiring encouragement and intellectual advice throughout my PhD study. His patience and strong belief to me is greatly appreciated. I would also like to thank Assoc. Prof. Dr. Liu Chuan-Fa as my co-supervisor for his help to finish my PhD study.

My sincere appreciation is also due to two of my senior colleagues, Dr. Ma Jimei and Dr. Zeng Jing for their valuable guidance and suggestions. I am also grateful to Xiang Shaohua, Dr. Leow Min Li, Dr. Cai Shuting, Dr. Wu Junliang, Le Mai Hoang Kim, Dr. Seenuvasan Vedachalam, Tan Yu Jia, Leng Wei Lin and Liao Hongze for their continuous support, helpful collaboration and inspiring discussion.

I would also like to thank Dr. Li Yongxin and Dr. Rakesh Ganguly for their help of X-ray crystallographic analysis, and my thanks are also extended to Goh Ee Ling and Zhu Wenwei for their training and support on NMR and mass spectroscopy.

I am also thankful to NTU for the Nanyang President's Graduate Scholarship for supporting my PhD study and all CBC staffs for their generous help in different areas.

I would also like to give my special thanks to NTU Chinese Debating Squad for nurturing my philosophy by discussing and sharing topics such as art, humanity,

philosophy and economics. I would like to convey tremendous gratitude to my coach Dr. Xu Hailou for his precious guidance and to my friends Peng Shuai, Chan Wei Ping, Zhong Zhaohang and Hou Zhaoqi for preparing every debate topic together.

Lastly, I give my deepest thanks to my parents for their constant support from the first day of my life, and to my wife for providing me a home of comfort, peace and happiness in Singapore.

TABLE OF CONTENTS

Chapter 1. Palladium-Catalyzed Direct Cross-Coupling of Glycals with Activated Alkenes

Chapter 2. Palladium Catalyzed Stereoselective *C*-Glycosylation of Glycals with Enol Triflates

Chapter 3. Oxidative Heck Reaction of Glycals and Aryl Hydrazines: a Palladium-Catalyzed *C*-Glycosylation

Chapter 4. Palladium and N-Heterocyclic Carbene Dual Catalyzed *C*-Glycosylation of Glycals and (*o*-azaaryl)carboxaldehydes

ABSTRACT

Glycals are a group of carbohydrate derivatives which were first synthesized more than a century ago. The reactive carbon-carbon double bond between C1 and C2 has stimulated a huge number of efforts to develop new carbon-carbon bond formation methods to transform glycals into other carbohydrate analogues and various useful synthetic building blocks.

Palladium catalyzed carbon–carbon bond formation reaction has become a fast growing area of chemistry due to its versatility and chemo selectivity. Palladium catalyzed reactions such as Heck–Mizoroki reaction, Suzuki reaction and Tsuji–Trost reaction have been intensively studied in the past decades. This thesis focuses on applying palladium chemistry to glycals to develop new methodologies on glycal functionalizations.

In the first chapter, a new $Pd(OAc)_2$ catalyzed direct alkene-alkene coupling of glycals and other alkenes such as acrylates and styrenes is described. The concept of this methodology is to apply the palladium catalyzed C–H activation on glycal functionalizations. The coupling reaction selectively takes place on C2 of the glycals to form sugar containing dienes.

In the second chapter, a Heck type *C*-glycosylation of glycals and enol triflates is demonstrated. In this reaction, the Nobel winning Heck reaction is applied on glycals to give exclusively C1 regioselectivity and α stereoselectivity. The substrate scope includes glycals from different sugar origins and enol triflates of different sizes.

Another Heck type α selective *C*-glycosylation methodology of glycals and aryl hydrazines towards aryl-*C*-glycosides is reported in the third chapter. The mechanism of α selectivity is also studied in this chapter.

In the last chapter, a dual catalyzed reaction by integrating the renowned palladium catalyzed Tsuji–Trost reaction and NHC catalysis is introduced. The two catalysts exert their effects simultaneously and parallelly to afford the nucleophilic addition product. The concept is first tried on simple allylic system and then on glycals with ethoxycarbonyloxyl protecting group on C3. In both cases, the aldehyde origins of the nucleophilic Breslow intermediate are *o*-azaarylcarboxaldehydes.

INDEX OF ABBREVIATIONS

δ	chemical shift
^{o}C	degree centigrade
Ac	acetyl
AcOH	acetic acid
Aq	aqueous
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	1,4-benzoquinone
brs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
calcd.	calculated
cat.	catalytic
CDCl$_3$	deuterated chloroform
CHCl$_3$	chloroform
conc.	concentrated
d	doublet
DABCO	1,4-diazabicyclo[2.2.2] octane
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
DCE	dichloroethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(*N*,*N*-dimethyl-amino) pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DiPPF	1,1'-bis(diisopropylphosphino)ferrocene
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
DPPPen	1,5-bis(diphenylphosphino)pentane
DtBPF	1,1'-bis(ditertbutylphosphino)ferrocene
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
E	electrophile
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
Et$_3$N	triethylamine
EtOAc	ethylacetate
EtOH	ethanol

FTIR	fourier transfer infrared spectroscopy	NMR	nuclear magnetic resonance
g	gram	Nu	nucleophile
h	hour	*o*	ortho
HRMS	high resolution mass spectroscopy	OTf	trifluromethanesulfonate
Hz	hertz	*p*	para
IR	infrared	PDC	pyridinium dichromate
*i*Pr	isopropyl	Ph	phenyl
J	coupling constants	PMB	*p*-methoxybenzyl
kg	kilogram	PMP	*p*-methoxyphenyl
M	concentration (mol/L)	PPh_3	triphenylphosphine
M^+	parent ion peak	ppm	parts per million
m	multiplet	PPTS	pyridinium *p*-toluenesulfonate
m	meta		
Me	methyl	Py	pyridine
MeCN	acetonitrile	q	quartet
MeOH	methanol	rt	room temperature
mg	milligram	s	singlet
MHz	megahertz	sat	saturated
min	minute	t	triplet
mL	milliliter	TBAF	tetrabutylammonium fluoride
µm	micrometer		
mm	millimeter	TBS	tert-butyldimethylsilyl
mmol	millimoles	TBDPS	tert-butyldiphenylsilyl
mol	moles	TFA	trifluoroacetic acid
M.S.	mass spectrum	Tf_2O	triflic anhydride
Ms	methane sulfonyl	THF	tetrahydrofuran
*n*Bu	*n*-butyl	Ts	*p*-toluenesulfonyl
NHC	N-heterocyclic carbene	TMS	trimethylsilyl
NMP	N-methyl-2-pyrrolidone	v	volume

Chapter 1. Palladium-Catalyzed Direct Cross-Coupling of Glycals with Activated Alkenes

1.1 Introduction

Carbohydrates are a class of structurally similar molecules present ubiquitously in the world. Carbohydrate polymers can be found as main components of the cell wall in Tubacteria, Protista, Fungi, Archaebacteria and Plantae which constitute 5 out of 6 kingdoms of life. Other than acting as crucial cell structure materials, carbohydrate polymers such as glycogen and starch are common sources of energy in living organisms. Carbohydrates also play crucial roles in various physiological and pathological processes including cellular recognition, inter-cellular communication, immune responses, signal transduction, viral and bacterial infection and tumour metastasis.[1]

The abundant presence also makes carbohydrates and their derivatives ideal chiral starting materials in synthetic chemistry.[2] Of which, glycals are carbohydrate derivatives possessing a double bond between C1 and C2 of the 5 or 6-membered ring. The double bond provides lots of potential for further chemical transformations.[3] Chemical reactions on C1, namely the anomeric carbon, have provided a wide access to biologically and chemically important glycosides.[4] However, chemistry on C2 has been relatively unexplored.[5] Reactions on C2 can offer a cluster of C2 functionalized dihydropyrans whose utility has increased tremendously over the past decades as an important class of heterocycles. Functionalized dihydropyrans are widely present in natural products with various biological activities (**Figure 1.1**).[6]

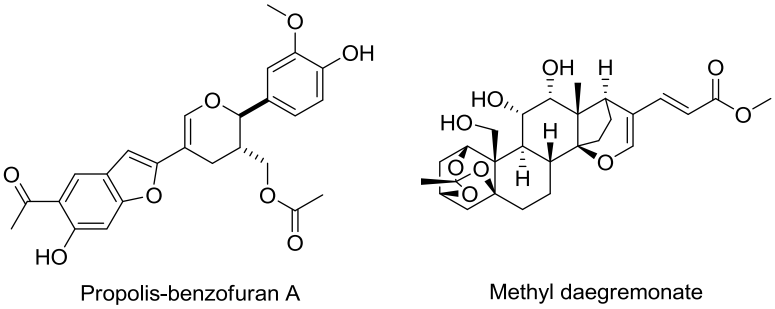


Figure 1.1. Pyran-containing natural products

Numerous methods to furnish multi-functionalized dihydropyran rings have been developed. Reported methods include Lewis acid and transition metal promoted intramolecular cyclizations,[7] Prins cyclizations[8] and heteroatom Diels-Alder reactions (**Figure 1.2**).[9] Most of these methods mainly focus on cyclization reactions to obtain pyran rings from precursors with existing functional groups.

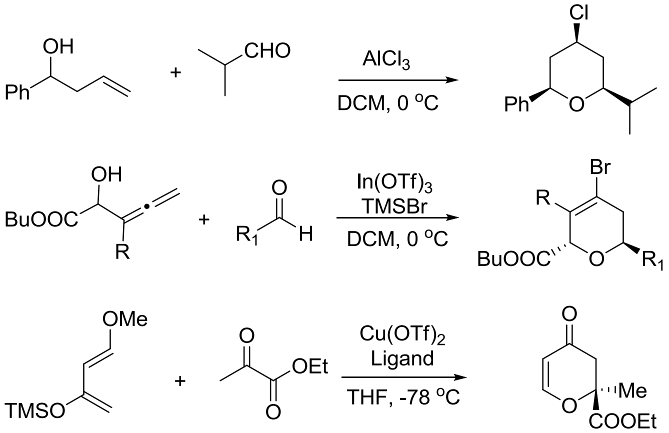


Figure 1.2. Recent publications on pyran formation

Since glycals are a group of optically pure unsaturated pyran compounds which can be potentially transformed to a wide range of functionalized pyran compounds, C2 functionalized glycals can offer the access to a large number of natural products. Amongst C2 functionalized glycals, formation of diene moiety (**Figure 1.3**) by attaching another alkene molecule has become increasingly promising because the diene can potentially serve as ideal building block to bi-cyclic natural products, such as Olivin,[10] Forslolin[11] and Jamesoniellede[12] by Diels-Alder cyclization (**Figure 1.4**).[13]

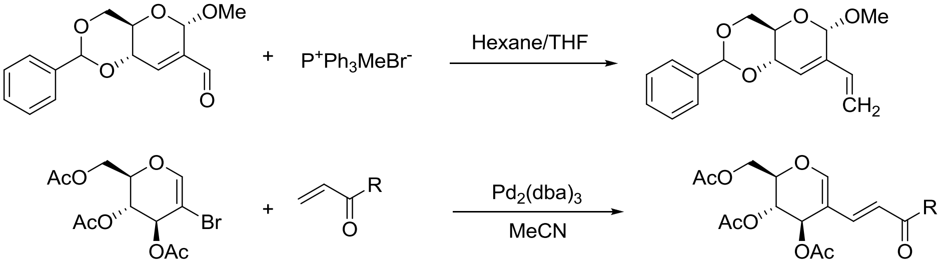


Figure 1.3. Reported methods for dihydropyran dienes

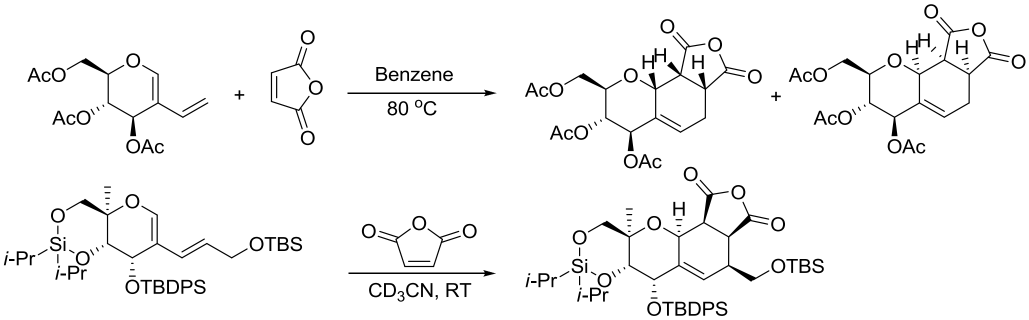


Figure 1.4. Diels-Alder cyclization of carbohydrate derived dienes

In the past decade, palladium catalyzed alkene-alkene direct coupling have attracted considerable attention.[14] Back in 1987, Maki's group reported the first palladium catalyzed alkene-alkene coupling of 5-(1-alkenyl)uracil derivatives and olefins.[15] In 2004, Ishii *et al*. published a $Pd(OAc)_2$ catalyzed oxidative coupling of acrylates with vinyl carboxylates.[16] A direct O_2 oxidative cross-coupling reaction of styrenes and acrylates was reported by Loh's group in 2009.[17] Another C–H alkenylation example using tetrahydronpyrido[1,2-*a*]pyrimidines and olefins was published in 2009 by Gallagher's group.[18] In 2010, Yu's group reported another direct coupling reaction of terminal alkenes and functionalized *α*-oxoketene dithioacetals (**Figure 1.5**).[19] All these reactions listed here have something in common. In all the cases, a palladium catalyst, usually palladium acetate was used as the catalyst. An oxidant is required as well in the form of oxygen gas or metal oxidants or both. Heating condition and polar solvent was also key conditions for C-H activation reaction.

Inspite of all these outstanding findings in C-H activation, the C-H activation reactions, especially alkene-alkene coupling reactions still need more efforts from chemists for the following reactions.

First, the substrate scope of this reaction is still limited. Among all of the five in **Figure 1.5**, three (reaction 1~3) of them can only report 8 examples due to the very narrow range of the left coupling partner. Not only in terms of product numbers, the substrate scope is also quite limited in the aspect of the types of starting material. Only one (reaction 1) example in the figure utilize the starting material from DNA and RNA. In the rest of the examples, all the materials are synthetic.

Second, none of the product in the previous reports is quite synthetically useful. The main value of all these examples is the value of the chemical method not the potential applications of the product. As a result, it is still necessary to add some synthetically useful products such as the glycal dienes to the C-H activation product library.

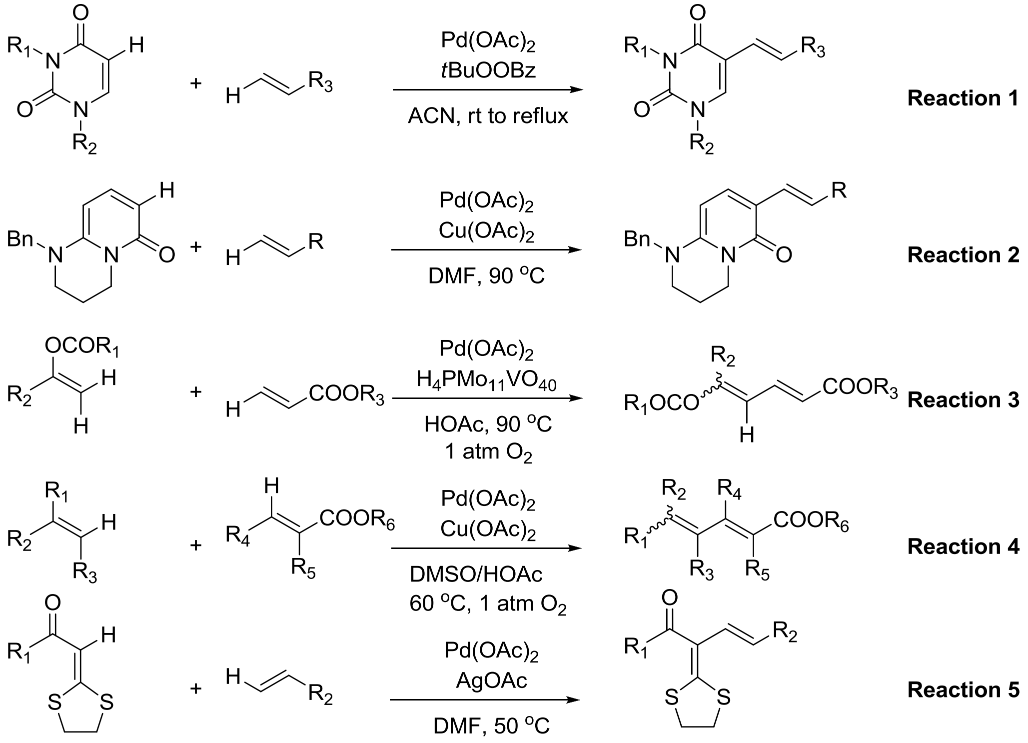


Figure 1.5. Recent palladium catalyzed alkene-alkene couplings

All these reactions proceed *via* similar mechanisms (**Figure 1.6**). The palladium catalyst attaches to the first alkene by acetoxypalladation or direct C-H bond activation to form **2a** or **2b**. Then another carbopalladation takes place to insert another molecule of alkene to generate **4a** or **4b**. The subsequent *β*-elimination leads to the dissociation of the precursor of the product **5** and the simultaneous release of Pd(0). The final product **6** is formed by another elimination of acetic acid and the Pd(II) catalyst is regenerated *via* oxidation. To realize this catalytic cycle, the proton of compound **1** which is abstracted in the first step needs to be relatively acidic in order to stabilize the C–Pd bond. Since the C2 carbon on glycal is more electron-rich, we envisioned that the palladium catalyzed oxidative alkene-alkene coupling would be a suitable tool to form the C–C bond between glycal and another molecule of alkene.

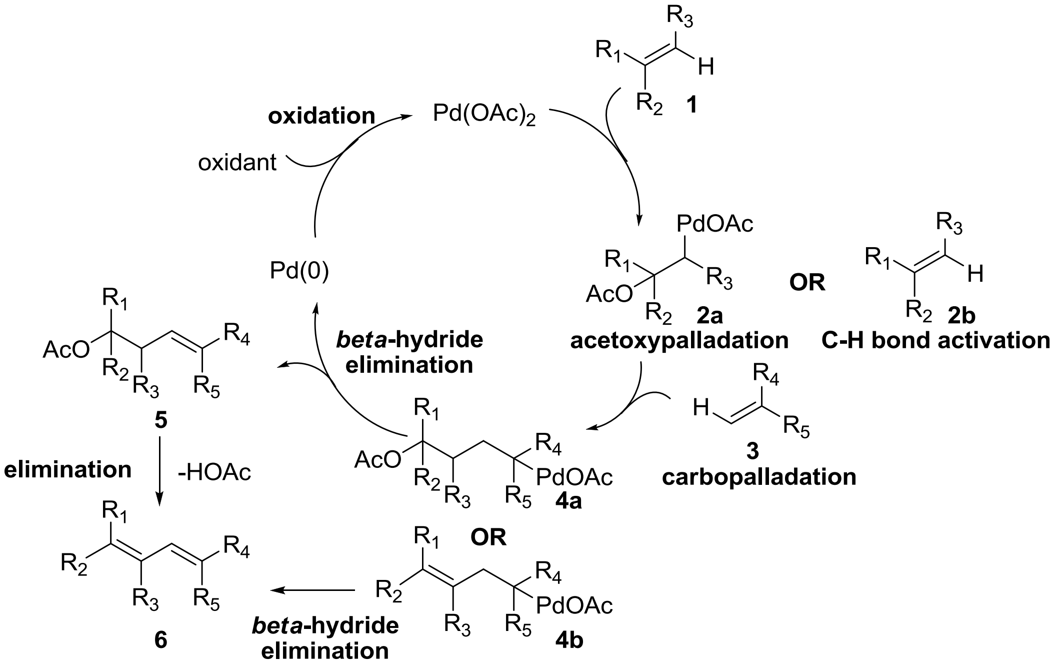


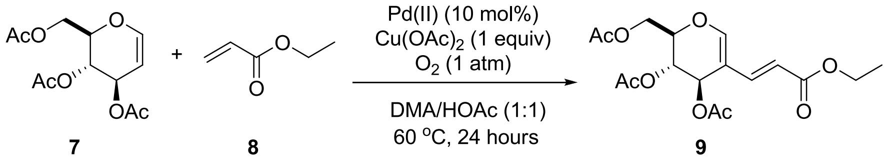
Figure 1.6. General mechanism of palladium catalyzed alkene-alkene couplings

1.2 Results and Discussion

1.2.1 Conditions Optimization

Initially, the trial reactions between peracetylated glycal **7** and ethyl acrylate **8** with different palladium sources and oxidative condition were conducted. Under 1 atm oxygen in the mixed solvent of DMA and acetic acid and with $Cu(OAc)_2$ as oxidant, examination of various palladium catalysts revealed that $Pd(OAc)_2$ (entry 1, Table 1.1) gave the coupling product **9** in higher yield than other commonly used palladium catalysts such as $PdCl_2$ (entry 2, Table 1.1), $Pd(TFA)_2$ (entry 4, Table 1.1), $Pd(PPh_3)_2Cl_2$ (entry 3, Table 1.1) and $Pd(PhCN)_2Cl_2$ (entry 5, Table 1.1).

Table 1.1. Screening of palladium catalysts[a], [b]

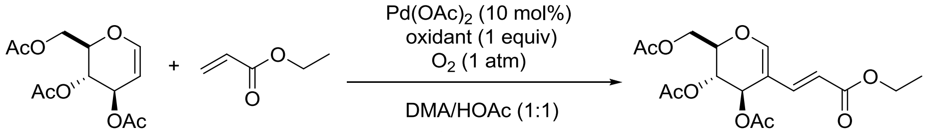


Entry	Catalyst	Conversion (%)	Yield (%)
1	$Pd(OAc)_2$	82	61
2	$PdCl_2$	37	14
3	$Pd(PPh_3)_2Cl_2$	0	0
4	$Pd(TFA)_2$	75	56
5	$Pd(PhCN)_2Cl_2$	0	0

[a] Reaction conditions unless otherwise specified: **7** (1 equiv), **8** (2 equiv), oxidant (1 equiv), O_2 (1 atm), in the mixture of HOAc and DMA. [b] Isolated yields.

After the optimal catalyst was identified, the efficiency of different oxidants was screened. Interestingly, the yield was much higher when copper(II) triflate (entry 2, Table 1.2) was employed as compared to copper(II) acetate (entry 1, Table 1.2), copper(II) sulfate (entry 3, Table 1.2), silver oxide (entry 4, Table 1.2) and silver carbonate (entry 5, Table 1.2). It was deduced that the ligand exchange took place between the palladium acetate and copper(II) triflate, which made the Pd(II) centre more electron-poor and thus more prone to electrophilic substitution towards C2 on glycal.

Table 1.2. Screening of oxidants[a], [b]



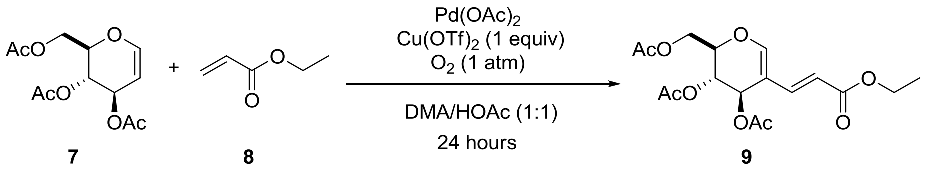
7 **8** **9**

Entry	Oxidant	Conversion (%)	Yield (%)
1	$Cu(OAc)_2$	82	61
2	$Cu(OTf)_2$	>90	71
3	$CuSO_4$	52	36
4	Ag_2O	<10	trace
5	Ag_2CO_3	41	23

[a] Reaction conditions unless otherwise specified: **7** (1 equiv), **8** (2 equiv), oxidant (1 equiv), O_2 (1 atm), in the mixture of HOAc and DMA. [b] Isolated yields.

It was noticed that if the catalyst loading was reduced to 0.05 equivalent, the yield decreased sharply to 53% (entry 1, Table 1.3). Adjusting reaction temperature and reaction time indicated that the best yield was obtained at 70 °C in a period of 24 hours (entry 3 and 5, Table 1.3). When the catalyst loading was increased to 0.2 equivalent, the isolated yield was only enhanced by 3% (entry 4, Table 1.3). Upon screening of different conditions, it was concluded that when the reaction underwent in mixed solvent of DMA and acetic acid (v/v=1/1) with 0.1 equivalent of palladium acetate and 1 equivalent of copper(II) triflate, the desired diene product was obtained in pure *E* form with an isolated yield of 82%. Other polar solvent such as DMSO, DMF, DMSO/HOAc, DMF/HOAC and DMF/DMSO were also tested. The results showed DMA/HOAc remained as the best solvent for this reaction.

Table 1.3. Optimization of the catalyst loading and reaction temperature[a], [b]



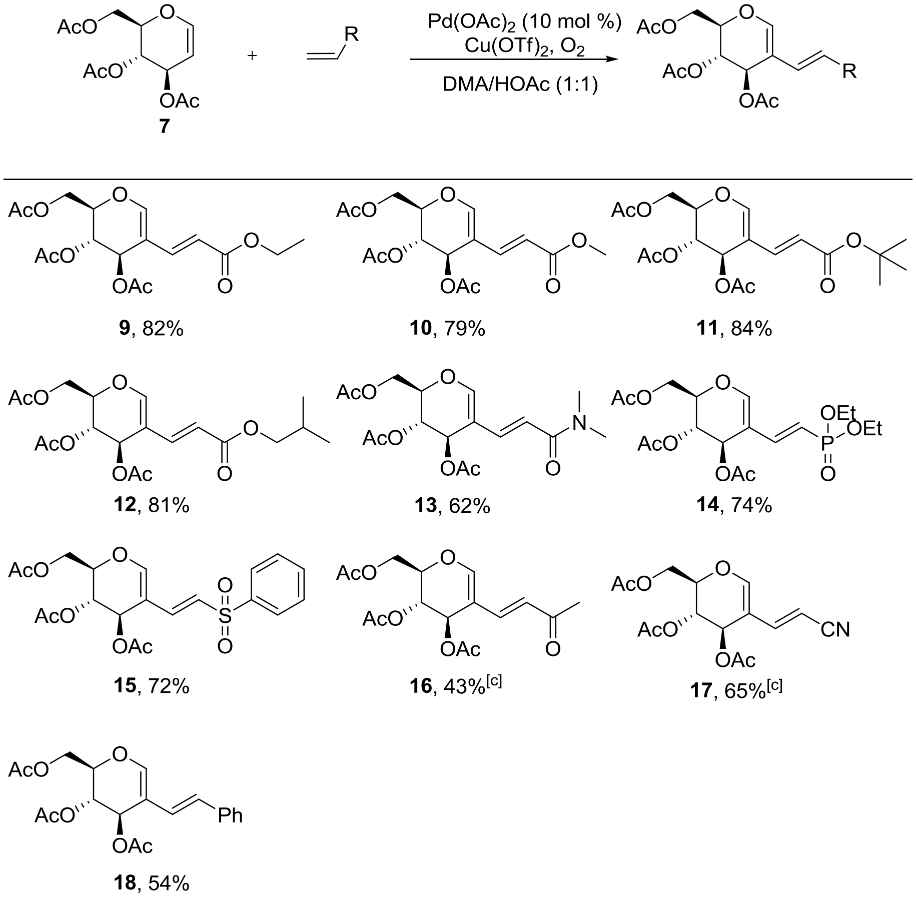
Entry	Catalyst (mol%)	Temp. (°C)	Conversion (%)	Yield (%)
1	5	60	79	53
2	10	60	>90	71
3	10	70	100	82
4	20	70	100	85
5	10	80	100	59[c]

[a] Reaction conditions unless otherwise specified: **7** (1 equiv), **8** (2 equiv), oxidant (1 equiv), O_2 (1 atm), in the mixture of HOAc and DMA. [b] Isolated yields. [c] Yield obtained after 12 hours of reaction time

1.2.2 Substrate Scope

After the reaction conditions were optimized, we proceeded to apply the conditions to different alkene coupling partners. An array of acrylates was first tested under the conditions (**Scheme 1.1**). To our delight, we found that all the

Scheme 1.1. Direct coupling of peracetylated glucal with activated alkenes. [a],[b]



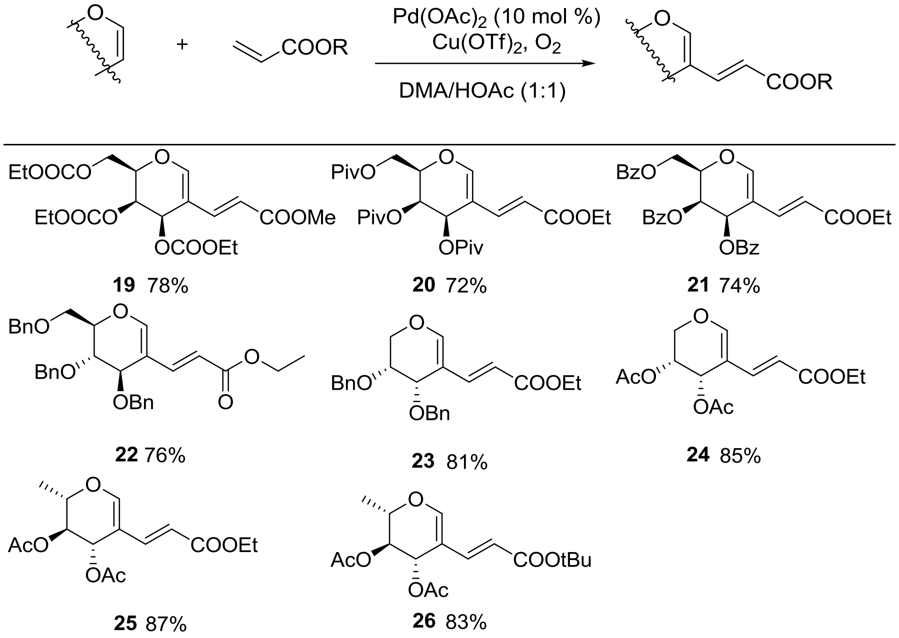
[a] Reaction conditions unless otherwise specified: **7** (1 equiv), alkene (2 equiv), $Cu(OTf)_2$ (1 equiv), O_2 (1 atm) at 70 °C in the mixture of AcOH and DMA for 24 hours. [b] All yields in Table 2 are isolated yields. [c] Reactions were carried out at 45 °C for 72 hours.

tested acrylates including ethyl acrylate **9**, methyl acrylate **10**, *t*-butyl acrylate **11** and *i*-butyl acrylate **12** gave the corresponding products in good to excellent yields. Subsequently, acrylamide **13**, acrylphosphonate **14** and acrylsulfonate **15** were examined and the results showed that the standard conditions worked well with these substrates to give the products in good yields. Besides acrylates, terminal alkenes such as methyl vinyl ketone **16** and acrylnitrile **17** afforded the desired products as well. Surprisingly, the relatively electron-rich alkenes such as styrene **18** also gave the corresponding product in moderate yield.

Glycals derived from various mono-sugars with different protecting groups were also studied (**Scheme 1.2**). Glycals derived from D-glucose with a variety of protecting groups were tested first. It was found that glycals with other commonly used acid-resistant protecting groups such as ethyoxycarbonyloxyl **19**, pivaloyl **20**, benzoyl **21** and benzyl **22, 23** groups gave the desired products in good to excellent yields. On the contrary, glycals with acid-sensitive protecting groups such as trimethylsilyl, *t*-butydimethylsilyl or isopropylidene failed to give any desired product due to the decomposition of the starting material in the acidic standard reaction conditions.

Besides D-glucose, glycals synthesized from other monosaccharides including D-galactose **19-21**, D-ribose **23, 24** and L-6-deoxyl-glucose **25, 26** also afforded the corresponding products in good to excellent yields. The structure the product **24** was confirmed by X-ray crystallography (**Figure 1.7**).

Scheme 1.2. Direct coupling of protected glycals with acrylates. [a], [b], [c]



[a] All reactions were carried out with glycal (1 equiv), activated alkene (2 equiv), $Cu(OTf)_2$ (1 equiv), O_2 (1 atm) for 24 hours. [b] All yields are isolated yields. [c] All the products are in *E* configuration.

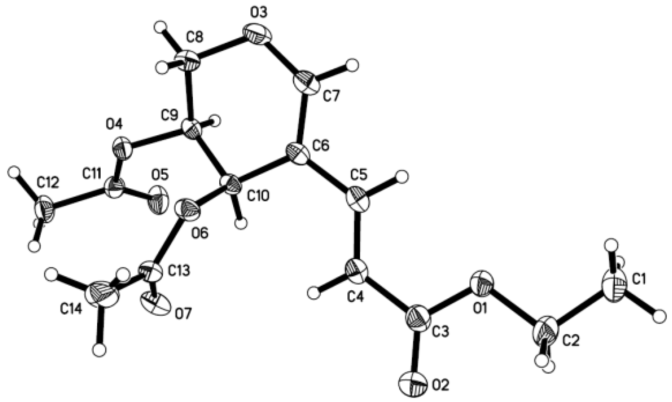
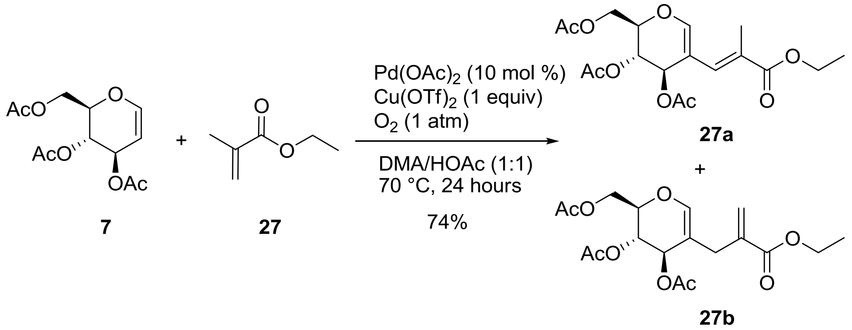


Figure 1.7. X-ray structure of **24**

1.2.3 Plausible Mechanism

It was interesting that when peracetylated glycal **7** and ethyl methacrylate **27** were subjected to the standard conditions, two different coupling products **27a** and **27b** were isolated and identified to be in a ratio of 1:2.5 in 74% total yield (**Scheme 1.3**).

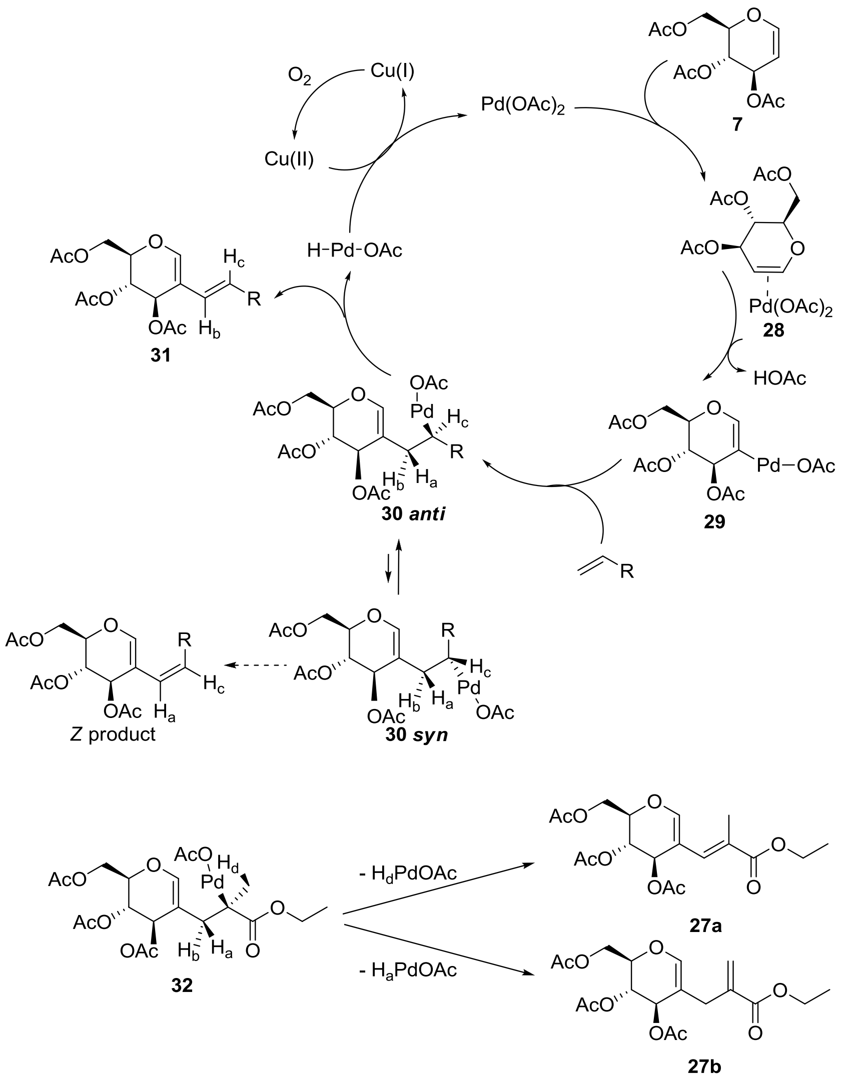
Scheme 1.3. Direct coupling of peracetylated glucal with ethyl methacrylate.



27a : **27b** = 1 : 2.5

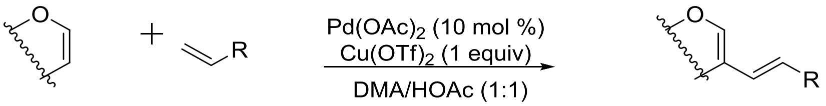
Together with the fact that this reaction is *E* selective, a plausible mechanism of this reaction is depicted (**Scheme 1.4**). For display purpose, we assume that the reaction takes place following the direct C-H activation mechanism although both of the two mechanisms are possible. Owing to the higher electron density on C2, the C2-Pd complex **29** was formed by C-H activation or acetoxypalladation followed by elimination. Then the insertion of a molecule of activated alkene took place to give compound **30**. The conformation of **30-*anti*** was relatively more stable than conformation **30-*syn*** as the two bulky groups (R and glycal) were located at *anti* positions. The stability of the two conformations explained the observation that only *E* products were identified from all substrates. Final product **31** was generated by the *syn* β-hydride elimination. The formation of both products **27a** and **27b** could be justified by the two possible ways of *β*-hydride elimination (H_a and H_d of **32**). The resulting palladium(0) was then oxidized by Cu(II) to recycle the active Pd(II) catalyst.

Scheme 1.4. Plausible mechanism



1.3 Conclusion

In conclusion, we have developed an efficient Pd(II) catalyzed direct alkene-alkene coupling reaction between glycals and activated alkenes. The reactions proceeded under mild conditions in good yields. The reaction displayed high tolerance of a vast scope of substrates, including a diversified range of terminal alkenes and glycals protected by various protecting groups. Dihydropyran dienes were obtained in pure *E* form. It is noteworthy that the functionalized pyran-containing products potentially provide access to many natural products, signifying their immense potential in synthetic organic chemistry.

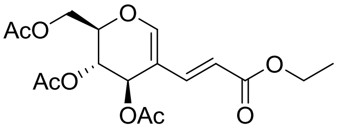


1.4 Experimental Section

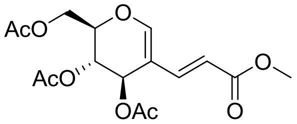
General**:** All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

Materials: Dimethylacetamide (DMA) and acetic acid (HOAc) were purchased from commercial suppliers and used without further purification. 3, 4, 6-tri–*O*–acetyl–D–glucal, 3, 4–*O*–acetyl–6–deoxy–L–glucal and all alkene reagents were purchased from commercial suppliers. 1, 2–unsaturated glucals with protecting groups as benzyl,[20] pivaloyl[21] and benzoyl[22] were prepared from 3, 4, 6-tri–*O*–acetyl–D–glucal by reported methods.

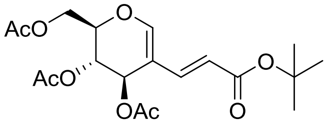
General procedure of Pd catalyzed cross-coupling of 1,2-unsaturated carbohydrate and alkene: To a solution of glycal (0.2 mmol), palladium diacetate (9 mg, 0.04 mmol) and copper(II) trifluoromethanesulfonate (72 mg, 0.2 mmol) in dimethylacetamide (0.2 mL) and acetic acid (0.2 mL) under 1 atm oxygen at 70 °C, activated alkene (0.4 mmol) was added dropwise. The mixture was allowed to stir at 70 °C for 24 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by column chromatography to afford the product.



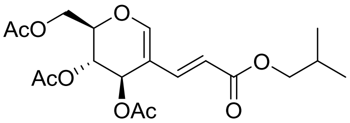
(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-ethoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (9) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford the product as colorless oil (61 mg, 82%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ.1.25 (t, *J* = 7.2 Hz, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 4.10–4.20 (m, 3H) , 4.33–4.51 (m, 2H), 5.14 (t, *J* = 3.3 Hz, 1H), 5.64 (s, 1H), 5.60 (d, *J* = 15.9 Hz, 1H), 6.96 (s, 1H), 7.18 (d, *J* = 15.9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ14.3, 20.6, 20.7(2C), 60.2, 61.0 62.7, 66.3, 74.3, 109.3, 114.2, 140.7, 152.1, 166.9, 169.3, 169.8, 170.3; IR (neat) 2983, 2339, 1732, 1714, 1643, 1614, 1444, 1427, 1371, 1222, 920, 736 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 7.1 (*c* 1.38, CHCl$_3$); HRMS (ESI) calcd for $C_{17}H_{22}O_9Na[M+Na]^+$: 393.1162, found 393.1171.



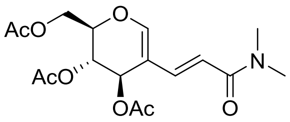
(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-methoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (10) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford the product as pale yellow oil (56 mg, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 3.72 (s, 3H), 4.18 (dd, J = 3.3, 11.1 Hz, 1H), 4.41–4.51 (m, 2H), 5.16 (t, J = 3.6 Hz, 1H), 5.59 (d, J = 2.4 Hz, 1H), 5.63 (d, J = 15.9 Hz, 1H), 6.98 (s, 1H), 7.20 (d, J = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 20.7(2C), 51.5, 61.0, 62.8, 66.4, 74.4, 109.3, 113.8, 141.0, 152.2, 167.4, 169.3, 169.8, 170.3; IR (neat) 3020, 2358, 1747, 1714, 1625, 1435, 1371, 1288, 1226, 1166, 756 cm^{-1}; $[\alpha]_{D}^{20}$ = 17.9 (c 0.86, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{20}O_9Na$ $[M+Na]^+$: 379.1005, found 379.1003.



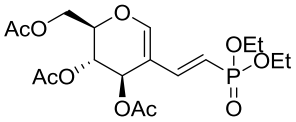
(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-tert-butoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (11) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford the product as colorless oil (67 mg, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 2.06 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 4.16 (dd, J = 3.3, 10.8 Hz, 1H), 4.39–4.47 (m, 2H), 5.13 (t, J = 3.3 Hz, 1H), 5.53 (d, J = 15.9 Hz, 1H), 5.54 (d, *J* = 2.4 Hz, 1H), 6.93 (s, 1H), 7.08 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6, 20.7(2C), 28.1, 61.6, 62.7, 66.3, 74.2, 80.2, 109.2, 116.1, 139.6, 151.5, 166.3, 169.3, 169.8, 170.3; IR (neat) 3020, 2978, 1743, 1735, 1697, 1627, 1390, 1369, 1226, 1151, 1024, 756 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 2.7 (*c* 0.88, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{26}O_9Na$ [M+Na]$^+$: 421.1475, found 421.1476.



(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-isobutoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (12) Following the general procedure, the crude product was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford the product as pale yellow oil (64 mg, 81%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, *J* = 6.6 Hz, 6H), 2.06 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 3.82–3.95 (m, 2H), 4.16 (dd, *J* = 3.3, 11.1 Hz, 1H), 4.39–4.47 (m, 2H), 5.14 (t, *J* = 3.0 Hz, 1H), 5.56 (d, *J* = 3.0 Hz, 1H), 5.61 (d, *J* = 15.9 Hz, 1H), 6.96 (s, 1H), 7.18 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 20.6(2C), 20.7, 27.7, 61.0, 62.7, 66.3, 70.4, 74.3, 109.3, 114.2, 140.7, 152.0, 167.0, 169.3, 169.8, 170.3; IR (neat) 2964, 2895, 2875, 1766, 1643, 1469, 1222, 1006, 732 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -11.8 (*c* 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{26}O_9Na$ [M+Na]$^+$: 421.1475, found 421.1480.

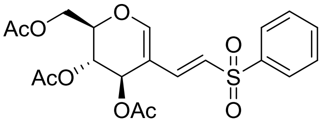


(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-(dimethylamino)-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (13) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford the product as yellow oil (46 mg, 62%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.04 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.96 (s, 3H), 2.98 (s, 3H), 4.17–4.21 (m, 1H), 4.36–4.46 (m, 2H), 5.10 (t, J = 3.3 Hz, 1H), 5.67 (t, J = 2.7 Hz, 1H), 6.14 (d, J = 15.3 Hz, 1H), 6.92 (s, 1H), 7.14 (d, J = 15.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 20.6, 20.7, 35.7, 37.1, 61.1, 62.7, 66.7, 74.2, 109.8, 113.4, 138.2, 151.0, 166.5, 169.4, 170.0, 170.3; IR (neat) 3003, 2358, 1747, 1645, 1392, 1371, 1219, 1206, 732 cm^{-1}; $[\alpha]_{\mathrm{D}}^{20}$ = -8.0 (c 0.93, CHCl$_3$); HRMS (ESI) calcd for $C_{17}H_{23}NO_8Na$ [M+Na]$^+$: 392.1321, found 392.1324.

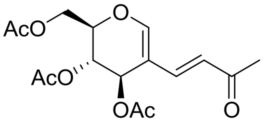


(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-2-(diethoxyphosphoryl)vinyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (14) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 1/1) to afford the product as yellow oil (64 mg, 74%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.22–1.32 (m, 6H), 2.04 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 3.97–4.08 (m, 4H), 4.16 (dd, J = 3.3, 11.1 Hz, 1H), 4.38–4.48 (m, 2H), 5.12 (t, J = 3.3 Hz, 1H), 5.35 (t, J = 17.1 Hz, 1H), 5.58 (d, J = 2.7 Hz, 1H), 6.92 (s, 1H), 6.97 (dd, J =

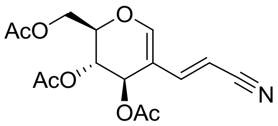
17.4, 22.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3(2C), 20.6, 20.7, 61.0, 61.6, 61.7, 62.6, 66.4, 74.3, 108.0, 109.7, 110.0, 110.6, 144.7, 144.8, 152, 169.3, 169.8, 170.3; IR (neat) 2985, 2349, 2231, 1766, 1645, 1600, 1446, 1371, 1249, 736 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -2.7 (*c* 0.60, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{27}O_{10}NaP$ $[M+Na]^+$: 457.1240, found 457.1236.



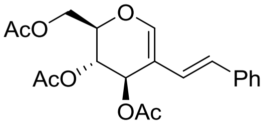
(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-2-(phenylsulfonyl)vinyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (15) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 2/1) to afford the product as colorless oil (63 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.93 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 4.16 (dd, *J* = 3.9, 14.7 Hz, 1H), 4.39–4.45 (m, 2H), 5.10 (t, *J* = 3.3 Hz, 1H), 5.49 (d, *J* = 2.1 Hz, 1H), 6.08 (d, *J* = 15.3 Hz, 1H), 7.05 (s, 1H), 7.17 (d, *J* = 15.3 Hz, 1H), 7.48–7.58 (m, 3H), 7.83–7.84 (m ,2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 20.6, 20.7, 60.9, 62.4, 66.2, 108.0, 123.1, 127.3, 129.2, 133.1, 138.8, 141.1, 153.9, 169.2, 169.8, 170.2; IR (neat) 3022, 1745, 1625, 1446, 1371, 1217, 1145, 846, 754 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 3.9 (*c* 0.60, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{22}O_9SNa$ $[M+Na]^+$: 461.0882, found 461.0880.



(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-3-oxobut-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (16) To a solution of **7** (54 mg, 0.2 mmol) palladium diacetate (4 mg, 0.02 mmol) and copper(II) triflate (72 mg, 0.2 mmol) in dimethylacetamide (0.2 mL) and acetic acid (0.2 mL) under 1 atm oxygen at 50 °C, but-3-en-2-one (50 mg, 0.4 mmol) was added dropwise. The mixture was allowed to stir at 45 °C for 72 hours. Then the mixture was diluted with ethyl acetate (2 mL), filtered, washed with water (5 mL) and brine (5 mL). Then the organic layer was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 4/1) to afford the product as pale yellow oil (28 mg, 43%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.21 (s, 3H), 4.16 (dd, J = 3.9 Hz, 11.4 Hz, 1H), 4.40–4.50 (m, 2H), 5.14 (t, J = 3.3 Hz, 1H), 5.56 (d, J = 2.1 Hz, 1H), 5.93 (d, J = 16.2 Hz, 1H), 7.00 (s, 1H), 7.04 (d, J = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.6(2C), 20.7, 61.0, 62.5, 66.2, 74.5, 109.3, 123.0, 139.6, 152.8, 169.3, 169.8, 170.3, 197.4; IR (neat) 3018, 2415, 1747, 1666, 1620, 1595, 1371, 1226, 1172, 1026, 756, 667 cm^{-1}; $[\alpha]^{20}_{D}$ = -7.26 (c 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{20}O_8Na$ $[M+Na]^+$: 363.1056, found 363.1060.

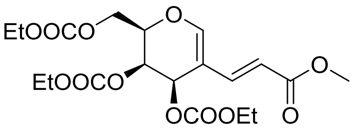


(2R,3S,4R)-2-(acetoxymethyl)-5-((E)-2-cyanovinyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (17) To a solution of **7** (54 mg, 0.2 mmol) palladium diacetate (4 mg, 0.02 mmol) and copper(II) triflate (72 mg, 0.2 mmol) in dimethylacetamide (0.2 mL) and acetic acid (0.2 mL) under 1 atm oxygen at 50 °C, acrylnitrile (21 mg, 0.4 mmol) was added dropwise. The mixture was allowed to stir at 45 °C for 72 hours. Then the mixture was diluted with ethyl acetate (2 mL), filtered, washed with water (5 mL) and brine (5 mL). Then the organic layer was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 3/2) to afford the product as yellow oil. (42 mg, 65%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.09 (s, 3H), 2.09 (s, 3H), 2.09 (s, 3H), 4.15–4.20 (m, 1H), 4.44–4.48 (m, 1H), 4.50–4.52 (m, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 5.13 (d, *J* = 3.3 Hz, 1H), 5.55 (d, *J* = 3.0 Hz, 1H), 6.85 (d, *J* = 16.5 Hz, 1H), 6.96 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 20.6, 20.7, 60.9, 61.7, 66.1, 74.7, 91.9, 109.5, 146.3, 152.7, 169.2, 169.8, 170.3; IR (neat) 2954, 2850,2812, 1598, 1427, 1114, 736, 698 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -6.3 (*c* 1.00, CHCl$_3$); HRMS (ESI) calcd for $C_{15}H_{17}NO_7Na$ [M+Na]$^+$: 346.0903, found 346.0905.

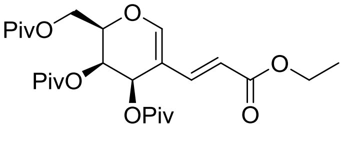


(2R,3S,4R)-2-(acetoxymethyl)-5-styryl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (18) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 3/1) to afford the product as colorless oil (40mg, 54%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.09 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 4.20–4.23 (m, 1H), 4.43–4.51 (m, 2H), 5.19 (t, *J* = 3.9 Hz, 1H), 5.76 (d, *J* = 3.3 Hz, 1H), 6.26 (t, *J* = 16.2 Hz, 1H), 6.56 (d, *J* = 16.5 Hz, 1H), 6.81 (s, 1H), 7.17–7.22 (m, 1H) 7.29–7.35 (m, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz)

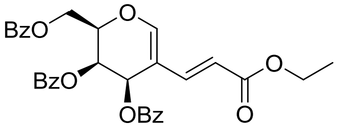
δ 20.7, 20.8, 61.3, 63.6, 67.1, 73.8, 77.2, 110.7, 123.9, 124.9, 125.9, 127.1, 128.6, 137.3, 146.4, 169.5, 170.2, 170.4; IR (neat) 3024, 2358, 1747, 1732, 1639, 1371, 1228, 1163, 1026, 754 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -11.85 (*c* 0.93, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{22}O_7Na$ [M+Na]$^+$: 397.1263, found 397.1262.



(2R,3R,4R)-5-((E)-3-methoxy-3-oxoprop-1-enyl)-2-(propionyloxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl dipropionate (19) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 2/1) to afford the product as pale yellow oil (70 mg, 78%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.32 (m, 9H), 3.69 (s, 3H), 4.15–4.27 (m, 6H), 4.34-4.39 (m, 1H), 4.48–4.54 (m, 2H), 5.30 (t, *J* = 3.6 Hz, 1H), 5.69 (d, *J* = 15.6 Hz, 1H), 5.71 (d, *J* = 3.9Hz, 1H), 6.89 (s, 1H), 7.16 (d, *J* = 15.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ14.0, 14.1(2C), 51.4, 64.4, 64.5, 64.7, 65.0, 65.1, 68.1, 73.3, 109.6, 114.5, 140.1, 152.0, 153.9, 154.5, 154.7, 167.3; IR (neat) 2985, 2398, 1768, 1614, 1444, 1006, 734 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 18.1 (*c* 0.84, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{26}NaO_{12}$[M+Na]$^+$: 469.1322, found 469.1323.

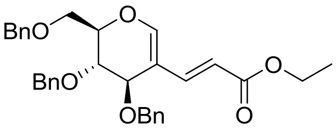


(2R,3R,4R)-5-((E)-3-ethoxy-3-oxoprop-1-enyl)-2-(pivaloyloxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl bis(2,2-dimethylpropanoate) (20) Following the general procedure, the crude product was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 5/1) to afford the product as colorless oil (71 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17–1.23 (m, 30H), 4.08–4.18 (m, 3H), 4.45–4.48 (m, 2H), 5.39 (t, *J* = 4.2 Hz, 1H), 5.51 (d, *J* = 15.9 Hz, 1H), 5.88 (d, *J* = 4.5 Hz, 1H), 6.87 (s, 1H), 7.13 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 27.0(2C), 38.7, 38.9, 38.9, 60.1, 61.2, 61.4, 65.1, 73.5, 110.7, 114.3, 140.1, 151.6, 166.9, 176.6, 177.3, 176.1; IR (neat) 2976, 1732, 1714, 1627, 1481, 1367, 1280, 1155, 758 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 32.7 (*c* 0.80, $CHCl_3$); HRMS (ESI) calcd for $C_{26}H_{40}O_9Na$ $[M+Na]^+$: 519.2570, found 519.2574.

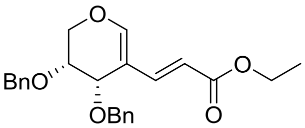


(2R,3R,4R)-2-(benzoyloxymethyl)-5-((E)-3-ethoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl dibenzoate (21) Following the general procedure, the crude product was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 2/1) to afford the product as colorless oil (82 mg, 74%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, *J* = 6.6 Hz, 3H), 4.07–4.19 (m, 2H), 4.62 (dd, *J* = 3.0, 12.0 Hz, 1H), 4.87–4.99 (m, 1H), 5.02–5.06 (m, 1H), 5.76 (d, *J* = 15.9 Hz, 1H), 5.89 (t, *J* = 4.2 Hz, 1H), 6.34 (d, *J* = 4.2 Hz, 1H), 7.09 (s, 1H), 7.27–7.34 (m, 3H), 7.39–7.44 (m, 4H), 7.49–7.58 (m, 3H), 7.82–7.85 (m, 2H), 7.97-8.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 60.2, 62.2, 62.3, 65.8, 73.6, 110.5, 114.8, 128.4, 128.6, 128.7, 128.9, 129.4, 129.7, 129.8, 129.4, 129.7, 129.8, 129.8, 133.3, 133.5, 133.5, 140.1, 152.2, 165.0, 165.8, 166.3, 167.0;

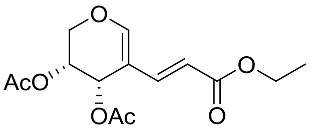
IR (neat) 2976, 1732, 1699, 1627, 1315, 1267, 1111, 768 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 47.7 (*c* 0.90, CHCl$_3$); HRMS (ESI) calcd for $C_{32}H_{28}O_9Na$ [M+Na]$^+$: 579.1631, found 579.1631.



(E)-ethyl 3-((2R,3S,4R)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-yl)acrylate (22) Following the general procedure, the crude product was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 4/1) to afford the product as yellow oil (78 mg, 76%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.29 (t, J = 7.2 Hz, 3H), 3.62–3.68 (m, 1H), 3.75–3.81 (m, 1H), 4.01 (t, J = 3.0 Hz, 1H), 4.16–4.23 (m, 3H), 4.43–4.50 (m, 4H), 4.54–4.56 (m, 1H), 4.65–4.66 (m, 2H), 5.68 (d, J = 15.6 Hz, 1H), 6.94 (s, 1H), 7.19–7.34 (m, 15H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 14.4, 59.9, 68.0, 69.9, 70.0, 70.7, 71.8, 73.4, 76.4, 111.0, 113.2, 127.7, 127.7, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 137.3, 137.4, 137.7, 142.8, 152.0, 167.4; IR (neat) 3030, 2868, 2355, 1714, 1614, 1496, 1454, 1165, 1028, 736, 698 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 14.9 (*c* 1.83, CHCl$_3$); HRMS (ESI) calcd for $C_{32}H_{34}O_6Na$ [M+Na]$^+$: 537.2253, found 537.2255.

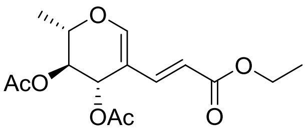


(E)-ethyl 3-((3R,4S)-3,4-bis(benzyloxy)-3,4-dihydro-2H-pyran-5-yl)acrylate (23) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 4/1) to afford the product as colorless oil (64 mg, 81%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.30 (t, J = 6.9 Hz, 3H), 3.79–3.86 (m, 1H), 4.14–4.24 (m, 4H), 4.38 (dd, J = 1.2, 3.0 Hz, 1H), 4.71–4.77 (m, 2H), 4.99 (d, J = 11.4 Hz, 1H), 5.67 (d, J = 15.9 Hz, 1H), 6.80 (s, 1H), 7.20–7.39 (m, 11H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 14.3, 60.0, 63.2, 67.5, 71.7, 73.8, 74.2, 112.2, 112.5, 127.5, 127.7, 128.0, 128.3, 128.6, 137.6, 138.3, 142.5, 153.4, 167.4; IR (neat) 2976, 1714, 1697, 1614, 1454, 1398, 1278, 1165, 752, 698 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 18.3 (c 1.50, CHCl$_3$); HRMS (ESI) calcd for $C_{24}H_{26}O_5Na$ [M+Na]$^+$: 417.1678, found 417.1690.

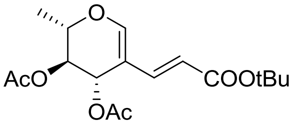


(3R,4S)-5-((E)-3-ethoxy-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (24) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 3/1) to afford the product as a white solid (51 mg, 85%): mp 107 – 109 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3H), 2.03 (s, 1H), 2.07 (s, 1H), 3.99–4.21 (m, 4H), 5.14–5.21 (m, 1H), 5.69 (d, J = 15.6 Hz, 1H), 5.89 (dd, J = 1.2, 3.6 Hz, 2H), 6.94 (s, 1H), 7.17 (d, J = 15.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 14.3, 20.5, 20.7, 60.2, 61.0, 62.5, 65.4, 109.9, 113.8, 140.4, 154.1, 167.1, 169.4, 170.3; IR (neat) 2976, 2358, 1747, 1625, 1371, 1282, 1168, 756, 667 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 243.0 (c 0.65,

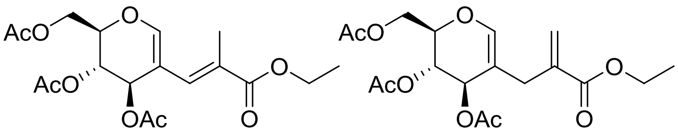
$CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{18}O_7Na$ $[M+Na]^+$: 321.0950, found 321.0955.



(2S,3S,4S)-5-((E)-3-ethoxy-3-oxoprop-1-enyl)-2-methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (25) Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 3/1) to afford the product as colorless oil (54 mg, 87%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.37 (d, *J* = 7.2 Hz, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 4.10–4.20 (m, 2H), 4.35–4.39 (m, 1H), 4.97 (t, *J* = 3.6 Hz, 1H), 5.54 (dd, *J* = 1.2, 3.3 Hz, 1H), 5.55 (d, *J* = 15.6 Hz, 1H), 6.95 (s, 1H), 7.19 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.3, 16.1, 20.7, 20.8, 60.1, 63.6, 70.2, 73.0, 108.7, 113.4, 141.3, 152.8, 167.1, 169.6, 170.0; IR (neat) 2983, 2389, 1747, 1625, 1446, 1371, 1033, 732 cm^{-1}; $[\alpha]_D^{20}$ = 41.8 (*c* 0.88, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{20}O_7Na$ $[M+Na]^+$: 335.1107, found 335.1111.



(2S,3S,4S)-5-((E)-3-tert-butoxy-3-oxoprop-1-enyl)-2-methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (26) Following the general procedure, the crude product was evaporated and the residue was purified by flash column chromatography (Hexane/EtOAc = 3/1) to afford the product as colorless oil (56 mg, 83%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.36 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 2.04 (s, 3H), 2.05 (s, 3H), 4.34–4.38 (m, 1H), 4.96 (t, J = 3.3 Hz, 1H), 5.47 (d, J = 15.6 Hz, 1H), 5.51 (s, 1H), 6.91 (s, 1H), 7.08 (d, J = 15.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 16.1, 20.7, 20.8, 28.1, 63.6, 70.1, 72.9, 80.0, 108.5, 115.2, 140.3, 152.3, 166.5, 169.58, 170.09; IR (neat) 2976, 2358, 1743, 1697, 1625, 1369, 1282, 1215, 1153, 710, 667 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 32.0 (*c*0.94, CHCl$_3$); HRMS (ESI) calcd for $C_{17}H_{24}O_7Na$ [M+Na]$^+$: 363.1420, found 363.1424.



(2R,3S,4R)-2-(acetoxymethyl)-5-(3-ethoxy-2-methyl-3-oxoprop-1-enyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (27a) and **(2R,3S,4R)-2-(acetoxymethyl)-5-(2-(ethoxycarbonyl)allyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (27b)** Following the general procedure, the crude product was purified by flash column chromatography (Hexane/EtOAc = 7/3) to afford both products as colorless oil (57 mg, 74%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 4.3H), 1.94 (d, J = 1.2 Hz, 1.3H), 2.02–2.09 (m, 13.2H), 2.92 (dd, J = 15.9, 22.5 Hz, 2H), 4.12–4.26 (m, 5.6H), 4.36–4.44 (m, 1H), 4.46–4.50 (m, 0.4H), 5.14 (dd, J = 4.8, 6.6 Hz, 1H), 5.18–5.22 (m, 0.4H), 5.37 (d, J = 4.8 Hz, 1H), 5.52 (d, J = 4.2 Hz, 0.4H), 5.55 (d, J = 1.2 Hz, 1H), 6.18 (s, 1H), 6.40 (s, 1H), 6.77 (s, 0.4H), 6.90 (s, 0.4H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 14.1, 14.2, 14.2, 20.7, 20.7, 20.8, 20.8, 30.7, 60.7, 61.0, 61.4, 66.7, 67.0, 67.3, 67.8, 73.5, 73.8, 107.2, 108.4, 125.9, 126.6, 133.4, 138.0, 143.6, 148.8, 166.5, 169.5, 170.3, 170.5; IR (neat) 2983, 1747, 1608, 1444, 1371, 1219, 1016, 648 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{24}O_9Na$ [M+Na]$^+$: 407.1318, found 407.1317.

Crystal Data

Basic crystal data of Compound **24**

Empirical formula	C14 H18 O7	
Formula weight	298.28	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.2675(2) Å	a= 90°.
	b = 11.6231(4) Å	b= 90°.
	c = 17.7142(6) Å	g = 90°.
Volume	1496.33(8) Å^3	
Z	4	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	632	
Crystal size	0.40 x 0.40 x 0.16 mm^3	
Theta range for data collection	2.10 to 31.08°.	
Index ranges	-8<=h<=10, -16<=k<=15, -22<=l<=25	

Reflections collected	23938
Independent reflections	2732 [R(int) = 0.0615]
Completeness to theta = 31.08°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9831 and 0.9585
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2732 / 0 / 193
Goodness-of-fit on F^2	1.100
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0994
R indices (all data)	R1 = 0.0440, wR2 = 0.1127
Largest diff. peak and hole	0.385 and -0.292 e.Å^{-3}

1.5 References

1. (a) Sznaidman, M. in *Bioorganic Chemistry : Carbohydrates* (Ed.: Hecht, S. M.), Oxford University Press, New York, **1999**, pp. 1 – 56. (b) Rauter, A. P.; Lindhorst, T. K. in *Carbohydrate Chemistry: Volume 38*, The Royal Society of Chemistry, London, **2012**, pp. 7 – 8. (c) Sinnott, M. in *Carbohydrate Chemistry and Biochemistry*, The Royal Society of Chemistry, London, **2007**, pp. 5 – 7. (d) Horton, D. in *Carbohydrate Chemistry, Biology and Medical Applications*, Elsevier, Amsterdam, **2008**, pp. 1 – 27.

2. Kovač, P. in *Carbohydrate Chemistry – Proven Synthetic Methods, Volume 1,* CRC Press, Boca Raton, **2011**

3. (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742. (b) Larrosa, I.; Romea, P.; Urpí, F. *Org. Lett.* **2006**, *8*, 527.(c) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761. (c) Nishikawa, T.; Koide, Y.; Kanakubo, A.; Yoshimura, H.; Isobe, M. *Org. Biomol. Chem.* **2006**, *4*, 1268. (d) Bililign, T. G., B. R.; Thorson, J. S. *Curr. Top. Med. Chem*. **2005**, *5*, 1299. (e) Wei, Z. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (f) Qin, H.-L.; Lowe, J. T.; Panek, J. S. *J. Am. Chem. Soc.* **2006**, *129*, 38.

4. (a) Ferrier, R. J. In *Glyoscience: Epimerisation, Isomerisation and Rearrangement Reactions of Carbohydrates*; Stutz, A. E., Ed. 2001; Vol. 215, p 153. (b) Descotes, G.; Martin, J. C. *Carbohydr. Res.* **1977**, *56*, 168. (c) Klaffke, W.; Pudlo, P.; Springer, D.; Thiem, J. L. *Ann. Chem.* **1991**, *6,* 509. (d) Bettadaiah, B. K.; Srinivas, P. *Tetrahedron Lett.* **2003**, *44*, 7257. (e)

Gorityala, B. K.; Cai, S.; Lorpitthaya, R.; Ma, J.; Pasunooti, K. K.; Liu, X.-W. *Tetrahedron Lett.* **2009**, *50*, 676. (f) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357; (g) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683. (h) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (i) Varki, A. *Glycobiology* **1993**, *3*, 97. (j) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137.

5. (a) Mamat, C.; Hein, M.; Miethchen, R. *Carbohydr. Res.* **2006**, *341*, 1758.(b) Priebe, W.; Grynkiewicz, G.; Neamati, N. *Tetrahedron Lett.* **1992**, *33*, 7681. (c) Lopez, J. C.; Lameignere, E.; Lukacs, G. *Chem. Commun.* **1988**, 514. (d) Hayashi, M.; Tsukada, K.; Kawabata, H.; Lamberth, C. *Tetrahedron* **1999**, *55*, 12287.

6. (a) Adio, A.M.; König, W.A. *Phytochemistry* **2005**, *66*, 599. (b) Banskota, A.H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1227. (c) Supratman, U.; Fujita, T.; Akiyama, K.; Hayashi, H. *Phytochemistry* **2001**, *58*, 311. (d) Valcic, S.; Zapp, J.; Becker, H. *Phytochemistry* **1997**, *44*,89.

7. (a) Baeckvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374.(b) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (d) Huang, H.-L.; Liu, R.-S. *J. Org. Chem.* **2002**, *68*, 805.

8. (a) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. L. *Org. Lett.* **2005**, *7*, 2683. (b) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319. (c) Hart, D. J.;

Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499.(d) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 1733. (e) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (f) Hu, X.-H.; Liu, F.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 1741.

9. (a) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949. (b) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599.
10. Franck, R. W.; John, T. V. *J. Org. Chem.* **1983**, *48*, 3269.
11. Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065.
12. Tazaki, H.; Zapp, J.; Becker, H. *Phytochemistry* **1995**, *39*, 859.
13. Arrayás, R. G.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816.
14. For reviews, see: (a) Dong, V.; Yeung, C. S.; *Chem. Rev.* **2011**, *111*, 1215. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Shul'pin, G. B.; Shilov, A. E. *Chem. Rev.* **1997**, *97*, 2879. (d) Lautens, M.; Alberico, D.; Scott, M. E. *Chem. Rev.* **2007**, *107*, 174
15. Hirota, K.; Isobe, Y.; Kitade, Y.; Make, Y. *Synthesis* **1987**, 495
16. Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, *6*, 4623.
17. Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc.* **2009**, *131*, 1372.
18. Cheng, D.; Gallagher, T. *Org. Lett.* **2009**, *11*, 2639
19. Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 5792.
20. Bovin, N. V.; Zurabyan, S. É.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25.
21. Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res.* **1982**, *101*, 197

22. Takahashi, Y.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 156

Chapter 2 Palladium Catalyzed Stereoselective *C*-Glycosylation of Glycals with Enol Triflates

2.1 Introduction

2.1.1 Glycosides and Glycosylation

Carbohydrates in nature generally do not exist in their monomeric forms. The natural forms of carbohydrates such as starch, cellulose, glycogen, glycoprotein and glycolipid are composed of carbohydrate monomers linked to other monomers or to peptides or lipids. The linkage, in carbohydrate chemistry, is named as glycosidic bond and the process to form glycosidic bond is named as glycosylation. Since the isolation and purification of polysaccharides from nature is tough and unproductive, chemical glycosylation becomes a very powerful tool to construct various oligo- and polysaccharides for biological studies.

2.1.2 *C*-Glycosides

Compounds with O-C, C-C, S-C and N-C glycosidic bonds are called *O*-glycosides, *C*-glycosides, *S*-glycosides and *N*-glycosides respectively (**Figure 2.1**).

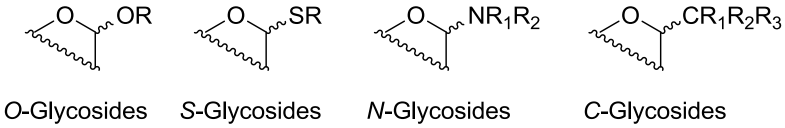


Figure 2.1. *O*, *S*, *N* and *C*-glycosides

Amongst all these glycosides, *O*-glycosides are the most widely present glycosides found in the most abundant polysaccharides such as cellulose, glycogen and starch. Despite the wide presence of *O*-glycosides, *C*-glycosides have thrived as an intensively studied research area for past decades for several reasons:

1. Due to the higher bond energy of C–C bond, *C*-glycosidic bonds are chemically more stable. Since *C*-glycosides are not universally present in organisms, they exhibit great resistance against enzyme catalyzed transformations. This feature suggests the huge potential of *C*-glycosides in the inhibition of carbohydrate processing enzymes, blocking of pathogenesis and modulation of immune pathways. On top of that, structure-activity relationship studied by medicinal chemists indicates that molecules with similar 3D structures tend to exhibit similar biological activities. Thus, as compared to *O*-glycosides, *C*-glycosides possess similar biological activities but enhanced stability.[1] One example is described in **Figure 2.2**.[2] KRN 7000 is a synthetic biologically active synthetic *O*-glycoside modified from natural agelasphins. Interestingly, the *C*-glycoside analogue of KRN 7000 was found to be 100 times more effective against melanoma and 1000 times more effective against malaria.

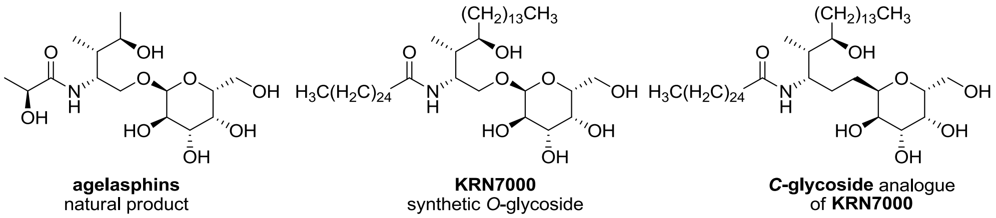


Figure 2.2. Natural product and their synthetic glycosides

2. Although not exhibited as widely as *O*-glycosides, *C*-glycosides are still quite abundant in nature (**Figure 2.3**). Many natural occurring *C*-glycosides have been isolated, identified and studied.[3] Some of these *C*-glycosides have shown promising pharmacological and biological properties.

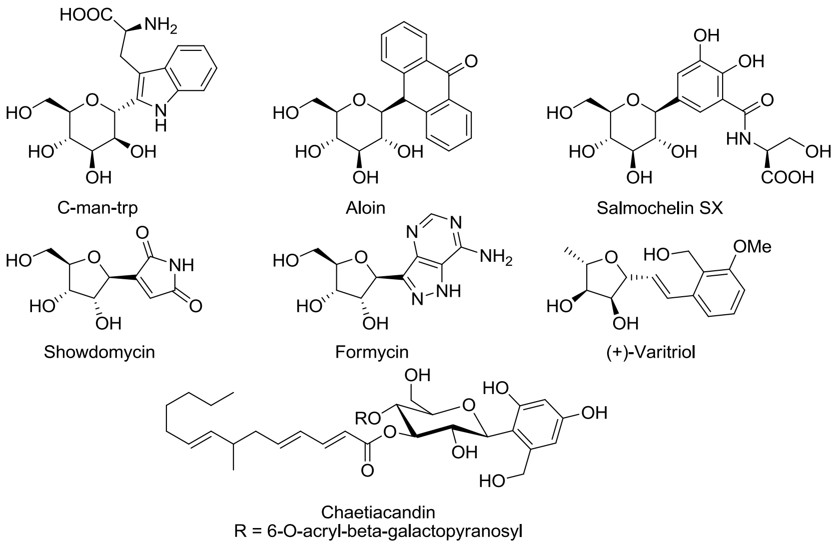


Figure 2.3. Natural occurring *C*-glycosides

3. *C*-glycosides are also useful building blocks for syntheses of many natural products (**Figure 2.4**).[4] The pre-existing chiral centres and high availability of carbohydrate make *C*-glycosides ideal starting materials for synthetic chemistry.

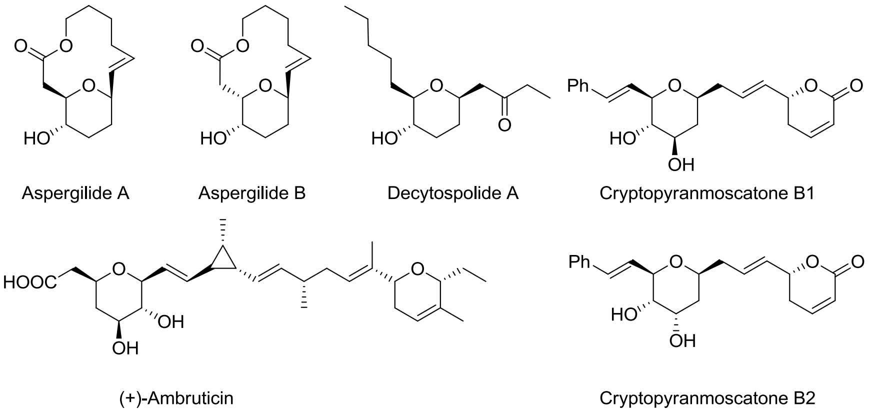


Figure 2.4. *C*-glycoside moieties present in natural products

2.1.3 *C*-Glycosylation

Undoubtedly, these irreplaceable properties of *C*-glycosides have encouraged carbohydrate chemists to pursue efficient and selective *C*-glycosylation methods. So far, there are mainly two pathways to construct *C*-glycosidic bond which are Lewis acid catalyzed *C*-glycosylation and Heck-type palladium catalyzed *C*-glycosylation.

2.1.3.1 Lewis acid catalyzed *C*-glycosylation

The basic mechanism of Lewis acid catalyzed *C*-glycosylation begins with the coordination of the electron lone pair of the C1 or C3 leaving group and the empty orbital of the Lewis acid (**Figure 2.5**). After the dissociation of the induced leaving group, the resulting electrophilic oxocarbenium is then attacked by the *C*-nucleophile to form the C-C glycosidic bond.

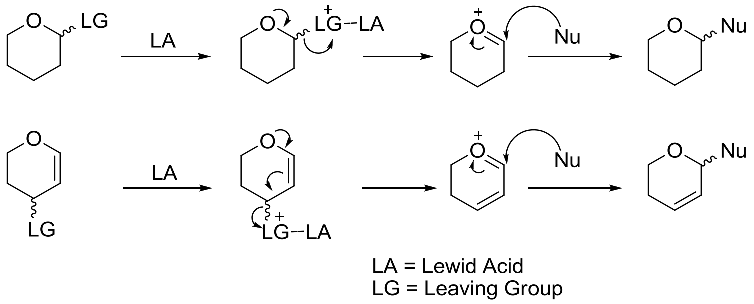


Figure 2.5. General mechanism of Lewis acid catalyzed *C*-glycosylation

The research of constructing *C*-glycoside from glycals (C3 activation) started since 1981 (**Figure 2.6**).[5] $BF_3.OEt_2$ and $AlCl_3$ were first employed stoichiometrically to promote the *C*-glycosylation reaction of glycals and silyl enol ethers. The enolates generated *in situ* captured oxocarbenium ions to form

C-glycosides. It was found that DCM and MeCN gave the best yields and selectivities. The reaction was *α*-favored and this observation was justified by a kinetically controlled mechanism. After this initial study, Yb(OTf)$_2$[6], TiCl$_4$[7], InCl$_3$[7], InBr$_3$[8], Bi(OTf)$_3$[9], ZrCl$_2$[10], Eu(OTf)$_3$[11], Yb(OTf)$_3$[11], Sc(OTf)$_3$[12] and MgClO$_4$[13] were found to be effective to catalyze the similar reactions as well.

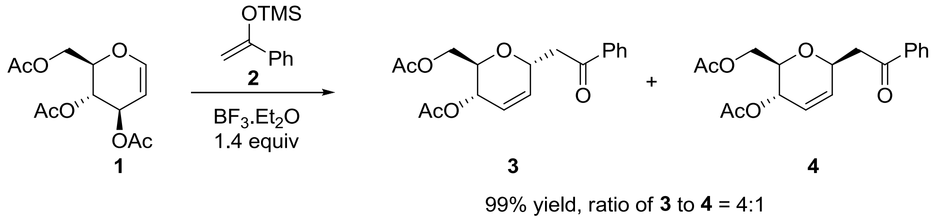


Figure 2.6. Lewis acid promoted *C*-glycosylation of glycals and silyl enol ethers

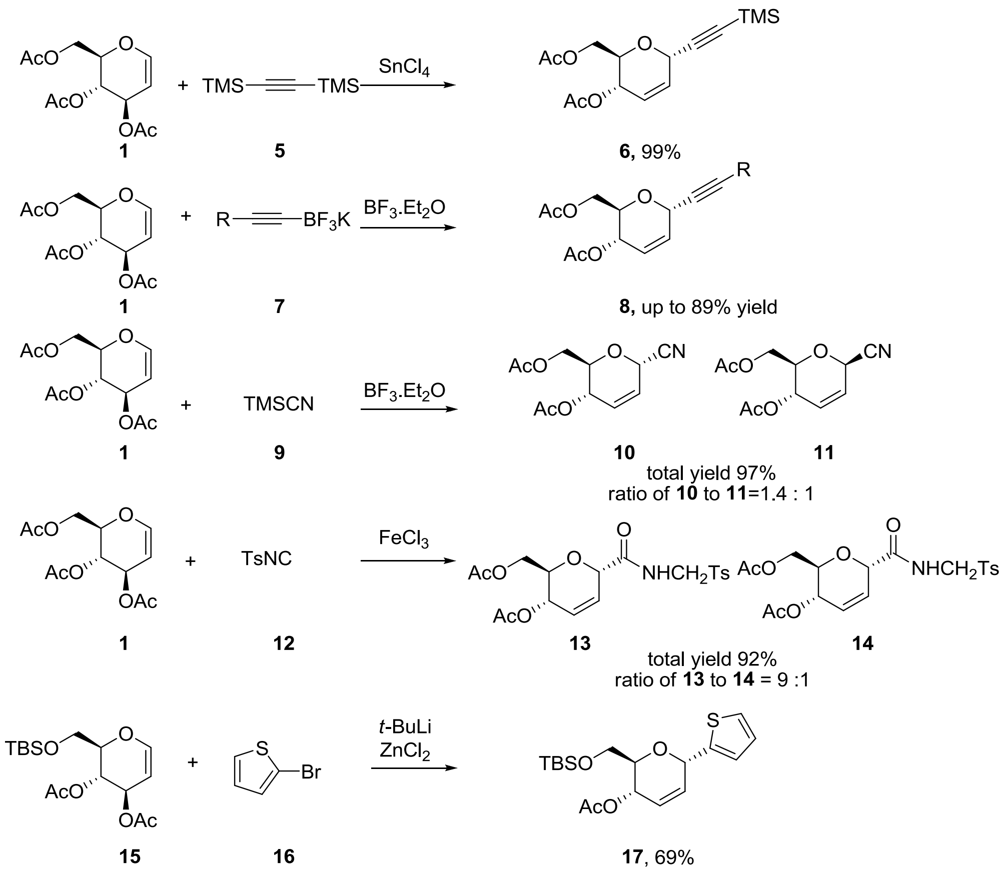


Figure 2.7. Examples of Lewis acid promoted *C*-glycosylation of glycals

Other than silyl enol ethers, other nucleophiles including TMS-protected terminal acetylenes,[14] potassium alkynyltrifluoroborates,[15] TMSCN,[16] isocyanides,[17] organozinc reagents,[18] organoaluminum reagents[19] and organoindium reagents[20] were also reported as good partners for *C*-glycosylation (**Figure 2.7**).

Besides glycals, carbohydrate derivatives with leaving groups on anomeric carbon are also a group of suitable starting materials for Lewis acid catalyzed *C*-glycosylation. The reactions proceed *via* the similar mechanism as glycal based glycosylations. Silyl enol ethers,[21] potassium alkynyltrifluoro-borates,[22] organozinc reagents,[23] organocopper reagents[24] and organotin reagents[25] are found as good partners for *C*-glycosylation (**Figure 2.8**). Notably, Friedel-Crafts reaction of carbohydrate substrates and electron rich arenes could also be realized using certain Lewis acid catalysts.[26]

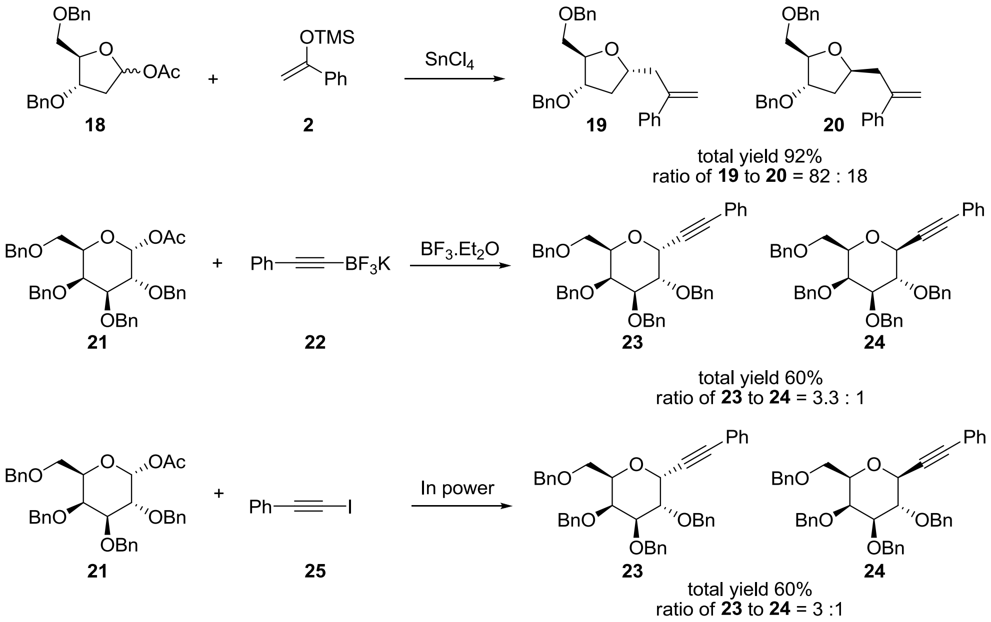


Figure 2.8. Examples of Lewis acid promoted *C*-glycosylation of C-1 substituted carbohydrate derivatives

2.1.3.2 Heck Type *C*-glycosylation

The Nobel-winning Heck reaction has been widely applied for olefin functionalizations. Given the vinyl feature of glycals, Heck reaction is expected to be a reliable synthetic method towards *C*-glycosides. The general mechanism of Heck type *C*-glycosylation reaction is depicted in **Figure 2.9**. The reactive R`PdX **25** is generated through oxidative addition or transmetalation. A subsequent migratory-insertion on glycal molecule takes place to form complex **28**. Then, the palladium metal attached to C2 potentially has two pathways to dissociate from the carbohydrate. One is through the *syn-β*-hydride elimination to form **29** with a C–C double bond between C2 and C3 while the protecting group on C3 keeps intact. The other pathway is through the *anti-β*-heteroatom elimination which removes the C3 protecting group, generating **30** with a C–C double bond between C2 and C3.

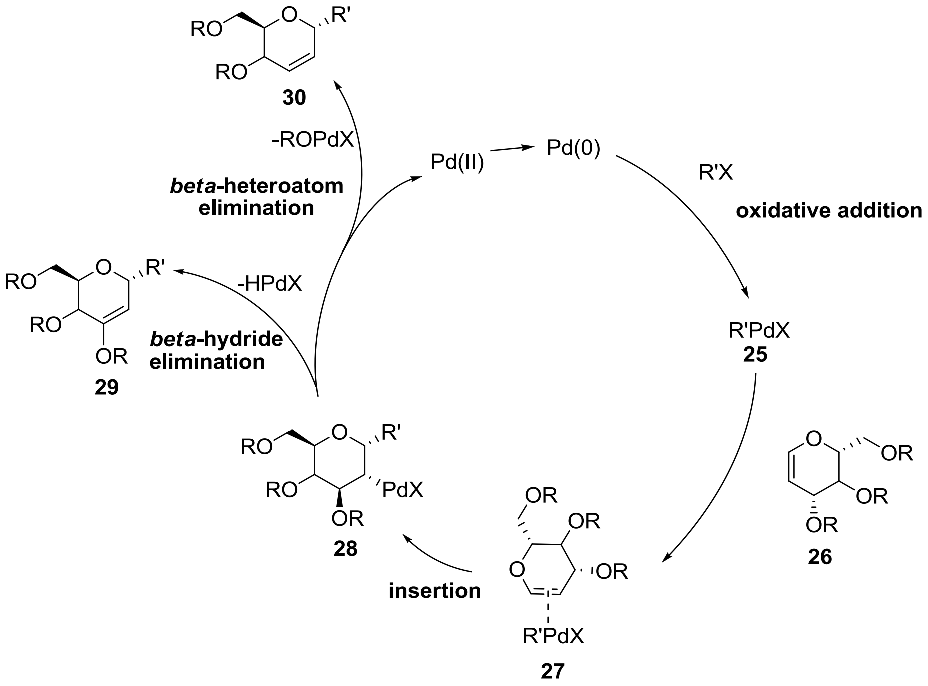


Figure 2.9. General mechanism of Heck type *C*-glycosylation

The Heck type *C*-glycosylation has been intensively studied in past decades. In order to prepare *C*-nucleosides, Daves established a highly regio- and stereoselective coupling reaction of furanose glycals and organomercuric salts (**Figure 2.10**). The exclusive selectivity is attributed to the steric control by the protecting groups on C3 and C4. The steric hindrance caused by the bulky protecting groups results in the Pd complex to only approach glycals from the less hindered face *via syn* addition.[27]

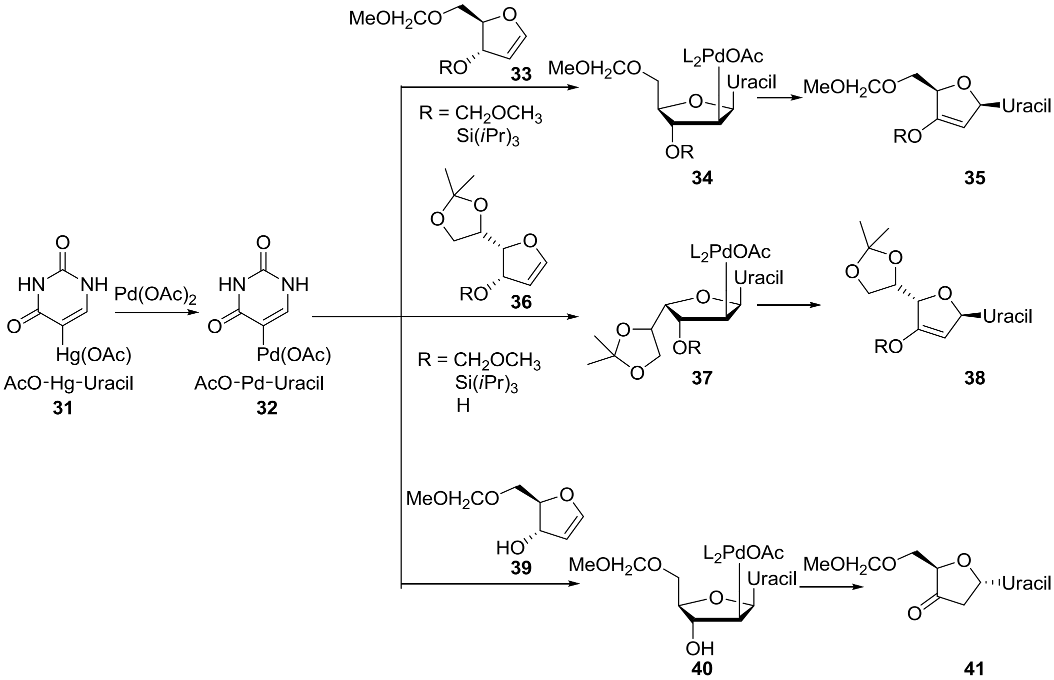


Figure 2.10. Heck type *C*-glycosylation of glycals and organomercuric salt

Aryl iodides are the most commonly used coupling partner in Heck reaction, which implies their utility in Heck type *C*-glycosylations.[28] Both furanose and pyranose glycals have been introduced to couple with aryl iodides (**Figure 2.11**).

Since the stereoselectivity is assumed to be determined by the stereo configuration of C3, the glycosidic bond is expected to form on the opposite side of the C3 protecting group. Interestingly, silyl protecting groups seem to facilitate the reaction since the most commonly used protecting groups such as acetyl or benzyl groups failed to give any product under the same conditions.

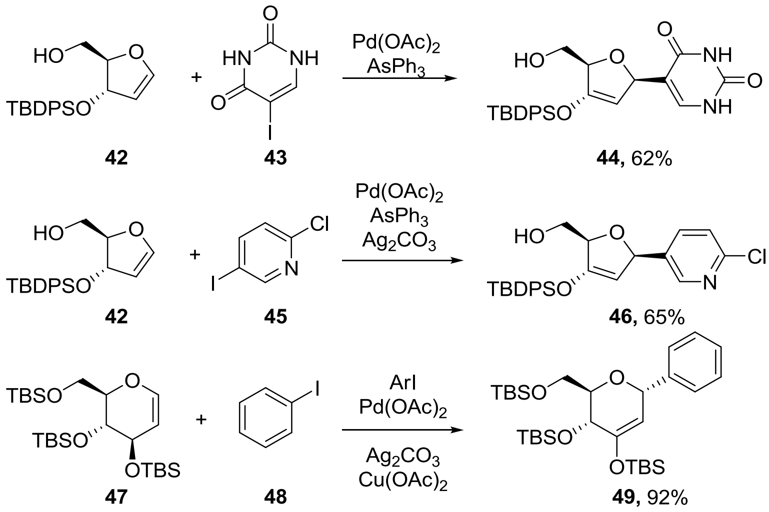


Figure 2.11. Examples of Heck type *C*-glycosylation of glycals and aryl iodides

Other coupling partners such as aryl boronic acids,[29] and electron-rich benzoic acids[30] are also employed to couple with glycals (**Figure 2.12**). All the reported methods give α selectivity exclusively.

However, almost all of the existing Heck type *C*-glycosylation methods focused on the *C*-aryl glycosides. Few palladium catalyzed *C*-glycosylation reactions of glycals and non-aryl groups has been realized. Amongst all the commonly used non-aryl coupling partners, enol triflates have shown great efficiency, indicating their underlying reactivity with glycals (**Figure 2.13**).[31]

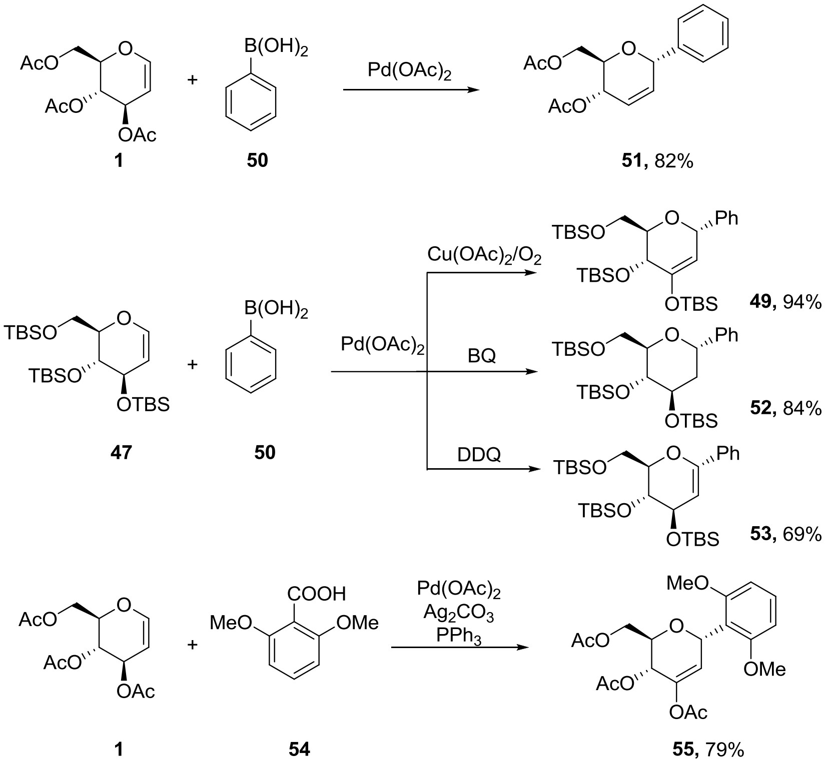


Figure 2.12. Examples of Heck type *C*-glycosylation from glycals and acids

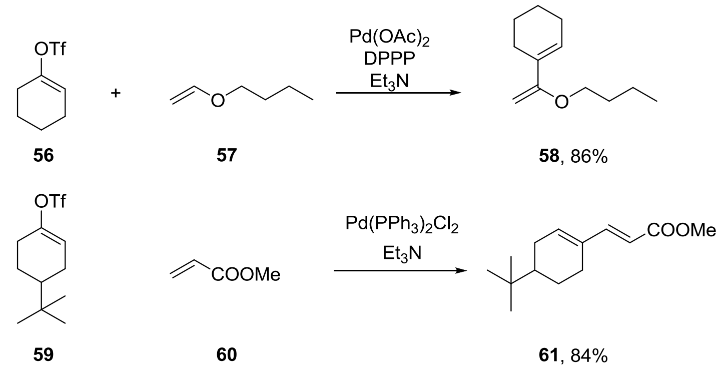


Figure 2.13. Examples of Heck reactions of enol triflate

2.2 Results and Discussion

2.2.1 Condition Optimizations

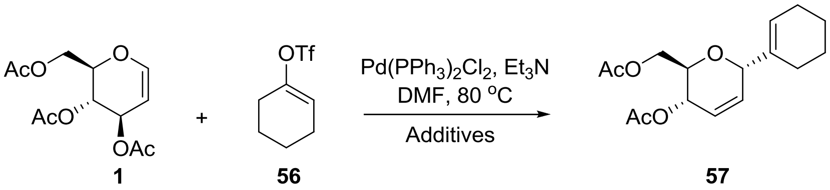
Table 2.1. Screening of palladium catalysts.[a], [b]

Entry	Pd Source	Yield (%)
1	$Pd(OAc)_2$	0
2	$Pd(TFA)_2$	0
3	$Pd(PhCN)_2Cl_2$	0
4	$Pd(PPh_3)_2Cl_2$	46

[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 1.5 equivalents of **56**, 10% catalyst and 3 equivalents of triethylamine in a sealed tube for 36 hours. [b] Isolated yields.

The initial test reaction of peracetylated glucal **1** and cyclohexenyl triflate **56** was conducted with 10% palladium acetate, 1 equivalent of triethylamine in DMF at 80 °C. Unfortunately, this reaction could not afford any *C*-glycosides after prolonged reaction time (entry 1, Table 2.1). Upon screening various palladium catalysts, it was found that bis(triphenylphosphine)palladium chloride (entry 4, Table 2.1) was the only effective palladium catalyst comparing to other palladium sources including palladium trifluoroacetate (entry 2, Table 2.1) and bis(benzylnitrile)palldium chloride (entry 3, Table 2.1).

Table 2.2. Screening of ligands and additives.[a], [b]

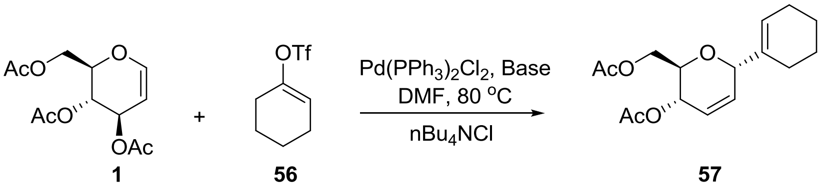


Entry	Additive	Yield (%)
1	DPPE	0
2	DPPP	53
3	DPPPen	0
4	*n*Bu$_4$NCl	62
5	*n*Bu$_4$NBr	51
6	*n*Bu$_4$NI	46
7	*n*Bu$_4$NOAc	30

[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 1.5 equivalents of **56**, 10% catalyst, 150% additives and 3 equivalents of triethylamine in a sealed tube for 36 hours. [b] Isolated yields.

In order to further increase the yield, an array of organic and inorganic additives was investigated. The addition of commonly used phosphine ligands was found to be futile to enhance the yield (entry 1-3, Table 2.2). To our delight, tetrabutylammonium salts could significantly increase the yield. Tetrabutylammonium salts with various anions were further screened and it was found that the chloride salt gave the desired product in the highest yield (entries 4-7, Table 2.2). [32]

Table 2.3. Screening of bases.[a], [b]

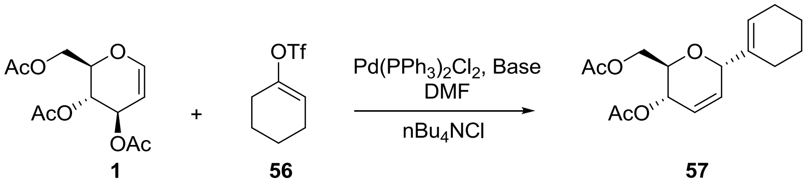


Entry	Base	Yield (%)
1	Et_3N	62
2	$n$$Bu_3N$	41
3	DIPEA	59
4	DABCO	32
5	DBU	43
6	K_2CO_3[c]	22
7	KOH[c]	10
8	Cs_2CO_3[c]	<5
9	KOAc[c]	34
10	K_3PO_4[c]	43
11	Na_2CO_3[c]	15

[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 1.5 equivalents of **56**, 10% catalyst, 150% $n\mathrm{Bu_4NCl}$ and 3 equivalents of base in a sealed tube for 36 hours. [b] Isolated yields. [c] 1 equivalent of PPh_3 was added.

Then, we proceeded to test the effects of different bases towards the yield by using the only effective catalyst (Table 2.3). After screening various organic and inorganic bases, no other base was found to be more effective than triethylamine.

Table 2.4. Screening of solvents and reaction temperatures.[a], [b]



Entry	Temp (°C)	Solvent	Yield (%)
1	80	DMF	62
2	100	DMF	65
3	120	DMF	78
4	135	DMF	69
5	120	DMSO	45
6	100	MeCN	12
7	120	NMP	56
8	110	toluene	23

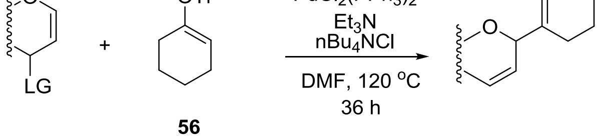
[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 1.5 equivalents of **56**, 10% catalyst, 150% *n*Bu_4NCl and 3 equivalents of Et_3N in a sealed tube for 36 hours. [b] Isolated yields.

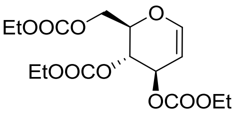
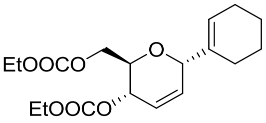
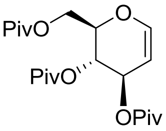
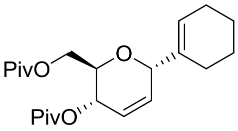
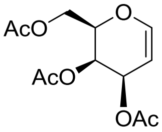
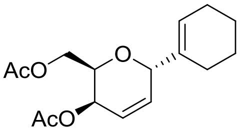
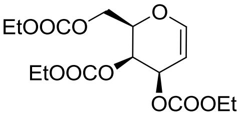
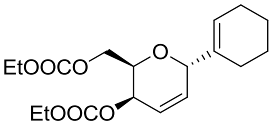
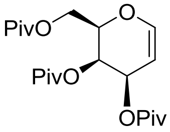
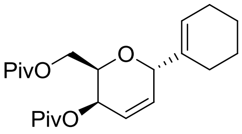
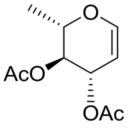
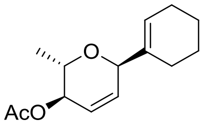
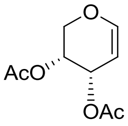
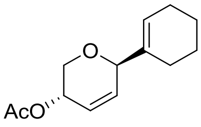
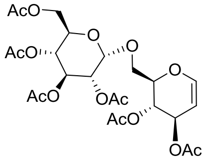
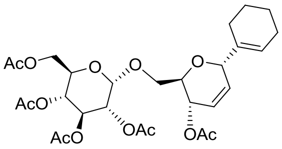
Gratifyingly, a further increase of the reaction temperature to 120 °C (entry 2, Table 2.4) led to the *β*-heteroatom elimination product in good yield with an acceptable period of time. Several solvents with high boiling point were examined and DMF was found to be the most effective solvent (entry 5-8, Table 2.4).

2.2.2 Substrate Scope

With the optimal reaction conditions in hand, we first studied the substrate scope by varying the glycal part (**Table 2.5**). Glycals derived from D-glucose with different protecting groups were tested for their reactivities under standard reaction conditions. The results revealed that only glycals protected by good leaving groups such as acetyl (**1**, **62**), pivaloyl (**60**, **66**) and ethoxycarbonylxoyl (**58**, **64**) gave corresponding *C*-glycosides (**57**, **59**, **61**, **63**, **65**, **67**). Other glycals protected by commonly used protecting groups such as benzyl, benzoyl, TBS or Boc failed to afford any desired product. Among all the reactive protecting groups, ethoxycarbonyl protected glycals gave the highest yields whereas pivaloyl protected glycal were shown to be the least efficient. Next, glycals prepared from different carbohydrates were examined. The results showed that glycals from D-galactose (**62**, **64**, **66**), L-6-deoxyglucose (**68**), D-ribose (**70**) and synthetic disaccharide (**72**) also coupled with cyclohexenyl triflate to give the corresponding *C*-glycosides (**63**, **65**, **67**, **69**, **71**, **73**) in moderate to high yields. The structure of *C*-glycoside **63** was confirmed by X-ray crystallography (**Figure 2.14**). Notably, glycals derived from D-galactose generally provided higher yields than their D-glucose equivalents.

Table 2.5. *C*-glycosylation coupling reaction of glycals and cyclohexenyl triflates.[a]



Entry	Glycals	Products	Yield[b] (%)
1	 **58**	 **59**	80
2	 **60**	 **61**	25
3	 **62**	 **63**	84
4	 **64**	 **65**	86
5	 **66**	 **67**	34
6	 **68**	 **69**	49
7	 **70**	 **71**	52
8	 **72**	 **73**	62

[a] Reactions were carried out with 1 equivalent of glycal, 1.5 equivalents of enol triflate, 10% catalyst, 150% $n\mathrm{Bu_4NCl}$ and 3 equivalents of triethylamine in a sealed tube for 36 hours. [b] Isolated yields.

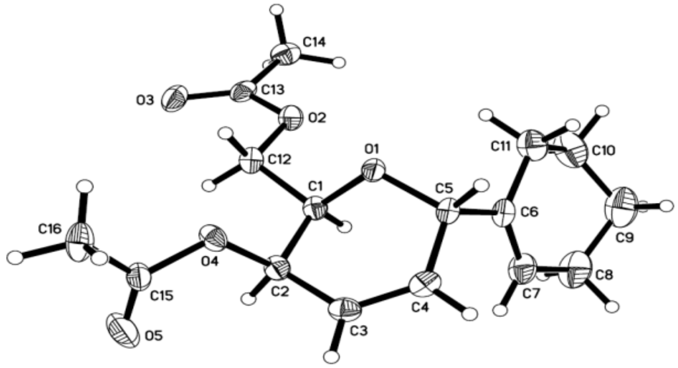
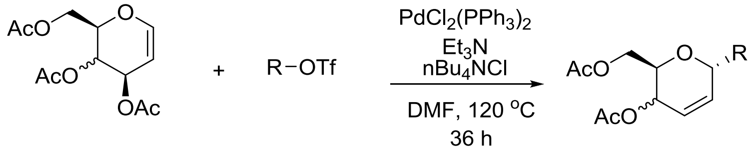
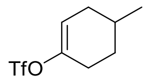
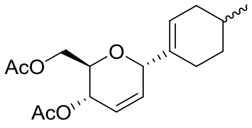
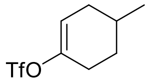
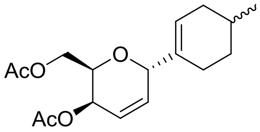
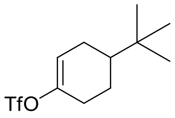
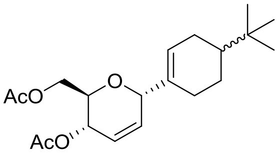
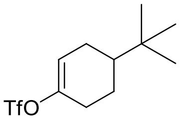
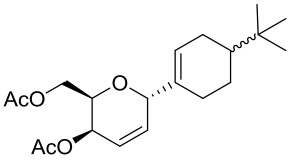
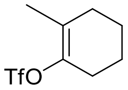
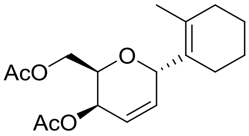
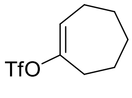
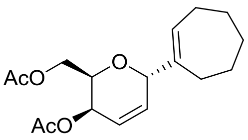


Figure 2.14. X-ray structure of compound **63**

Various enol triflates were also subjected to the standard reaction condition towards glycals (**Table 2.6**). To our delight, cyclohexenyl triflates with substituents including 4-methyl (**74**), 4-*t*-butyl (**77**) and 2-methyl (**80**) groups afforded their corresponding *C*-glycosides (**75**, **76**, **78**, **79**, **81**). After that, enol triflates with different ring sizes were tested and the results were not promising. Enol triflate with smaller ring size such as cyclopentenyl triflate failed to give any product due to its low boiling point. Enol triflates with larger rings such as cycloheptenyl, cyclooctenyl triflate were also synthesized and tested. However, only the reaction of cycloheptenyl triflate (**82**) and acetyl glycal from D-galactose (**62**) could give the product (**83**) in poor yields. In addition, some aliphatic enol triflates such as hexenyl triflate and octenyl triflate could not give any products.

Table 2.6. *C*-glycosylation coupling reactions of glycals and enol triflates[a]

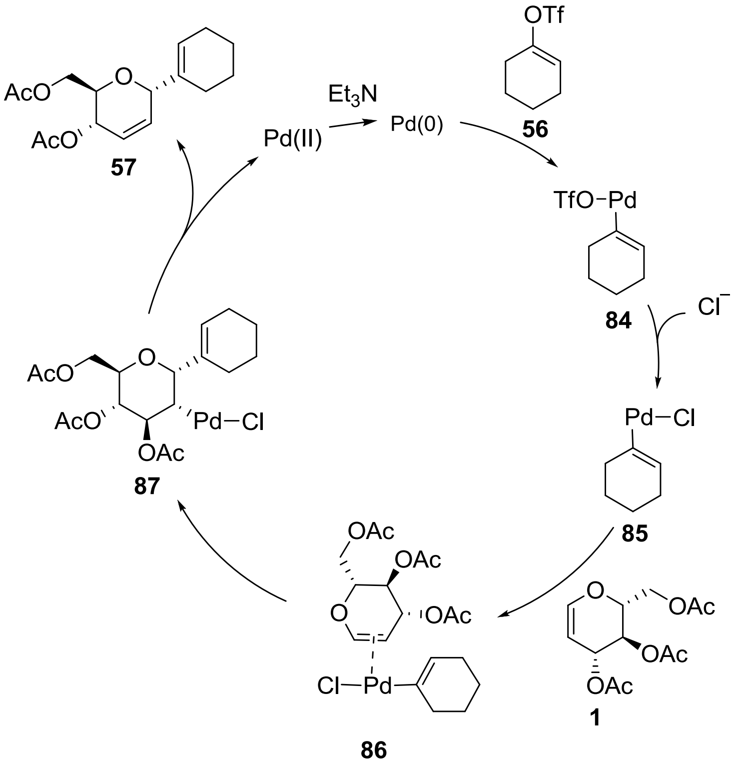


Entry	Enol triflate	Product	Yield[b] (%)
1	 **74**	 **75**	68% (1:1)
2	 **74**	 **76**	71% (1:1)
3	 **77**	 **78**	51% (1:1)
4	 **77**	 **79**	62% (1:1)
5	 **80**	 **81**	54%
6	 **82**	 **83**	31%

[a] Reactions were carried out with 1 equivalent of glycal, 1.5 equivalents of enol triflate, 10% catalyst, 150% *n*Bu$_4$NCl and 3 equivalents of triethylamine in a sealed tube for 36 hours. [b] Isolated yields.

2.2.3 Plausible Mechanism

Scheme 2.1. Plausible Mechanism

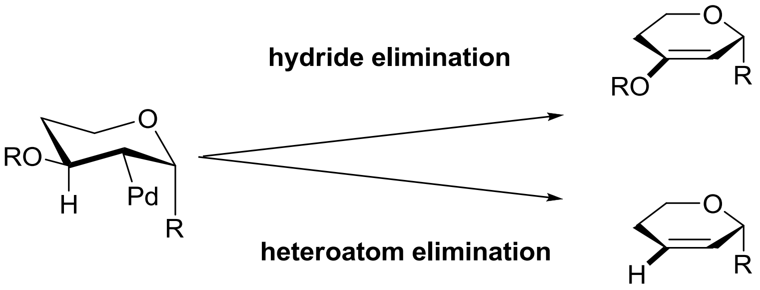


A plausible mechanism for this reaction depicted in **Scheme 2.1**. Pd(II) from the catalyst was first reduced by base to generate Pd(0) species. Oxidative addition gave the alkenyl-Pd cation complex **84**, **85** and the complex subsequently added to the double bond on glycal *via* migratory addition to form complex **86**. Then, anti Pd-leaving group elimination took place to release the final *C*-glycoside **57** and Pd(II) species which was reduced to its active Pd(0) by another molecule of base to start a new catalytic cycle.[33]

Two possible pathways of the Pd elimination are shown in **Scheme 2.2**. One is the syn-β-hydride elimination and the other is the anti-β-heteroatom elimination.

The difference between the two pathways is the electron density on the Pd center. If the Pd is electron deficient, then the reaction usually favors the β-hydride elimination since hydride is more electron rich than the leaving group anion. For the same reason, if the Pd center is electron rich, the reaction favors β-heteroatom elimination. Chloride ion from the catalyst and additive, as a rigid and electron rich ligand, can significantly increase the electron density of the Pd center through coordination. In this reaction, due to the multi-equivalent of chloride ion (from the catalyst and the additive) in the reaction mixture, the Pd center becomes electron rich so that it prefers the β-heteroatom elimination pathway.

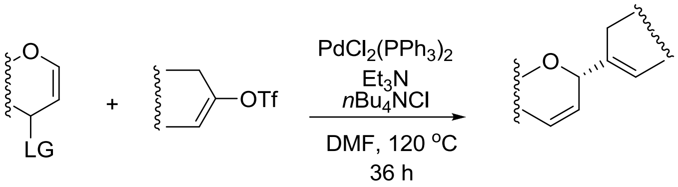
Scheme 2.2. Pd Elimination Mechanism



There are mainly two functions of the *n*-tetrabutyl ammonium salt. First it acts as a phase transfer agent to increase the reactivity of the ionic intermediate. The other function is that the halogen anion can promote the *anti*-heteroatom elimination.[34]

2.3 Conclusion

In summary, a novel and efficient palladium catalyzed Heck type coupling reaction of glycals and enol triflate was developed. This cross coupling reaction proceeded with high regioselectivity (C1 only) and stereoselectivity (α selective). Glycals with good leaving groups and a certain range of enol triflates were screened and yielded the product in moderate to good yields. The products showed possibilities for the further transformations to other functionalities.

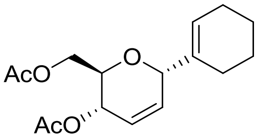


2.4 Experimental Section

General**:** All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

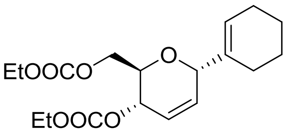
Material: Dimethylformamide (DMF) and triethylamine (Et_3N) were purchased from commercial suppliers and used without further purification. 3, 4, 6-tri–*O*–acetyl–D–glucal and 3, 4, 6-tri-*O*-acetyl-D-galactal, 3, 4–*O*–actyl–6–deoxy–L–glucal, and cyclohexenyl trifluoromethanesulfonate were purchased from commercial suppliers. 1, 2–unsaturated glucals with protecting groups as benzyl, pivaloyl and benzoyl were prepared from 3, 4, 6-tri–*O*–acetyl–D–glucal by reported methods.[35] Glycals derived from D-ribose and disaccharide are synthesized by reported methods.[36] Other enol triflates were prepared by reported methods.[37]

General procedure of Pd catalyzed cross-coupling of glycals and enol triflates: synthesis of ((2R,3S,6S)-3-acetoxy-6-cyclohexenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (57). To a sealed tube containing the solution of glucal (54 mg, 0.2 mmol) bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutyl-ammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow oil. (49 mg, 78%)



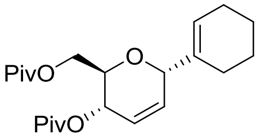
((2R,3S,6S)-3-acetoxy-6-cyclohexenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (57): To a sealed tube containing the solution of tri-acetyl-O-glucal (54 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutyl-ammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography

(EtOAc/Hexane = 1/2) to afford the product as yellow oil. (46 mg, 78%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.55-1.67 (m, 4H), 1.93–1.96 (m, 1H), 1.98–2.08 (m, 8H), 2.14–2.22 (m, 1H), 3.82–3.86 (m,1H) , 4.12 (dd, *J* = 3.0, 11.9 Hz, 1H), 4.20 (dd, *J* = 6.2, 11.5 Hz, 1H), 4.51 (s, 1H), 5.20 (ddd, *J* = 2.2, 4.0, 9.8 Hz, 1H), 5.67 (d, *J* = 1.2 Hz, 1H), 5.81–5.84 (m, 1H), 5.94 (ddd, *J* = 1.5, 3.0, 10.4 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 20.8, 20.9, 22.2, 22.6, 25.1, 26.3, 63.1, 64.2, 67.8, 75.8, 122.8, 127.0, 133.7, 134.8, 170.6, 170.7; IR (neat) 3018, 2931, 1737, 1371, 1236, 1215, 1095, 1047, 1022, 756 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 6.9 (*c* 1.00, CHCl$_3$); HRMS (ESI) calcd for $C_{16}H_{22}O_5Na$ [M+Na]$^+$: 317.1365, found 317.1365.

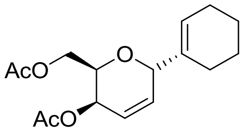


((2R,3S,6S)-6-cyclohexenyl-2-((ethoxycarbonyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl) methyl ethyl carbonate (59): To a sealed tube containing the solution of tri-*O*-ethoxycarbonyloxyl-D-glucal (72 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 2/5) to afford the product as colorless oil (57 mg, 80%). ^{1}H NMR (CDCl$_3$, 400

MHz) δ 1.28-1.33 (m, 6H), 1.54–1.65 (m, 4H), 2.03–2.04 (m, 1H), 2.04 (m, 2H), 2.14–2.17 (m, 1H), 3.88–3.92 (m, 1H), 4.16–4.31 (m, 6H), 4.51 (s, 1H), 5.10 (dd, J = 1.6, 8.0 Hz, 1H), 5.66 (d, J = 1.1 Hz, 1H), 5.90 (dd, J = 2.0, 12.4 Hz, 1H), 5.97 (ddd, J = 1.4, 3.5, 10.4 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.2, 14.2, 22.1, 22.6, 25.1, 26.3, 64.1, 64.3, 66.3, 68.2, 68.8, 75.8, 124.2, 127.4, 132.1, 135.2, 154.6, 155.1; IR (neat) 3018, 2933, 2320, 1743, 1373, 1253, 1215, 1012, 756 cm^{-1}; $[\alpha]^{20}_{D}$ = -2.6 (*c* 0.5, CHCl$_3$); HRMS (ESI) calcd for $C_{18}H_{26}O_7Na$ [M+Na]$^+$: 377.1576, found 377.1579

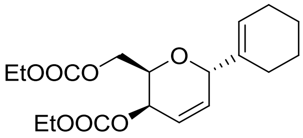


(2R,3S,6S)-6-cyclohexenyl-2-(pivaloyloxymethyl)-3,6-dihydro-2H-pyran-3-yl pivalate (61): To a sealed tube containing the solution of tri-*O*-pivaloyl-D-glucal (80 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/12) to afford the product as colorless oil (19 mg, 25%). This compound was prepared by the general procedure described above and was obtained as a yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.23–1.27 (m, 18H), 1.64-1.69 (m, 4H), 1.97–2.24 (m, 4H), 3.87–3.91 (m, 1H), 4.10–4.20 (m, 2H), 4.52 (s, 1H), 5.14 (ddd, *J* = 2.2, 4.0, 7.4 Hz, 1H), 5.71 (d, *J* = 1.1 Hz, 1H), 5.80–5.84 (m,1H), 5.94 (ddd, *J* = 1.6, 2.9, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 22.6, 25.1, 26.0, 27.0, 27.2, 29.7, 38.8, 63.4, 65.3, 69.3, 75.7, 124.8, 126.7, 131.5, 135.7, 177.9, 178.3; IR (neat) 2960, 2929, 1732, 1479, 1396, 1365, 1280, 1259, 1147, 1095, 1031, 798 cm^{-1}; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -10.1 (*c* 0.25, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$: 401.2304, found 401.2324

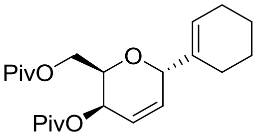


((2R,3R,6S)-3-acetoxy-6-cyclohexenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (63): To a sealed tube containing the solution of tri-*O*-acetyl-D-galactal (54 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as a colorless crystal (49 mg, 84%). mp 75 - 78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.69 (m, 4H), 1.89–1.94 (m, 1H), 2.04–2.07 (m, 8H), 2.18–2.23 (m, 1H), 3.98–4.01 (m, 1H) , 4.12–4.22 (m, 2H), 4.56 (s, 1H), 5.02 (dd, *J* = 2.6, 4.9 Hz, 1H), 5.59 (d, *J* = 1.3 Hz, 1H), 6.02

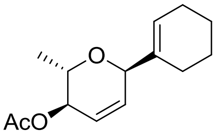
(ddd, *J* = 1.9, 5.0, 10.2 Hz, 1H), 6.12 (dd, *J* = 3.4, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 21.1, 22.2, 22.6, 25.1, 26.2, 63.2, 65.5, 68.7, 75.7, 124.7, 127.1, 131.6, 135.5, 170.5, 170.9; IR (neat) 3018, 2399, 2341, 1734, 1519, 1371, 1215, 756 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -264.2 (*c* 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: 317.1365, found 317.1363



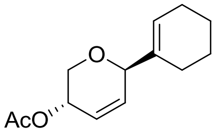
((2R,3R,6S)-6-cyclohexenyl-2-((ethoxycarbonyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl) methyl ethyl carbonate (65): To a sealed tube containing the solution of tri-*O*-ethoxycarbonyloxyl-D-galactal (72 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 2/5) to afford the product as pale yellow oil (61 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27-1.31 (m, 6H), 1.53–1.66 (m, 4H), 1.88–1.93 (m, 1H), 2.02–2.05 (m, 2H), 2.17–2.21 (m, 1H), 4.04–4.07 (m, 1H), 4.18 (dd, *J* = 3.1, 14.3 Hz, 4H), 4.28–4.30 (m, 2H), 4.56 (s, 1H), 4.88 (dd, *J* = 2.6, 4.6 Hz, 1H), 5.58 (d, *J* = 1.3 Hz, 1H), 6.06–6.10 (m, 1H), 6.13 (dd, *J* = 3.2, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 14.2, 22.2, 22.6, 25.1, 26.2, 64.1, 64.2, 66.2, 67.3, 67.9, 75.8, 122.2, 126.9, 134.4, 134.8, 154.8, 155.0; IR (neat) 2932, 2347, 1990, 1747, 1271, 1217, 756 cm^{-1}; $[\alpha]_{\mathrm{D}}^{20}$ = -180.3 (*c* 1.5, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{26}O_7Na$ [M+Na]$^+$: 377.1576, found 377.1588



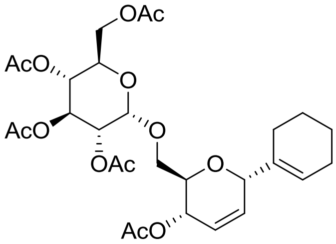
(2R,3R,6S)-6-cyclohexenyl-2-(pivaloyloxymethyl)-3,6-dihydro-2H-pyran-3-yl pivalate (67): To a sealed tube containing the solution of tri-*O*-pivaloyl-D-galactal (80 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/12) to afford the product as yellow oil (26 mg, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.20 (m, 18H), 1.52–1.68 (m, 4H), 1.90-1.94 (m, 1H), 2.03–2.05 (m, 2H), 2.26–2.30 (m, 1H), 4.00–4.04 (m, 1H), 4.13–4.20 (m, 2H), 4.56 (s, 1H), 4.97 (dd, *J* = 2.6, 5.0 Hz, 1H), 5.60 (d, *J* = 1.3 Hz, 1H), 6.01 (ddd, *J* = 1.9, 5.0, 10.2 Hz, 1H), 6.10 (dd, *J* = 3.5, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 22.6, 25.1, 26.4, 27.0, 27.1, 27.1, 63.4, 64.0, 68.0, 75.7, 122.8, 126.9, 133.6, 134.9, 177.9, 178.2; IR (neat) 2972, 2933, 1730, 1479, 1396, 1367, 1282, 1155, 756 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -105.0 (*c* 0.7, $CHCl_3$); HRMS (ESI) calcd for $C_{22}H_{34}O_5Na$ [M+Na]$^+$: 401.2304, found 401.2308



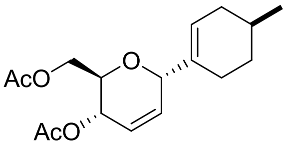
(2S,3R,6R)-6-cyclohexenyl-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate (69): To a sealed tube containing the solution of L-6-deoxyl-3,4-diacetyglucal (44 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetrabutylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/4) to afford the product as colorless oil (23 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, *J* = 6.5 Hz, 3H), 1.55–1.66 (m, 4H), 2.04–2.13 (m, 7H), 3.78–3.85 (m, 1H), 4.93 (s, 1H), 4.92–4.95 (m, 1H), 5.68 (d, *J* = 4.7 Hz, 1H), 5.81 (ddd, *J* = 2.0, 7.2, 10.3, 1H), 5.92 (ddd, *J* = 1.3, 2.7, 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, 21.2, 22.3, 22.7, 25.1, 25.8, 67.7, 70.2, 74.8, 124.0, 126.1, 132.3, 136.1, 170.7; IR (neat) 3018, 2931, 2399, 1730, 1373, 1244, 1215, 1136.0, 923, 753 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -4.6 (*c* 0.8, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{20}O_3Na$ [M+Na]$^+$: 259.1310, found 259.1304



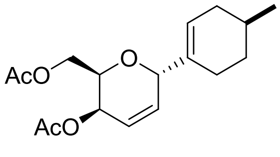
(3S,6R)-6-cyclohexenyl-3,6-dihydro-2H-pyran-3-yl acetate (71): To a sealed tube containing the solution of (3R,4S)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (40 mg, 0.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/5) to afford the product as pale yellow oil (23 mg, 52%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54–1.65 (m, 4H), 1.93–1.97 (m, 1H), 2.03–2.04 (m, 3H), 2.06–2.08 (m, 3H), 3.60 (dd, J = 5.0, 11.8 Hz, 1H), 4.01 (dd, J = 4.3, 7.8 Hz, 1H), 4.56 (s, 1H), 5.12–5.15 (m, 1H), 5.66 (d, J = 0.8 Hz, 1H), 5.89–5.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 22.2, 22.6, 25.1, 25.4, 64.1, 64.9, 77.2, 124.2, 126.7, 133.3, 135.7, 170.7; IR (neat) 2929, 1747, 1435, 1367, 1224, 1039 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 58.6 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$: 245.1154, found 245.1164



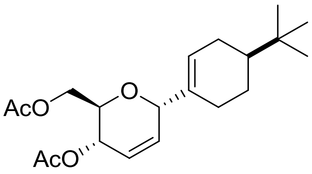
(2S,3R,4S,5R,6R)-2-(((2R,3S,6S)-3-acetoxy-6-cyclohexenyl-3,6-dihydro-2H-pyran-2-yl)methoxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (73): To a sealed tube containing the solution of **72** (112 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cyclohexenyl triflate (54 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/1) to afford the product as colorless oil (71 mg, 62%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.60–1.69 (m, 4H), 2.03–2.11 (m, 19H), 3.79–3.81 (m, 1H), 4.07–4.15 (m, 3H), 4.27–4.31 (m, 3H), 4.50 (s, 1H), 4.85 (dd, J = 3.8, 10.3 Hz, 1H), 5.05–5.10 (m, 1H), 5.32 (d, J = 3.8 Hz, 1H), 5.44–5.49 (m, 1H), 5.66 (s, 1H), 5.81–5.84 (m, 1H), 5.96 (td, J = 1.4, 10.4 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 20.6, 20.6, 20.7, 20.8, 22.2, 22.6, 25.1, 26.2, 61.7, 63.5, 67.9, 68.3, 69.3, 69.9, 70.2, 70.8, 75.5, 94.1, 124.2, 127.1, 131.8, 135.3, 169.6, 170.1, 170.6, 170.7; IR (neat) 3018, 2931, 2860, 2837, 2399, 1730, 1435, 1371 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 25.1 (c 2.0, CHCl$_3$); HRMS (ESI) calcd for C$_{28}$H$_{38}$O$_{13}$Na [M+Na]$^{+}$: 605.2210, found 605.2206



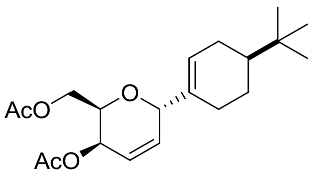
((2R,3S,6S)-3-acetoxy-6-(4-methylcyclohex-1-enyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (75): To a sealed tube containing the solution of tri-*O*-acetyl-D-glucal (54 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, 4-methyl-cyclohexenyl triflate (50 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow oil (42 mg, 68%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.95 (d, J = 6.3 Hz, 3H), 1.23–1.25 (m, 1H), 1.63–1.73 (m, 3H), 2.07–2.17 (m, 9H), 3.81–3.86 (m, 1H), 4.11–4.21 (m, 2H), 4.52 (s, 0.5H), 4.54 (s, 0.5H), 5.19–5.22 (m, 1 H), 5.64 (s, 1H), 5.81-5.85 (m, 1H), 5.92–5.94 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 20.8, 20.8, 21.1, 21.4, 21.6, 25.9, 26.5, 28.0, 28.3, 30.8, 33.6, 33.7, 63.2, 63.3, 65.4, 65.6, 68.7, 75.4, 75.8, 124.7, 124.9, 126.5, 127.0, 131.5, 131.7, 135.0, 135.2, 170.5, 170.9; IR (neat) 3020, 2953, 2926, 2910, 2877, 1737, 1456, 1435, 1371, 1234, 1217, 1076, 1049, 906, 759 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_5Na$ [M+Na]$^+$: 331.1521, found 311.1529



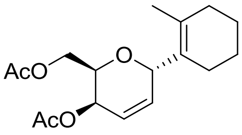
((2R,3R,6S)-3-acetoxy-6-(4-methylcyclohex-1-enyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (76): To a sealed tube containing the solution of tri-acetyl-D-galatcal (54 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, 4-methyl-cyclohexenyl triflate (50 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow oil (44 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 6.2 Hz, 3H), 1.19–1.27 (m, 1H), 1.62–1.74 (m, 3H), 2.02–2.11 (m, 9H), 3.98–4.00 (m, 1H), 4.16–4.20 (m, 2H), 4.58 (s, 0.5 H), 4.60 (s, 0.5H), 5.01-5.04 (m, 1H), 5.56 (d, J = 1.1 Hz, 1H), 6.02–6.05 (m, 1H), 6.11–6.14 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 20.8, 20.9, 21.4, 21.5, 25.9, 26.7, 28.0, 28.3, 30.3, 30.8, 33.5, 33.7, 63.1, 63.2, 64.2, 64.2, 67.7, 68.0, 75.4, 76.0, 122.8, 122.9, 126.4, 126.9, 133.8, 133.8, 134.3, 134.5, 170.6, 170.7; IR (neat) 3020, 2951, 2910, 1745, 1737, 1454, 1435, 1371, 1232, 1070, 1047, 910, 756 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}O_5Na$ $[M+Na]^+$: 331.1521, found 331.1522



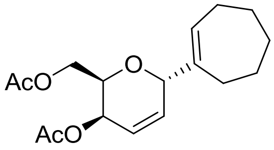
((2R,3S,6S)-3-acetoxy-6-(4-tert-butylcyclohex-1-enyl)-3,6-dihydro-2H-pyran-2-yl) methyl acetate (78): To a sealed tube containing the solution of tri-*O*-acetyl-D-glucal (54 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, 4-*tert*-butyl-cyclohexenyl triflate (52 µL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow oil (35 mg, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 9H), 1.12–1.25 (m, 3H), 1.85–1.90 (m, 2H), 2.07–2.08 (m, 8H), 3.83–3.84 (m, 1H), 4.11–4.14 (m, 1H), 4.18–4.23 (m, 1H), 4.52 (s, 0.5H), 4.55 (s, 0.5H), 5.20–5.23 (m, 1 H), 5.68–5.69 (m, 1H), 5.81-5.85 (m, 1H), 5.92–5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 20.8, 21.0, 23.9, 24.1, 26.7, 26.8, 27.1, 27.2, 27.4, 28.0, 32.1, 32.2, 43.9, 44.1, 63.1, 63.3, 65.4, 65.6, 68.7, 68.8, 75.1, 75.8, 124.6, 124.8, 127.0, 127.7, 131.5, 131.7, 135.2, 135.4, 170.4, 170.8; IR (neat) 3018, 2960, 2870, 2841, 1732, 1367, 1232, 1186, 1047, 970, 756 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{30}O_5Na$ [M+Na]$^+$: 373.1991, found 373.1993



((2R,3R,6S)-3-acetoxy-6-(4-tert-butylcyclohex-1-enyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (79): To a sealed tube containing the solution of tri-*O*-acetyl-D-galactal (54 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, 4-*tert*-butyl-cyclohexenyl triflate (52 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as colorless oil (42 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 6.3 Hz, 9H), 1.23–1.36 (m, 3H), 1.78–1.92 (m, 3H), 2.02–2.10 (m, 6H), 2.34–2.38 (m, 1H), 3.97–4.02 (m, 1H), 4.13–4.23 (m, 2H), 4.58 (s, 0.5H), 4.61 (s, 0.5H), 5.01–5.05 (m, 1 H), 5.57–5.60 (m, 1H), 6. 01-6.05 (m, 1H), 6.11–6.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 20.8, 20.9, 23.9, 24.0, 26.7, 26.8, 27.1, 27.2, 27.3, 28.4, 32.1, 44.0, 44.1, 63.0, 63.1, 64.2, 64.2, 67.7, 68.9, 75.0, 76.1, 122.7, 122.9, 126.9, 127.6, 133.7, 133.8, 134.6, 134.7, 170.6, 170.6; IR (neat) 3018, 2692, 1732, 1371, 1232, 1215, 1188, 1068, 1047, 1016, 923, 751, 704 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{30}O_5Na$ [M+Na]$^+$: 373.1991, found 373.1999



((2R,3R,6S)-3-acetoxy-6-(2-methylcyclohex-1-enyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (81): To a sealed tube containing the solution of tri-*O*-acetyl-D-galactal (54 mg, 0.2 mmol), bis(triphenylphosphine)-palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, 2-methyl-cyclohexenyl triflate (52 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as colorless oil (33 mg, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50–1.64 (m, 5H), 1.72 (s, 3H), 1.84–1.88 (m, 1H), 1.92–1.99 (m, 2H), 2.08 (d, *J* = 4.4 Hz, 6H), 4.09–4.13 (m, 1H), 4.15–4.19 (m, 1H), 4.37 (dd, *J* = 7.5, 11.3 Hz, 1H), 4.94–4.96 (m 1H), 5.11 (d, *J* = 2.0, 1H), 5.83–5.86 (m, 1 H), 5.92–5.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 20.8, 21.1, 22.8, 22.9, 24.8, 32.4, 61.9, 64.3, 68.9, 72.6, 121.7, 128.0, 134.6, 170.7, 170.8; IR (neat) 2929, 2858, 1737, 1732, 1371, 1232, 1188, 1124, 1047, 1022, 972, 756 cm^{-1}; $[\alpha]_D^{20}$ = 5.0 (*c* 1.5, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{24}O_5Na$ [M+Na]$^+$: 331.1521, found 331.1520



((2R,3R,6S)-3-acetoxy-6-cycloheptenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (83): To a sealed tube containing the solution of tri-*O*-acetyl-D-galactal (54 mg, 0.2 mmol), bis(triphenylphosphine) palladium(II) dichloride (14 mg, 0.02 mmol) and tetra-butylammonium chloride (83 mg, 0.3 mmol) in dimethylformamide (1 mL) at 120 °C, cycloheptenyl triflate (60 μL, 0.3 mmol) was added dropwise. The mixture was allowed to stir at 120 °C for 36 hours. The mixture was then quenched, diluted with dichloromethane (5 mL), and filtered. The filtrate was washed with water (10 mL) and brine (10 mL). The organic layer was removed and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as yellow oil (19 mg, 31%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37–1.42 (m, 3H), 1.55–1.68 (m, 2H), 1.80–1.88 (m, 1H), 2.04–2.16 (m, 8H), 2.24–2.26 (m, 2H), 4.04 (dd, *J* = 2.6, 6.3 Hz, 1H), 4.18–4.19 (m, 2H), 4.61 (s, 1H), 5.03 (dd, *J* = 2.6, 4.7 Hz, 1H), 5.69–5.73 (m, 1 H), 6.03–6.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 20.9, 26.6, 26.9, 28.4, 31.3, 32.4, 63.2, 64.2, 67.5, 77.1, 122.9, 132.6, 133.8, 140.8, 170.5, 170.7; IR (neat) 3018, 2924, 2850, 1737, 1732, 1454, 1371, 1232, 1217, 1049, 1026, 756 cm^{-1}; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -52.5 (*c* 1.5, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{24}O_5Na$ [M+Na]$^+$: 331.1521, found 331.1521

Crystal data

Basic crystal data of Compound **63**

Empirical formula	C16 H22 O5	
Formula weight	294.34	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 29.342(4) Å	a= 90°.
	b = 5.0975(5) Å	b= 105.4(5)°.
	c = 10.8993(13) Å	c = 90°.
Volume	1571.9(3) Å^3	
Z	4	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	632	
Crystal size	0.40 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.94 to 27.16°.	
Index ranges	-37<=h<=37, -6<=k<=6, -14<=l<=14	
Reflections collected	11179	
Independent reflections	1945 [R(int) = 0.0556]	
Completeness to theta = 27.16°	99.7 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9909 and 0.9643
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1945 / 107 / 230
Goodness-of-fit on F^2	1.182
Final R indices [I>2sigma(I)]	R1 = 0.0370, wR2 = 0.1003
R indices (all data)	R1 = 0.0474, wR2 = 0.1269
Largest diff. peak and hole	0.481 and -0.279 e.Å^{-3}

2.5 References

1. (a) Härle, J.; Günther, S.; Lauinger, B.; Weber, M.; Kammerer, B.; Zechel, David L.;Luzhetskyy, A.; Bechthold, A. *Chem. Biol.* **2011**, *18*, 520. (b) Weatherman, R. V.;Kiessling, L. L. *J. Org. Chem.* **1996**, *61*, 534. (c) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (d) Zhou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (e) Compain, P.;Martin, O. R. *Biorg. Med. Chem.* **2001**, *9*, 3077. (f) Yang, G.; Schmieg, J.; Tsuji, M.;Franck, R. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 3818. (g) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown: NY, **1995**.

2. Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. chem., Int. Ed.* **2004**, *43*, 3818

3. (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742.(b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Wei, Z. *Curr. Top. Med. Chem.* **2005**, *5*, 1363.

4. (a) Connor, D. T.; Greenough, R. C.; Von Strandtmann, M. *J. Org. Chem.***1977**, *41*, 3664. (b) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2007**, *10*, 225.(c) Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364. (d) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 1853. (e) Larrosa, I.; Romea, P.; Urpí, F. *Org. Lett.* **2006**, *8*, 527. (f) Nagasawa, T.; Kuwahara, S. *Org. Lett.* **2009**, *11*, 761. (g) Nishikawa, T.; Koide, Y.; Kanakubo, A.; Yoshimura, H.; Isobe, M. *Org. Biomol. Chem.*

2006, *4*, 1268. (h) Yeager, A. R.; Min, G. K.; Porco, J. A.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065.

5. Dawe, R. D.; Fraser-Reid, B. *J. C. S. Chem. Comm.* **1981**, 1180.

6. Takhi, M.; Rahman, A.; Schmidt, R. R. *Tetrahedron Lett.* **2001**, *42*, 4053.

7. (a) Ghosh, R.; De, D.; Shown, B.; Maiti, S. B. *Carbohydr. Res.* **1999**, *321*, 1. (b) Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K.; Sachwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 4507.

8. Yadav, J. S.; Reddy, B. V. S. *Synthesis* **2002**, 511.

9. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. S.; Chandraiah, L.; Sunitha, V. *Synthesis* **2004**, 2523.

10. Smitha, G.; Reddy, C. S. *Synthesis* **2004**, 834.

11. Takhi, M.; Rahman, A.; Schmidt, R. R. *Tetrahedron Lett.* **2001**, *42*, 4053.

12. Yadav, J. S.; Reddy, B. V. S.; Chand, P. K. *Tetrahedron Lett.* **2001**, *42*, 4057.

13. Kamble, V. T.; Bandgar, B. P.; Khobragade, C. N.; Gacche, R. N.; Kamble, V. A. *Lett. in Org. Chem.* **2006**, *3*, 658.

14. (a) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem.Comm.* **1998**, 2665. (b) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211. (c) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahedron Lett.* **2002**, *43*, 5437. (d) Smitha, G.; Reddy, S. C. *Synthesis* **2004**, 834. (e) Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Russo, B.; Tagarelli, A. *Synthesis* **2006**, 332. (f) Yeager, A. R.; Min, G. K.; Porco, J. A.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 5065.

15. Vieira, A. S.; Fiorante, P. F.; Hough, T. L. S.; Ferreira, F. P.; Ludtke, D. S.; Stefani, H. A. *Org. Lett.* **2008**, *10*, 5215.

16. (a) Delasheras, F. G.; Felix, A. S.; Fernandezresa, P. *Tetrahedron* **1983**, *39*, 1617. (b) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Chand, P. K.; Prasad, A. R. *Synlett* **2001**, 1638. (c) Franz, A. H.; Wei, Y. Q.; Samoshin, V. V.; Gross, P. H. *J. Org. Chem.* **2002**, *67*, 7662.

17. Yadav, J. S.; Reddy, B. V. S.; Chary, D. N.; Madavi, C.; Kunwar, A. C. *Tetrahedron Lett.* **2009**, *50*, 81.

18. (a) Orsini, F.; Pelizzoni, F. *Carbohydr. Res.* **1993**, *243*, 183. (b) Thorn, S. N.; Gallagher, T. *Synlett* **1996**, 185. (c) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293. (d) Cook, M. J.; Fletcher, M. J. E.; Gray, D.; Lovell, P. J.; Gallagher, T. *Tetrahedron* **2004**, *60*, 5085.

19. Deelertpaiboon, P.; Reutrakul, V.; Jarussophon, S.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *Tetrahedron Lett.* **2009**, *50*, 6233.

20. (a) Price, S.; Edwards, S.; Wu, T.; Minehan, T. *Tetrahedron Lett.* **2004**, *45*, 5197. (b)Lubin-Germain, N.; Hallonet, A.; Huguenot, F.; Palmier, S.; Uziel, J.; Augé, J. *Org. Lett.* **2007**, *9*, 3679.

21. (a) Narasaka, K.; Ichikawa, Y.; Kubota, H. *Chem. Lett.* **1987**, 2139; (b) Mukaiyama, T.; Kobayashi, S. *Carbohydr. Res.* **1987**, *171*, 81.

22. Zeng, J.; Vedachalam, S.; Xiang, S. H., Liu, X. -W. *Org. Lett.* **2011**, *13*, 42

23. Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480.

24. Hainke, S.; Singh, I.; Hemmings, J.; Seitz, O. *J. Org. Chem.* **2007**, *72*, 8811.

25. Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (b) Leteux, C.; Veyrieres, A. *J. Chem. Soc, Perkin Trans. 1* **1994**, 2647.

26. (a) Bárta, J.; Pohl, R.; Klepetářová, B.; Ernsting, N. P.; Hocek, M. *J. Org. Chem.* **2008**, *73*, 3798. (b) Hamamichi, N.; Miyasaka, T. *J. Org. Chem.* **1991**, *56*, 3731. (c) Kwok, D. I.; Daves, G. D. *J. Org. Chem.* **1989**, *54*, 4496. (d) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1984**, *25*, 2085.

27. (a) Arai, I.; Hanna, R.; Daves, G. D. *J. Am. Chem. Soc.***1981**, *103*, 7684. (b) Arai, I.; Daves, G. D. *J. Am. Chem. Soc.* **1978**, *100*, 287.(c) Hacksell, U.; Daves, G. D. *J. Org. Chem.* **1983**, *48*, 2870. (d) Cheng, J. C. Y.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 3083.

28. (a) Zhang, H. C.; Daves, G. D. *J. Org. Chem.* **1992**, *57*, 4690. (b) Joubert, N.; Pohl, R.; Klepetářová, B.; Hocek, M. *J. Org. Chem.* **2007**, *72*, 6797. (c) Li, H.-H.; Ye, X.-S. *Org. Biomol. Chem*. **2009**, *7*, 3855.

29. (a) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2009**, *11*, 1709. (b) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013.

30. Xiang, S. H.; Cai, S. T.; Zeng, J.; Liu, X. -W. *Org. Lett.* **2011**, *13*, 4608.

31. (a) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537. (b) Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S. J.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 2302. (c) Kaukoranta, P.; Källström, K.; Andersson, P. G. *Adv. Synth. Catal.* **2007**, *349*, 2595. (d) Mata, Y.; Pàmies, O.; Diéguez, M. *Chem.—Eur. J.* **2007**, *13*, 3296.

32. (a) Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Org. Lett.* **2011**, *13*, 1126.(b) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745.

33. Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Org. Lett.* **2011**, *13*, 2184.

34. Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724.

35. (a) Bovin, N. V.; Zurabyan, S. É.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25. (b) Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res.* **1982**, *101*, 197. (c)Takahashi, Y.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 1563.

36. (a) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2010**, *12*, 4624. (b) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955.

37. Pal, K. *Synthesis* **1995**, *1995*, 1485.

Chapter 3. Oxidative Heck Reaction of Glycals and Aryl Hydrazines: a Palladium-Catalyzed *C*-Glycosylation

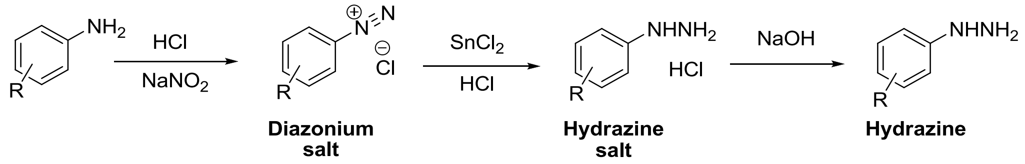
3.1 Introduction

The core concept of organic reactions is the cleavage and formation of chemical bonds. Since most of the chemical bonds in organisms are carbon-carbon bond, the formation of a chemical bond between two carbon atoms has been developed as the most important research area in organic chemistry. In order to form one new C–C bond, two other bonds need to be cleaved to form carbon ions or carbon radicals. The activation of C–X bond where X is a halogen atom has been most intensively studied in the last century. Activation of C–X bond by metals such as magnesium, zinc, tin and palladium results in Grignard reagents, organozinc, organotin and Heck or Suzuki type intermediates, which are widely used in synthetic chemistry to construct C–C bonds. In the past decade, C–H[1] and C–C[2] activation has emerged as other promising areas for C–C bond formation. The number of steps to synthesize target compound could be reduced by abstracting the proton directly from the carbon backbone, mediated by transition metal.

Besides C–X and C–H activation, transition metal catalyzed C–N activation[3] to form a new C–C bond also has great potential in synthetic chemistry due to the wide presence of C–N bond in natural products such as amino acids and proteins. Therefore C–N activation is potentially a helpful method to synthesize *C*-

glycosides. The general approaches to activate C–N bonds include the conversion of amines into diazonium salts[4] or hydrazines.[5] (**Scheme 3.1**)

Scheme 3.1. General synthesis of diazonium salts and hydrazines from aniline



Diazonium salts are generally more widely used reagent for C-N activation (**Figure 3.1**) whereas hydrazines have been rarely explored (**Figure 3.2**).

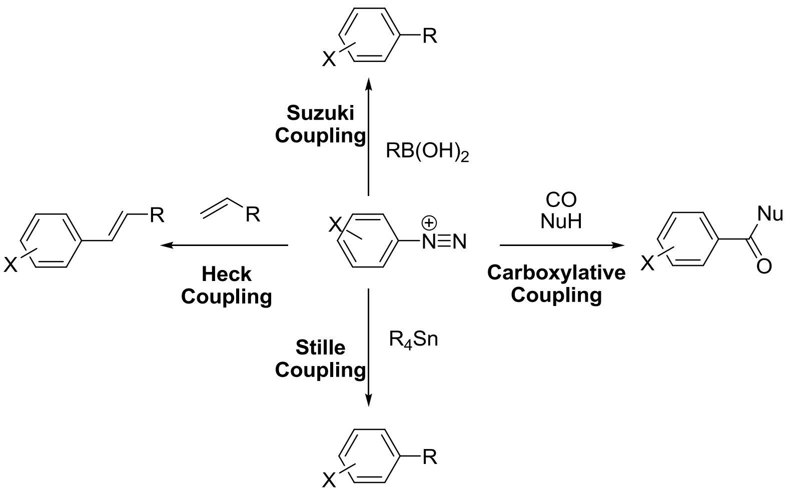


Figure 3.1. Transition metal catalyzed C-N activations of diazonium salts

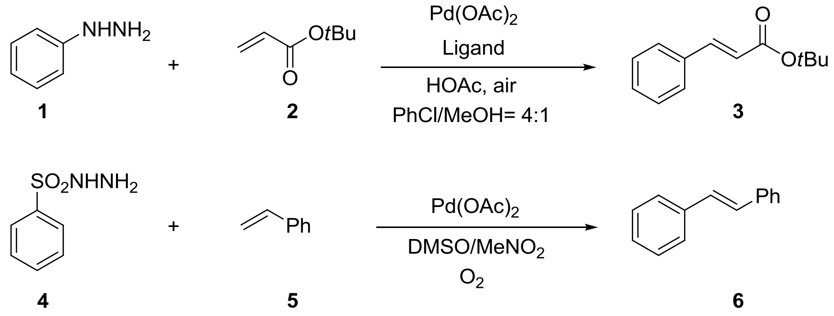


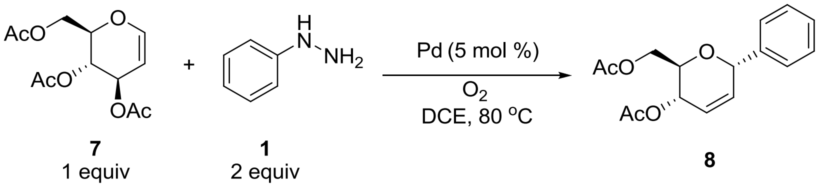
Figure 3.2. Transition metal catalyzed C-N activations of hydrazines

After inspecting the properties of both types of reagents, we decided to explore the *C*-glycosylation reaction with hydrazines as the coupling partners to glycals because the relatively safe diazonium compounds such as its tetrafluoroborate or hexafluorophosphate salts are not chemically stable upon heating.[6] Since heating is usually required for Heck type C–N activation reaction, we selected hydrazines as the ideal coupling partners to glycals.

3.2 Results and Discussion

3.2.1 Conditions Optimization

Table 3.1. Screening of Pd Catalysts[a]



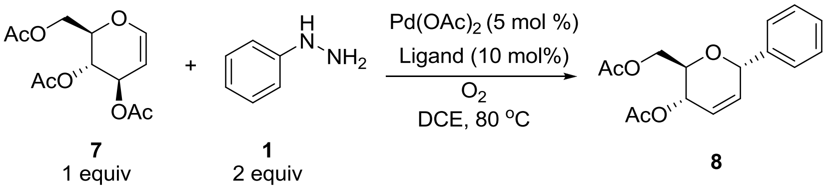
Entry	Pd Source	Yield[b] (%)
1	$Pd(OAc)_2$	33
2	$Pd(TFA)_2$	20
3	$PdCl_2$	<5
4	$Pd(MeCN)_4(BF_4)_2$	0

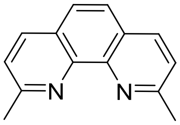
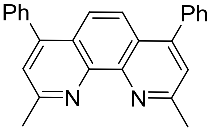
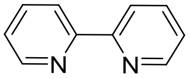
[a] Reactions were carried out with 1 equivalent of **7**, 2 equivalents of **1**, 5% catalyst, 10% ligand and 1 atm of oxygen for 6-12 hours. [b] Isolated yields.

Reported conditions[5b] of 5 mol% $Pd(OAc)_2$ in dichloroethane under air were first applied to the commercially available peracetylated glucal **7** and phenyl hydrazine **1**. Unfortunately, no desired product was identified after 12 hours. Considering that reactions of glycals usually require higher reaction temperature than simple alkenes, the reaction was tested again with the reaction temperature raised to 80 °C. To our delight, the desired aryl-*C*-glycoside **8** was formed in 33% yield (entry 1, Table 3.1). Following the successful conditions, an array of palladium catalysts was first screened. Commonly used palladium sources such as $Pd(TFA)_2$ (entry 2, Table 3.1), $PdCl_2$ (entry 3, Table 3.1) and

$Pd(MeCN)_4(BF_4)_2$ (entry 4, Table 3.1) were applied to the conditions and the results showed that $Pd(OAc)_2$ provided the desired product in highest yield.

Table 3.2. Screening of ligands[a]



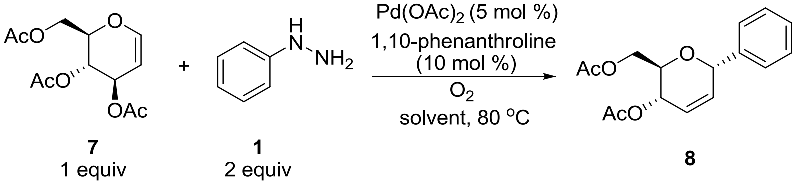
Entry	Ligand	Yield[b] (%)
1		43
2		31
3		25
4		0

[a] Reactions were carried out with 1 equivalent of **7**, 2 equivalents of **1**, 5% catalyst, 10% ligand and 1 atm of oxygen for 6-12 hours. [b] Isolated yields.

Ligand and temperature effects were subsequently investigated. As suggested by the reported methods, bipyridine ligands were tested in the reaction (**Table 3.2**). Gratifyingly, it was found that the use of 1,10-phenanthroline (entry 1, Table 3.2) raised the yield to 43%. Other nitrogen containing ligands such as 2,9-dimethyl-1,10-phenanthroline, 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline and 2,2'-

bipyridine (entry 2-4, Table 3.2) were found to be less effective than 1,10-phenanthroline.

Table 3.3. Screening of solvents and reaction temperatures[a]



Entry	Solvent	Temp (°C)	Yield[b] (%)
1	DCE	80	43
2	1,4-dioxane	80	<5
3	PhCl	80	55
4	DMF	80	<5
5	DMA	80	18
6	PhCl/HOAc (1:1)	80	71
7	HOAc	80	82
8	HOAc	50	35
9	HOAc	60	77
10	HOAc	65	90

[a] Reactions were carried out with 1 equivalent of **7**, 2 equivalents of **1**, 5% catalyst, 10% ligand and 1 atm of oxygen for 6-12 hours. [b] Isolated yields.

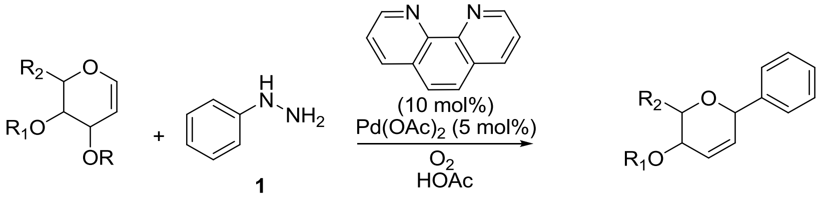
After identifying the optimal catalyst, different solvents were tested for this reaction. Besides dichloroethane (entry 1, Table 3.3), solvents such as 1,4-dioxane (entry 2, Table 3.3), chlorobenzene (entry 3, Table 3.3), DMF (entry 4,

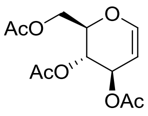
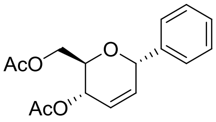
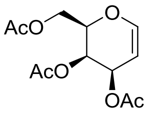
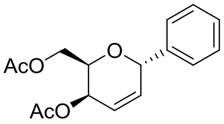
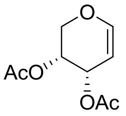
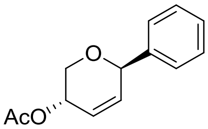
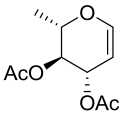
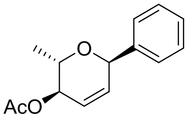
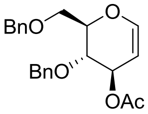
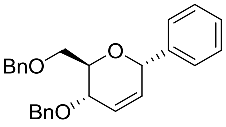
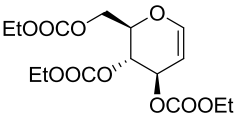
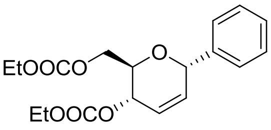
Table 3.3) and DMA (entry 5, Table 3.3) were examined and no significant increase in yield was found. The mixed solvent of chlorobenzene and acetic acid (entry 6, Table 3.3) was found to enhance the yield to 71%. Further adjustment of solvent by using acetic acid (entry 7, Table 3.3) as the only solvent afforded the desired product **8** in higher yield. Adjusting the reaction temperature (entry 8-10, Table 3.3) revealed that 65 ^{o}C was the optimal temperature for this Heck type *C*-glycosylation.

3.2.2 Substrate Scope

After the optimal reaction conditions were determined, we proceeded to explore the substrate scope of the glycal part and the results were summarized in **Table 3.4**. The protecting group studies showed that the desired *C*-glycosides were formed only when the C-3 protecting groups were acetyl (**7**, **9**, **11**, **13**, **15**) or ethoxycarbonyloxyl (**17**). Glycals with other C3 protecting groups such as TMS and TBS, as well as the acid tolerant benzyl and benzoyl groups, failed to provide any product. It could be that the use of acetic acid as the only solvent was too harsh for most of the commonly used protecting groups on C3. Next, the glycals from various carbohydrate origins were tested under the standard conditions. Results showed that glycals from D-galactose **9**, L-6-deoxyglucose **13** and D-ribose **11** could also couple with phenyl hydrazine to give the corresponding products (**10**, **14** and **12**).

Table 3.4. *C*-Glycosylation coupling reaction of glycals and phenyl hydrazine[a],[b]

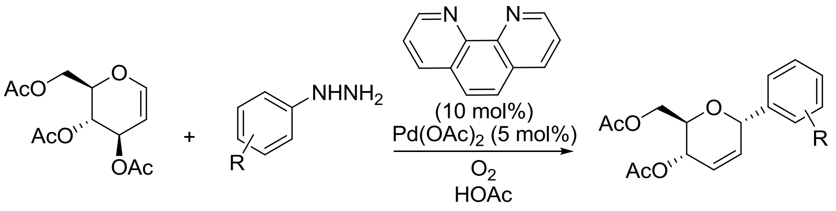


Entry	Glycal	Product	Yield (%)
1	 **7**	 **8**	90
2	 **9**	 **10**	85
3	 **11**	 **12**	81
4	 **13**	 **14**	83
5	 **15**	 **16**	72
6	 **17**	 **18**	43

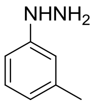
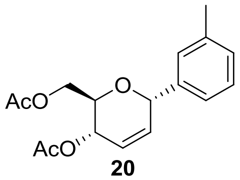
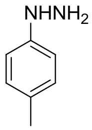
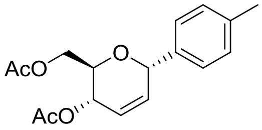
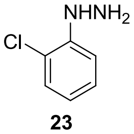
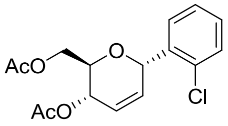
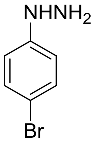
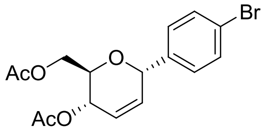
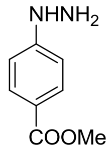
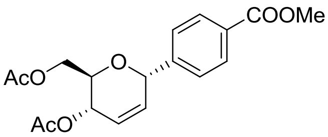
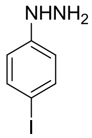
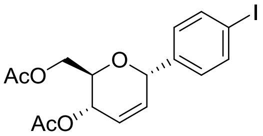
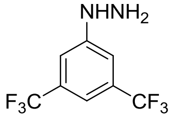
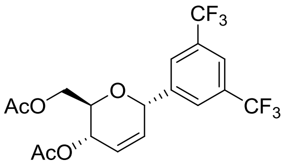
[a] Reactions were carried out with 1 equivalent of glycal, 2 equivalents of **1**, 5% catalyst, 10% ligand and 1 atm of oxygen for 6 hours. [b] Isolated yields.

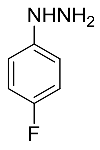
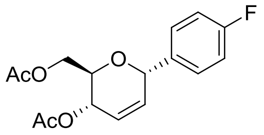
After identifying the substrate scope of glycals, various aryl hydrazines were subjected to peracetylated glucal **7** under standard conditions and the results were summarized in **Table 3.5**. Notably, hydrazine hydrochloric salt failed to give any desired product even after prolonged reaction time. *Ortho*-substituted aryl hydrazines were first tested and the results were not promising. Unless *o*-chlorophenyl hydrazine **23** which afforded the desired product **24** only in moderate yield, other *o*-aryl hydrazines such as *o*-tolylphenylhydrazine or *o*-bromophenylhydrazine were futile under the standard conditions. These results suggested that the greater steric hindrances caused by bromo or methyl groups prevented the aryl-palladium complex from approaching glycals and therefore the insertion step was inhibited.[7] By contrast, *meta*- or *para*-substituted aryl hydrazines **19**, **21**, **23**, **25**, **27**, **29**, **31, 33** generally provided the corresponding *C*-glycosides **20**, **22**, **24**, **26**, **28**, **30**, **32**, **34** in good to excellent yields. The desired products were not obtained when aryl hydrazine with strong electron donating groups, like methoxyl or ethoxyl, were used due to them being thermally unstable under high temperature. For each example in **Table 3.5**, pure α selectivity was obtained.

Table 3.5. *C*-Glycosylation coupling reaction of peracetylated glucal and various aryl hydrazines.[a]



7

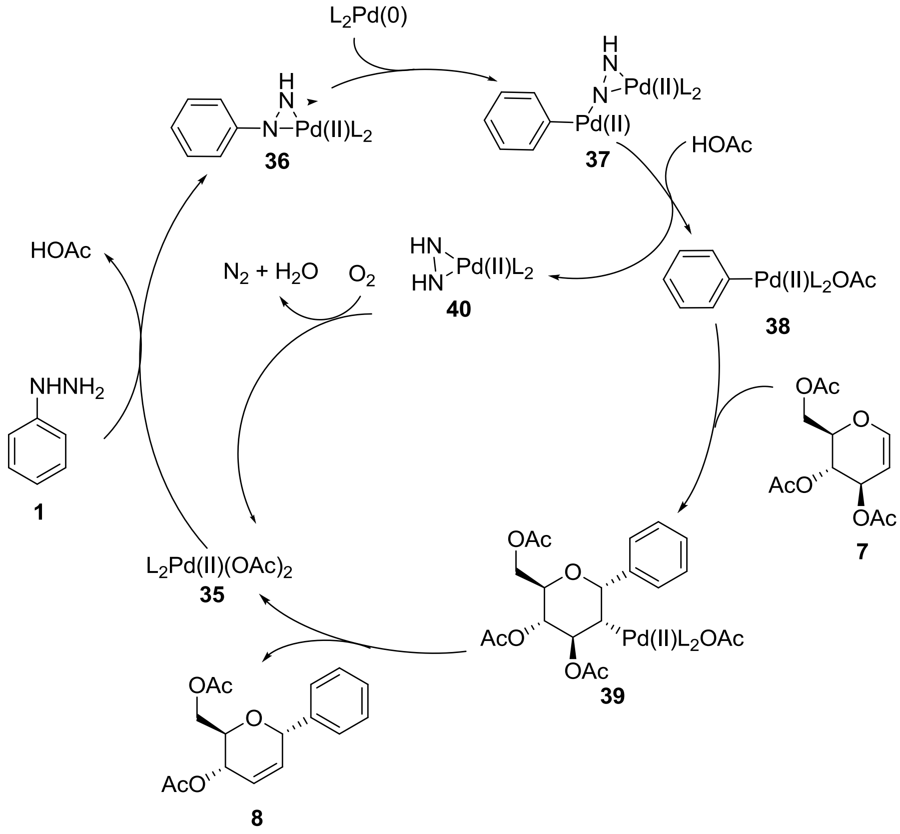
Entry	Hydrazine	Product	Time (h)	Yield[b](%)
1	 **19**	 **20**	4	80
2	 **21**	 **22**	3	86
3	 **23**	 **24**	8	43
4	 **25**	 **26**	6	85
5	 **27**	 **28**	10	51
6	 **29**	 **30**	2	30
7	 **31**	 **32**	8	64

8	 **33**	 **34**	4	79

[a] Reactions were carried out with 1 equivalent of **7**, 2 equivalents of aryl hydrazine, 5% catalyst, 10% ligand and 1 atm of oxygen. [b] Isolated yields.

3.2.3 Mechanism Study

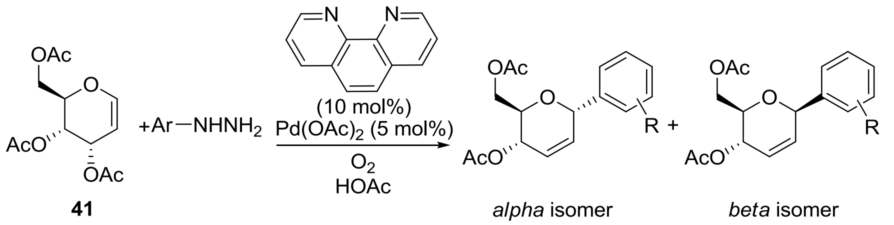
Scheme 3.2. Plausible Mechanism



The plausible mechanism of this Pd catalyzed *C*-glycosylation was described in **Scheme 3.2**. A substitution reaction first took place between the catalyst **35** and phenyl hydrazine **1**, forming two Pd-N bonds on both of the N atoms and releasing two molecules of acetic acid. Then, the active Pd-hydrazine complex **36** underwent an oxidative addition by another Pd(0) species which was reduced by the excess hydrazines. The resulting complex **37** underwent another substitution reaction with acetic acid to generate complex **38** and **40**. Complex **38** then inserted into the double bond of the glycal to form the Pd-glycal adduct **39**. Finally, the β-heteroatom elimination took place to afford the desired *C*-glycoside and regenerated the active catalyst **35**. Complex **40** was oxidized by oxygen to release nitrogen gas and regenerate the active catalyst **35**.

Next, efforts were made to elucidate the reaction selectivity of this Heck type *C*-glycosylation reaction. The reported palladium catalyzed *C*-glycosylation reactions of pyranose glycals gave exclusively *α* selectivity but the reason of this selectivity remains relatively unexplored. Each of the three pre-existing chiral centers on glycals could be responsible for the selectivity. Based on the research on *C*-glycosylation reaction of furanose glycals and aryl iodides, Daves[8] concluded that the selectivity was attributed to the geometry of protecting groups on C3 and C4. In 2009, Ye's group deduced that the stereochemistry of the protecting group on C3 determined the α selectivity.[9] The reason for the selectivity was concluded that the *C*-glycosidic bond was formed on the opposite side of the C3 protecting group. To justify this hypothesis, the C3 diastereomer of peracetylated glucal (3*S*, 4*S*, 6*R*)-tri-*O*-acetyl-D-glucal **41** was prepared by reported method.[10] According to the hypothesis, this uncommon glycal was expected to give pure *β* *C*-glycosides. This C3 inverted glucal was treated with different aryl hydrazines and the result was summarized in **Table 3.6**. However, instead of giving pure *β* selectivity, a mixture of *α* and *β* isomers was obtained, with *α* to *β* ratios ranging from 1:1 to 1:0.6, which indicated that the stereochemistry of C3 is not the only determining factor responsible for the *α* selectivity.

Table 3.6. *C*-Glycosylation coupling reaction of (3*S*, 4*S*, 6*R*)-tri-*O*-acetyl-D-glycal and various aryl hydrazines.[a]

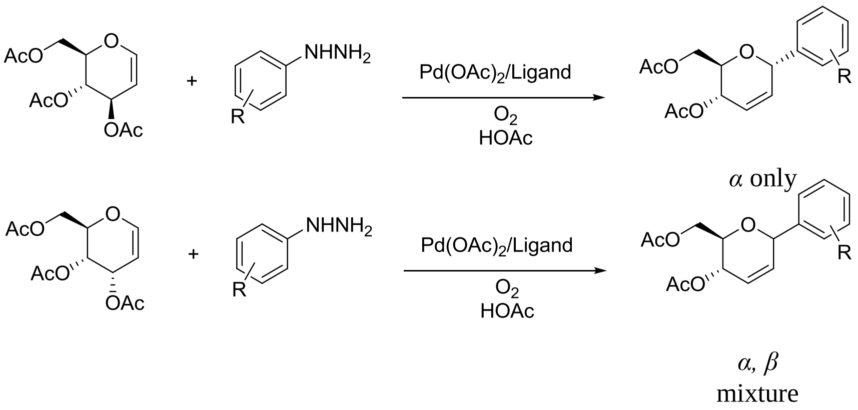


Entry	R of *C*-glycoside	Time (h)	Yield[b] (%)	α : β
1	Ph (*α* **8**, *β* **42**)	6	79	1:1
2	4-F-C_6H_4(*α* **26**, *β* **43**)	4	75	1:0.81
3	4-Br-C_6H_4 (*α* **22**, *β* **44**)	6	83	1:0.6
4	3-Me-C_6H_4(*α* **19**, *β* **45**)	4	74	1:0.87

[a] Reactions were carried out with 1 equivalent of **41**, 2 equivalents of aryl hydrazine, 5% catalyst, 10% ligand and 1 atm of oxygen. [b] Total isolated yields.

3.3 Conclusion

In conclusion, an efficient oxidative Heck type *C*-glycosylation reaction of glycals and aryl hydrazine has been developed. This reaction proceeded *via* the Pd(II) promoted C-N bond cleavage on hydrazines. The substrate scope included glycals with good leaving groups on C3 as protecting groups and aryl hydrazines with different substituents. Exclusive *α* selectivity was achieved when 3*R* glycals substrate were used. By contrast, *α* and *β* mixtures with the ratio ranging from 1:1 to 1:0.6 were obtained when 3*S* glycals were used. As far as we know, this is the first example for the formation of *β* aryl-*C*-pyranose glycosides *via* Heck type reaction. Since aryl hydrazines could be prepared by concise procedures from their corresponding anilines, this protocol presents promising potential to be applied to the syntheses of aryl-*C*-glycosides containing natural products.



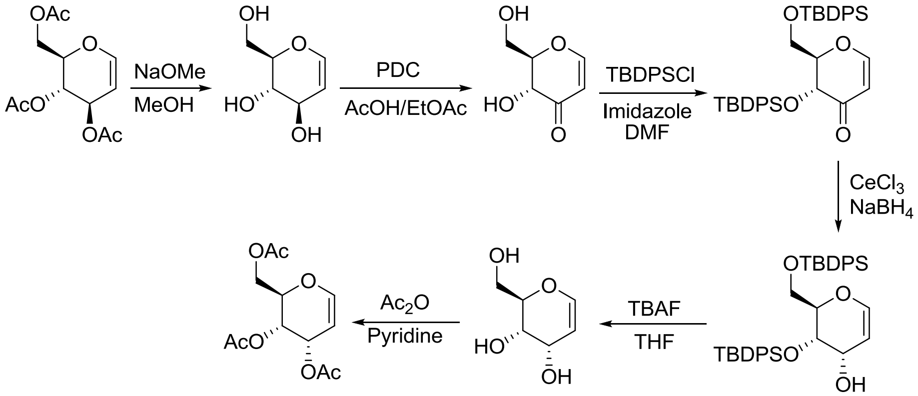
3.4 Experimental Section

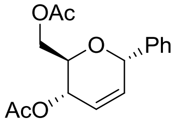
General**:** All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

Materials: Acetic acid, palladium catalysts and ligands were purchased from commercial suppliers and used without further purification. 3, 4, 6-tri–*O*–acetyl–D–glucal, 3, 4–*O*–actyl–6–deoxy–L–glucal and 3, 4, 6–tri–*O*-acetyl-D-galactal reagents were purchased from commercial suppliers. Glycals with protecting groups as benzyl,[11] pivaloyl[12] and benzoyl[13] were prepared from 3, 4, 6–tri–*O*–acetyl–D–glucal by reported methods. Substituted phenyl hydrazines were prepared by reported procedures[14] from corresponding hydrochloric salts.

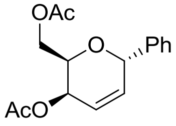
General procedure of Pd catalyzed cross-coupling of glycals and aryl hydrazines: synthesis of ((2R,3S,6S)-3-acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (8). To a round bottom flask containing the solution of glucal **7** (54 mg, 0.2 mmol) palladium(II) diacetate (5 mg, 0.02 mmol) and 1, 10-phenantroline (7 mg, 0.04 mmol) in acetic acid (0.5 mL) at 65 °C, phenyl hydrazine (54 μL, 0.3 mmol) in acetic acid (1 mL) was added dropwise. The mixture was allowed to stir at 65 °C for 6 hours. Then the mixture was diluted with ethyl acetate (2 mL), filtered, washed with water (5 mL) and brine (5 mL). The organic layer was evaporated and the residue was purified by flash column chromatography (EtOAc/Hexane = 1/4) to afford the product as yellow oil. (52 mg, 90%)

Synthesis of 3-inverted acetyl glucal ((2R,3S,4S)-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (41) from commercially available acetyl glucal ((2R,3S,4R)-2-(acetoxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (7)

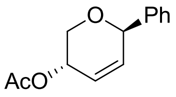




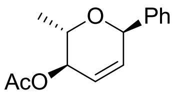
((2*R*,3*S*,6*S*)-3-acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (8). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as colorless oil (52 mg, 90%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.32–7.39 (m, 5H), 6.19 (ddd, *J* = 1.5, 3.0, 10.4 Hz, 1H), 5.97–6.01 (m, 1H), 5.29–5.33 (m, 2H), 4.25 (dd, *J* = 5.9, 12 Hz, 1H), 4.09 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.83–3.97 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.9, 170.5,138.8, 131.5, 128.5, 128.3,127.9, 125.0, 73.7, 69.3, 65.0, 62.9, 21.1, 20.8; $[\alpha]_{\mathrm{D}}^{20}$ = 13.9 (*c* 2.00, CHCl$_3$); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ $[M+Na]^+$ 313.1052, found 313.1053.



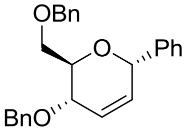
((2*R*,3*R*,6*S*)-3-acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (10). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as pale yellow oil (49 mg, 85%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.30–7.35 (m, 5H), 6.41 (ddd, *J* = 0.5, 3.6, 10.2 Hz, 1H), 6.20 (ddd, *J* = 2.1, 5.2, 10.2 Hz, 1H), 5.39–5.41 (m, 1H), 5.11 (dd, *J* = 2.6, 5.1 Hz, 1H), 4.14–4.23 (m, 2H), 3.92–3.95 (m, 1H), 2.11 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.6, 170.6, 138.3, 133.3, 128.5, 128.2, 127.8, 123.5, 73.8, 68.3, 63.8, 62.8, 20.9, 20.7; $[\alpha]_D^{20}$ = -371.1 (*c* 3.00, CHCl$_3$); HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M+Na]$^+$ 313.1052, found 313.1060.



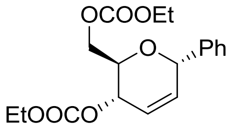
(3*S*,6*R*)-6-phenyl-3,6-dihydro-2H-pyran-3-yl acetate (12). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (10:1 to 8:1) to give the product as yellow oil (35 mg, 81%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.30–7.39 (m, 5H), 6.16 (ddd, *J* = 1.2, 2.6, 10.4 Hz, 1H), 6.03–6.07 (m, 1H), 5.22–5.29 (m, 1H), 5.21 (t, *J* = 2.1, 1H), 4.04 (dd, *J* = 4.4, 11.9 Hz, 1H), 3.69 (dd, *J* = 5.2, 11.9 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.7, 139.1, 133.3, 128.6, 128.3, 127.8, 124.5, 75.1, 64.7, 64.7, 21.1; $[\alpha]_D^{20}$ = 170.0 (*c* 3.00, CHCl$_3$); HRMS (ESI) calcd for $C_{13}H_{14}O_3Na$ [M+Na]$^+$ 241.0841, found 241.0842.



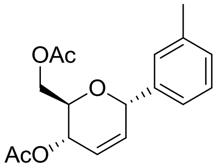
(2*S*,3*R*,6*R*)-2-methyl-6-phenyl-3,6-dihydro-2H-pyran-3-yl acetate (14). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (8:1) to give the product as bright yellow oil (38 mg, 83%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.30–7.42 (m, 5H), 6.13 (ddd, *J* = 1.4, 2.8, 10.3 Hz, 1H), 5.95 (ddd, *J* = 2.1, 3.2, 10.3 Hz, 1H), 5.23 (q, *J* = 2.2 Hz, 1H), 5.05 (m, 1H), 3.87 (t, *J* = 6.3 Hz, 1H), 2.10 (s, 3H), 1.25 (d, *J* = 6.44 Hz, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.8, 139.6, 132.2, 128.5, 128.1, 127.9, 124.2, 72.8, 69.8, 68.0, 21.2, 17.3; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = -34.8 (*c* 1.50, CHCl$_3$); HRMS (ESI) calcd for $C_{14}H_{16}O_3Na$ [M+Na]$^+$ 255.0997, found 255.0989.



(2*R*,3*R*,6*S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-6-phenyl-3,6-dihydro-2H-pyran (16). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (10:1 to 6:1) to give the product as colorless oil (56 mg, 72%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.43–7.46 (m, 2H), 7.25–7.37 (m, 13H), 6.08–6.16 (m, 2H), 5.32 (d, *J* = 1.5 Hz, 1H), 4.58–4.64 (m, 2H), 4.45–4.51 (m, 2H), 4.18–4.21 (m, 2H), 3.68–3.72 (m, 2H), 3.60–3.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 139.6, 138.2, 129.6, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.2, 77.2, 74.1, 73.3, 71.2, 70.7, 70.2, 69.2; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 22.8 (*c* 1.20, CHCl$_3$); HRMS (ESI) calcd for $C_{26}H_{26}O_3Na$ [M+Na]$^+$ 409.1780, found 409.1779.

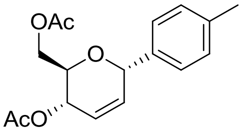


((2*R*,3*S*,6*S*)-6-phenyl-2-((ethoxycarbonyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl)methyl ethyl carbonate (18). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (4:1 to 3:1) to give the product as brown oil (30 mg, 43%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.32–7.41 (m, 5H), 6.20 (ddd, J = 1.6, 3.1, 10.4 Hz, 1H), 6.06 (dt, J = 2.2, 10.4 Hz, 1H), 5.33 (d, J = 2.4 Hz, 1H), 5.21 (dd, J = 1.9, 7.6 Hz, 1H), 4.30–4.33 (m, 1H), 4.15–4.28 (m, 5H), 3.87–3.91 (m, 1H), 1.27–1.34 (m, 6H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ154.9, 154.4, 138.3, 131.7, 128.4, 128.3, 128.1, 127.9, 124.4, 77.0, 73.7, 68.5, 68.1, 66.0, 64.3, 64.1, 14.1, 14.1; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 19.8 (c 0.80, CHCl$_3$); HRMS (ESI) calcd for $C_{18}H_{22}O_7Na$ $[M+Na]^+$ 373.1263, found 373.1263.

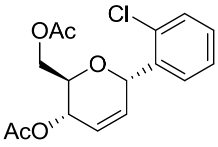


((2*R*,3*S*,6*S*)-3-acetoxy-6-(m-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (20). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as colorless oil (49 mg, 80%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.13–7.25

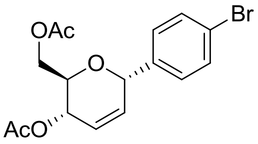
(m, 4H), 6.17–6.20 (m, 1H), 5.96–6.00 (m, 1H), 5.29–5.32 (m, 2H), 4.27 (dd, *J* = 5.9, 12 Hz, 1H), 4.10 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.84–3.88 (m, 1H), 2.37 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.5, 138.8, 138.2, 131.6, 129.0, 128.6, 128.4, 124.9, 124.9, 73.7, 69.3, 65.0, 62.9, 21.5, 21.1, 20.8;$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 19.5 (*c* 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ $[M+Na]^+$ 327.1208, found 327.1204.



((2*R*,3*S*,6*S*)-3-acetoxy-6-(p-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (22). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as pale yellow oil (52 mg, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (m, 2H), 7.18 (m, 2H), 6.17 (ddd, *J* = 1.4, 2.9, 10.4 Hz, 1H), 5.98 (dt, *J* = 2.1, 10.3 Hz, 1H), 5.30–5.33 (m, 2H), 4.26 (dd, *J* = 5.7, 12.0 Hz, 1H), 4.08 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.80–3.84 (m, 1H), 2.36 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.5, 138.1, 135.8, 131.6, 129.2, 128.0, 125.0, 73.7, 69.0, 65.1, 62.9, 21.2, 21.1, 20.8; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 5.2 (*c* 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ $[M+Na]^+$ 327.1208, found 327.1198.

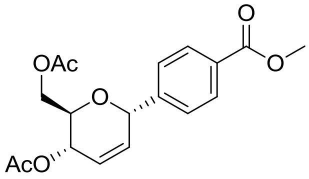


((2*R*,3*S*,6*S*)-3-acetoxy-6-(2-chlorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (24). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as pale yellow oil (28 mg, 43% yield). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.47 (m, 1H), 7.30–7.42 (m, 1H), 7.27–7.30 (m, 2H), 6.12 (dd, J = 1.2, 2.6, 10.4 Hz, 1H), 6.04 (ddd, J = 2.0, 3.1, 10.4 Hz, 1H), 5.71 (dd, J = 2.2, 2.2 Hz, 1H), 5.23–5.26 (m, 1H), 4.34 (dd, J = 6.6, 12 Hz, 1H), 4.10 (dd, J = 3.7, 12.0 Hz, 1H), 3.95–3.99 (m, 1H), 2.11 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 170.9, 170.5, 135.9, 134.2, 131.4, 130.0, 129.6, 129.3, 126.7, 124.7, 77.2, 70.2, 64.8, 62.5, 21.1, 20.8; $[\alpha]^{20}_{D}$ = 16.8 (*c* 1.50, CHCl$_3$); HRMS (ESI) calcd for C$_{16}$H$_{17}$O$_5$ClNa [M+Na]$^+$ 347.0662, found 347.0669.

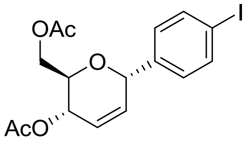


((2*R*,3*S*,6*S*)-3-acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (26). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (4:1) to give the product as colorless oil (62 mg, 85%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.48–

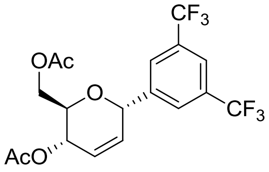
7.51 (m, 2H), 7.26–7.29 (m, 2H), 6.12–6.16 (m, 1H), 5.97–6.00 (m, 1H), 5.27–5.29 (m, 2H), 4.25 (dd, *J* = 6.0, 12.0 Hz, 1H), 4.08 (dd, *J* = 3.0, 12.0 Hz, 1H), 3.77–3.81 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 170.4, 137.9, 131.7, 130.9, 129.6, 125.5, 122.4, 73.0, 69.4, 64.9, 62.8, 21.1, 20.8; $[\alpha]_D^{20}$ = -22.0 (*c* 3.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$ $[M+Na]^+$ 391.0157, found 391.0155.



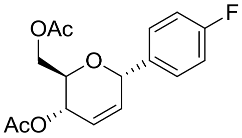
Methyl-4-((2*S*,5*S*,6*R*)-5-acetoxy-6-(acetoxymethyl)-5,6-dihydro-2H-pyran-2-yl)benzoate (28). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (4:1 to 3:1) to give the product as yellow oil (35 mg, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.17–6.21 (m, 1H), 5.98–6.02 (m, 1H), 5.36 (s, 1H), 5.28–5.30 (m, 1H), 4.20–4.28 (m, 1H), 4.11 (dd, *J* = 3.0, 12.0 Hz, 1H), 3.92 (S, 3H), 3.80–3.84 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 170.4, 166.7, 144.0, 130.8, 129.9, 129.8, 127.5, 125.4, 73.1, 69.7, 64.8, 62.7, 52.1, 21.0, 20.8; $[\alpha]_D^{20}$ = -6.0 (*c* 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{20}O_7Na$ $[M+Na]^+$ 371.1107, found 371.1111.



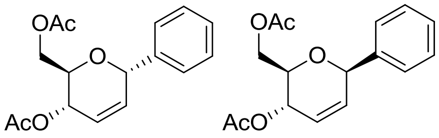
((2*R*,3*S*,6*S*)-3-acetoxy-6-(4-iodophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (30). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (4:1) to give the product as dark brown oil (25 mg, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, J = 1.8, 6.6 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.13–6.16 (m, 2H), 5.98–6.01 (m, 1H), 5.26–5.31 (m, 2H), 4.26 (dd, J = 6.0, 12.0 Hz, 1H), 4.09 (dd, J = 3.1, 12.0 Hz, 1H), 3.78–3.82 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.5, 138.7, 137.7, 130.9,, 129.8, 125.5, 94.1, 73.2, 69.5, 64.9, 62.9, 21.1, 20.9; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 1.4 (*c* 1.00, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5INa$ $[M+Na]^+$ 439.0018, found 439.0014.



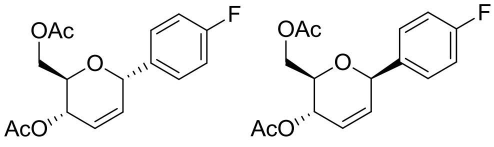
((2*R*,3*S*,6*S*)-3-acetoxy-6-(3,5-bis(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (32). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as colorless oil (54 mg, 64% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 2H), 7.85 (s, 1H), 6.26 (ddd, J = 1.5, 3.1, 10.4 Hz, 1H), 6.08 (ddd, *J* = 2.2, 2.8, 10.4 Hz, 1H), 5.42 (d, *J* = 1.84 Hz, 1H), 5.25–5.28 (m, 1H), 4.28 (dd, *J* = 7.4, 12.0 Hz, 1H), 4.16 (dd, *J* = 2.9, 12.0 Hz, 1H), 3.81–3.86 (m, 1H), 2.11 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) *δ* 170.8, 170.4, 132.1, 131.8, 129.9, 127.4, 126.3, 122.0, 72.0, 70.4, 64.7, 62.9, 29.9, 21.0, 20.6; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 24.4 (*c* 0.80, CHCl$_3$); HRMS (ESI) calcd for $C_{18}H_{16}O_5F_6Na$ [M+Na]$^+$ 449.0800, found 449.0811.



((2*R*,3*S*,6*S*)-3-acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (34). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc eluent as (6:1 to 4:1) to give the product as colorless oil (48 mg, 79%). ^{1}H NMR (CDCl$_3$, 400 MHz) *δ* 7.36–7.40 (m, 2H), 7.04–7.08 (m, 2H), 6.19 (m,1H), 5.98–6.01 (m, 1H), 5.28–5.30 (m, 2H), 4.26 (dd, *J* = 6.0, 12.0 Hz, 1H), 4.08 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.79–3.83 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) *δ* 170.8, 170.5, 163.9, 161.4, 134.7, 134.6, 131.3, 129.8, 129.7, 125.2, 115.5, 115.3, 73.0, 69.3, 64.9, 62.8, 21.1, 20.8; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 15.8 (*c* 2.50, CHCl$_3$); HRMS (ESI) calcd for $C_{16}H_{17}O_5FNa$ [M+Na]$^+$ 331.0960, found 331.0958.

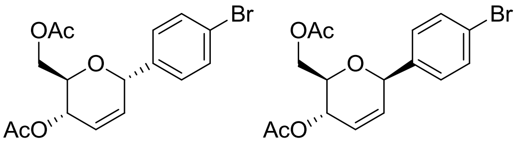


((2*R*,3*S*,6*S*)-3-acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (8) and ((2*R*,3*S*,6*R*)-3-acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (42). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as yellow oil (46 mg, 79%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.31–7.42 (m, 10H), 5.91–6.18 (m, 1H), 5.83 (dt, J = 2.1, 10.3 Hz, 1H), 5.40–5.44 (m, 1H), 5.30–5.34 (m, 2H), 5.21–5.22 (m, 1H), 4.18–4.30 (m, 3H), 4.10 (dd, J = 3.1, 12.0 Hz, 1H), 3.92–3.96 (m, 1H), 3.83–3.87 (m, 1H), 2.11 (s, 3H), 2.07–2.09 (m, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.0, 170.9, 170.5, 170.4, 139.8, 138.8, 132.8, 131.5, 128.7, 128.5, 128.4, 128.3, 127.9, 127.2, 125.0, 124.9, 77.6, 77.2, 74.8, 73.7, 69.3, 65.5, 65.0, 63.8, 62.9, 21.1, 20.9, 20.8; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M+Na]$^+$ 313.1052, found 313.1053.

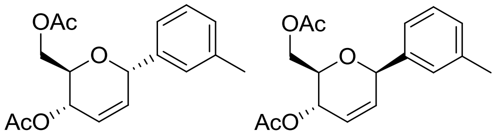


((2*R*,3*S*,6*S*)-3-acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (26) and ((2*R*,3*S*,6*R*)-3-acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (43). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as colorless oil (46 mg, 75%). ^{1}H NMR

(CDCl$_3$, 400 MHz) δ 7.37–7.38 (m, 2.45H), 7.29–7.33 (m, 2H), 7.02–7.08 (m, 4.47H), 6.13–6.16 (m, 1.25H), 5.98–6.02 (m, 1.24H), 5.82–5.90 (m, 2H), 5.39–5.42 (m, 1H), 5.20–5.30 (m, 2.45H), 5.20 (s, 1H), 4.24–4.29 (m, 2.27H), 4.19 (dd, *J* = 5.9, 12.1 Hz, 1H), 4.08 (dd, *J* = 3.1, 12.0 Hz, 1.28H), 3.91–3.95 (m, 1H), 3.79–3.83 (m, 1.24H), 2.11 (s, 2.89H), 2.09 (s, 3.63H), 2.08 (s, 3.15H), 2.07 (s, 3.56H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.0, 170.8, 170.5, 170.4, 163.9, 163.9, 161.5, 161.4, 135.7, 135.7, 134.7, 134.7, 132.5, 131.3, 129.8, 129.7, 129.1, 129.0, 125.2, 115.7, 115.5, 115.4, 115.3, 77.2, 76.9, 74.9, 73.0, 69.3, 65.3, 64.9, 63.7, 62.8, 21.1, 20.9, 20.8; HRMS (ESI) calcd for $C_{16}H_{17}O_5FNa$ [M+Na]$^+$ 331.0958, found 331.0956.



((2*R*,3*S*,6*S*)-3-acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (22) and ((2*R*,3*S*,6*R*)-3-acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (44). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (4:1 to 3:1) to give the product as yellow oil (61 mg, 83%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.47–7.52 (m, 3.2H), 7.26–7.30 (m, 2H), 7.20–7.24 (m, 1.25H), 6.13 –6.16 (m, 1H), 6.00 (dt, *J* = 2.1, 10.4 Hz, 1H), 5.84–5.86 (m, 1.22H), 5.38–5.41 (m, 0.61H), 5.28–5.31 (m, 2H), 5.18 (s, 0.60H), 5.18 (s, 0.87H), 4.25–4.30 (m, 1.66H), 4.17–4.24 (m, 0.67H), 4.09 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.91–3.94 (m, 0.64H), 3.78–3.82 (m, 1H), 2.11 (s, 1.77H), 2.09 (s, 3H), 2.08 (s, 1.68H), 2.08 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.0, 170.8, 170.4, 170.4, 138.8, 137.9, 132.2, 132.0, 131.8, 131.7, 130.9, 129.6, 128.9, 125.5, 125.4, 122.4, 122.3, 77.2, 76.9, 74.8, 73.0, 69.4, 65.3, 64.9, 63.6, 62.8, 21.1, 20.9, 20.8; HRMS (ESI) calcd for $C_{16}H_{17}O_5BrNa$ [M+Na]$^+$ 391.0157, found 391.0156.



((2*R*,3*S*,6*S*)-3-acetoxy-6-(*m*-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (19) and ((2*R*,3*S*,6*R*)-3-acetoxy-6-(*m*-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (45). The compound was synthesized by the general procedure and purified by column chromatography using hexane/EtOAc as eluent (6:1 to 4:1) to give the product as pale yellow oil (45 mg, 84%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.24–6.29 (m, 0.87H), 7.11–7.23 (m, 6.72H), 6.19 (m, 1H), 5.93 (dt, *J* = 1.6, 10.2 Hz, 1H), 5.82 (dt, *J* = 2.1, 10.3 Hz, 0.87H), 5.41–5.44 (m, 0.87H), 5.18–5.32 (m, 2H), 5.18 (s, 0.87H), 4.25–4.29 (m, 2H), 4.20 (dd, *J* = 6.0, 12.1 Hz, 0.88H), 4.10 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.91–3.95 (m, 0.87H), 3.84–3.88 (m, 1H), 2.37 (s, 3H), 2.35 (s, 2.62H), 2.11 (s, 2.59H), 2.09 (s, 3H), 2.08 (s, 5.35H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 171.0, 170.9, 170.5, 170.4, 139.7, 138.8, 138.4, 138.2, 132.9, 131.6, 129.2, 129.0, 128.6, 128.4, 128.0, 124.9, 124.9, 124.8, 124.4, 77.7, 77.2, 74.8, 73.7, 69.3, 65.5, 65.1, 63.8, 62.9, 21.5, 21.4, 21.1, 20.9, 20.8; HRMS (ESI) calcd for $C_{17}H_{20}O_5Na$ [M+Na]$^+$ 327.1208, found 327.1204.

3.5 References

1. For reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res*. **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (d) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Bras, J. L.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (g) Dong, V.; Yeung, C. S.; *Chem. Rev.* **2011**, *111*, 1215.

2. (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc*. **2002**, *124*, 11250. (b) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (c) Goossen, L. J.; Deng, G. J.; Levy, L. M. *Science* **2006**, *313*, 662. (d) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103. (e) Goossen, L. J.; Rodriguez, N.;Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (f) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (g) Bi, H. P.; Zhao, L.; Liang,Y. M.; Li, C. J. *Angew. Chem., Int. Ed.* **2009**, 48, 792.

3. For recent reviews on the classic Mizoroki-Heck reaction, see: (a) Crisp, G. T. *Chem. Soc. Re*v. **1998**, *27*, 427. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Re*v. **2000**, *100*, 3009. (c) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (d) Bhanage, B. M.; Arai, M. *Catal. Re*v. **2001**, *43*, 315. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.

4. (a) Galli, C. *Chem. Re*v. **1988**, *88*, 765. (b) Hanson, P.; Rowell, S. C.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc.*, *PerkinTrans. 2* **2002**, 1126. (c) Hanson, P.; Jones, J. R.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1135. (d)Kikukawa, K.; Nagira, K.; Terao, N.; Wada, F.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2609. (e) Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31. (f) Kikukawa, K.; Nagira, K.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2207. (g) Cai, M. Z.; Hu, R. H.; Zhou, J. *Chin. Chem. Lett.* **2001**, *12*, 861. (h) Hu, R.-H.; Liu, X.-L.; Cai, M.-Z. *Jiangxi Shifan Daxue Xuebao, Ziran Kexueban* **2001**, *25*, 246; *Chem. Abstr*. **2001**, *136*, 5024.(i) Masllorens, J.; Bouquillon, S.; Roglans, A.; He´nin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822.

5. (a) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *Org. Lett*. **2011**, *13*, 6308. (b) Yang, F.-L.; Ma, X.-T.; Tian, S.-K. *Chem. Eur. J.* **2012**, *18*, 1582

6. Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186.

7. (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Miburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (b) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166

8. (a) Arai, I.; Hanna, R.; Daves, G. D. *J. Am. Chem. Soc*. **1981**, *103*, 7684. (b) Arai, I.; Daves, G. D. *J. Am. Chem. Soc.* **1978**, *100*, 287.(c) Hacksell, U.; Daves, G. D. *J. Org. Chem.* **1983**, *48*, 2870. (d) Cheng, J. C. Y.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 3083.

9. Li, H.-H.; Ye, X.-S. *Org. Biomol. Chem.* **2009**, *7*, 3855.

10. (a) Czernecki, S.; Vijayakumaran, K.; Ville, G. *J. Org. Chem.* **1986**, *51*, 5472.

(b) Fujiwara, T.; Hayashi, M. *J. Org. Chem.* **2008**, *73*, 9161.

11. Bovin, N. V.; Zurabyan, S. É.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25.

12. Hadfield, A. F.; Sartorelli, A. C. *Carbohydr. Res.* **1982**, *101*, 197

13. Takahashi, Y.; Vasella, A. *Helv. Chim. Acta.* **1992**, *75*, 1563.

14. Liu, Y.; Shi, H.; Li, Y.; Zhu, H. J. *Heterocycl. Chem.* **2010**, *47*, 897.

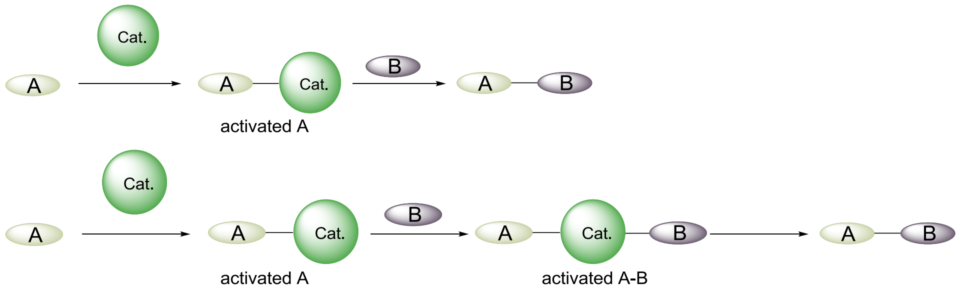
Chapter 4. Palladium and N-Heterocyclic Carbene Dual Catalyzed *C*-glycosylation of Glycals and (*o*-azaaryl)carboxaldehydes

4.1 Introduction

4.1.1 Dual Catalysis

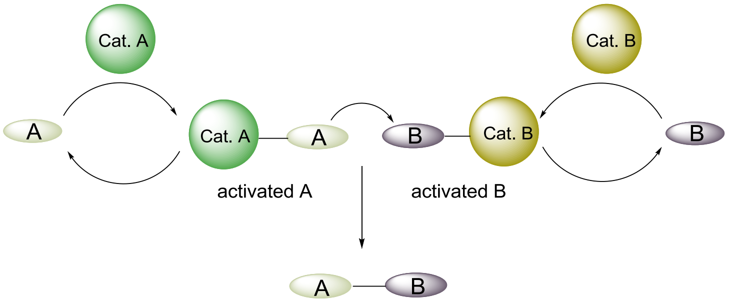
Catalysis, in principle, is the increase in the rate of a chemical reaction of two or more reactants due to the participation of an additional substance called catalyst. The catalyst functions as a substance to raise the overall energy of the reactant and therefore significantly lowering the energy barrier for a reaction to take place. Since the early time of catalytic chemistry, most of the chemists focused their efforts on using a single catalyst to raise the energy of one reactant, following which the activated reactant would react with the other reactant to form the product (**Scheme 4.1**).

Scheme 4.1. Traditional catalysis



With the development of catalytic chemistry, more catalysts and catalytic reactions have been discovered. Chemists then embarked on the exploration of the possibilities to apply two catalysts to simultaneously activate two reactants. This new catalytic method is called dual catalysis. Dual catalysis is a new direction of catalytic chemistry which involves the simultaneous activation of the relatively unreactive nucleophiles and electrophiles (**Scheme 4.2**). The activated nucleophile and electrophile generated *in situ* then react with each other to form the nucleophilic addition product. By adopting dual catalysis strategy, chemists can avoid the use of stoichiometric amount of activating reagents and obtain the products which are not achievable by the conventional synthetic methods. Two requirements need to be met in order to achieve dual catalysis. The first is that the two catalysts need to be inert to each other. If the two catalysts react with each other, they would be mutually poisoned. The second requirement is that the working reaction conditions such as temperature, solvent and pH of the two catalysts need to be compatible with each other.

Scheme 4.2. Dual catalysis



In 2003, Krische *et al.* reported an elegant intramolecular dual catalyzed reaction by integrating Morita-Baylis-Hillman[1] reaction with Tsuji-Trost[2] reaction (**Figure 4.1**). In this report, the allylic system, functioned as an electrophile, was activated by $Pd(PPh_3)_4$ and the 1,4-conjugated system was activated by PBu_3 to give a nucleophile.[3] The nucleophilic addition then took place between the nucleophile and electrophile generated *in situ* to complete the cyclization reaction.

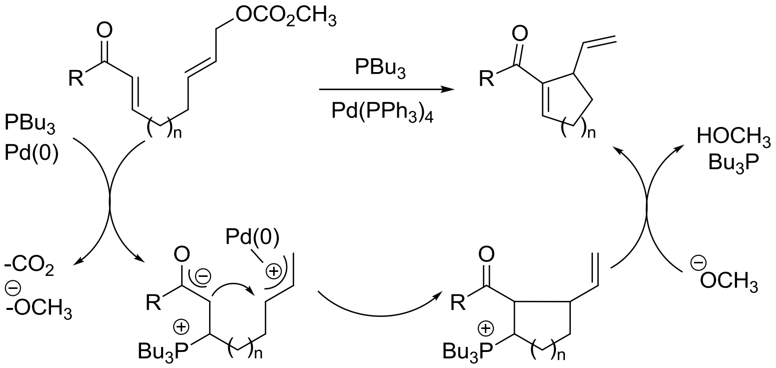


Figure 4.1. Mechanism of Morita-Baylis-Hillman and Tsuji-Trost dual catalysis

Three years later, Córdova's group reported another dual catalyzed reaction with the combination of Tsuji-Trost reaction and enamine chemistry (**Figure 4.2**).[4] Unlike the previous report, this dual catalyzed reaction took place intermolecularly. Allyl acetate was activated by $Pd(PPh_3)_4$ to form the electrophile whereas the nucleophilic enamine was formed from aldehydes or ketones by pyrrolidine (**Figure 4.3**). The allylation of the α-carbon of aldehydes and ketones provided great potential for carbon chain elongation. A chiral version of this reaction was published in 2012 by the same group and good to excellent yields were obtained by the nicely designed chiral pyrrolidine.[5]

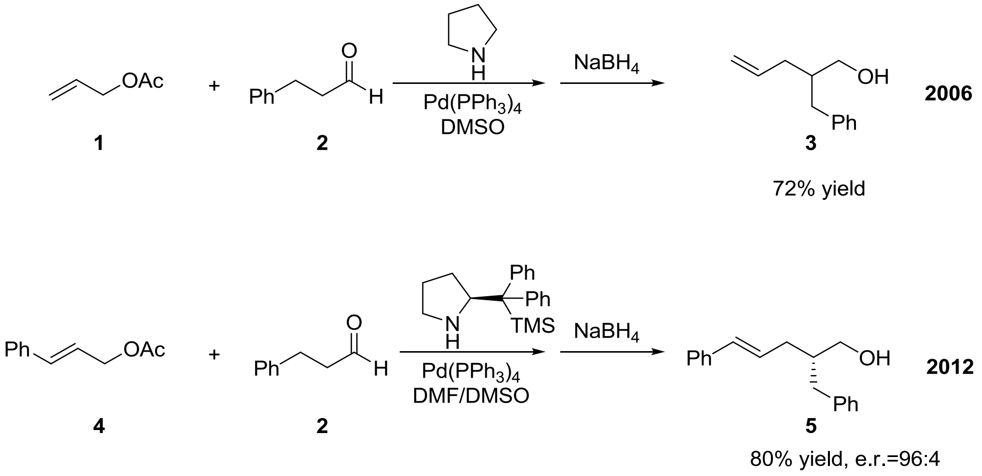


Figure 4.2. Enamine and Tsuji-Trost dual catalysis

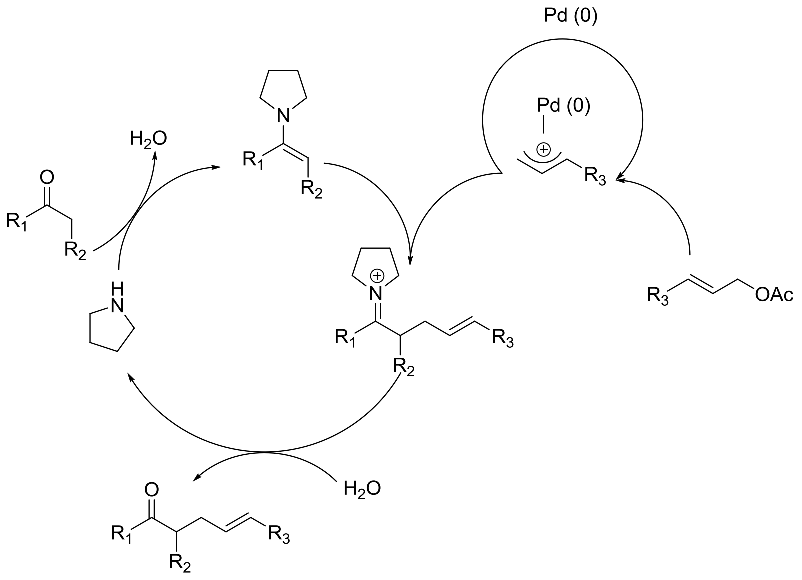


Figure 4.3. Mechanism of enamine and Tsuji-Trost dual catalysis

One year after Córdova's pioneering work of jointly applying the Tsuji-Trost and enamine chemistry, List *et al.* published the first enantioselective dual catalysis by introducing a chiral phosphoric acid cocatalyst as a proton donor as well as a chiral ligand to control the stereoselectivity (**Figure 4.4**, **Figure 4.5**).[6] A broad spectrum of aldehydes were tested under the standard conditions and all gave good to excellent yields and enantioselectivity.

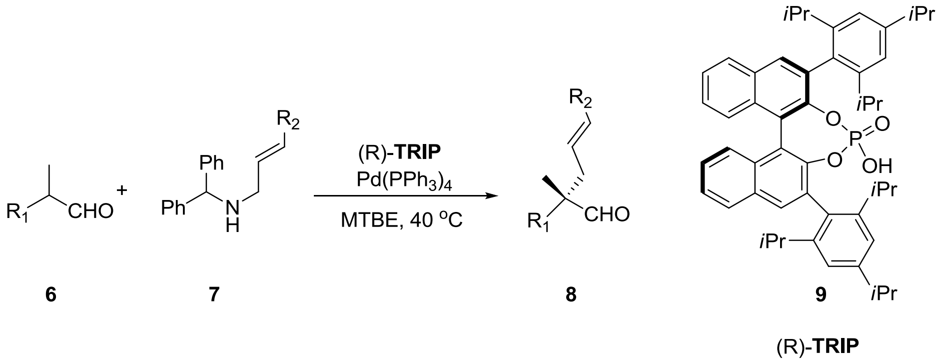


Figure 4.4. Enamine and Tsuji-Trost dual catalysis

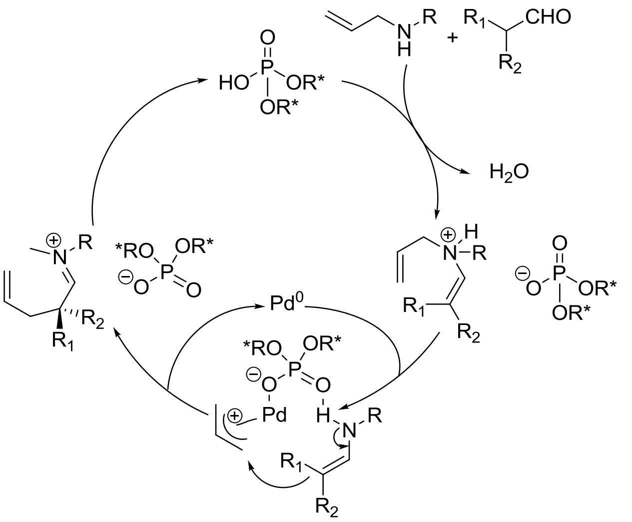


Figure 4.5. Mechanism of Enamine and Tsuji-Trost dual catalysis

In 2011, Zhang's group reported another dual catalyzed reaction of Tsuji-Trost reaction and enamine chemistry.[7] In this work, instead of allyl acetate, the less reactive allylamine was utilized as the source of allylation. The author claimed that methanol as solvent formed hydrogen bond with allylamine, which can effectively activate the C-N bond. Chiral reactions by using a chiral ligand were also included in the report and excellent yield and *ee* was obtained.

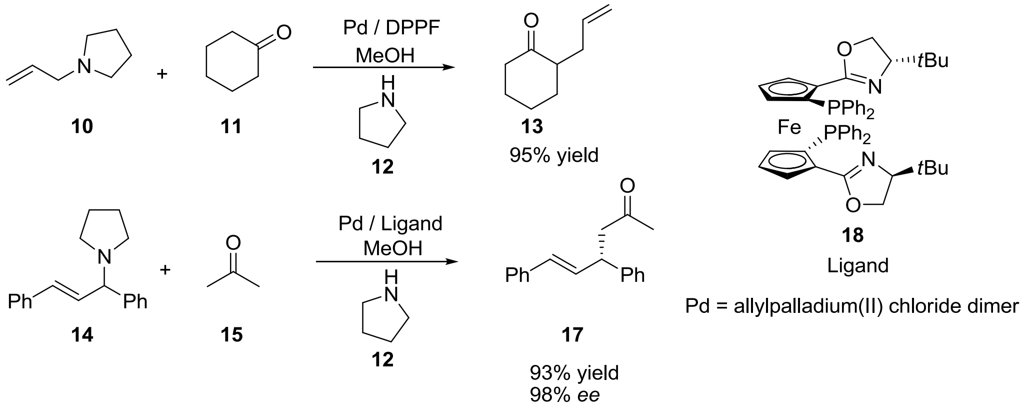


Figure 4.6. Mechanism of enamine and Tsuji-Trost dual catalysis

Besides the dual catalysis of Tsuji-Trost reaction and enamine chemistry, Trost's group published a novel dual catalysis method by merging the Tsuji-Trost reaction and vanadium-allenoate chemistry (**Figure 4.7**).[8] By treatment with the vanadium catalyst, the propargylic alcohol underwent rearrangement to generate the nucleophilic allenoate. The resulting allenoate then spontaneously reacted with the electrophilic π-allyl Pd complex generated by its allylic precursor to form the addition product (**Figure 4.8**). Interestingly, either of the two catalysts could independently catalyze the reaction to give respective products. However, when the two catalysts were applied simultaneously, these products were only obtained as by-products of only trace amount.

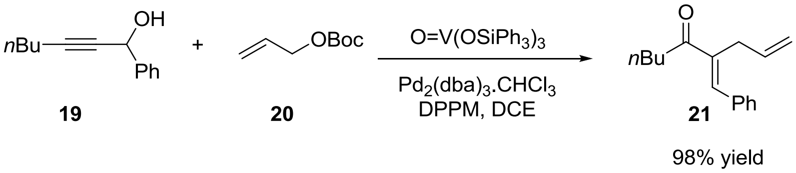


Figure 4.7. Allenoate and Tsuji-Trost dual catalysis

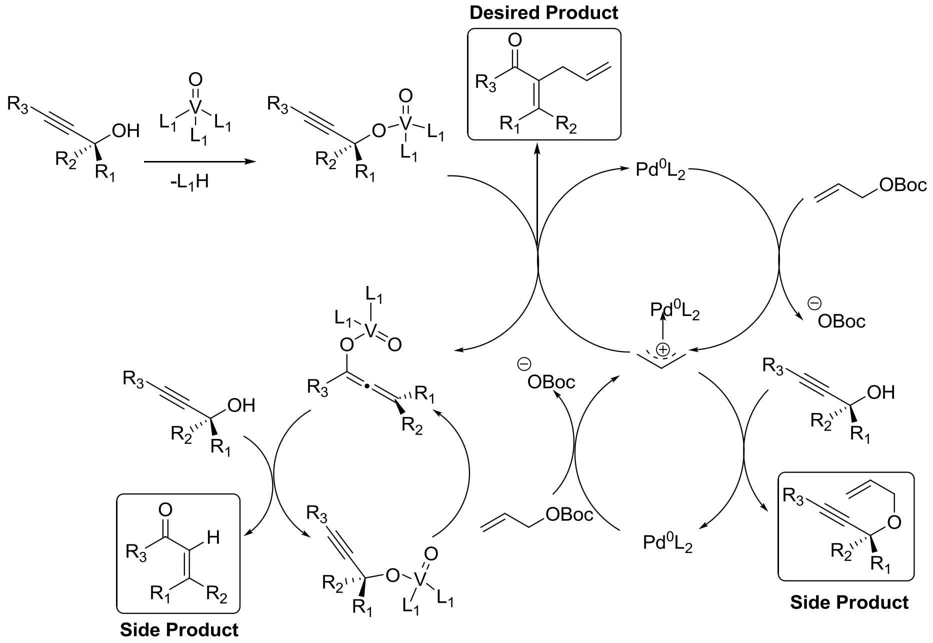


Figure 4.8. Mechanism of allenoate and Tsuji-Trost dual catalysis

4.1.2 Tsuji-Trost Type *C*-Glycosylation

Since glycals are also a group of compounds possessing allylic system, the versatility of Tsuji-Trost reaction in dual catalyzed reaction inspired us to develop a new *C*-glycosylation method of glycals. The basic concept of Tsuji-Trost *C*-glycosylation of glycals is generally the same as classic Tsuji-Trost reactions (**Figure 4.9**). We postulated that the palladium catalyst could coordinate to the allylic system of C1 to C3 on glycal to form the glycal-Pd complex. Following which, the carbon nucleophile would undergo a nucleophilic addition to the relatively electron deficient C1 on glycal to form the *C*-glycosidic bond.

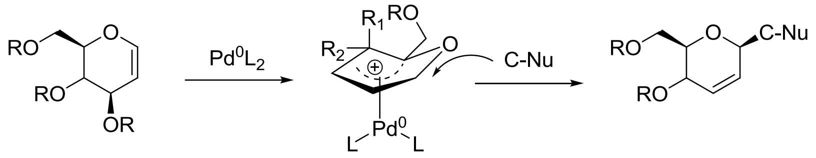
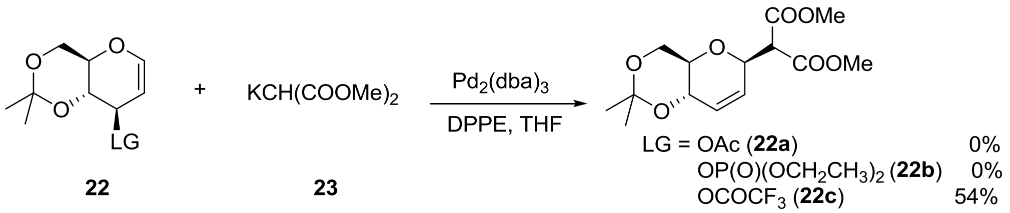


Figure 4.9. General mechanism of Tsuji-Trost type *C*-glycosylation

The pioneer work of Tsuji-Trost type *C*-glycosylation was done by RajanBabu *et al*. by applying the potassium malonate salt as nucleophile (**Figure 4.10**).[9] Glycals are generally more electron-rich than allyl ester or allyl amine, which reduce the affinity of allylic systems on glycals for palladium. The common C3 protecting groups such as acetyl group or phosphoric group failed to give any product. Only the strong electron withdrawing trifluoroacetyl group afforded the *C*-glycoside in acceptable yield. Regarding the nucleophile, only the strong *C*-nucleophile such as potassium and sodium melonate salts and their analogues were strong enough to form the C-C glycosidic bond. The restrictions on both glycals and nucleophiles limited the application of this method.



22 **23**

Figure 4.10. Tsuji-Trost type *C*-glycosylation of glycals and melonate salts

An alternative method to bypass the electron-rich property of glycals is to use the pre-activated pyranose system (**Figure 4.11**).[10] Compound such as **24** and **27** significantly increased the yield to satisfactory level. Notably, for these two examples, the stereochemistry on anomeric carbon were retained. The retention of the stereochemistry confirmed that the palladium catalyst approached the glycal from less hindered side and the subsequence SN2 reaction took place opposite to the bulky Pd catalyst to regain the stereochemistry of the anomeric carbon. However, the scope of *C*-nucleophile was still very limited.

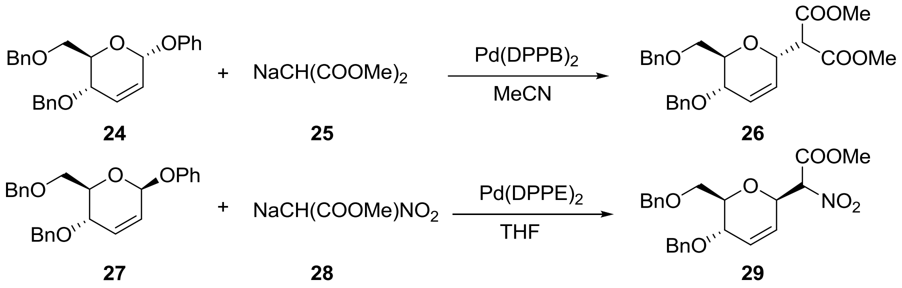


Figure 4.11. Tsuji-Trost type *C*-glycosylation from *O*-glycosides

The Tsuji-Trost type *C*-glycosylation of other *C*-nucleophiles remained blank until a breakthrough is made in 2013. Our group published a palladium catalyzed *C*-glycosylation reaction (**Figure 4.12** and **Figure 4.13**) by using the decarboxylative strategy to generate the Pd-glycal system and nucleophilic enolate simultaneously.[11] The reactions proceeded with high yields and exclusive β selectivities.

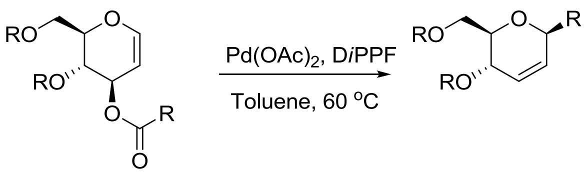
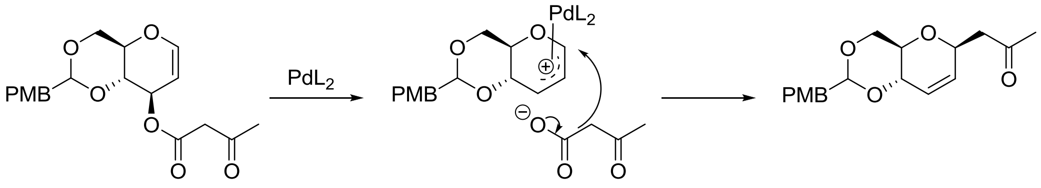


Figure 4.12. Tsuji-Trost type decarboxylative *C*-glycosylation



30 31 32

Figure 4.13. Mechanism of Tsuji-Trost type decarboxylative *C*-glycosylation

This intramolecular C3-decarboxylative approach has then been expanded to *N* and *O*-glycosylation (**Figure 4.14**).[12] After that, efforts have been made to realize the intermolecular version of decarboxylative glycosylation. Our group have found that ethoxycarbonyloxyl on C3 can serve as a good leaving group through decarboxylation for *O*-glycosylation (**Figure 4.15**). Inspired by this result, we proceeded to explore the Tsuji-Trost *C*-glycosylation reaction by using C3 ethoxycarbonyloxyl protecting glycals.

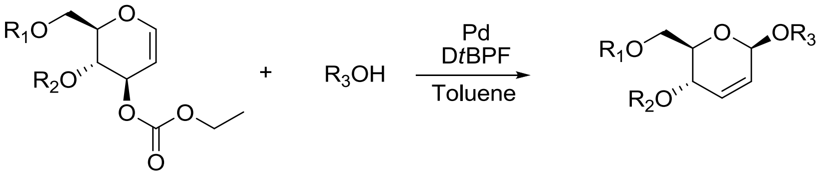


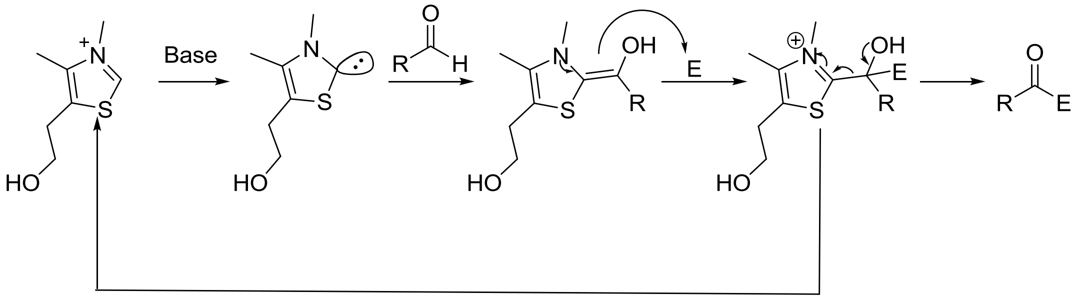
Figure 4.14. Tsuji-Trost decarboxylative *O*-glycosylation

4.1.3 NHC Catalysis and Stetter Reaction

After choosing the suitable glycals, we moved on to identify the proper *C*-nucleophile. Preliminary results showed that the reported nucleophiles for Tsuji-Trost reaction such as allenoate and enamine didn't work for glycals. As a result, we need to find another *C*-nucleophile for the dual catalyzed *C*-glycosylation reaction.

Recently, N-Heterocyclic carbenes (NHC) as a new member in the organocatalysis family have attracted remarkable attention.[13] The umpolung of an aldehyde by treatment of NHC turns aldehyde from an electrophile into a nucleophile (**Scheme 4.3**). The nucleophilic intermediate of aldehyde, namely Breslow intermediate, can capture electrophiles such as another molecule of aldehyde *via* 1,2-addition or α, β-unsaturated ketone *via* 1,4-addition. We envisioned that the NHC catalysis could be further applied on the Pd-allylic system. Since to our knowledge, there is only limited number of reports regarding the combination of Tsuji-Trost reaction and NHC catalysis[14], we determined to explore the possibility of this reaction by simple allylic system first.

Scheme 4.3. Formation and reactivity of Breslow intermediate



4.2 Application of Tsuji-Trost Reaction and NHC Catalysis on Allyl Acetate

4.2.1 Conditions Optimization

Two challenges need to be overcome in order to apply the palladium-NHC dual catalysis. The first one is that since NHCs are also a group of ligands which can bind to palladium, the two catalysts could potentially poison each other. The other problem is that the Breslow intermediates can also undergo 1,2-addition with another molecule of aldehyde, which may generate benzoins **37** as the byproduct. In 2006, Hamada *et al.* reported the one-pot sequential multi-catalytic reaction by integrating Stetter reaction and Pd catalyzed allylation reaction in one reaction vessel (**Figure 4.15**).[14] This was the first report in which the Pd and NHC catalyst exert their respective catalytic property individually.

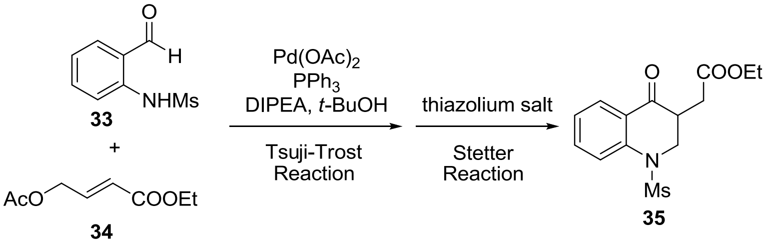


Figure 4.15. One-pot Tsuji-Trost and Stetter tandem reaction

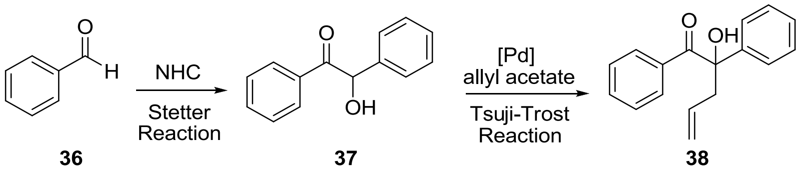
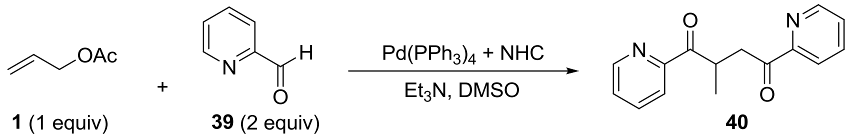


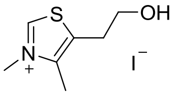
Figure 4.16. One-pot Tsuji-Trost and Stetter tandem reaction

In 2008, Glorius *et al*. published another tandem palladium-NHC catalytic method (**Figure 4.16**).[15] Interestingly, in both reports, thiazolium salts were found to work independently as NHC catalysts, not Pd ligands. This finding implied that thiazolidinylidenes are the suitable NHC catalysts for Pd-NHC dual catalyzed *C*-glycosylation. After targeting the NHC catalyst, we found that recent research has shown that nitrogen on *o*-azaaryl heterocycle exhibits great affinity towards Pd catalyst.[16] This suggested that the coordination between the nitrogen atom and Pd catalyst can shorten the distance between the π-allyl Pd complex and the Breslow intermediate to avoid the formation of benzoin products.

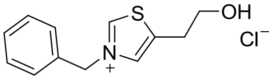
Inspired by the literature review, we started the initial trial with 1 equivalent of allyl acetate **1** as the allylic source, 2 equivalent of pyridine-2-carboxaldehyde **39** as the *o*-azaaryl aldehyde in presence of 5 mol% of $Pd(PPh_3)_4$, 10 mol% of 5-(2-hydroxylethyl)-3, 4-dimethylthiazolium iodide **41** and 3 equivalent of Et_3N as base (entry 1, Table 4.1). To our delight, 53% percent of product **40** in the form of 2-methyl-1,4-di(pyridin2-yl)butane-1,4-dione was obtained. This product suggested a double addition on allylic system. Notably, benzaldehyde provided the 1,2-addition benzoin as the only product, implying the effect of N-Pd coordination for this reaction. The subsequent control reactions (entry 2-3, Table 4.1) revealed that both Pd and NHC catalysts played crucial roles to this coupling reaction. Other NHC catalysts such as imidazolium (entry 5, Table 4.1), triazolium (entry 6, Table 4.1) and thiazolium (entry 7, Table 4.1) catalysts were screened. In agreement with the literature, only another thiazolium NHC **42** gave comparable yield.

Table 4.1. Screening of NHCs and control reactions[a]

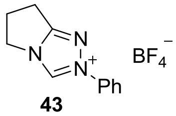




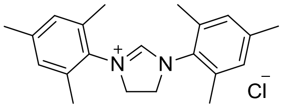
41



42



43



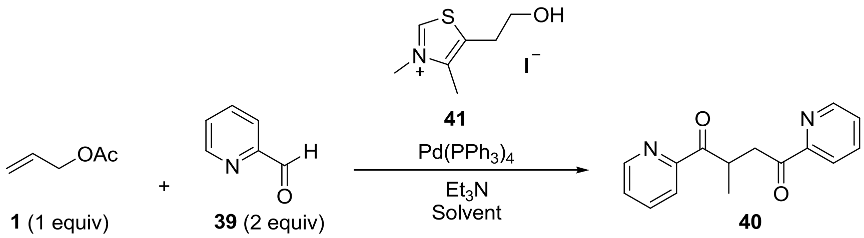
44

Entry	Pd source	NHC	Yield[b] (%)
1	$Pd(PPh_3)_4$	**41**	53
2	-	**41**	<5
3	$Pd(PPh_3)_4$	-	0
4	$Pd(PPh_3)_4$	**42**	50
5	$Pd(PPh_3)_4$	**43**	0
6	$Pd(PPh_3)_4$	**44**	0

[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 2 equivalents of **39**, 5% Pd catalyst, 10% NHC catalyst, and 3 equivalents of triethylamine under argon for 3 hours at room temperature. [b] Yields determined by NMR with 1,3,5-trimethoxybenzene as an internal reference.

A variety of commonly used Pd catalysts including $Pd(OAc)_2$ (entry 1-2, Table 4.2), $(Pd(allyl)Cl)_2$ (entry 3, Table 4.2) and $Pd_2(dba)_3$ (entry 4, Table 4.2) were tested under the same conditions. The results showed that $Pd(PPh_3)_4$ was the only active catalyst for this dual catalytic reaction. It was found that among the commonly used solvents such as DMSO, DMF (entry 5, Table 4.2), THF (entry 6, Table 4.2), acetone (entry 7, Table 4.2) and DCM (entry 8, Table 4.2), DMSO was the most effective solvent. The yield of the product **40** was significantly enhanced to 90% by the slow addition of aldehyde as a 1M solution in DMSO over 2 hours by a syringe pump (entry 9, Table 4.2).

Table 4.2. Screening of Pd catalysts and solvents[a]

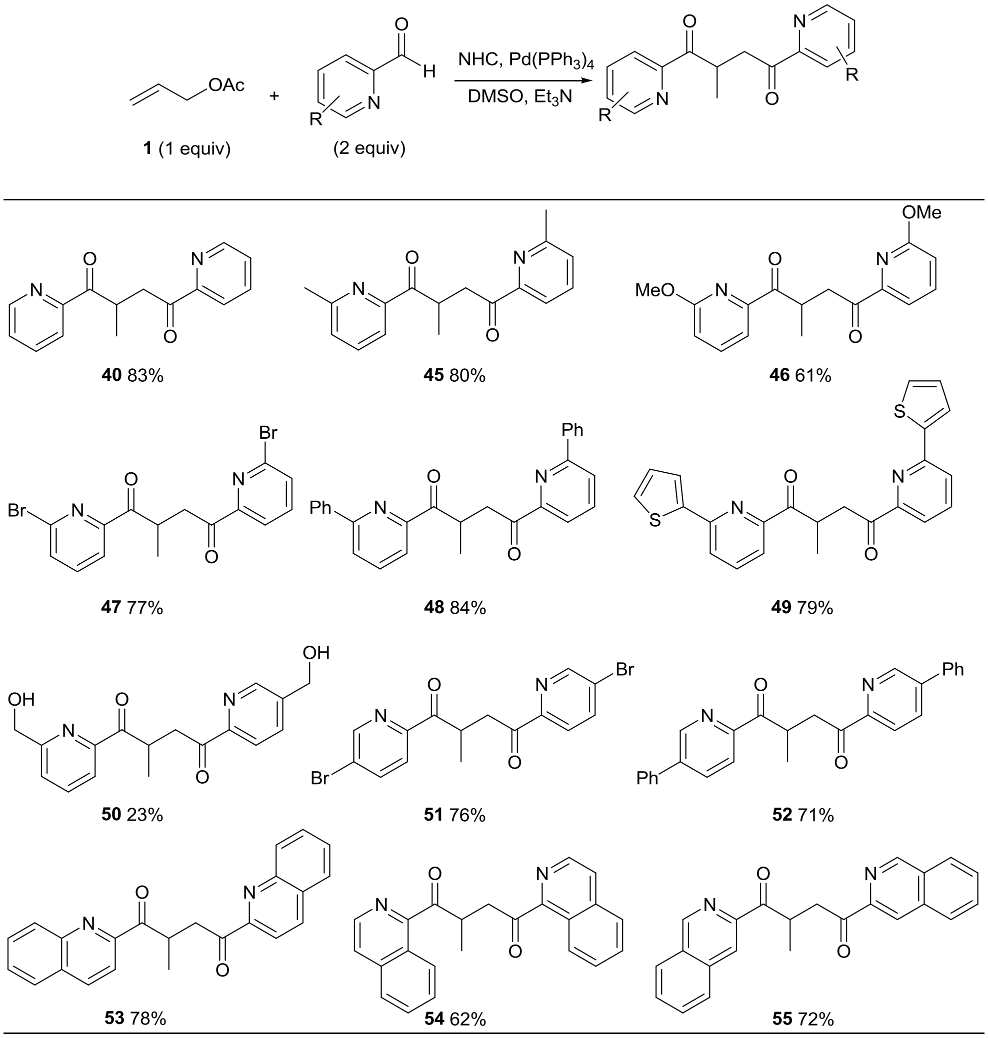


Entry	Pd Source	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	DMSO	0
2	$Pd(OAc)_2$+DiPPF[d]	DMSO	0
3	$(Pd(allyl)Cl)_2$	DMSO	0
4	$Pd_2(dba)_3$	DMSO	0
5	$Pd(PPh_3)_4$	DMF	0
6	$Pd(PPh_3)_4$	THF	23
7	$Pd(PPh_3)_4$	Acetone	44
8	$Pd(PPh_3)_4$	DCM	9
9[c]	$Pd(PPh_3)_4$	DMSO	90

[a] Unless otherwise specified, reactions were carried out with 1 equivalent of **1**, 2 equivalents of **39**, 5% Pd catalyst, 10% NHC catalyst, and 3 equivalents of Et_3N under argon for 3 hours at room temperature. [b] Yields determined by NMR with 1,3,5-trimethoxybenzene as internal reference. [c] **39** was added by a syringe pump as a 1M solution in DMSO in 2 hours. [d] Ligand added in 20 mol%

4.2.2 Substrate Scope

Scheme 4.4 Substrate scope[a], [b], [c]



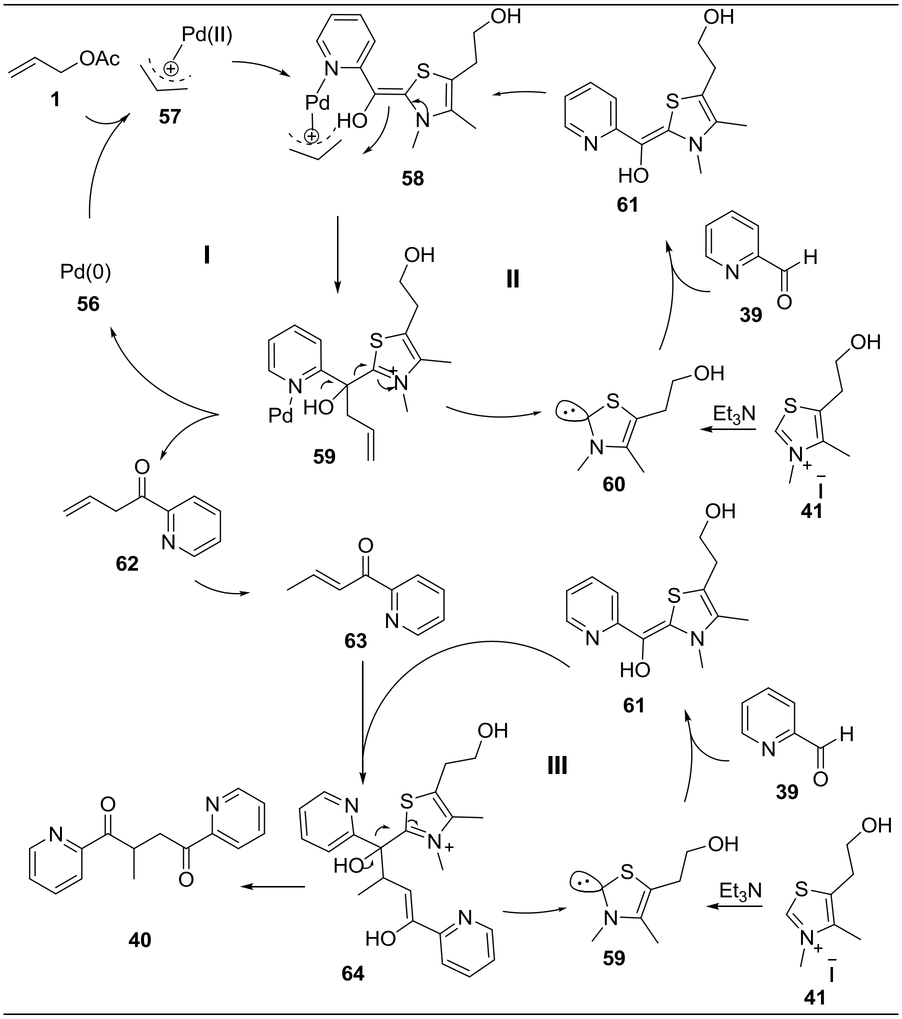
[a] Reactions were carried out with 1 equivalent of **1**, 2 equivalents of aldehyde, 5% Pd catalyst , 10% NHC catalyst, and 3 equivalents of triethylamine under argon for 3 hours at room temperature. [b] Aldehyde was added with syringe pump as a 1M solution in DMSO within 2 hours. [c] Isolated yields

With the optimal conditions in hand, the scope of *o*-azaaryl aldehyde was first studied. Besides pyridine-carboxaldehyde, some *o*-azaaryl aldehydes, such as pyrrole-2-carboxaldehyde, imidazole-2-carboxaldehyde and pyrimidine-2-carboxaldehyde, were not reactive under standard conditions. On the other hand, *o*-azaaryl aldehydes, including quinoline-2-carboxaldehyde **53**, isoquinoline-1-carboxaldehyde **54** and isoquinoline-3-carboxaldehyde **55**, generally provided the corresponding products in good to excellent yields. Next, an array of substituted pyridine-2-carboxaldehydes were examined under standard conditions. The results showed that except 6-methoxy-pyridine-2-carboxaldehyde **46** and 6-hydroxymethyl-pyridine-2-carboxaldehyde **50**, other pyridine-2-carbxaldehyde generally gave the products **47**, **48**, **49**, **51**, **52** in good to excellent yields. Surprisingly, no desired product was obtained when 3-methyl-pyridine-2-carboxaldehyde was applied under standard conditions. It was deduced that the methyl group prevented the π-allyl Pd complex from approaching the aldehyde to form the Pd-N coordination.[17] Other allyl acetate derivatives, such as 2-methylallyl acetate, (*E*)-but-2-enyl acetate, and 1-phenylallyl acetate, were tested in the reaction and disappointingly, no corresponding product was obtained.

4.2.3 Mechanism Study

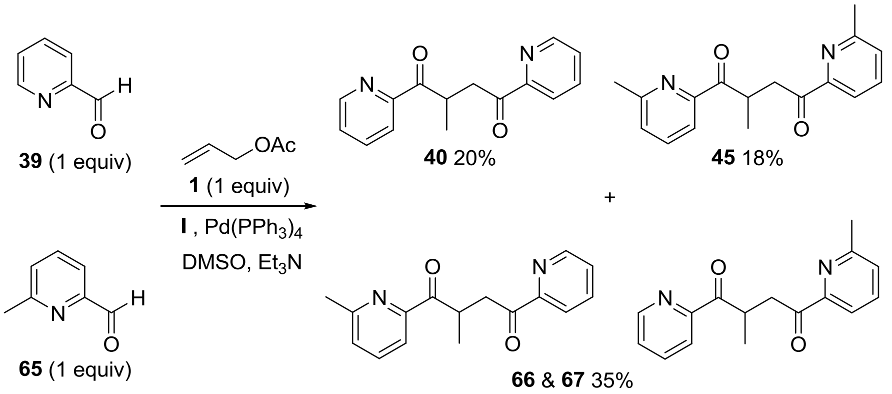
A plausible mechanism was described in **Scheme 4.5**. After the formation of Breslow intermediate **61** from aldehyde and π-allyl Pd complex **57** from allyl acetate, the two intermediates were brought closer by the Pd-N coordination to form complex **58**. Then, a nucleophilic substitution reaction took place to form intermediate **62** as an β, γ-unsaturated ketone. Under the basic reaction conditions, proton transfer took place to form the α, β-unsaturated ketone **63**. A subsequent 1,4-addition of another Breslow intermediate towards compound **63** gave the final product as a 1,4-dione **40**.

Scheme 4.5. Plausible mechanism

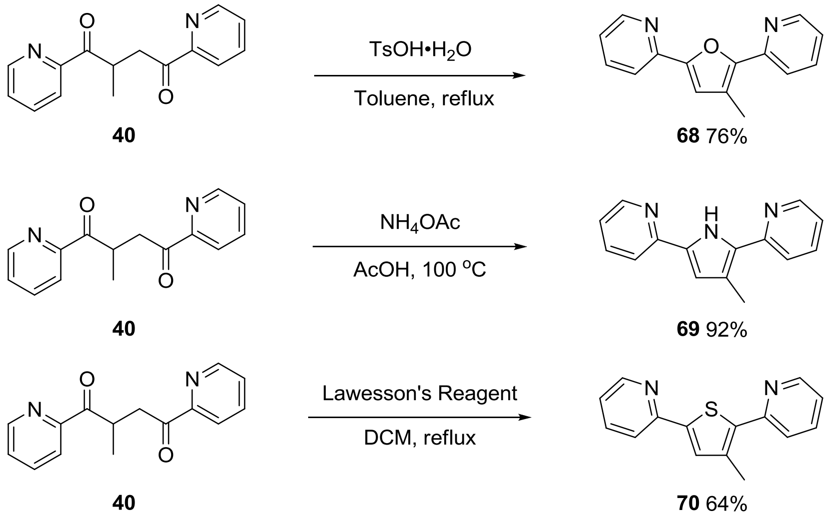


A cross experiment was conducted to justify the proposed mechanism (**Scheme 4.6**). In this experiment, allyl acetate was simultaneously treated by 1 equivalent of pyridine-2-carboxaldehyde **39** and 1 equivalent of 6-methyl-pyridine-2-carboxaldehyde **65**. The results showed that all of the four products **40**, **45**, **66**, **67** predicted by the mechanism were obtained in almost the same yields.

Scheme 4.6. Cross reaction of pyridine-2-carboxaldehyde and 6-methyl-carboxaldehyde towards allyl acetate



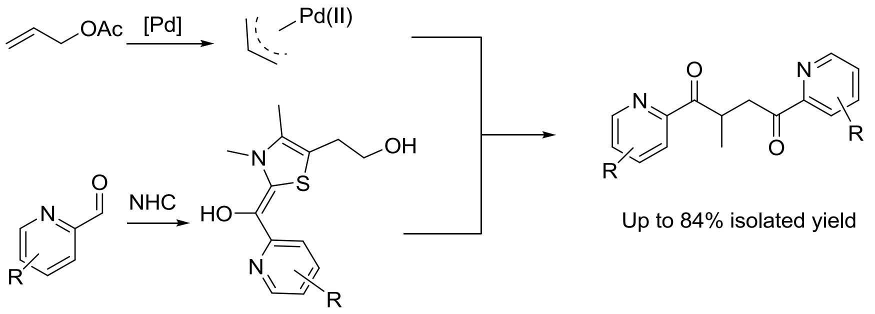
Scheme 4.7. Synthesis of various heterocyclic compounds by 1,4-dione



Transformations of product **40** towards furan **68**,[18] pyrrole **69**,[19] and thiophene **70**[20] were conducted by Paal-Knorr synthesis (**Scheme 4.7**). The 1,4-dione products are an class of ideal starting material towards 2, 5-diheterocycle furans, pyrroles and thiophenes which has shown wide applications in medicinal[21], organometallic[22] and polymer chemistry.[23] Current methods to synthesize 1,4-dicarbonyl compounds bearing heterocycle terminus require harsh conditions, long reaction steps or the formation of undesired products.[24] This dual catalysis method provides a milder and 1-step method towards the heterocycle containing 1,4-diones.

4.2.4 Conclusion

In summary, the first dual intermolecular catalytic of Pd and NHC catalysts between allyl acetate and *o*-azaaryl carboxaldehydes has been established. The reaction proceeded under mild conditions in short reaction time. The substrate scope included a plethora of *o*-azaaryl aldehydes with different substituents and ring sizes. The 1,4-dione products could be converted into other useful heterocyclic compounds. This reaction proves the feasibility of a Pd-NHC dual catalytic system and this system shows great potential for the Pd-NHC *C*-glycosylation.

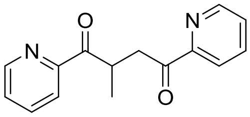


4.2.5 Experimental Section

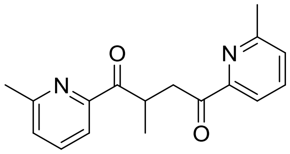
General: All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 400 MHz Bruker AVIII 400. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^1H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

Material: Dimethyl sulfoxide (DMSO) and triethylamine (Et_3N) were purchased from commercial suppliers and used without further purification. NHC catalysts, tetrakis-triphenylphosphine palladium(0), Allyl acetate, pyridine-2-carboxaldehyde, 6-methylpyridine-2-carboxaldehyde, 6-methoxylpyridine-2-carboxaldehyde, 6-bromopyridine-2-carboxaldehyde, 6-(2-Thienyl)pyridine-2-carboxaldehyde, 5-bromopyridine-2-carboxaldehyde, 2-quinolinecarboxaldehyde were purchased from commercial suppliers. 6-phenylpyridine-2-carboxaldehyde,[25] 6-hydroxymethylpyridine-2-carboxaldehyde,[26] 5-phenylpyridine-2-carboxaldehyde,[25] 1-isoqunoline-carboxaldehyde[27] and 3-isoquinolinecarboxaldehyde[28] were prepared by reported methods.

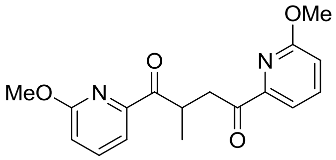
General experimental procedure of direct coupling by dual catalysis: To a solution of **1** (0.4 mmol), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol) and triethylamine (1.2 mmol) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, (*o*-azaaryl)carboxaldehyde (0.8 mmol) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump within a 2-hour period. The mixture was allowed to stir at room temperature for another 1 hour. Then the mixture was diluted with ethyl acetate (10 mL), filtered, washed with water (20 mL) and brine (15 mL) and dried over Na_2SO_4. The organic layer was evaporated and the residue was purified by flash column chromatography to afford the product.



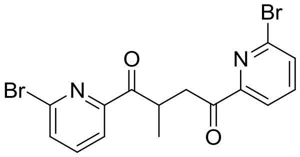
2-methyl-1,4-di(pyridin-2-yl)butane-1,4-dione (40) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, pyridine-2-carboxaldehyde (0.8 mmol, 76 μL) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a brown solid (85 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34-1.36 (d, J = 7.2 Hz, 3H), 3.49–3.54 (dd, J = 4.4, 18.8 Hz, 1H), 3.91–3.99 (dd, J = 9.7, 18.8 Hz, 1H), 4.64–4.70 (m, 1H), 7.45–7.50 (m, 2H), 7.79-7.99 (m, 2H), 8.08-8.10 (m, 2H), 8.69-8.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, 35.1, 41.9, 121.7, 122.5, 126.9, 127.1, 136.8, 136.9, 148.9, 149.0, 152.8, 153.1, 200.2, 204.4; IR (neat) 3055, 2972, 2933, 2358, 2330, 1693, 1680, 1583, 1435, 1348, 1219, 955, 746, 619 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_2$ [M+H]$^+$: 255.1134, found 255.1138.



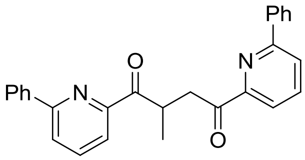
2-methyl-1,4-bis(6-methylpyridin-2-yl)butane-1,4-dione (45) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-methylpyridine-2-carboxaldehyde (0.8 mmol, 96 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a dark brown solid (91 mg, 80%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.30-1.32 (d, *J* = 7.2 Hz, 3H), 2.61 (s, 6H), 3.45–3.51 (dd, *J* = 4.9, 18.7 Hz, 1H), 3.83–3.90 (dd, *J* = 9.2, 18.7 Hz, 1H), 4.62–4.71 (m, 1H), 7.28–7.30 (m, 2H), 7.63-7.69 (m, 2H), 7.71-7.77 (m, 1H), 7.85-7.87 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.5, 24.4, 24.5, 35.2, 41.7, 118.7, 119.4, 126.4, 126.6, 136.7, 136.8, 152.3, 152.8, 157.9, 157.9, 200.7, 204.8; IR (neat) 3020, 2358, 2341, 1693, 1591, 1456, 1344, 1215, 975, 756, 667 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_2$ [M+H]$^+$: 283.1447, found 283.1443



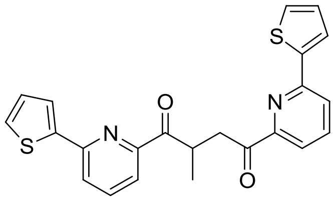
1,4-bis(6-methoxypyridin-2-yl)-2-methylbutane-1,4-dione (46) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-methoxylpyridine-2-carboxaldehyde (0.8 mmol, 109 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a white solid (77 mg, 61%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.33-1.35 (d, *J* = 7.1 Hz, 3H), 3.37–3.43 (dd, *J* = 5.2, 18.6 Hz, 1H), 3.79–3.86 (dd, *J* = 8.7, 18.6 Hz, 1H), 3.98 (s, 3H), 4.00 (s, 3H), 4.54–4.63 (m, 1H), 6.91-6.94 (m, 2H), 7.56-7.58 (m, 1H), 7.64-7.70 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.3, 35.5, 41.7, 53.4, 53.5, 114.9, 115.1, 115.2, 115.7, 139.0, 139.1, 150.1, 150.7, 163.2, 163.3, 200.1, 204.0; IR (neat) 2976, 2953, 1693, 1591, 1573, 1433, 1338, 1274, 1230, 1035, 812 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_4$ [M+H]$^+$: 315.1345, found 315.1339



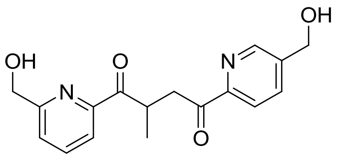
1,4-bis(6-bromopyridin-2-yl)-2-methylbutane-1,4-dione (47) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine) palladium (0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-bromopyridine-2-carboxaldehyde (0.8 mmol, 149 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 2:1) to afford the product as a yellow solid (126 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.34 (d, J = 7.2 Hz, 3H), 3.43–3.49 (dd, J = 4.2, 19.1 Hz, 1H), 3.81–3.88 (dd, J = 9.9, 19.1 Hz, 1H), 4.47–4.56 (m, 1H), 7.64-7.72 (m, 4H), 7.89-7.91 (m, 1H), 8.00-8.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4, 35.3, 41.8, 120.6, 121.3, 131.7, 131.9, 139.1, 139.2, 141.4, 153.4, 153.8, 198.7, 202.7; IR (neat) 2929, 1697, 1556, 1431, 1396, 1338, 1273, 1217, 985, 754 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2Br_2$ $[M+H]^+$: 410.9344, found 410.9349



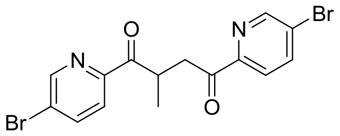
2-methyl-1,4-bis(6-phenylpyridin-2-yl)butane-1,4-dione (48) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-phenylpyridine-2-carboxaldehyde (0.8 mmol, 146 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a yellow solid (137 mg, 84%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44-1.46 (d, J = 7.2 Hz, 3H), 3.66–3.72 (dd, J = 4.9, 18.5 Hz, 1H), 4.00–4.07 (dd, J = 9.0, 18.5 Hz, 1H), 4.83–4.92 (m, 1H), 7.43-7.53 (m, 6H), 7.82-7.85 (m, 1H), 7.87-7.94 (m, 4H), 8.00-8.02 (m, 1H), 8.10-8.11 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.6, 35.6, 41.9, 119.9, 120.7, 123.2, 123.6, 126.9, 126.9, 128.8, 128.8, 129.3, 129.4, 137.6, 137.7, 138.4, 138.5, 152.5, 153.0, 156.2, 156.4, 200.7, 204.7; IR (neat) 3064, 2972, 1693, 1579, 1448, 1392, 1348, 1217, 1028, 985, 754 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{23}N_2O_2$ [M+H]$^+$: 407.1760, found 407.1756



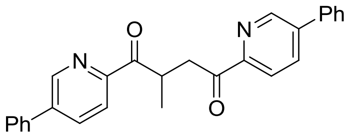
2-methyl-1,4-bis(6-(thiophen-2-yl)pyridin-2-yl)butane-1,4-dione (49) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-(2-Thienyl)pyridine-2-carboxaldehyde (0.8 mmol, 151 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a pale yellow solid (132 mg, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.43 (d, J = 7.1 Hz, 3H), 3.59–3.65 (dd, J = 5.2, 18.4 Hz, 1H), 3.93–4.00 (dd, J = 8.7, 18.4 Hz, 1H), 4.79–4.84 (m, 1H), 7.37-7.42 (m, 2H), 7.75-7.85 (m, 7H), 7.96-7.99 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 35.7, 41.7, 119.6, 120.3, 123.0, 123.3, 124.1, 124.2, 126.2, 126.3, 126.5, 137.5, 137.6, 141.5, 141.6, 152.4, 152.5, 152.6, 153.0, 200.5, 204.5; IR (neat) 3018, 2972, 1693, 1587, 1465, 1392, 1342, 1215, 989, 756 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2S_2$ [M+H]$^+$: 419.0888, found 419.0883



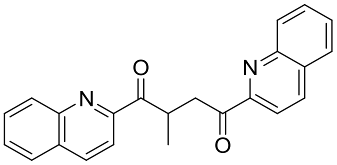
4-(5-(hydroxymethyl)pyridin-2-yl)-1-(6-(hydroxymethyl)pyridin-2-yl)-2-methyl-butane-1,4-dione (50) To a solution of **1** (0.4 mmol, 44 μL), tetrakis-(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-hydroxymethylpyridine-2-carboxaldehyde (0.8 mmol, 110 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 1:2) to afford the product as a white solid (29 mg, 23%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.34 (d, J = 7.2 Hz, 3H), 3.37–3.43 (dd, J = 5.1, 18.2 Hz, 1H), 3.78-3.82 (m, 2H), 3.91–3.98 (dd, J = 9.0, 18.2 Hz, 1H), 4.67–4.72 (m, 1H), 4.84 (s, 4H), 7.42-7.44 (m, 2H), 7.80-7.91 (m, 3H), 7.99-8.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.2, 35.4, 42.0, 63.9, 64.0, 120.6, 121.4, 124.0, 124.1, 137.6, 137.7, 151.4, 151.9, 158.55, 158.5, 199.6, 203.5; IR (neat) 3012, 2931, 2854, 1942, 1681, 1589, 1446, 1373, 1338, 1219, 995, 753 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_4$ $[M+H]^+$: 315.1345, found 315.1354



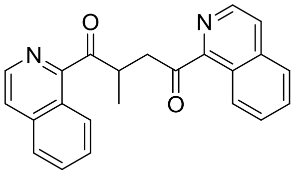
1,4-bis(5-bromopyridin-2-yl)-2-methylbutane-1,4-dione (51) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 5-bromopyridine-2-carboxaldehyde (0.8 mmol, 149 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 2:1) to afford the product as a white solid (124 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31-1.33 (d, J = 7.2 Hz, 3H), 3.42–3.48 (dd, J = 4.3, 18.9 Hz, 1H), 3.84-3.91 (dd, J = 9.8, 18.9 Hz, 1H), 4.53–4.62 (m, 1H), 7.84-7.86 (m, 1H), 7.94-8.01 (m, 3H), 8.74-8.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3, 35.1, 41.8, 123.0, 123.8, 125.1, 125.4, 139.6, 139.6, 150.1, 150.1, 150.9, 151.3, 199.3, 203.3; IR (neat) 3093, 2088, 1953, 1693, 1566, 1454, 1317, 1209, 981, 756 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2Br_2$ $[M+H]^+$: 410.9344, found 410.9342



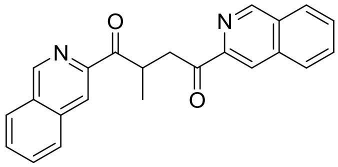
2-methyl-1,4-bis(5-phenylpyridin-2-yl)butane-1,4-dione (52) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 5-phenylpyridine-2-carboxaldehyde (0.8 mmol, 146 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 4:1) to afford the product as a yellow solid (115 mg, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.39 (d, J = 7.2 Hz, 3H), 3.53–3.59 (dd, J = 4.4, 18.8 Hz, 1H), 3.97-4.04 (dd, J = 9.7, 18.7 Hz, 1H), 4.68–4.77 (m, 1H), 7.43-7.53 (m, 6H), 7.60-7.65 (m, 4H), 7.96-8.06 (m, 3H), 8.16-8.18 (m, 1H), 8.91-8.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 35.2, 42.1, 121.9, 122.6, 127.3, 127.3, 128.7, 128.8, 129.2, 129.2, 135.0, 135.1, 136.9, 137.1, 139.6, 139.9, 147.4, 147.5, 151.4, 151.8, 199.9, 204.0; IR (neat) 3018, 2399, 1689, 1587, 1471, 1379, 1340, 1215, 927, 756 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{23}N_2O_2$ [M+H]$^+$: 407.1760, found 407.1763



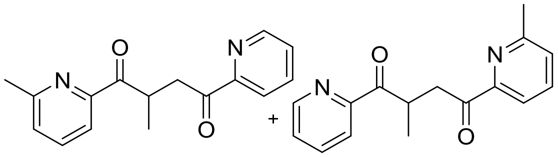
2-methyl-1,4-di(quinolin-2-yl)butane-1,4-dione (53) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, quinoline-2-carboxaldehyde (0.8 mmol, 126 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 6:1) to afford the product as a brown solid (110 mg, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.47 (d, J = 7.1 Hz, 3H), 3.77–3.82 (dd, J = 5.0, 18.6 Hz, 1H), 4.08-4.15 (dd, J = 9.1, 18.6 Hz, 1H), 4.95–5.00 (m, 1H), 7.61-7.65 (m, 2H), 7.74-7.79 (m, 2H), 7.83-7.87 (m, 2H), 8.04-8.06 (m, 1H), 8.16-8.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6, 35.3, 41.7, 118.1, 118.8, 127.5, 127.6, 128.3, 128.5, 129.6, 129.6, 129.9, 130.6, 130.8, 136.8, 136.8, 147.2, 147.3, 152.4, 152.8, 200.8, 204.9; IR (neat) 3018, 2974, 1693, 1593, 1456, 1375, 1215, 987, 835, 710 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2$ $[M+H]^+$: 355.1447, found 355.1448



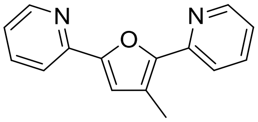
1,4-di(isoquinolin-1-yl)-2-methylbutane-1,4-dione (54) To a solution of **1** (0.4 mmol, 44 µL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 µL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, isoquinoline-1-carboxaldehyde (0.8 mmol, 126 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 6:1) to afford the product as a dark brown solid (88 mg, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.43 (d, J = 7.2 Hz, 3H), 3.65–3.71 (dd, J = 4.8, 18.4 Hz, 1H), 3.99-4.06 (dd, J = 9.0, 18.4 Hz, 1H), 4.69–4.74 (m, 1H), 7.56-7.73 (m, 4H), 7.79-7.88 (m, 4H), 8.57-8.62 (m, 2H), 8.77-8.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3, 38.5, 44.2, 124.0, 124.5, 125.7, 126.3, 126.8, 126.8, 126.9, 126.9, 128.7, 128.9, 130.2, 130.3, 137.0, 137.0, 141.0, 141.2, 152.8, 153.4, 202.8, 206.6; IR (neat) 2958, 2852, 1732, 1683, 1456, 1361, 1215, 1091, 943, 755 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2$ [M+H]$^+$: 355.1447, found 355.1450



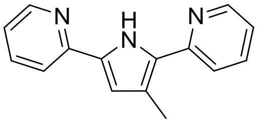
1,4-di(isoquinolin-3-yl)-2-methylbutane-1,4-dione (55) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, isoquinoline-3-carboxaldehyde (0.8 mmol, 126 mg) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2). The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 6:1) to afford the product as a yellow solid (102 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.43 (d, J = 7.2 Hz, 3H), 3.61–3.67 (dd, J = 4.6, 18.7 Hz, 1H), 4.07-4.14 (dd, J = 9.5, 18.6 Hz, 1H), 4.79–4.88 (m, 1H), 7.70-7.78 (m, 4H), 7.93-8.00 (m, 2H), 8.04-8.07 (m, 2H), 8.42 (s, 1H), 8.54 (s, 1H), 9.30-9.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 35.8, 42.8, 120.3, 121.0, 127.5, 127.5, 128.6, 128.6, 129.2, 129.3, 130.1, 130.2, 130.7, 130.9, 135.5, 135.7, 147.0, 147.4, 151.8, 151.9, 200.4, 204.6; IR (neat) 3018, 1685, 1624, 1492, 1388, 1215, 1170, 1128, 933, 904, 810 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2$ $[M+H]^+$: 355.1447, found 355.1443



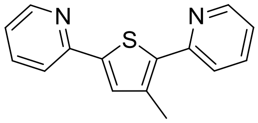
2-methyl-1-(6-methylpyridin-2-yl)-4-(pyridin-2-yl)butane-1,4-dione (66) & 2-methyl-4-(6-methylpyridin-2-yl)-1-(pyridin-2-yl)butane-1,4-dione (67) To a solution of **1** (0.4 mmol, 44 μL), tetrakis(triphenylphosphine)palladium(0) (0.02 mmol, 23 mg), 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide (0.04 mmol, 12 mg) and triethylamine (1.2 mmol, 165 μL) in dimethyl sulfoxide (1.2 mL) under argon at room temperature, 6-methylpyridine-2-carboxaldehyde (0.4 mmol, 48 mg) and pyridine-2-carboxaldehyde (0.4 mmol, 47.5 μL) in dimethyl sulfoxide (0.8 mL) was added by a syringe pump with a 2 hours period. The mixture was allowed to stir at room temperature for another 1 hour. The mixture was diluted with DCM (15 mL), washed with saturated ammonium chloride solution (20 mL×3) and water (15 mL×2).The solvent of the organic layer was removed by evaporation and the crude was purified by flash column chromatography (Hexane:EtOAc = 6:1) to afford the product as a yellow solid (102 mg, 72%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.29-1.31 (m, 3H), 2.58-2.59 (m, 3H), 3.41-3.53 (m, 1H), 3.85-3.93 (m, 1H), 4.64-4.65 (m, 1H), 7.27-7.29 (m, 1H), 7.42-7.45 (m, 1H), 7.61-7.69 (m, 1H), 7.72-7.85 (m, 2H), 7.96-8.06 (m, 1H), 8.65-8.71 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.4, 17.5, 24.4, 24.5, 35.1, 35.1, 41.7, 41.9, 118.7, 119.5, 121.7, 122.4, 126.5, 126.7, 126.8, 127.1, 136.8, 136.8, 136.8, 148.9, 148.9, 152.2, 152.2, 152.8, 153.2, 157.9, 157.9, 200.2, 200.6, 204.5, 204.6; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_2$ [M+H]$^+$: 269.1290, found 269.1289



2,2'-(3-methylfuran-2,5-diyl)dipyridine (68) A solution of 2-methyl-1,4-di(pyridin-2-yl)butane-1,4-dione (**40**) (51 mg, 0.2 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol) in toluene (10 mL) was heated to reflux for 5 hours under nitrogen. Then the solvent of the organic layer was removed under reduce pressure and the residue was purified by column chromatography (Hexane:EtOAc = 6:1) to afford the product as white solid (36 mg, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 7.06 (s, 1H), 7.11-7.18 (m, 2H), 7.70-7.75 (m, 2H), 7.78-7.83 (m, 2H), 8.59-8.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1, 114.6, 118.7, 119.7, 121.1, 122.0, 123.6, 136.2, 136.5, 148.4, 149.1, 149.3, 149.7, 151.0, 152.1; IR (neat) 2926, 2852, 1620, 1589, 1556, 1471, 1429, 1273, 1151, 937, 752 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$: 237.1028, found 237.1031



2,2'-(3-methyl-1H-pyrrole-2,5-diyl)dipyridine (69) A solution of 2-methyl-1,4-di(pyridin-2-yl)butane-1,4-dione (**40**) (51mg, 0.2mmol) and ammonium acetate (770mg, 10 mmol) in acetic acid (8 mL) was heated to 100 °C under nitrogen for 12 hours. Then ethyl acetate (20 mL) was added and the reaction mixture was washed with water (20 mL) and saturated sodium bicarbonate solution (20 mL) and dried over sodium sulfate. The solvent of organic layer was removed under reduce pressure and the residue was purified by column chromatography (Hexane:EtOAc = 1:1) to afford the product as pale yellow solid (43 mg, 92%). ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.44 (s, 3H), 6.60-6.61 (d, J = 2.8 Hz), 7.02-7.07 (m, 2H), 7.51-7.54 (m, 2H), 7.61-7.68 (m, 2H), 8.51-8.57 (m, 2H), 10.48 (s, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.1, 111.6, 118.3, 119.1, 120.1, 120.4, 120.6, 129.1, 131.1, 136.2, 136.2, 149.2, 149.3, 150.1, 150.8; IR (neat) 3001, 1642, 1566, 1473, 1288, 1269, 1511, 1072, 948, 756 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{14}N_3$ [M+H]$^+$: 236.1188, found 236.1185



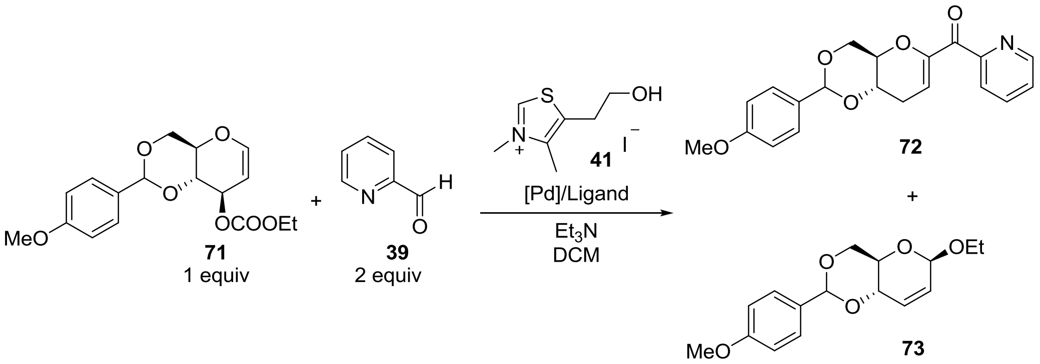
2,2'-(3-methylthiophene-2,5-diyl)dipyridine (70) A solution of 2-methyl-1,4-di(pyridin-2-yl)butane-1,4-dione (**40**) (51mg, 0.2mmol) and Lawesson's Reagent (89 mg, 0.22 mmol) in dichloromethane (3 mL) was stirred at 40 °C under nitrogen for 6 hours. Then EtOAc (20 mL) was added and the reaction mixture was washed with water (10 mL) and saturated sodium bicarbonate solution (10 mL) and dried over sodium sulfate. The solvent of organic layer was removed under reduce pressure and the residue was purified by column chromatography (Hexane:EtOAc = 4:1) to afford the product as yellow solid (32 mg, 64%).^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.55 (s, 3H), 7.13-7.18 (m, 2H), 7.48 (s, 1H), 7.60-7.74 (m, 4H), 8.57-8.59 (m, 1H), 8.63-8.65 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 16.4, 188.9, 121.4, 121.5, 121.9, 136.4, 136.6, 139.7, 143.4, 149.6, 149.6, 152.4, 153.5; IR (neat) 2960, 1747, 1681, 1581, 1471, 1259, 1153, 1004, 781 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}N_2S$ $[M+H]^+$: 252.0799, found 252.0799

4.3 Pd-NHC Dual Catalyzed *C*-Glycosylation

4.3.1 Conditions Optimization

Since the dual catalytic method of Pd and NHC has been developed, we intended to apply the method to *C*-glycosylation. Our initial effort began with the reaction of 3-ethoxycarbonyloxy-4, 6-para-methoxybenzylidene-D-glucal **71** and pyridine-2-carboxaldehyde **39** in presence of the previous reactive catalyst $Pd(PPh_3)_4$, 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide **41** and triethylamine in the solution of DCM under 50 ^oC (entry 1, Table 4.3). However, no new compound was observed after prolonged stirring time. It was observed that when DPPB was added as ligand, the desired *C*-glycoside was obtained in 20% yield (entry 2, Table 4.3). Unlike the dual catalysis of allyl acetate, the structure of the product **72** indicated that only one molecule of aldehyde was added to the glycal moiety, which further confirmed that the dual catalysis of allyl acetate underwent a stepwise addition. On top of that, to the best of our knowledge, this is the first report to directly synthesize a C1, C2 unsaturated, C3 deoxy *C*-glycoside. On the other hand, due to the formation of the nucleophilic ethanol by decarboxylation, the ethoxyl-*O*-glycoside **73** was also isolated in a comparable yield. Control reactions by solely using NHC or Pd catalyst were conducted and no desired product was identified (entry 3-4, Table 4.3). Starting from this result, we proceeded to screen the commonly used palladium catalysts and ligands. The results revealed that Pd(II) sources like $Pd(OAc)_2$ (entry 5, Table 4.3) and $Pd(TFA)_2$ (entry 6, Table 4.3) were not successful in catalyzing this reaction, comparing to Pd(II) catalyst, Pd(0) catalysts such as $Pd(PPh_3)_4$, $Pd(dba)_2$ (entry 9, Table 4.3) and $Pd_2(dba)_3$.

Table 4.3. Screening of Pd catalysts and ligands[a], [b]

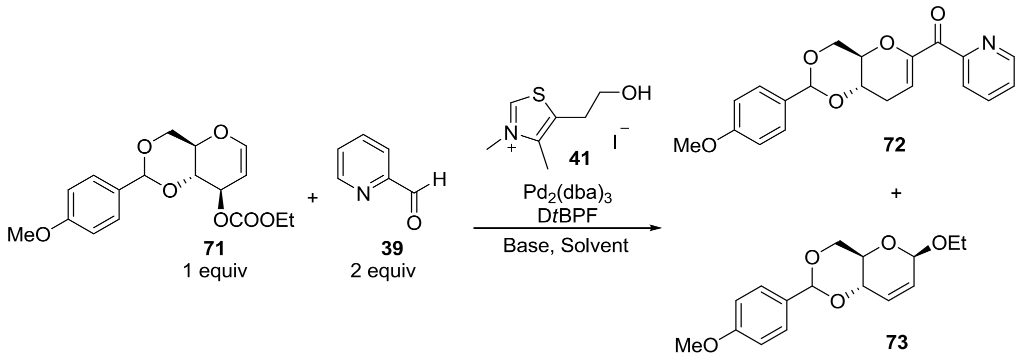


Entry	Pd Source	Ligand	Yield **72** (**73**) (%)
1	$Pd(PPh_3)_4$	-	0
2	$Pd(PPh_3)_4$	DPPB	20 (22)
3	-	-	0 (0)
4[c]	$Pd(PPh_3)_4$	DPPB	0 (60)
5	$Pd(OAc)_2$	DPPB	trace (25)
6	$Pd(TFA)_2$	DPPB	0 (<5)
7	$Pd(PPh_3)_4$	D*i*PPF	35 (50)
8	$Pd_2(dba)_3$	D*i*PPF	45 (38)
9	$Pd(dba)_2$	D*i*PPF	24 (45)
10	$Pd_2(dba)_3$	D*t*BPF	57 (23)

[a] Unless otherwise specified, reactions were carried out with 2 equivalents of aldehyde **39**, 1 equivalent of base, 10 mol% Pd catalyst, 15 mol% Ligand, 20 mol% NHC. [b] Isolated yields. [c] No NHC catalyst added

(entry 8, Table 4.3) generally gave better results and among them, $Pd_2(dba)_3$ provided the desired *C*-glycoside in highest yield. With regards to ligands, two ligands were reported for decarboxylative reactions on glycals, namely D*i*PPF (entry 7-9, Table 4.3) and D*t*BPF (entry 10, Table 4.3) and they were tested in this case. Both ligands gave the higher yield of proudct **72** than DPPB and D*t*BPF was found to be the optimal ligand.

Table 4.4. Screening of solvents, bases and temperatures



Entry	Base	Solvent	Temp. (^{o}C)	Yield **72**[**73**] (%)
1	Et_3N	Toluene	80	71 (10)
2	DBU	Toluene	80	85 (<5)
3	Cs_2CO_3	Toluene	80	40 (15)
4	K_2CO_3	Toluene	80	62 (12)
5	DBU	Toluene	70	72 (10)

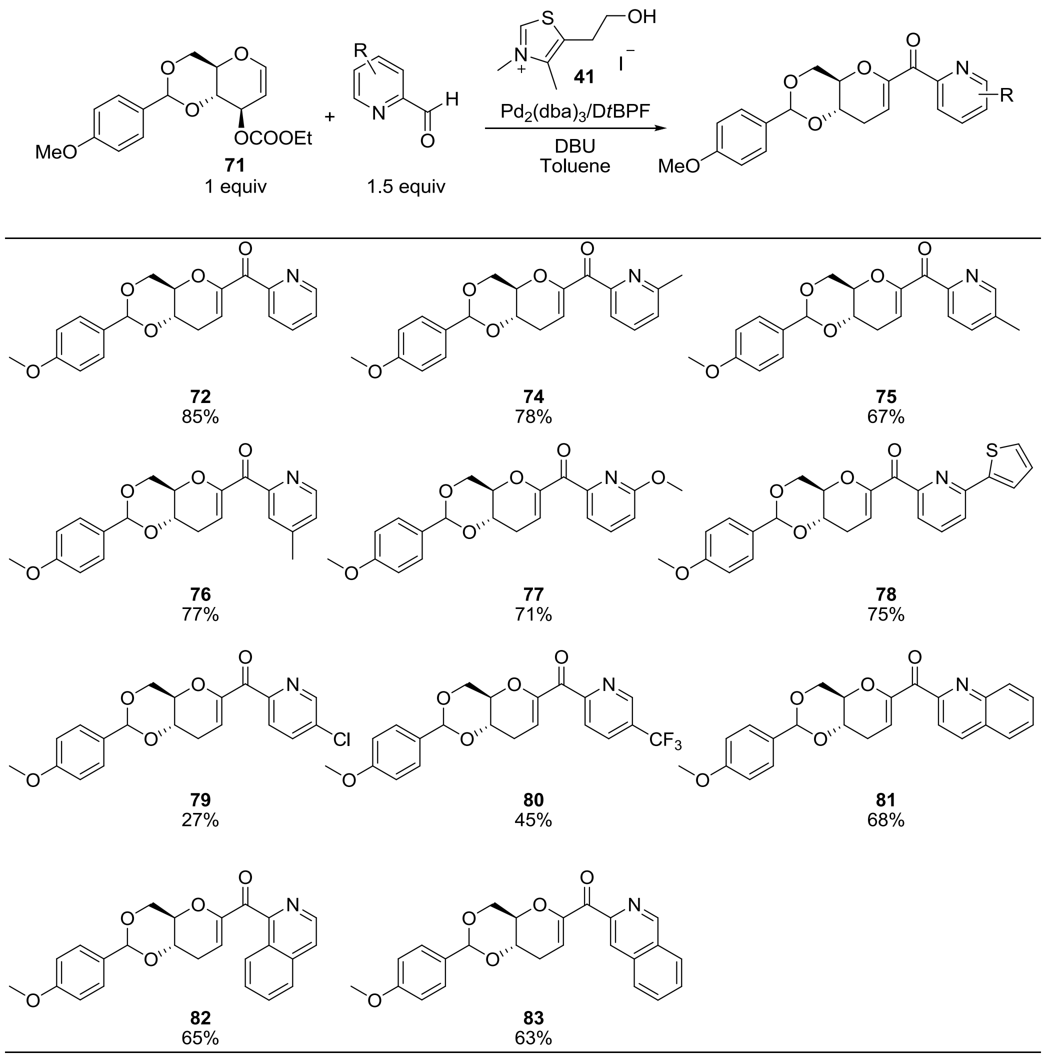
[a] Unless otherwise specified, reactions were carried out with 1.5 equivalents of aldehyde **39**, 1 equivalent of base, 10 mol% Pd catalyst, 15 mol% ligand, 20 mol% NHC. [b] Isolated yields.

Due to the fact that the allylic activation on glycal generally required more energy than the activation on simple allylic system, the solvent was changed to toluene and the reaction temperature was increased to 80 ^{o}C. To our delight, the yield of the desired product **72** was enhanced to 71% and the yield of the byproduct **73** was reduced to 10% (entry 1, Table 4.4). This observation was justified by the evaporation of the ethanol to the nitrogen balloon under higher temperature. Then, the commonly used bases to activate the NHC catalyst were screened. Among some organic and inorganic base (entry 2-4, Table 4.4), it was found that DBU (entry 5, Table 4.4) was the best base for this coupling reaction.

4.3.2 Substrate Scope

After identifying the optimal reaction conditions, we first went on to study the substrate scope of the (*o*-azaaryl)carboxaldehyde. Similar to the results of the previous dual catalysis reaction, only pyridine **72**, quinoline **81** or isoquinoline carboxaldehyde **82**, **83** gave the desired *C*-glycosides, other (*o*-azaaryl)carboxaldehyde containing pyrimidine, imidazole and pyrrole failed to give any desired products. Next, a range of pyridine-2-carboxaldehydes with methyl group on different positions were tested under standard conditions. The results showed that except 3-methyl-pyridine-2-carboxaldehyde, 4-, 5- and 6-methyl pyridine-2-carboxaldehydes all afforded the corresponding products in satisfactory yields (**74**, **75**, **76**). Besides methyl groups, other substituents with different electro properties were also examined. Pyridine-2-carboxaldehyde with electron-donating group such as methoxyl **77** and thiophenyl **78** generally provided the products in good yields. On the contrary, pyridine-2-carboxaldehyde with strong electron-withdrawing groups such as chloro **79** and trifluoromethyl **80** only afforded the desired products in poor to moderate yields. The structure of *C*-glycoside **72** was confirmed by X-ray crystallography (**Figure 4.17**).

Scheme 4.8. Substrate scope of aldehydes[a], [b]



[a] Reactions were carried out with 1.5 equivalent aldehyde, 1 equivalent DBU, 5 mol% $Pd_2(dba)_3$ catalyst, 15 mol% D*t*BPF, 20 mol% NHC. [b] Isolated yields.

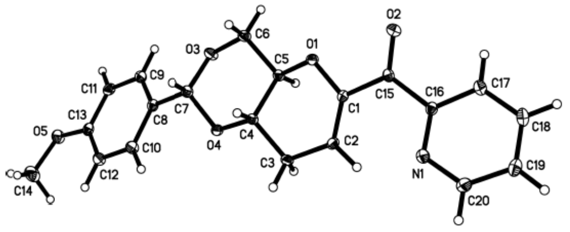
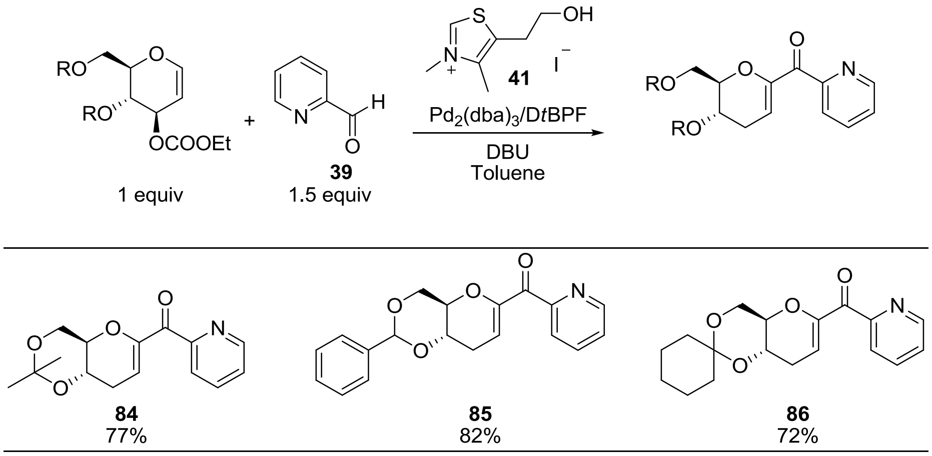


Figure 4.17. Crystal structure of **72**

As for the glycals, several 3-ethoxycarbonloxy D-glucals with different 4. 6-protecting groups were tested with pyridine-2-carboxaldehyde under standard conditions. The results showed that the acetal protecting groups such as isopropylidene **84**, benzylidene **85** and cyclohexylidene **86** provided the corresponding *C*-glycosides in good to excellent yields. Other glycals protected with commonly used protecting groups such as acetyl, *tert*-butyldimethylsilyl and benzyl groups failed to provide the desired product.

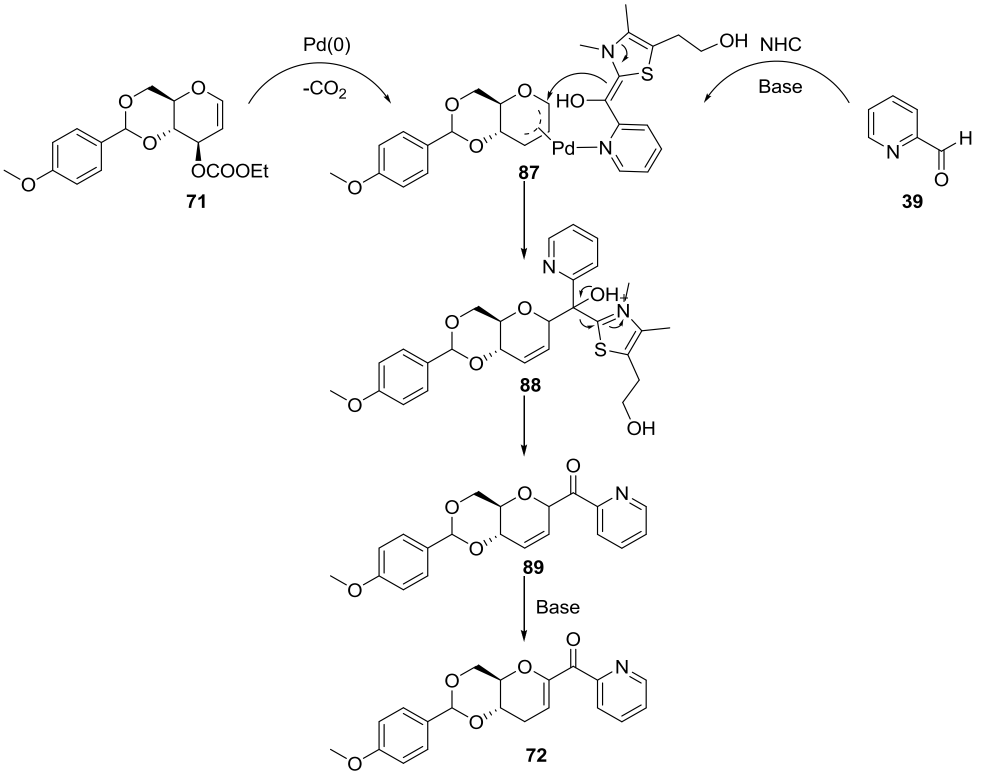
Scheme 4.9. Substrate scope of glycals[a], [b]



[a] reactions were carried out with 1.5 equivalent aldehyde **39**, 1 equivalent DBU, 5 mol% $Pd_2(dba)_3$, 15 mol% D*t*BPF, 20 mol% NHC. [b] isolated yields .

4.3.3 Plausible Mechanism

Scheme 4.10. Plausible mechanism

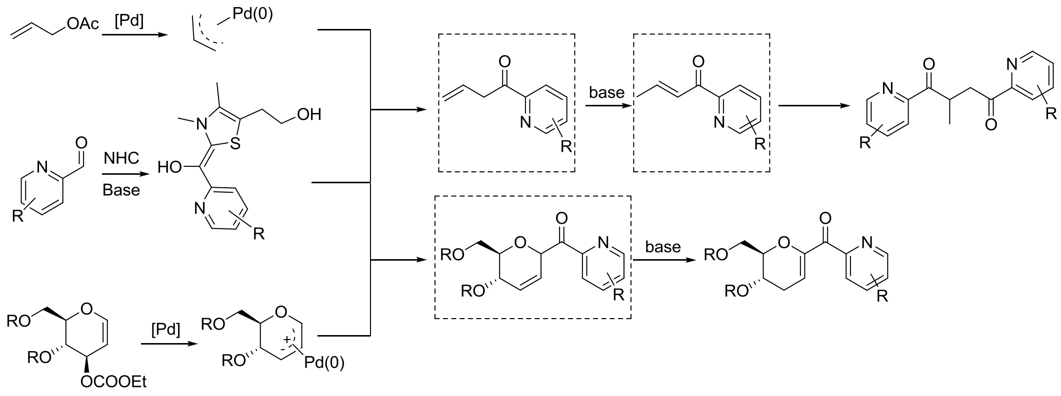


The plausible mechanism was proposed in **Scheme 4.10**. Similar to the allyl acetate and *o*-azaaryl carboxaldehyde dual catalysis, the dual activation first took place to afford the nucleophilic Breslow intermediate and electrophilic π-allyl Pd complex **87**. Then, the N-Pd coordination reduced the distance between the two intermediates to a suitable proximity for the nucleophilic addition. The subsequent nucleophilic addition generated *C*-glycoside as intermediate **88**. Final product **72** was transformed from compound **89** *via* proton transfer under basic conditions.

Unlike the previous report, the second 1,4-addition did not occur for two reasons. This first is that the glycal moiety is more steric hindered than the linear allyl acetate which makes it more difficult to accommodate another bulky Breslow intermediate. The second reason is that as stated in Chapter 1, the C2 position of glycal is more electron rich and thus the 1,4-conjugated system of the product is not a very good electrophile.

4.4 Conclusion

In conclusion, a novel dual catalysis system of palladium and N-heterocyclic carbene has been developed. The nucleophilic addition took place between the electrophilic Pd-allylic system and the nucleophilic Breslow intermediate. This catalysis system has been applied on simple allyl acetate as well as glycals. The application on *C*-glycosylation widens the scope of reacting glycosylation partners and opens up possibilities for future glycosylation.

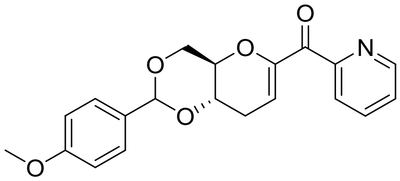


4.5 Experimental Section

General: All the reactions were carried out in a flame or oven dried glassware with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 400 MHz Bruker AVIII 400. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^1H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

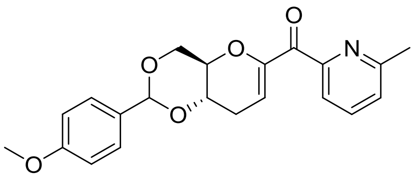
Material: All the palladium catalysts and phosphine ligands were purchased from commercial suppliers without any further purification. All the anhydrous solvent was purchase from commercial suppliers for direct use. Heterocyclic aldehydes for products **72**, **74**, **75**, **76**, **77**, **78**, **79**, **80**, **81** was purchased from commercial suppliers for direct use. Aldehydes for products **82**[27] and **83**[28] was synthesized by the reported synthetic methods. The glycal starting materials glycals were synthesized by their respective reported methods.[29]

General procedure of Pd-NHC dual catalysis of *C*-glycosylation of glycals and 2-pyridine carboxaldehyde: synthesis of ((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)(pyridin-2-yl)methanone (72): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 2-pyridinecarboxaldehyde **39** (28 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography (EtOAc/Hexane = 1/2) to afford the product as a yellow solid. (63 mg, 90%)



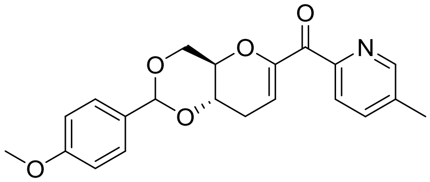
((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(pyridin-2-yl)methanone (72): This compound was prepared following the general procedure by the eluent EtOAc/Hexane = 1/2 as a yellow solid. (63 mg, 90%) mp 171–173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.51–2.59 (qd, J = 2.9, 9.6 Hz, 1H), 2.64–2.71 (dt, J = 5.8, 18.7 Hz, 1H), 3.80 (s, 3H), 3.92–

3.97 (m, 2H), 3.99–4.04 (m, 1H), 4.53–4.61 (m, 1H), 5.61 (s, 1H), 6.52–6.54 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.89–6.91 (d, *J* = 8.7 Hz, 2H), 7.42–7.47 (m, 3H), 7.82–7.88 (m, 2H), 8.65–8.66 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 27.9, 55.3, 68.8, 70.4, 73.8, 101.7, 113.8, 117.9, 124.5, 126.2, 127.5, 129.7, 137.1, 148.3, 149.5, 154.7, 160.2, 186.9; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 53.5 (*c* 2.20, CHCl$_3$); HRMS (ESI) calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$: 354.1341, found 354.1336.



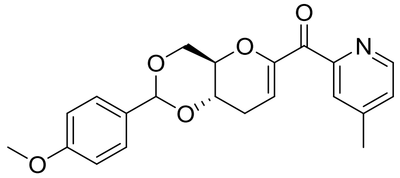
((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(6-methylpyridin-2-yl)methanone (74): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), Pd$_2$(dba)$_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 6-methyl-pyridine-2-carboxaldehyde (36 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH$_4$Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a brown solid. (61 mg, 83%) mp 182–184°C. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.50–2.58 (qd, *J* = 2.9, 9.5 Hz, 1H), 2.62

(s, 3H), 2.64–2.70 (m, 1H), 3.80 (s, 3H), 3.92–3.95 (m, 2H), 3.97–4.02 (m, 1H), 4.56–4.59 (m, 1H), 5.61 (s, 1H), 6.54–6.56 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.88–6.91 (d, *J* = 8.7 Hz, 2H), 7.28–7.30 (d, *J* = 7.6 Hz, 1H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.68–7.72 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.5, 28.0, 55.3, 68.9, 70.3, 73.8, 101.7, 113.7, 118.0, 121.5, 125.8, 127.5, 129.7, 137.1, 149.5, 154.3, 157.5, 160.2, 187.1; $[\alpha]^{20}_{D}$ = 53.7 (*c* 2.60, CHCl$_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ [M+H]$^+$: 368.1498, found 368.1498

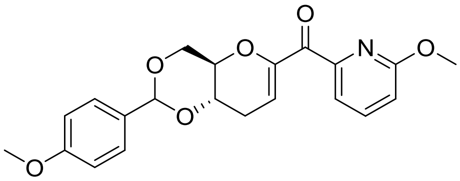


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(5-methylpyridin-2-yl)methanone (75): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), Pd$_2$(dba)$_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 5-methyl-pyridine-2-carboxaldehyde (36 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH$_4$Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a yellow solid. (57 mg, 78%) mp 160–

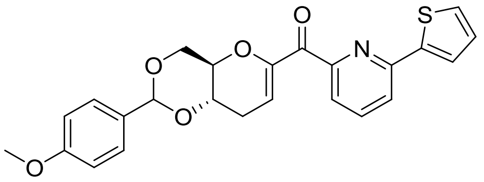
163 °C.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.51–2.58 (qd, J = 2.9, 9.6 Hz, 1H), 2.63–2.71 (dt, J = 5.9, 18.7 Hz, 1H), 3.80 (s, 3H), 3.92–3.94 (m, 2H), 3.98–4.04 (m, 1H), 4.55–4.58 (m, 1H), 5.61 (s, 1H), 6.53–6.55 (dd, J = 2.9, 5.7 Hz, 1H), 6.88–6.91 (m, 2H), 7.42–7.45 (m, 2H), 7.61–7.64 (m, 1H), 7.79–7.81 (d, J = 8.0 Hz, 1H), 8.47–8.47 (dd, J = 0.6, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 27.9, 55.3, 68.9, 70.4, 73.8, 101.7, 113.7, 117.3, 124.3, 127.5, 129.7, 136.6, 137.4, 148.8, 149.6, 152.1, 160.2, 186.8; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 58.1 (*c* 2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$: 368.1498, found 368.1501.



((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(4-methylpyridin-2-yl)methanone (76): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 4-methyl-pyridine-2-carboxaldehyde (36 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a yellow solid (60 mg, 82%). mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 2.51–2.59 (qd, J = 2.9, 9.6 Hz, 1H), 2.63–2.71 (dt, J = 5.8, 18.7 Hz, 1H), 3.80 (s, 3H), 3.89–3.96 (m, 2H), 3.98–4.04 (m, 1H), 4.54–4.59 (m, 1H), 5.61 (s, 1H), 6.51–6.53 (dd, J = 3.0, 5.6 Hz, 1H), 6.88–6.91 (m, 2H), 7.25–7.25 (d, J = 0.8 Hz, 2H), 7.42–7.45 (m, 1H), 7.68 (s, 1H), 8.49–8.50 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 27.9, 55.3, 68.8, 70.4, 73.8, 101.7, 113.7, 117.8, 125.3, 127.0, 127.5, 129.7, 148.1, 148.6, 149.5, 154.6, 160.2, 187.3; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 58.3 (c 2.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$: 368.1498, found 368.1497.

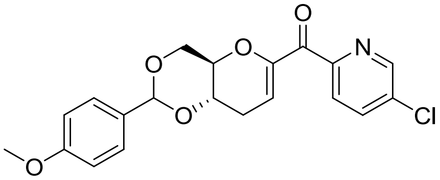


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(6-methoxypyridin-2-yl)methanone (77): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 6-methoxy-pyridine-2-carboxaldehyde (41 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a pale yellow solid (55 mg, 71%). mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50–2.57 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.62–2.70 (dt, *J* = 5.9, 18.6Hz, 1H), 3.81 (s, 3H), 3.91–3.95 (m, 2H), 3.97 (s, 3H), 4.00–4.04 (m, 1H), 4.56–4.59 (m, 1H), 5.62 (s, 1H), 6.61–6.63 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.89–6.92 (d, *J* = 8.8 Hz, 2H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.47–7.49 (d, *J* =7.4 Hz, 1H), 7.67–7.71 (dd, *J* = 7.4, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 53.6, 55.3, 68.9, 70.4, 73.9, 77.2, 101.7, 113.8, 114.2, 116.1, 117.7, 127.5, 129.8, 139.1, 149.8, 151.9, 160.3, 162.8, 186.5; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 28.8 (*c* 1.50, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 384.1447, found 384.1441.

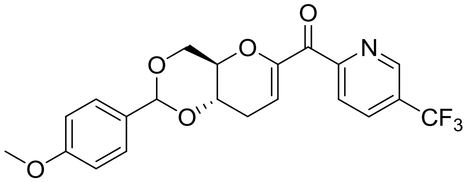


((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(6-(thiophen-2-yl)pyridin-2-yl)methanone (78): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 6-thiophenyl-pyridine-2-carboxaldehyde (57 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated

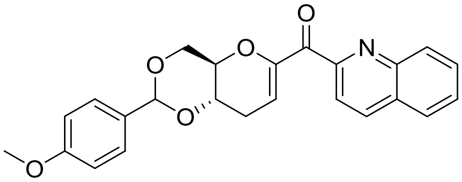
NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a bright yellow solid (74 mg, 85%). mp 171–172°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54–2.61 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.66–2.73 (dt, *J* = 5.9, 18.7 Hz, 1H), 3.81 (s, 3H), 3.95–3.97 (m, 2H), 3.99–4.05 (m, 1H), 4.56–4.63 (m, 1H), 5.63 (s, 1H), 5.91–5.93 (dd, *J* = 3.0, 5.6 Hz, 1H), 6.71–6.73 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.90–6.92 (d, *J* = 8.7, 2H), 7.42–7.44 (m,3H), 7.68–7.69 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.75–7.77 (d, *J* = 7.4 Hz, 1H), 7.82–7.86 (m, 1H), 7.94–7.94 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 55.3, 68.9, 70.4, 73.9, 101.7, 113.8, 117.5, 122.3, 122.4, 124.3, 126.2, 126.7, 127.5, 129.8, 137.7, 141.5, 149.6, 152.2, 154.4, 160.3, 186.8; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 44.0 (*c* 2.50, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5S$ $[M+H]^+$: 436.1219, found 436.1216



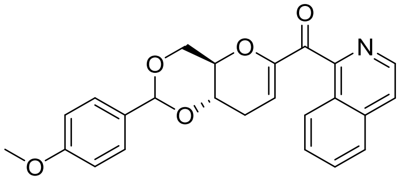
(5-chloropyridin-2-yl)((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)methanone (79): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 6-chloro-pyridine-2-carboxaldehyde (42 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with eluent EtOAc/Hexane = 1/2 to as a white solid (25 mg, 32%). mp 200–201 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 2.52–2.59 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.65–2.73 (dt, *J* = 5.9, 18.7 Hz, 1H), 3.81 (s, 3H), 3.92–3.95 (m, 2H), 3.98–4.02 (m, 1H), 4.55–4.58 (m, 1H), 5.62 (s, 1H), 6.55–6.57 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.92–6.92 (d, *J* = 2.9 Hz, 2H), 7.43–7.45 (d, *J* = 8.7, Hz, 2H), 7.80–7.83 (dd, *J* = 2.3, 8.4 Hz, 1H), 7.86–7.89 (d, *J* = 8.4 Hz, 1H), 8.60–8.61 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 55.3, 68.8, 70.5, 73.7, 101.7, 113.8, 117.7, 125.5, 127.5, 129.7, 135.2, 136.9, 147.3, 149.3, 152.4, 160.3, 186.8; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 16.1 (*c* 0.90, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{19}NO_5Cl$ $[M+H]^+$: 388.0952, found 388.0955.



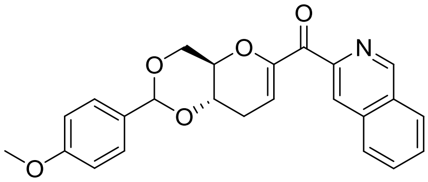
((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(5-(trifluoromethyl)pyridin-2-yl)methanone (80): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 5-trifluoromethyl-pyridine-2-carboxaldehyde (53 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a white solid (38 mg, 45%). mp 195–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52–2.60 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.66–2.74 (dt, *J* = 5.8, 18.9 Hz, 1H), 3.81 (s, 3H), 3.90–3.96 (m, 2H), 3.97–4.05 (m, 1H), 4.56–4.61 (m, 1H), 5.62 (s, 1H), 6.53–6.56 (dd, *J* = 3.0, 5.7 Hz, 1H), 6.89–6.92 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.45–7.45 (d, *J* = 1.8, Hz, 2H), 7.98–8.00 (d, *J* = 8.2 Hz, 1H), 8.08–8.11 (dd, *J* = 1.8, 8.2 Hz, 1H), 8.91–8.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 55.3, 68.8, 70.6, 73.6, 101.8, 113.8, 118.4, 124.2, 127.5, 129.6, 134.4, 134.4, 145.3, 145.3, 149.3, 160.3, 185.6; $[\alpha]_D^{20}$ = 28.8 (*c* 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 384.1447, found 384.1441.



((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]-dioxin-6-yl)(quinolin-2-yl)methanone (81): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then 2-quinolinecarboxaldehyde (47 mg, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a brown solid (59 mg, 73%). mp 162–164°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55–2.63 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.64–2.71 (dt, *J* = 5.9, 18.6Hz, 1H), 3.81 (s, 3H), 3.95–4.07 (m, 3H), 4.58–4.64 (m, 1H), 5.64 (s, 1H), 6.76–6.78 (dd, *J* = 2.9, 5.6 Hz, 1H), 6.89–6.93 (m, 2H), 7.44–7.47 (m, 2H), 7.63–7.67 (ddd, *J* = 1.1, 7.0, 8.1 Hz, 1H), 7.78–7.82 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1H), 7.87–7.89 (d, *J* = 8.2 Hz, 1H), 7.92–7.95 (d, *J* = 8.5 Hz, 1H), 8.18–8.20 (d, *J* = 8.6 Hz, 1H), 8.28–8.30 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1, 55.3, 68.9, 70.5, 73.8, 101.8, 113.8, 118.6, 120.7, 127.5, 127.7, 128.4, 128.9, 129.8, 130.3, 137.1, 146.6, 149.5, 154.3, 160.3, 187.1; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 49.2(*c* 1.60, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1493

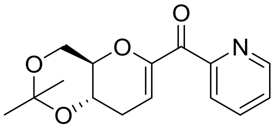


isoquinolin-1-yl((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro-pyrano-[3,2-d][1,3]dioxin-6-yl)methanone (82): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then isoquinoline-1-pyridinecarboxaldehyde (47 μL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a yellow solid (56 mg, 70%). mp 197–200°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46–2.33 (qd, *J* = 2.9, 9.4 Hz, 1H), 2.57–2.65 (dt, *J* = 5.8, 18.8Hz, 1H), 3.80 (s, 3H), 3.94–4.05 (m, 3H), 4.58–4.65 (m, 1H), 5.62(s, 1H), 5.91–5.93 (dd, *J* = 3.0, 5.6 Hz, 1H), 6.88–6.92 (m, 2H), 7.43–7.45 (d, *J* = 8.7 Hz, 2H), 7.62–7.66 (ddd, *J* = 1.2, 5.9, 8.2 Hz, 1H), 7.72–7.78 (m, 2H), 7.88–7.90 (d, *J* = 8.2 Hz, 1H), 8.10–8.12 (d, *J* = 8.4 Hz, 1H), 8.54–8.56 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 55.3, 68.8, 70.6, 73.7, 101.8, 113.8, 118.3, 122.7, 125.9, 126.2, 127.1, 127.5, 128.4, 129.7, 130.8, 136.6, 141.0, 150.6, 155.6, 160.3, 188.7; $[\boldsymbol{\alpha}]^{\mathbf{20}}_{\mathbf{D}}$ = 35.9 (*c* 1.20, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1491

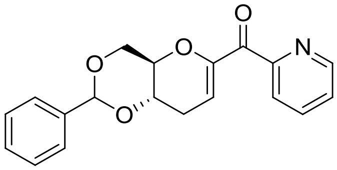


isoquinolin-3-yl((4aR,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro-pyrano-[3,2-d][1,3]dioxin-6-yl)methanone (83): To a round bottom flask containing the solution of **71** (67 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then isoquinoline-3-pyridinecarboxaldehyde (47 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/2 as a yellow solid (55 mg, 68%). mp 171–172°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55–2.62 (qd, *J* = 2.9, 9.6 Hz, 1H), 2.66–2.74 (dt, *J* = 5.8, 18.6 Hz, 1H), 3.81 (s, 3H), 3.94–3.99 (m, 2H), 4.01–4.08 (m, 1H), 4.56–4.63 (m, 1H), 5.63 (s, 1H), 6.58–6.60(dd, *J* = 2.9, 5.6 Hz, 1H), 6.90–6.92 (dd, *J* =2.0, 6.8, 2H), 7.44–7.46 (dd, *J* = 1.9, 6.8, 2H), 7.72–7.81 (m, 2H), 7.96–7.98 (d, *J* = 8.0 Hz, 1H), 8.05–8.07 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 55.3, 68.9, 70.5, 73.9, 101.7, 113.8, 117.0, 123.2, 127.5, 127.6, 128.1, 129.5, 129.7, 131.2, 135.6, 148.4, 150.0, 160.2, 187.2, 126.7, 127.5, 129.8, 137.7, 141.5, 149.6, 152.2, 154.4, 160.3, 186.8; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 53.4 (*c*

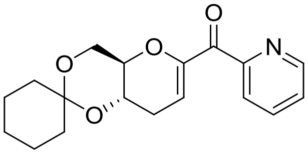
2.00, $CHCl_3$); HRMS (ESI) calcd for $C_{24}H_{22}NO_5$ $[M+H]^+$: 404.1498, found 404.1500



((4aR,8aS)-2,2-dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-(pyridin-2-yl)methanone (84): To a round bottom flask containing the solution of 3-ethoxycarbonyloxy-4, 6-isopropylidene-D-glucal (52 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then pyridine-2-carboxaldehyde **39** (28 μL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/5 as a white solid (45 mg, 82%). mp 84–86 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44 （s, 3H), 1.55 (s, 3H), 2.35–2.43 (qd, J = 2.9, 9.8 Hz, 1H), 2.48–2.56 (dt, J = 5.8, 18.5Hz, 1H), 3.74–3.80 (m, 1H), 3.95–4.00(t, J = 10.8 Hz, 1H), 4.02–4.09 (m, 1H), 4.15–4.19 (dd, J = 5.5, 11.0 Hz, 1H), 6.46–6.48 (q, J = 2.9 Hz, 1H), 7.42–7.46 (ddd, J = 2.0, 4.8, 6.9 Hz, 1H), 7.81–7.87 (m, 2H), 8.63–8.65(m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 28.4, 29.1, 62.1, 66.3, 71.5, 99.7, 118.0, 124.5, 126.1, 137.1, 148.3, 149.5, 154.7, 187.0; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ = 62.8 (*c* 1.50, CHCl$_3$); HRMS (ESI) calcd for $C_{15}H_{18}NO_4$ $[M+H]^+$: 276.1236, found 276.1233



((4aR,8aS)-2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-(pyridin-2-yl)methanone (85): To a round bottom flask containing the solution of 3-ethoxycarbonyloxy-4, 6-benzylidene-D-glucal (61 mg, 0.2 mmol), Pd$_2$(dba)$_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butylphosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then pyridine-2-carboxaldehyde **39** (28 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH$_4$Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/3 as a white solid (56 mg, 87%). mp 140–141°C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.53–2.61 (qd, *J* = 2.9, 12.6 Hz, 1H), 2.62–2.70 (dt, *J* = 5.9, 18.6Hz, 1H), 3.92–3.99 (m, 2H), 3.99–4.07 (m, 1H), 4.57–4.62 (m, 1H), 5.66 (s, 1H), 6.54–6.56 (dd, *J* = 2.9, 5.7 Hz, 1H), 7.35–7.41 (m, 3H), 7.43–7.47 (m, 1H), 7.50–7.53 (m, 2H), 7.82–7.89 (m, 2H), 8.64–8.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 27.9, 68.9, 70.4, 73.9, 77.2, 101.8, 117.8, 124.5, 126.2, 128.4, 129.2, 148.3, 149.5, 154.7, 186.9; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ = 90.9 (*c* 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{22}NO_6$ $[M+H]^+$: 324.1236, found 324.1227.



pyridin-2-yl((4a'R,8a'S)-4',4a',8',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano-[3,2-d][1,3]dioxine]-6'-yl)methanone (86): To a round bottom flask containing the solution of 3-ethoxycarbonyloxy-4, 6-cyclohexylidene-D-glucal (62 mg, 0.2 mmol), $Pd_2(dba)_3$ (9mg, 0.01mmol), 1,1'Bis(di-*tert*-butyl-phosphino)ferrocene (14 mg, 0.03 mmol) in toluene (2.0 mL), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.4 mmol) was added dropwise. The mixture was stirred at room temperature for 5 minutes. Then pyridine-2-carboxaldehyde **39** (28 µL, 0.3 mmol) was added in a period of 10 minutes. The resulting solution was then heated to 80 °C for 3.5 hours. The mixture was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (10×2 mL) and brine (10×2 mL). The organic layer was removed by evaporation and the crude product was purified by flash column chromatography with the eluent EtOAc/Hexane = 1/4 as a brown oil. (45 mg, 72%) ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41–1.53 (m, 4H), 1.58–1.67 (m, 4H), 1.90–1.93 (m, 1H), 2.04–2.08 (m, 1H), 2.36–2.44 (qd, *J* = 2.8, 9.7 Hz, 1H), 2.49–2.56 (dt, *J* = 5.9, 18.4 Hz, 1H), 3.75–3.82 (m, 1H), 3.95–4.00 (m, 1H), 4.06–4.10 (m, 1H), 4.12–4.18 (m, 1H), 6.45–6.48 (dd, *J* = 2.8, 5.7 Hz, 1H), 7.43–7.46 (m, 1H), 7.81–7.87 (m, 2H), 8.64–8.66 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 22.7, 25.6, 27.8, 28.5, 38.0, 61.4, 65.4, 71.8, 99.8, 118.1, 124.5, 126.1, 137.0, 148.3, 149.5, 154.8, 187.1; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = 21.1 (*c* 1.10, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1549, found 316.1551.

Crystal data

Basic crystal data of Compound **72**

Chemical formula	$C_{20}H_{19}NO_5$	
Formula weight	353.36	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.400 x 0.410 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3058(7) Å	α = 90°
	b = 6.2839(6) Å	β = 97.945(2)°
	c = 18.0298(16) Å	γ = 90°
Volume	819.78(13) $Å^3$	
Z	2	
Density (calculated)	1.432 g/cm^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	372	

4.6 References

1. For reviews, see: (a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659. (b) Wei, Y. Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (c) Martelli, G.; Orena, M.; Rinaldi, S. *Eur. J. Org. Chem.* **2012**, *2012*, 4140. (d) Liu, T-Y.; Xie, M.; Chen, Y-C. *Chem. Soc. Rev.* **2012**, *41*, 4101

2. For reviews, see: (a) Frost, C. G.; Howarth, J.; Williams, J.M.J. *Tetrahedron: Asymmetry*. **1992**, *3*, 1089. (b) Lu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258. (c) Helmchen, G. J. *Organomet. Chem.* **1999**, *576*, 203. (d) Trost, B.M. *Chem. Pharm. Bull.* **2002**, *50*, 1

3. Jellerichs, .B.G.; Kong, J. -R.; Krische, .M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758

4. Ibrahem, I.; Córdova, A. *Angew. Chem.,* **2006**, *118*, 1986; *Angew. Chem., Int. Ed.* **2006**, *45*, 1952

5. Afeweki, S. Ibrahem, I.; Rydfjord, J.; Breistein, P.; Córdova, A. *Chem. Eur. J.* **2012**, *18*, 2972

6. Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336

7. Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354

8. B. M. Trost, X. Luan, *J. Am. Chem. Soc.* **2011**, *133*, 1706

9. RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642.

10. Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890.

11. Zeng, J.; Ma, J.;Xiang, S.; Cai, S.; Liu, X. -W. *Angew. Chem. Int. Ed.,* **2013**, *52*, 5134.

12. (a) Xiang, S.; Lu, Z.; He, J.; Le, M. K.; Zeng, J.; Liu, X. -W. *Chem. Eur. J.* **2010**, *16*, 4533. (b) Xiang, S.; He, J.; Ma, J.; Liu, X. -W. *Chem. Comm.* **2014**, *50*, 4222

13. (a) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (b) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (e) Moore, J.; Rovis, T.; List, B., Ed.; Springer Berlin / Heidelberg: 2009; Vol. 291, p 77. (f) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

14. Nemoto, T.; Fukuda, T.; Hamada, Y.; *Tetrahedron Lett.* **2006**, *47*, 4365

15. Lebeuf, R. l.; Hirano, K.; Glorius, F. *Org. Lett.* **2008**, *10*, 4243.

16. (a) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 2643. (b) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650. (c) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391.

17. Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066.

18. Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *J. Med. Chem.* **2001**, *44*, 3838.

19. Duan, X.-G.; W. Rees, C. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3189.

20. Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7925.

21. Ismail, M. A.; Brun, R.; Easterbrook, J. D.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *J. Med. Chem.* **2003**, *46*, 4761.

22. Ciszek, J. W.; Keane, Z. K.; Cheng, L.; Stewart, M. P.; Yu, L. H.; Natelson, D.; Tour, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3179.

23. Jones, R. A.; Civcir, P. U. *Tetrahedron* **1997**, *53*, 11529.

24. Alan Jones, R.; Karatza, M.; Voro, T. N.; Civeir, P. U.; Franck, A.; Ozturk, O.; Seaman, J. P.; Whitmore, A. P.; Williamson, D. J. *Tetrahedron* **1996**, *52*, 8707.

25. Catherine A, F. *Tetrahedron Lett.* **2010**, *51*, 5621.

26. Ziessel, R.; Nguyen, P.; Douce, L.; Cesario, M.; Estournes, C. *Org. Lett.* **2004**, *6*, 2865.

27. Barrows, R. S.; Lindwall, H. G. *J. Am. Chem. Soc.* **1942**, *64*, 2430.

28. Jones, S. W.; Palmer, C. F.; Paul, J. M.; Tiffin, P. D. *Tetrahedron Lett.* **1999**, *40*, 1211.

29. (a) Ma, J.; Ng, S.; Zeng, J.; Chen, P.; Than, A.; Zhang, J.; Zhao, Y. *Chem. Eur. J.* **2010**, *16*, 4533. (b) Doetz, K. H.; Otto, F.; Nieger, M. *J. Organomet. Chem.* **2001**, *621*, 77.

List of Publications

1) A highly efficient dual catalysis approach for *C*-glycosylation: addition of (*o*-azaazryl)carboxaldehyde to glycals. **Bai, Yaguang**; Leng, Wei Lin; Li, Yongxin; Liu, Xue-Wei. *Chemical Communication*, **2014**, 50, 13391
2) Dual-function Pd/NHC Catalysts: Tandem Allylation-Isomerization-Conjugate Addition that Allows Access to Pyrroles, Thiophenes and Furans. **Bai, Yaguang**; Xiang, Shaohua, Liu, Xue-Wei. *Chemical Communication*, **2014**,*50*, 6168-6170
3) Oxidative Heck Reaction of Glycals and Aryl Hydrazines: A Palladium-Catalyzed *C*-Glycosylation. **Bai, Yaguang**; Hoang, Kim Le Mai; Liao, Hongze; Liu, Xue-Wei. *Journal of Organic Chemistry,* **2013,** *78*, 8821-8825.
4) Palladium Catalyzed Stereoselective C-Glycosylation of Glycals with Enol Triflates. **Bai, Yaguang**; Leow, Minli; Zeng, Jing; Liu, Xue-Wei. *Organic Letters*, **2011**, *13*, 5648
5) Palladium-Catalyzed Direct Cross-Coupling Reaction of Glycals with Activated Alkenes. **Bai, Yaguang**; Zeng, Jing; Cai, Shuting; Liu, Xue-Wei. *Organic Letters*, **2011**. *13*, 4394
6) Quick Access to Drug-like Heterocycles: Facile Silver-Catalyzed One-Pot Multi-component Synthesis of Aminoindolizines. **Bai, Yaguang**; Zeng, Jing; Ma, Jimei; Liu, Xue-Wei. *ACS Combinatorial Science*, **2010**, *12*, 696
7) Exploring the Native Chemical Ligation Concept for Highly Stereospecific Glycosylation Reactions. Hoang, Kim Le Mai; **Bai, Yaguang**; Ge, Xin; Liu, Xue-Wei. *Journal of Organic Chemistry*, **2013**, *78*, 5196

8) Direct Synthesis of Pyrroles *via* a Sliver-Promoted Three-Component Reaction Involving Unusual Imidazole Ring Opening. Zeng, Jing; **Bai, Yaguang**; Cai, Shuting; Liu, Xue-Wei. *Chemical Communications*, **2011**, *47*, 12855