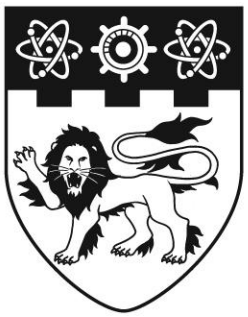

NANYANG TECHNOLOGICAL UNIVERSITY

PART I. PALLADIUM-CATALYSED *C*-GLYCOSYLATIONS
PART II. SYNTHESIS OF INDOLIZINES *VIA* INTRAMOLECULAR C-N BOND FORMATION

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SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

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TABLE OF CONTENTS

ABSTRACT

Allyl moiety can be commonly found in organic compounds. It serves as key intermediate in chemical reactions and can be stabilised by resonance. This thesis focuses on exploiting the allylic functionality in both sugar system and other organic compounds to bring about bond formation efficiently.

In the first chapter, a brief introduction of the various types of allylic systems will be covered. Allylic cation will be the main focus and methods to generate this allylic cation using palladium catalyst as well as reactions of this allylic cation will be discussed. In particular, a specific allylic system, glycal, which can generate π-allyl palladium species, will be highlighted.

In the second chapter, a one-pot synthesis of *C*-vinyl glycosides *via* palladium-catalysed decarboxylative allylation/Wittig reaction is described. The nucleophilic phosphorus ylide attacks π-allyl palladium species generated *in situ*, which can undergo subsequent Wittig reaction upon deprotonation.This methodology can form di- and trisubstituted alkenes in good β-anomeric stereoselectivities. Depending on the aldehydes' coordinating ability, opposing olefin selectivities can be obtained.

In the third chapter, *C*-glycosylation by adopting a dual catalytic system with Ir photocatalyst and Pd catalyst is demonstrated. The π-allyl palladium species generated *in situ* undergoes single electron reduction to form an allylic radical, which then quickly couples with another radical. This methodology showcases the utility of radical-radical coupling to achieve stereoselective α-*C*-glycosides.

In the last chapter, based on our previous understanding of allylic systems, an application to non-sugar system is attempted in the hope of obtaining bioactive *N*-heterocycles, which are commonly found in pharamaceutical products. The activation by electrophilic reagent results in π-allylic cation formation and subsequent cyclisation occurs to furnish multisubstituted indolizines. This methodology can lead to C-N bond formation and the multisubstituted indolizines can be utilised in further structure-activity relationship studies.

INDEX OF ABBREVIATIONS

Δ	chemical shift	Cl_2CH_2 CH_2Cl_2	1,2-dichloroethane
Φ	quantum yield	CH_3CN	acetonitrile
^oC	degree centigrade	C_6H_5CN	benzonitrile
Å	Ångström	cm^{-1}	inverse centimeter
Ac	acetyl	COD	1,5-cyclooctadiene
acac	acetylacetonate	d	doublet
AcOH	acetic acid	dba	dibenzylideneacetone
AIBN	azobisisobutyronitrile	DCC	*N*,*N*'-dicyclohexylcarbodiimide
Ar	aryl	dd	doublet of doublets
BBN	borabicyclo[3.3.1]nonane	ddd	doublet of doublets of doublets
BF_4	tetrafluoroborate	DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Bn	benzyl	dF	3,5-difluoro-2-[5-(trifluoro methyl)-2-pyridinyl]phenyl
Boc	*tert*-butoxycarbonyl	dq	doublet of quartets
bpy	2,2'-bipyridine	dt	doublet of triplets
brs	broad singlet	D*i*PPF	1,1'-bis(di-isopropyl phosphino)ferrocene
Bz	benzoyl	DMA	dimethylacetamide
calcd.	calculated	DMAP	4-(*N*,*N*-dimethylamino) pyridine
cat.	catalytic	DMF	*N*,*N*-dimethylformamide
$CDCl_3$	deuterated chloroform	DMSO	dimethyl sulfoxide
CF_3	trifluoromethyl	DPPB	1,4-bis(diphenylphosphino) butane
CH_2Cl_2	dichloromethane	DPPE	1,4-bis(diphenylphosphino) ethane
$CHCl_3$	chloroform	DPPPent	1,5-bis(diphenylphosphino) pentane

DPPF	1,1’-bis(diphenyl phosphino)ferrocene	M^+	parent ion peak(mass spectrum)
DtBPF	1,1’-bis(di-*tert*-butylphosphino)ferrocene	Me	methyl
dtbbpy	4,4'-bis(*tert*-butyl)-2,2'-bipyridine	MeOH	methanol
ee	enantiomeric excess	mg	milligram
EPR	electron paramagnetic resonance spectroscopy	MHz	megahertz
equiv.	equivalent	min	minute
ESI	electron spray ionisation	mL	milliliter
Et	ethyl	mm	millimeter
Et_2O	diethyl ether	mmol	millimoles
Et_3N	triethylamine	mol	moles
EtOAc	ethyl acetate	MS	mass spectrum
EtOH	ethanol	MS	molecular sieve
Fmoc	fluorenylmethoxycarbonyl	*n*-Bu	*n*-butyl
FTIR	fourier transfer infrared spectroscopy	N	concentration (normality)
g	gram	NMe_2	*N*,*N*-dimethylamino
h	hour (time)	NMO	4-methylmorpholine *N*-oxide
Hex	hexane	NMP	*N*-methyl-2-pyrrolidone
HRMS	high resolution mass spectroscopy	NMQ	*N*-methylquinolinium
Hz	hertz	NMR	nuclear magnetic resonance
IR	infrared	Nu	nucleophile
*i*Pr	isopropyl	OTf	trifluromethanesulfonate
J	coupling constant	*p*	*para*
M	concentration (mol/L)	P	protecting group
m	multiplet	PBN	*N*-*tert*-butyl-α-phenylnitrone

Pd/C	palladium on carbon	t	triplet
PF_6	hexafluorophosphate	TBAI	tetrabutylammonium iodide
Piv	pivaloyl; trimethylacetyl	TBAT	tetrabutylammonium triphenyldifluorosilicate
Ph	phenyl	TBDPS	*tert*-butyldiphenylsilyl
PMB	*p*-methoxybenzyl	TBS	*tert*-butyldimethylsilyl
PMP	*p*-methoxyphenyl	*t*-Bu	*tert*-butyl
ppm	parts per million	TFA	trifluoroacetic acid
ppy	2-phenylpyridine	THF	tetrahydrofuran
pyr	pyridine	TIPS	triisopropylsilyl
q	quartet	TLC	thin layer chromatography
RBF	round bottom flask	TMEDA	tetramethylethylenediamine
rt	room temperature	TMS	trimethylsilyl
s	singlet	v	volume
sat	saturated	XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1:

Allylic Systems in Organic Compounds

1.1 Allylic System: Allylic Cation, Radical and Anion

The allyl moiety is one of the most common functionalities in organic chemistry and it consists of a methylene moiety connected to the vinyl group. It can be classified into three types: allylic cation, radical and anion. The electron delocalisation of these allylic systems can be explained by molecular orbital theory, which provides a rationale for the distribution of electron density and strong resonance stabilisation (**Figure 1.1**). Computational studies have shown that the resonance stabilisation is similar for allylic cation and allylic anion, while that of the allylic radical is much lower, only half of their delocalisation energies as the charge distribution is favourable for the allylic ions.[1]

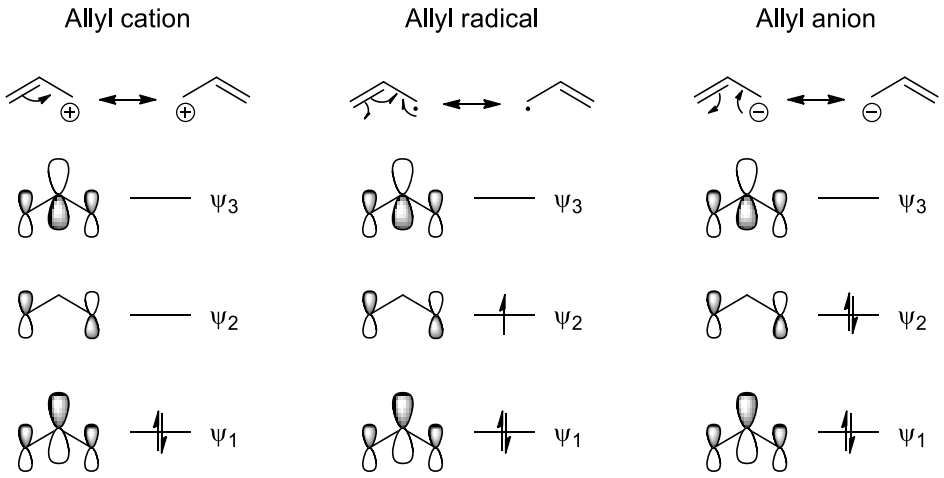


Figure 1.1 Molecular orbital diagrams for allyl cation, allyl radical and allyl anion

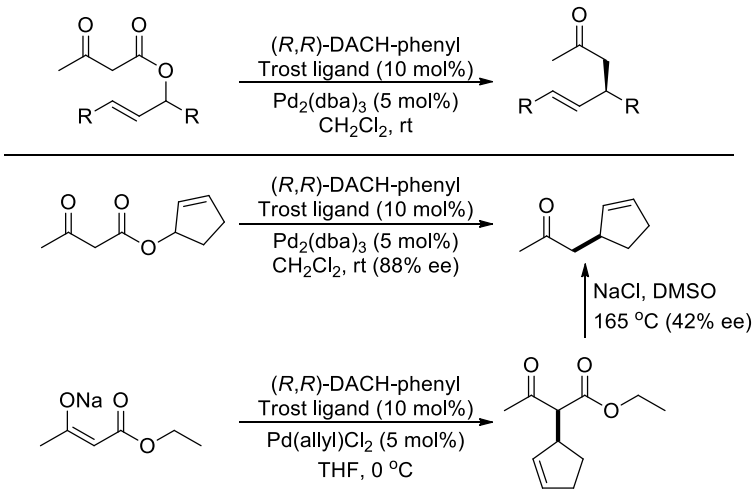
For the purpose of this thesis, discussion would be centered on allyl cation, with some coverage of a specific stabilised allyl radical.

1.2 Pd-Catalysed Allylic Reactions

For Tsuji-Trost allylation, allylic electrophiles are coupled successfully with nucleophiles. The typical reaction proceeds as such: an allylic functionality with a leaving group undergoes reaction with Pd(0) to displace the leaving group and the resultant Pd-allyl system is then attacked by a nucleophile.[2]

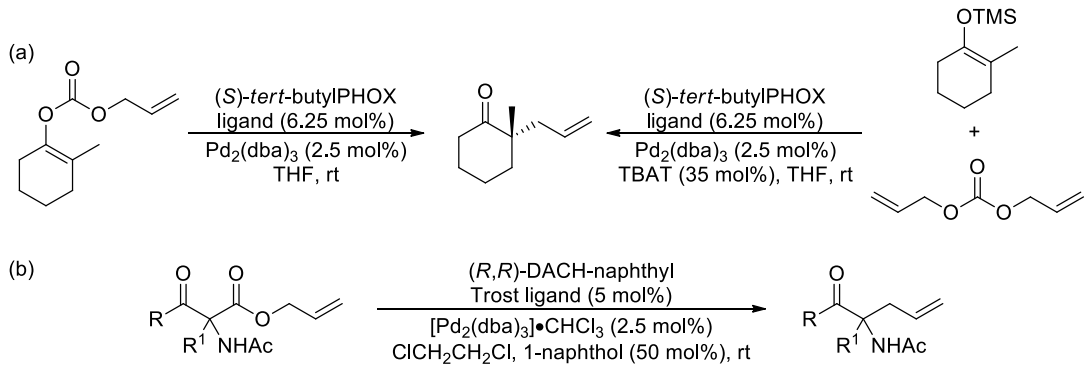
Pioneering work by Trost on asymmetric allylic substitution was reported in 1977.[3] In a seminal work by Tsuji in 1980, a decarboxylative variant of the allylation was demonstrated.[4] This method offers the advantage of starting from low-cost and easily accessible carboxylic acid starting material, enhancing the formation of reactive intermediate at milder conditions. This synthetic methodogy is able to achieve regioselectivity and comparatively easier purification as the byproduct is gaseous CO_2. While many substrates were later being utilised in such reactions since 1980s, the asymmetric decarboxylative allylation was not developed till 2004.[5]

Asymmetric decarboxylative allylation was first accomplished by Tunge and Burger (**Scheme 1.1**).[6] β-keto esters in the presence of a palladium catalyst and Trost's ligand were utilised. Chirality is introduced as the chiral Trost ligand favours the attack on one of the prochiral allyl carbon centers. Notably, when the keto ester functionality was installed on cyclic ring, the increased ring size enhanced the enantioselectivity. The efficiency and stereochemistry enhancement of the decarboxylation allylation reaction are also superior when compared to the sequential allylation/decarboxylation reaction.



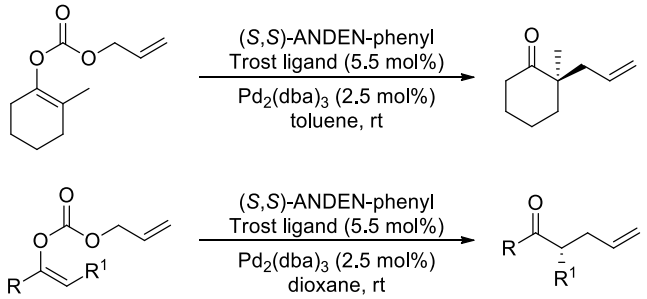
Scheme 1.1 Asymmetric decarboxylative allylation

The synthetic challenge of forming quaternary stereocenter was overcome by Stoltz and Behenna through decarboxylation of allyl enol carbonate by *tert*-butyl-phox ligand (**Scheme 1.2a**).[7] The intermolecular version can be realised by reacting trimethylsilyl enol ether with diallyl carbonate. This was later extended by Murakami using acetamido-*β*-keto carboxylate and Trost's ligand (**Scheme 1.2b**).[8] The use of acyclic *α*-acetamido-*β*-ketoesters was demonstrated and it was proposed that the enantioselectivity might be due to hydrogen bonding with the naphthol additive but there was no further investigation into applications of these acyclic substrates then.



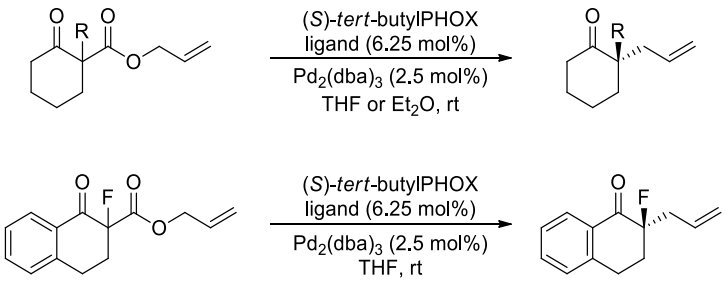
Scheme 1.2 Formation of quaternary stereocenters by decarboxylative allylation

In order to reduce the enolate concentration as well as utilise it at neutral conditions, Trost and Xu used allyl enol carbonate with chiral diphosphine ligand (**Scheme 1.3**).[9] Both cyclic and acyclic substrates could be applied, with high enantioselectivity without multiple alkylations. The reaction efficiency and stereoselectivity depended on the hybridisation of the substituents on enol carbonate, with sp^2 yielding better selectivity as compared to sp^3.[9]



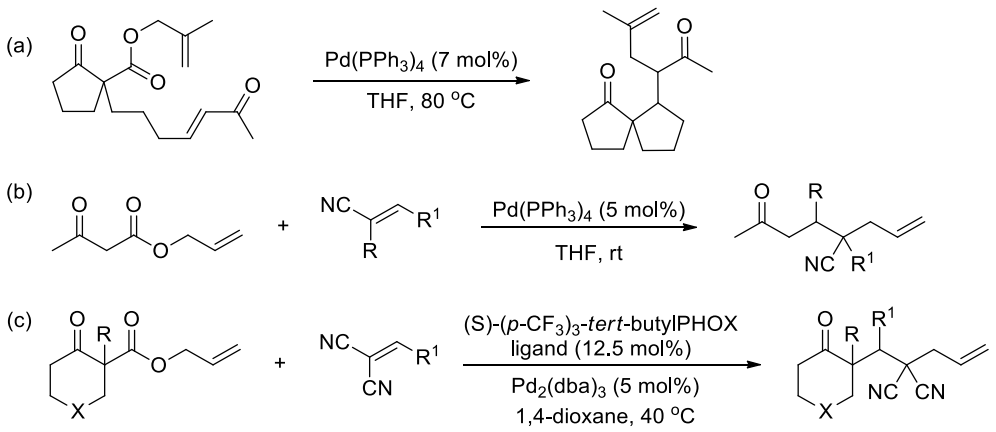
Scheme 1.3 Utilisation of cyclic and acyclic substrates in decarboxylative allylation

Another interesting finding by Stoltz and Nakamura groups allowed the application of racemic *β*-keto carboxylates to undergo decarboxylative allylation, achieving enantioselective quaternary stereocenters (**Scheme 1.4**).[10]



Scheme 1.4 Conversion of racemic substrates to enantioselective quaternary stereocenters

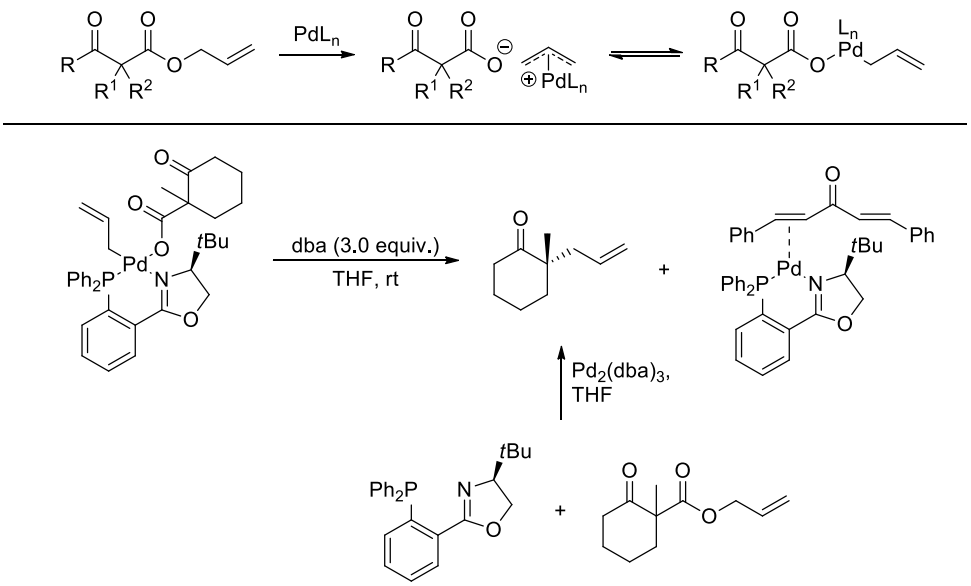
Research work discussed thus far is mostly based on utilising allylic ester containing both the nucleophile and electrophile. In an interesting work pioneered by Tsuji, the concept of interceptive decarboxylative allylation was brought out, whereby the post-decarboxylation intermediate was intercepted by Michael acceptor joined by intramolecular tethering (**Scheme 1.5a**).[11] Yamamoto later developed intermolecular variants of this reaction by utilising sufficiently electrophilic Michael acceptors (**Scheme 1.5b**).[12] However, these early works could only achieve minimal diastereoselectivity. The diastereoselectivity problem of this kind of interceptive decarboxylative allylation was addressed by Stoltz using PHOX-ligated palladium catalyst (**Scheme 1.5c**).[13]



Scheme 1.5 Interceptive decarboxylative allylation

Mechanistically, the first step of decarboxylative allylation occurs by oxidative addition or ionisation of the allyl carbonate or carboxylate, producing π-allyl palladium-carboxylate ion pair which is in equilibrium with σ-allyl palladium-complex (**Scheme 1.6**).[2a] Stoltz proved the formation of this kind of σ-allyl palladium complex for bidentate ligands, which is converted from π-allyl palladium-carboxylate,

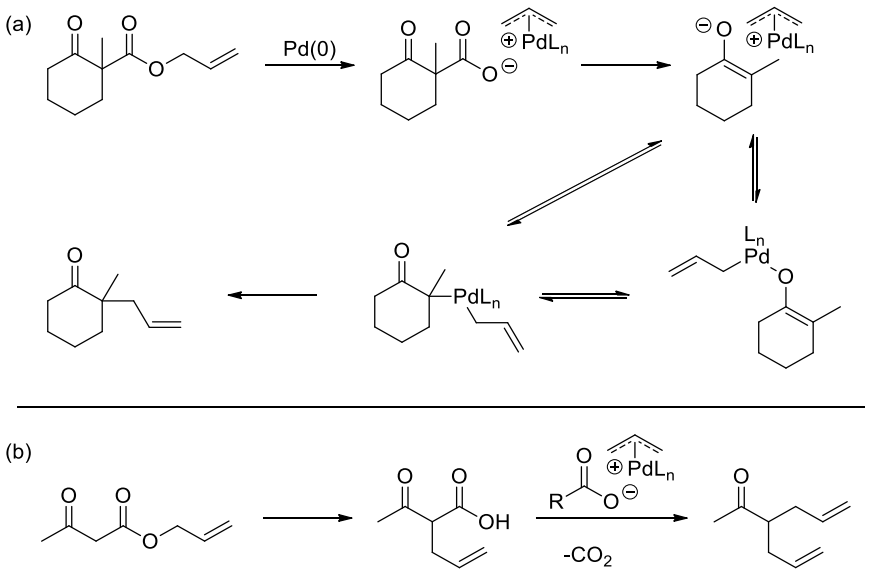
thereby allowing the coordination of carboxylate while preserving the favourable 16e$^-$ square planar geometry.[14]



Scheme 1.6 First step of decarboxylative allylation – oxidative addition or ionisation

The second step is comparatively not so distinguishable in some cases. While *α,α*-disubstituted substrates first undergo decarboxylation then allyation (**Scheme 1.7a**), *α*-hydrogen bearing substrates undergo proton transfer, followed by allylation and subsequent decarboxylation (**Scheme 1.7b**).[4, 15] In the latter case, outer-sphere attack of nucleophile then occurs *via* double-inversion mechanism but inner-sphere reductive elimination does occur to a small extent.[6, 16] However, the mechanism involving vinyl carbonates has hardly been elucidated. The order of decarboxylation and allylation reactions has yet to be confirmed and proven till date although it was mostly accepted that decarboxylation occurs prior to allylation.[9a] Notably, decarboxylation was believed to be the rate-determining elementary step. It was hypothesised that the "softness" of the metal facilitates decarboxylation through

spontaneous formation of palladium-carboxylate ion pair.[17] In the last step, reductive elimination occurs.



Scheme 1.7 (a) Decarboxylation preceding allylation; (b) Allylation preceding decarboxylation

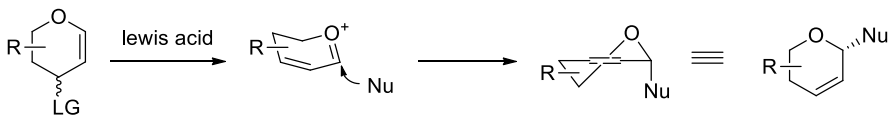
However, the outer-sphere or inner-sphere mechanism for certain substrates still presents some uncertainty despite great efforts to prove it.[6, 9a, 10b, 18] Research efforts today continue to seek the mechanistic explanations of this reaction.

1.3 Glycal as Allylic System

As previously discussed, transition metal-catalysed allylation is widely reported and present many opportunities for functionalisations. This method was later applied to glycosylation, commencing from glycal donor.

The choice of glycal as the glycosyl donor presents advantages over the saturated glycosyl donor as the unsaturated bond readily coordinates with metal, and these transition metal-catalysed reactions are widely reported with excellent selectivities. Moreover, the unsaturated glycosides provide sites for functionalisations, allowing easy access to a variety of sugars in a facile manner (**Scheme 1.8**).[19] Another point highlighted by O'Doherty was the advantage of needing less protecting groups.[20]

Prior to these transition metal-catalysed works, Ferrier reaction was mostly used for glycosylation from glycal donor. It utilises a Lewis acid activator such as $BF_3.OEt_2$ and TMSOTf to activate the leaving group at *C3* position to form the oxocarbenium ion, whereby a nucleophile can then attack.[21] The stereochemical outcome is predominantly α-anomer due to the favourable half-chair conformation formed.[21-22]

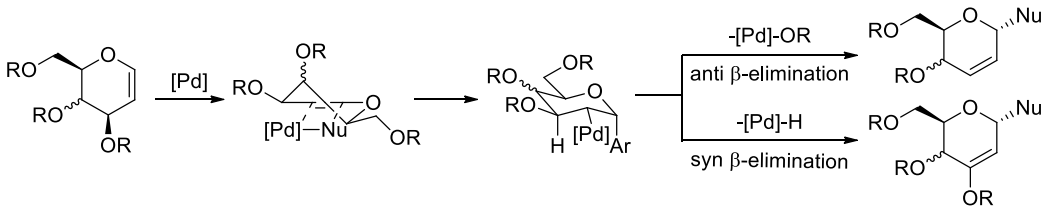


Scheme 1.8 Ferrier reaction yielding α-anomer

Transition metal-catalysed reactions were later applied to glycal scaffold.[23] Although the harsh heating conditions required in transition metal-catalysed reactions

might cause sugar decomposition, the usage of these catalysts offer the advantage of reducing the amount of waste generated as the activator loading is brought down from stoichiometric amounts, as in the case of Ferrier reaction, to catalytic amount. Furthermore, they allow stereocontrol through coordination of metal complex with double bond, offering potential for the *β*-anomer to be obtained. Five other common transition metal-catalysed cross-coupling reactions: Heck, Negishi, Suzuki, Stille and Tsuji-Trost reactions will be covered here, with main focus on Tsuji-Trost reaction.[24]

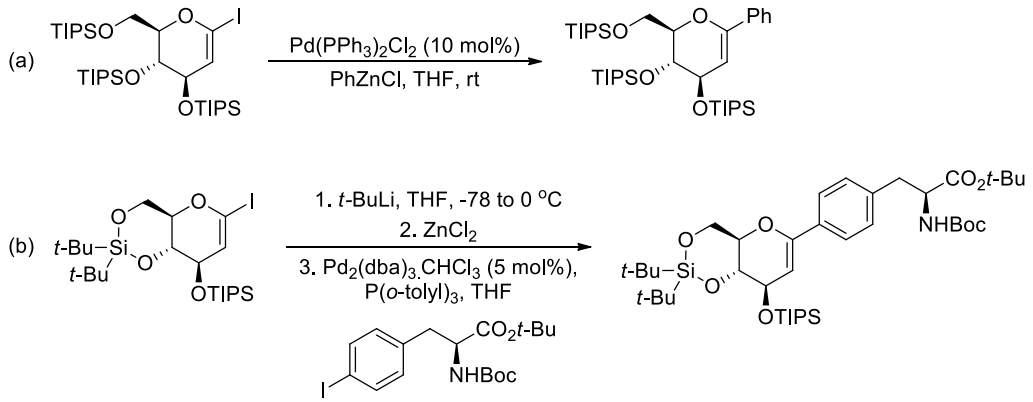
Heck type coupling is able to provide access to *C*-glycosides. The palladium complex adds across the double bond in *syn* manner, followed by *anti β*-alkoxy or *syn β*-hydride elimination to obtain the *β*-product (**Scheme 1.9**).[25-30] Substrates successfully applied include arenediazonium salts,[25] benzoic acids,[26] arylboronic acids,[27] aryl halides,[28] enol triflates[29] and sodium arylsulfinates.[30] It was noted that electron-rich Pd complex would result in *β*-alkoxy elimination as the anion was comparatively less electron-rich than hydride.



Scheme 1.9 Palladium-catalysed Heck reaction

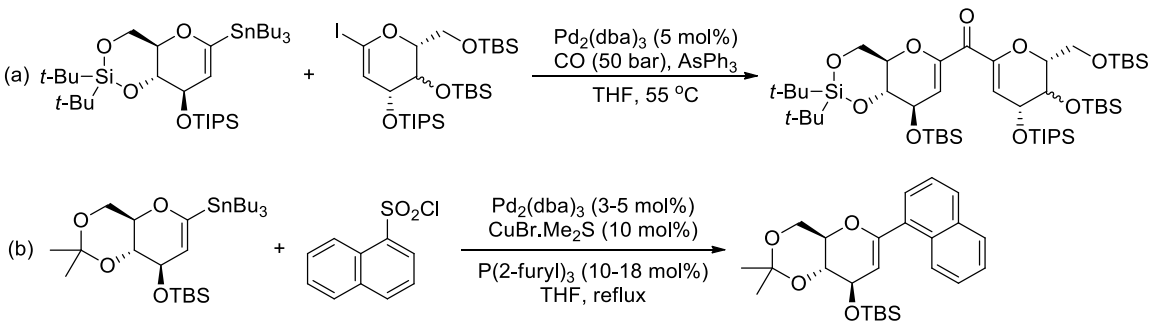
Another transition metal-catalysed glycosylation strategy is through Negishi reaction, in which organozinc can be either the glycosyl donor[31] or acceptor (**Scheme 1.10**).[32] Oxidative addition of the organic halide to palladium(0) catalyst precedes

transmetallation with organozinc, following which reductive elimination occurs to yield the product.



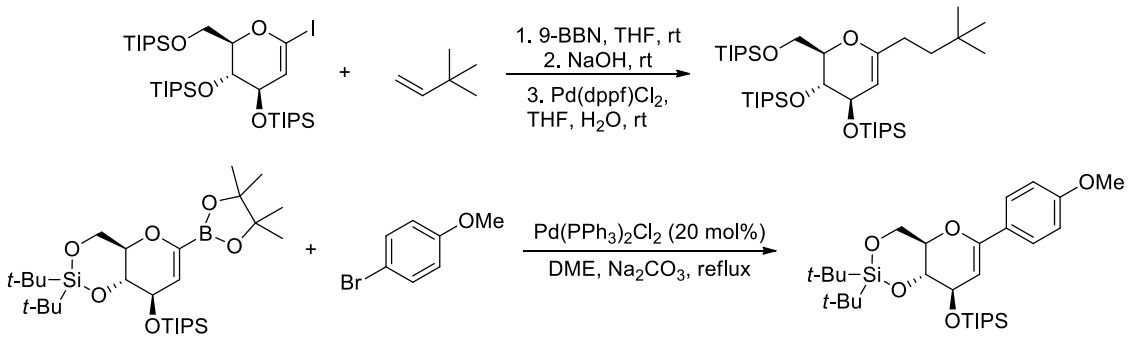
Scheme 1.10 Negishi reactions on glycals

Stannylated glycals can be applied in Stille reaction (**Scheme 1.11**).[33,34] This type of glycosylation proceeds *via* oxidative addition of organic halide to palladium(0), following which transmetallation with stannylated glycals and subsequent reductive elimination occurs to yield the desired product. Aryl halides, alkenyl halides and glycal halide were successfully applied[33] and interestingly, a desulfurative variant using aryl sulfonyl chloride was also reported.[34]



Scheme 1.11 Stille reactions in glycosylation

Suzuki reaction has been successfully applied in glycosylations, in which the glycosyl donor can exist as either organic halide[35] or organoboronic acid form[36] and the acceptor possesses the other coupling functionality (**Scheme 1.12**). After oxidative addition of organic halide to palladium, the halide is then displaced by base, forming the reactive organopalladium species. Upon transmetallation with organoboronic acid, reductive elimination occurs to furnish the glycoside.

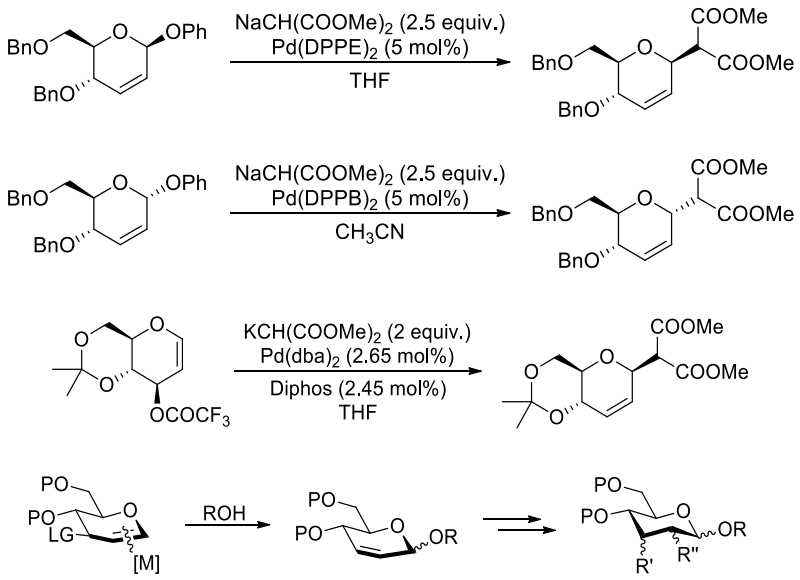


Scheme 1.12 Suzuki reactions in glycosylation

As discussed, the transition metal-catalysed glycosylations, apart from Heck reaction, often resulted in a substituted glycal after reductive elimination, instead of achieving a stereoselective anomer. Tsuji-Trost type allylation is an alternative to bring about stereoselective glycosylations. However, challenges persist, which include lack of neighbouring group participation and difficulties in generating cationic π-allylic system in the electron-rich glycal system.

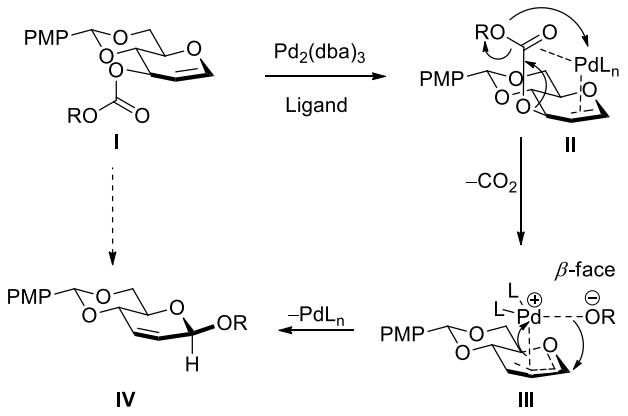
Seminal work by RajanBabu reported the installation of a strongly electron withdrawing leaving group, trifluoroacetyl functionality at the 3-*O* position to increase the affinity between glycal and palladium catalyst.[37] However, only strong *C*-nucleophile could be adopted as the acceptor. Sinou, Feringa and O'Doherty also

pioneered the study of preactivated glycal through the use of *pseudo*-glycals (**Scheme 1.13**).[38] In 2004, Lee reported the *in situ* activation of glycal by addition of diethylzinc to form *O*-glycosides.[39] Notably, all these efforts could yield the *β*-anomer.

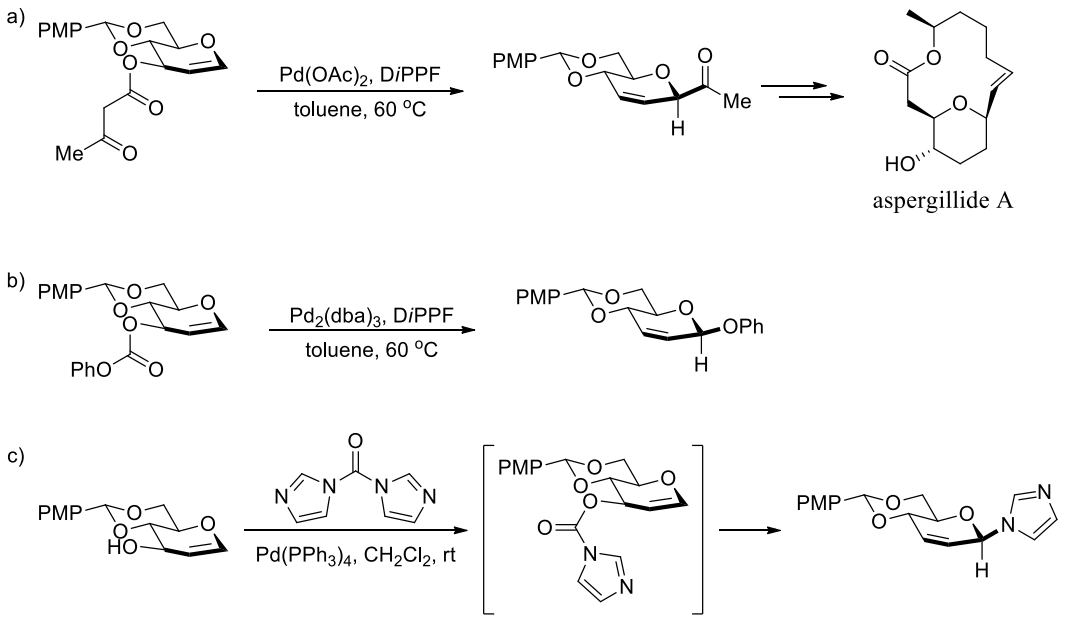


Scheme 1.13 Glycals as glycosyl donors

Inspired by these works, our group envisaged the development of a milder and flexible glycosylation strategy using transition metal-catalysed allylation approach. A series of glycal donors with *C3*-ester or carbonate moiety was designed to deliver *C*-, *O*- and *N*-nucleophiles intramolecularly (**Scheme 1.14**).[40,41] Excellent stereoselectivities as well as regioselectivities were obtained (**Scheme 1.15**).[40] Interestingly for the case of *N*-glycosylation, the installation of the *C3* carbamate could be performed *in situ* and in one-pot with glycal and carbonyldiimidazole.

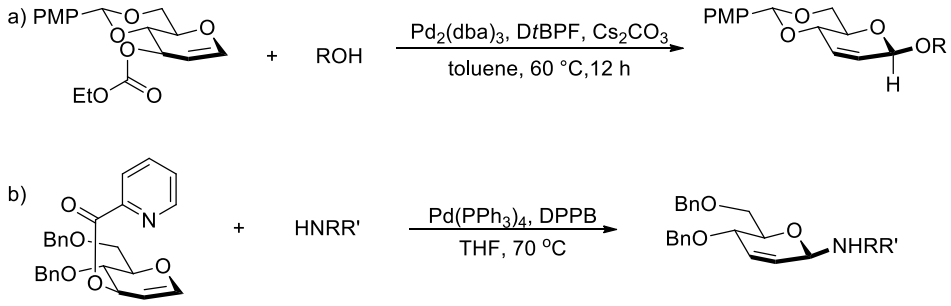


Scheme 1.14 Proposed mechanism of glycals with carbonate group



Scheme 1.15 Intramolecular decarboxylative allylation in: a) *C*-glycosylation; b) *O*-glycosylation; c) *N*-glycosylation

Later, we also developed intermolecular versions of this glycosylation using ethyl carbonate or picoloyl group connected to the *C3* hydroxyl group as the directing group (**Scheme 1.16**).[41] These *O*- and *N*-glycosylations occur by interceptive decarboxylative allylation, whereby the π-allyl palladium species is trapped by an external nucleophile introduced.



Scheme 1.16 Intermolecular decarboxylative allylation in: a) *O*-glycosylation; b) *N*-glycosylation

The importance of glycosylation could not be over emphasised as glycosides are involved in majority of the biological pathways as well as present in many natural products. As nature often presents these glycosides in heterogeneous forms, making it hard to extract them in bulk, there is a need for an efficient synthetic method to obtain pure glycosides for further biological and pharmaceutical research. As seen, allylic system generated from glycals is a general and useful strategy to target stereoselectivity. In this thesis, we will continue to investigate into utilisation of this allylic system in glycals as well as other organic compounds.

1.4 References

1. (a) Li, Z.; Bally, T.; Houk, K. N.; Borden, W. T. *J. Org. Chem.* **2016,** *81*, 9576-9584; (b) Linares, M.; Humbel, S.; Braida, B. *J. Phys. Chem. A* **2008,** *112*, 13249-13255; (c) Mo, Y. *J. Org. Chem.* **2004,** *69*, 5563-5567; (d) Mo, Y.; Lin, Z.; Wu, W.; Zhang, Q. *J. Phys. Chem.* **1996,** *100*, 6469-6474; (e) Wiberg, K. B.; Cheeseman, J. R.; Ochterski, J. W.; Frisch, M. J. *J. Am. Chem. Soc.* **1995,** *117*, 6535-6543; (f) Gobbi, A.; Frenking, G. *J. Am. Chem. Soc.* **1994,** *116*, 9275-9286.
2. (a) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011,** *111*, 1846-1913; (b) You, S. L.; Dai, L. X. *Angew. Chem. Int. Ed.* **2006,** *45*, 5246-5248; (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996,** *96*, 395-422.
3. Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977,** *99*, 1649-1651.
4. Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980,** *21*, 3199-3202.
5. (a) Shimizu, I.; Ishii, H.; Tasaka, A. *Chem. Lett.* **1989,** *18*, 1127-1128; (b) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987,** *20*, 140-145; (c) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987,** *52*, 2988-2995; (d) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983,** *24*, 1793-1796.
6. Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004,** *6*, 4113-4115.
7. Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004,** *126*, 15044-15045.
8. Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* **2005**, 3951-3952.
9. (a) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009,** *131*, 18343-18357; (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005,** *127*, 17180-17181; (c) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005,** *127*, 2846-2847.
10. (a) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005,** *44*, 7248-7251; (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005,** *44*, 6924-6927.
11. Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1989,** *30*, 4829-4832.
12. (a) Patil, N. T.; Yamamoto, Y. *Synlett* **2007**, 1994-2005; (b) Shim, J.-G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998,** *63*, 8470-8474.
13. Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010,** *2*, 192.
14. Sherden, N.; Behenna, D.; Virgil, S.; Stoltz, B. *Angew. Chem. Int. Ed.* **2009,** *48*, 6840-6843.
15. Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. A. *Org. Lett.* **2010,** *12*, 3042-3045.
16. (a) Yan, B.; Spilling, C. D. *J. Org. Chem.* **2008,** *73*, 5385-5396; (b) Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986,** *51*, 421-426; (c) Bäckvall, J.-E.; Nordbert, R. E.; Jan, V. *Tetrahedron Lett.* **1983,** *24*, 411-412; (d) Fiaud, J.; Aribi-Zouioueche, L. *Tetrahedron Lett.* **1982,** *23*, 5279-5282.
17. Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007,** *72*, 1652-1658.
18. (a) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2007,** *129*, 11876-11877; (b) Carcache, D. A.; Cho, Y. S.; Hua, Z.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J.*

Am. Chem. Soc. **2006,** *128*, 1016-1022; (c) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980,** *102*, 6381-6384.
19. Aljahdali, A. Z.; Shi, P.; Zhong, Y.; O'Doherty, G. A. *Adv. Carbohydr. Chem. Biochem.* **2013,** *69*, 55-123.
20. Babu, R. S.; Chen, Q.; Kang, S. W.; Zhou, M. Q.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2012,** *134*, 11952-11955.
21. Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. *Eur. J. Org. Chem.* **2013**, 7221-7262.
22. (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570-575; (b) Ferrier, R. J.; Prasad, N.; Sankey, G. H. *J. Chem. Soc. C* **1968**, 974-977; (c) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443-5449.
23. Li, X.; Zhu, J. *Eur. J. Org. Chem.* **2016**, 4724-4767.
24. Merino, P.; Tejero, T.; Marca, E. *Heterocycles* **2012,** *86*, 791-820.
25. Schmidt, B. *Chem. Commun.* **2003**, 1656-1657.
26. Xiang, S.; Cai, S.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011,** *13*, 4608-4611.
27. Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001,** *3*, 2013-2015.
28. Li, H.-H.; Ye, X.-S. *Org. Biomol. Chem.* **2009,** *7*, 3855-3861.
29. Bai, Y.; Leow, M.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011,** *13*, 5648-5651.
30. Ma, J.; Xiang, S.; Jiang, H.; Liu, X. W. *Eur. J. Org. Chem.* **2015**, 949-952.
31. Ousmer, M.; Boucard, V.; Lubin‐Germain, N.; Uziel, J.; Augé, J. *Eur. J. Org. Chem.* **2006**, 1216-1221.
32. Friesen, R. W.; Loo, R. W. *J. Org. Chem.* **1991,** *56*, 4821-4823.
33. (a) Conway, J. C.; Urch, C. J.; Quayle, P.; Xu, J. *Synlett* **2006**, 776-780; (b) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994,** *72*, 1262-1272; (c) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990,** *55*, 2572-2574.
34. Steunenberg, P.; Jeanneret, V.; Zhu, Y.-H.; Vogel, P. *Tetrahedron: Asymmetry* **2005,** *16*, 337-346.
35. Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004,** *45*, 1797-1801.
36. Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. *Tetrahedron* **2012,** *68*, 5744-5753.
37. RajanBabu, T. V. *J. Org. Chem.* **1985,** *50*, 3642-3644.
38. (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003,** *125*, 12406-12407; (b) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003,** *125*, 8714-8715; (c) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989,** *54*, 1890-1896.
39. Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004,** *126*, 1336-1337.
40. (a) Xiang, S. H.; He, J. X.; Ma, J. M.; Liu, X. W. *Chem. Commun.* **2014,** *50*, 4222-4224; (b) Xiang, S.; Lu, Z.; He, J.; Le, M. H. K.; Zeng, J.; Liu, X. W. *Chem. Eur. J.* **2013,** *19*, 14047-51; (c) Zeng, J.; Ma, J.; Xiang, S.; Cai, S.; Liu, X. W. *Angew. Chem. Int. Ed.* **2013,** *52*, 5134-7.
41. (a) Xiang, S. H.; He, J. X.; Tan, Y. J.; Liu, X. W. *J. Org. Chem.* **2014,** *79*, 11473-11482; (b) Ji, L.; Xiang, S.-H.; Leng, W.-L.; Le Mai Hoang, K.; Liu, X.-W. *Org. Lett.* **2015,** *17*, 1357-1360.

Chapter 2:

Palladium-Catalysed Decarboxylative Allylation/Wittig Reaction: Substrate-Controlled Synthesis of *C*-Vinyl Glycosides

**This chapter has been published in "Palladium-Catalyzed Decarboxylative Allylation/Wittig Reaction: Substrate-Controlled Synthesis of *C*-Vinyl Glycosides", Org. Lett., 2017, 19, 416–419.[1] Reproduced with permission from ref 1.

2.1 Introduction

2.1.1 Strategies and Challenges to Obtain *C*-Vinyl Glycosides

C-Glycosides are present in many biologically and pharmacologically active natural products.[2] Moreover, they are good mimics of the closely-related *O*-glycosides but with enhanced metabolic stability *in vivo*, making them suitable drug candidates.[3] In particular, *C*-vinyl glycosides are an interesting class of compounds, with several sites for further functionalisations, making them useful precursors to gain access to complex natural products (**Figure 2.1**).[2b, 4]

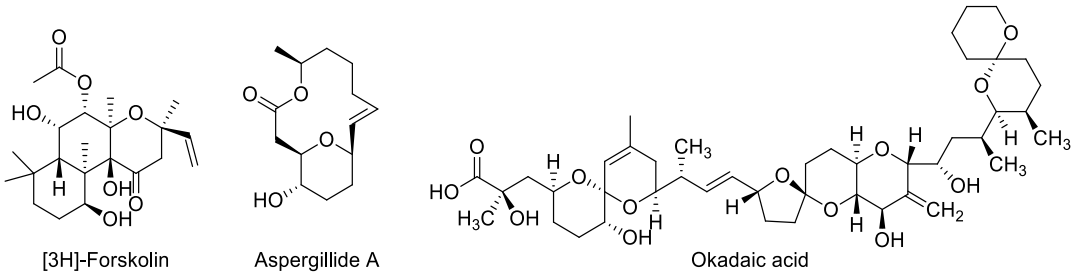
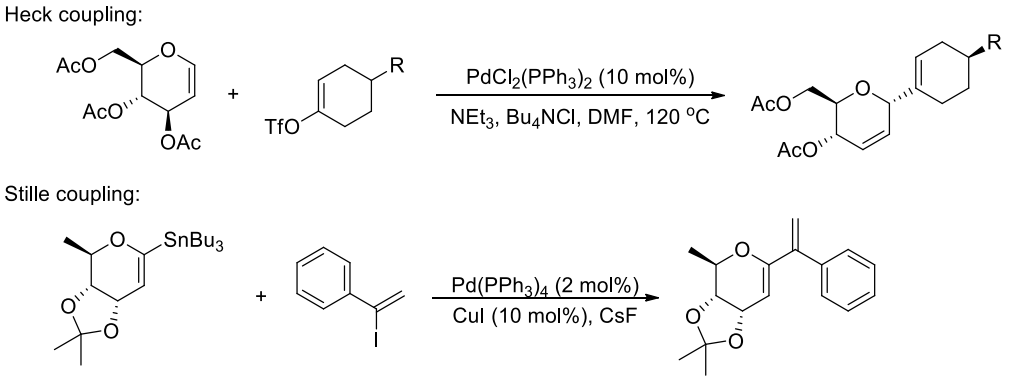


Figure 2.1 Natural products containing *C*-vinyl glycosidic linkage.

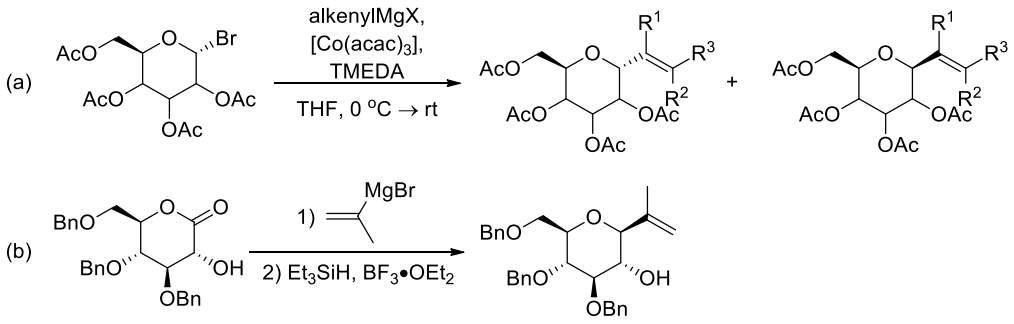
In spite of their synthetic importance, there are only a handful of methods to prepare these *C*-vinyl glycosides, which include metal-catalysed cross-coupling,[5] organometallic mediated reactions,[6] Ferrier-type reaction[7] as well as conventional organic reactions.[8]

Transition metal-catalysed cross-coupling is a popular strategy for introducing functional groups on unsaturated compounds. For the formation of *C*-vinyl glycosidic linkage, palladium-catalysed Heck[5a] and Stille[5b] type reactions can be used to mediate the reaction of glycals with alkenyl triflates and halides (**Scheme 2.1**).

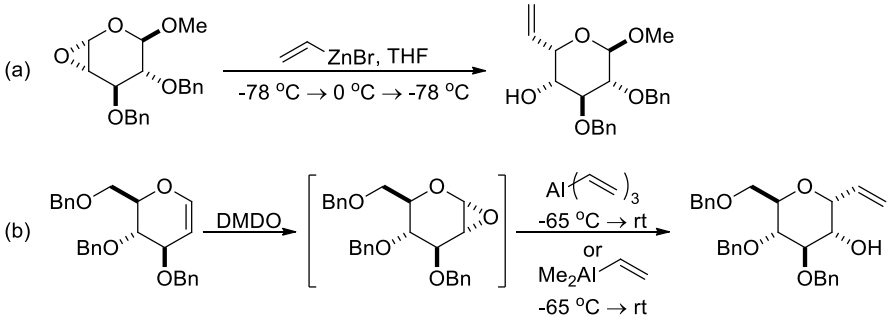


Scheme 2.1 Transition metal catalysed reactions to access *C*-vinyl glycosides

Organometallic reagents such as Grignard reagents, organozinc and organoaluminium reagents have been exploited to furnish the *C*-vinyl glycosides.[6] In 1998, Takahashi[6d] first reported the use of gluconolactone with Grignard reagent, followed by reduction and the same type of alkenyl Grignard reagent was utilised by Cossy[6a] to react with 1-bromo glycosides (**Scheme 2.2**). Epoxypyranoside can be adopted as the starting material, whereby the usage of organozinc reagents by Wei[6a] and organoaluminium reagents by Rainier[6c] led to the epoxide ring opening and formation of desired *C*-vinyl glycosides (**Scheme 2.3**).

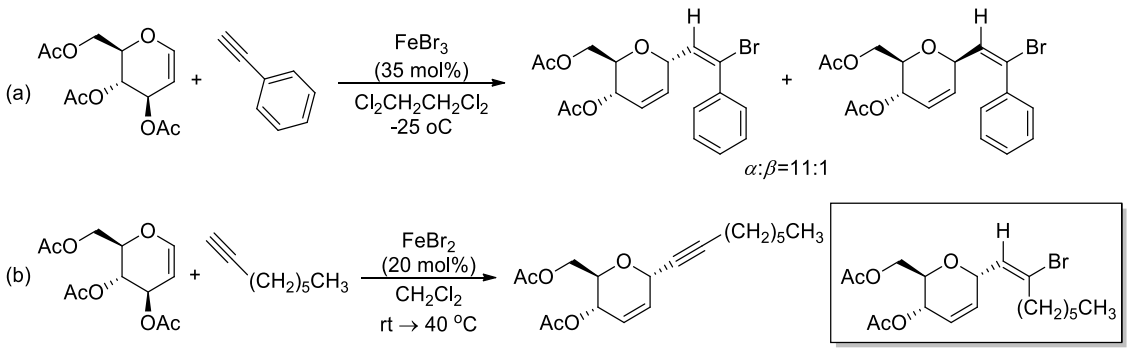


Scheme 2.2 Use of Grignard reagents for syntheses of *C*-vinyl glycosides



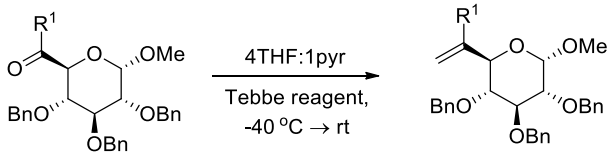
Scheme 2.3 Epoxide ring opening with organozinc and organoaluminium reagents

Ferrier approach was adopted by Mukherjee, in which aromatic terminal alkyne and glycal were utilised in the presence of iron(III) bromide Lewis acid to achieve Ferrier type-glycosylation/halogenation, yielding *C*-vinyl glycosides.[7b] *C*-Vinyl glycoside was also obtained as a side product through utilising aliphatic alkyne in his work on *C*-alkynylation (**Scheme 2.4**).[7a]

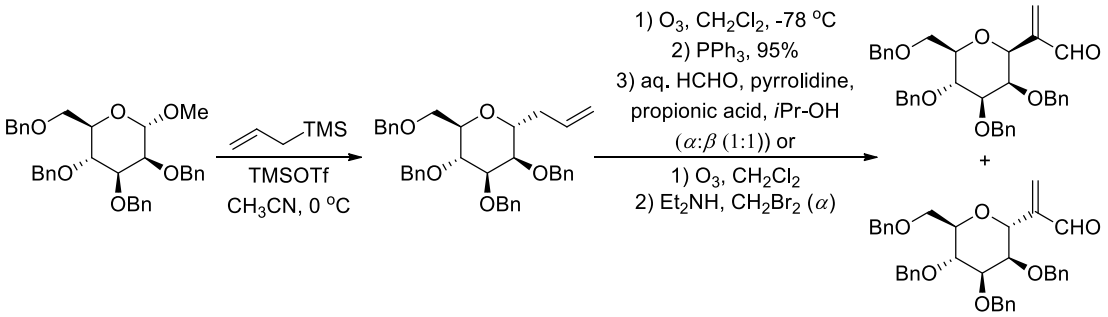


Scheme 2.4 Ferrier type glycosylation/halogenation

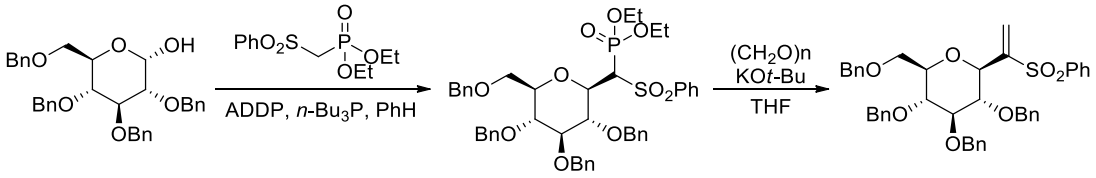
Other methods such as Tebbe methylenation by Fairbanks (**Scheme 2.5**),[8c] sequential reductive ozonolysis/α-methylenation by Roy (**Scheme 2.6**)[8b] and Mitsunobu/Horner Wadsworth Emmons by Pasetto could also successfully furnish *C*-vinyl glycosides (**Scheme 2.7**).[8a]



Scheme 2.5 Tebbe methylenation



Scheme 2.6 Ozonolysis-methylenation

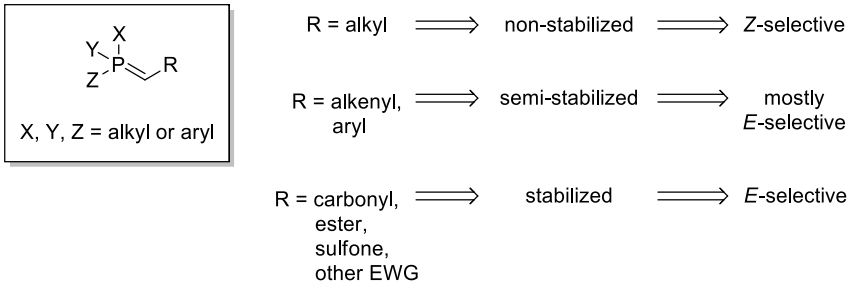


Scheme 2.7 Mitsunobu/Horner Wadsworth Emmons reaction

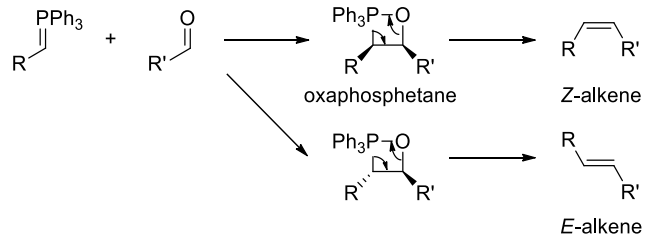
Despite the variety of methodologies to obtain *C*-vinyl glycosides, challenges in the syntheses of these compounds persist. Limitations of the existing methods include: 1) the formation of geminal alkenes only due to the incapability of forming *E* and *Z*-alkenes selectively; 2) achievement of moderate anomeric selectivity (α/β); and 3) requirement of stepwise isolation for some cases. Notably, such mediocre selectivity is a common problem in *C*-glycosides[9] in general due to the lack of anomeric effect and neighbouring group participation to direct stereoselectivity.[10] The problem is compounded in the case of *C*-vinyl glycosides, with the formation of two stereocenters, hence the issue of diastereoselectivity remains to be addressed.

2.1.2 Phosphonium Ylides: New Role as Nucleophiles

Since the discovery by Wittig in 1954,[11] phosphonium ylides have been extensively used in the formation of carbon-carbon double bond. However, till date, more than sixty years after its discovery, the detailed mechanism is still debatable as experimental observations under different reaction conditions with different ylides (non-, semi-, and stabilised ylides) have to be accounted for. *Z*-alkenes are typically obtained as the major product when most non-stabilised ylides are used, while *E*-alkenes have been achieved with most semi-stabilised and stabilised ylides (**Scheme 2.8**). In 2013, Byrne and Gilheany reviewed previously proposed mechanisms and experimental results, and hypothesised that in the absence of lithium, it is probable that [2+2] cycloaddition occurs between aldehyde or ketone and any phosphonium ylide to give oxaphosphetane as the first and only intermediate under kinetic control (**Scheme 2.9**).[12] They also proposed that decomposition of oxaphosphetane occurs in a single step, with simultaneous Berry pseudorotation as well as C-O and P-C bond-breaking. This decomposition is stereospecific according to the alkene formed.

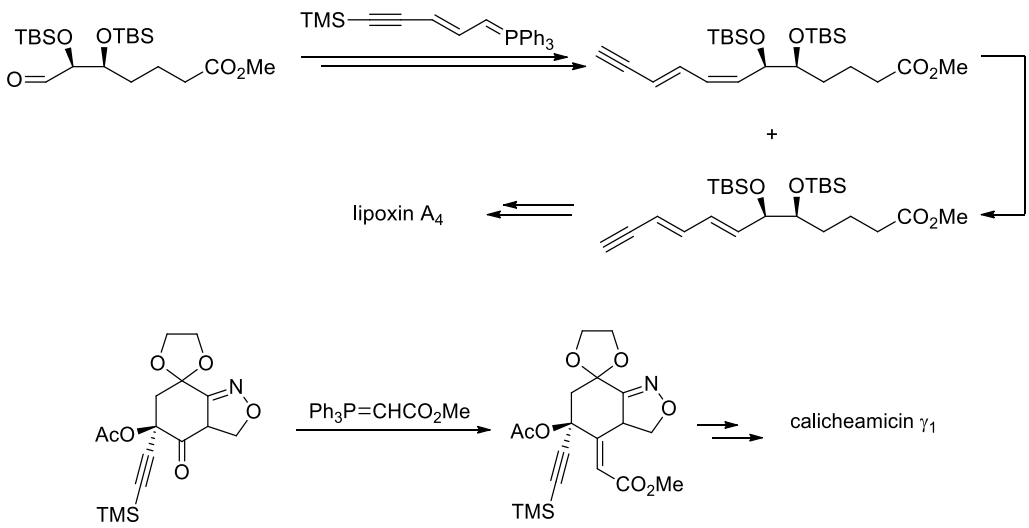


Scheme 2.8 Phosphorus ylides and corresponding preferred alkene stereoselectivities

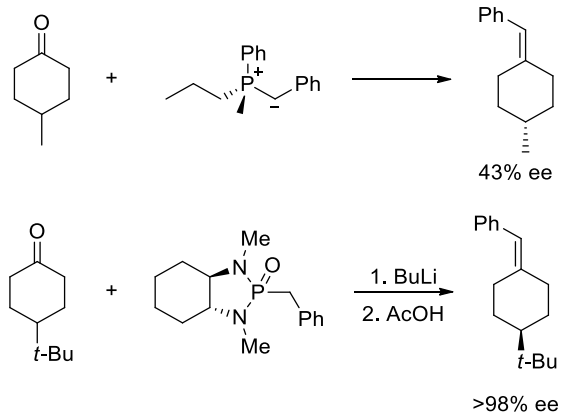


Scheme 2.9 Mechanism of Wittig reaction

Thus far, Wittig reaction continues to be an important organic synthetic strategy as seen by its prevalence in natural product syntheses (**Scheme 2.10**).[13] With the installation of a prostereogenic or stereogenic center some distance away from the reacting center, the asymmetric variant of Wittig reaction can also be achieved (**Scheme 2.11**).[14]

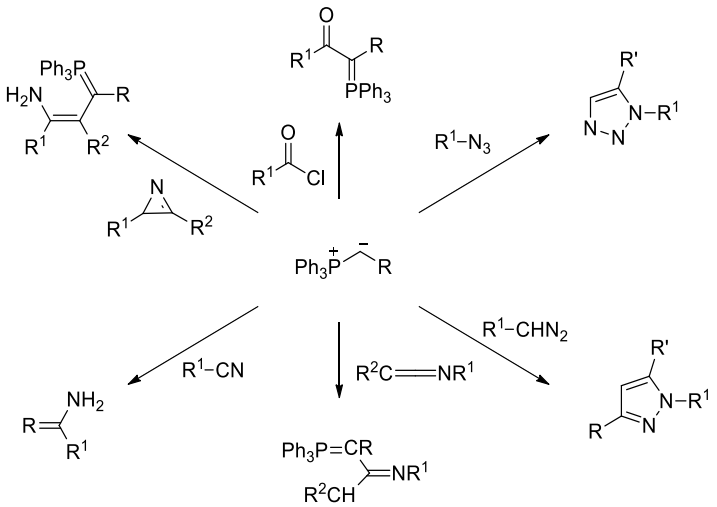


Scheme 2.10 Wittig reactions in natural product syntheses



Scheme 2.11 Asymmetric Wittig reactions

It is important to note that the phosphonium ylide zwitterion can also be viewed separately as carbanion and phosphonium cation, suggesting its role as a possible nucleophile. The nucleophilic property of phosphonium ylide has been demonstrated through reactions with a series of electrophiles such as nitriles,[15] diazo compounds,[16] azides,[17] allenes,[18] aziridines[19] and acyl chlorides[20] (**Scheme 2.12**).



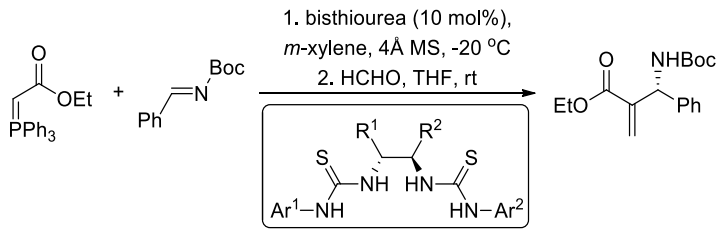
Scheme 2.12 Reactions of phosphorus ylide with electrophiles

This role of phosphorus ylides as nucleophiles in one-pot reactions has not been explored until recently. In these one-pot reactions, nucleophilic attack first occurs,

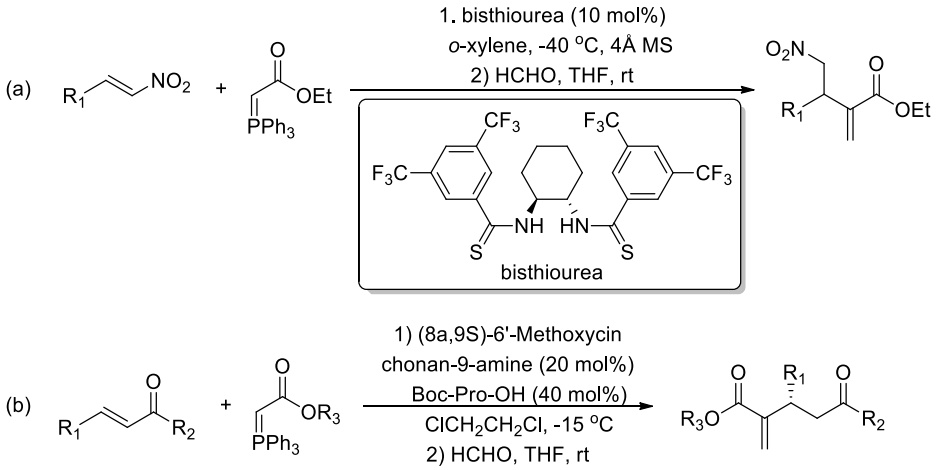
followed by deprotonation to regenerate phosphonium ylides for subsequent Wittig reaction *via* an oxaphosphetane intermediate. Their applications have been extended to one-pot Mannich/Wittig,[21] Michael/Wittig[22] and allylic substitution/Wittig.[23]

Organocatalysed Mannich/Wittig type reaction could be achieved as shown by Chen using bisthiourea (**Scheme 2.13**).[21] Singh and Cheng developed one-pot Michael/Wittig reactions using nitroolefins and *α,β*-unsaturated ketones with bisthiourea and chiral ion pair as catalysts respectively (**Scheme 2.14**).[22]

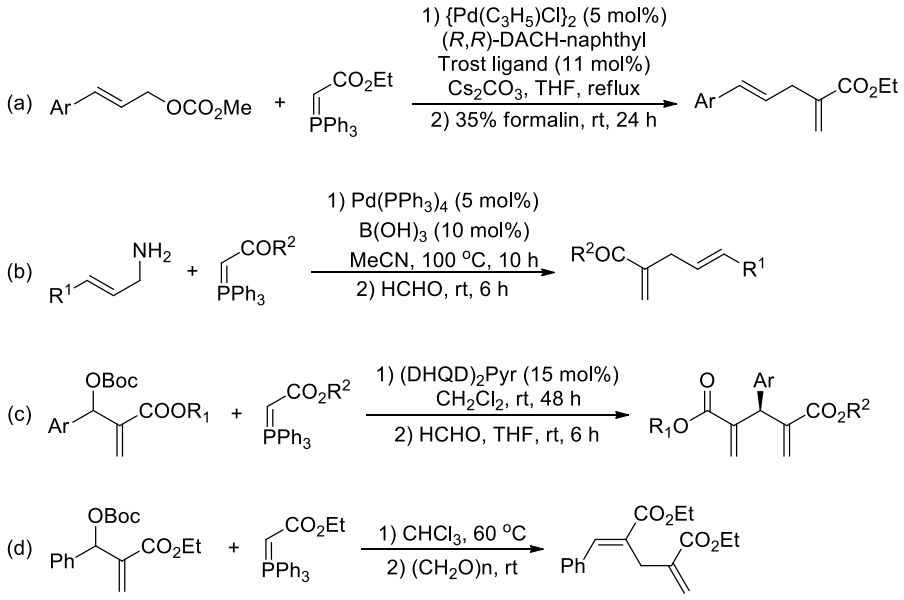
In 2010, You made a significant discovery by utilising the phosphorus ylides in a one-pot Pd-catalysed allylation/Wittig reaction, as opposed to organocatalysts used previously.[23d] Prior to that, ylides were less commonly used with transition metals due to the possibility of forming palladacycles. A series of allylation/Wittig reactions were later discovered by Zhu, Tian and Dou.[23a-c] Zhu utilised Morita-Baylis-Hillman carbonates for the one-pot reaction using chiral amine catalyst,[23c] while Tian performed palladium-catalysed allylation on allylic amine.[23b] Another interesting work was by Dou's group, whereby they managed to develop a catalyst-free variant (**Scheme 2.15**).[23a]



Scheme 2.13 One-pot Mannich/Wittig type reaction



Scheme 2.14 One-pot Michael/Wittig reactions

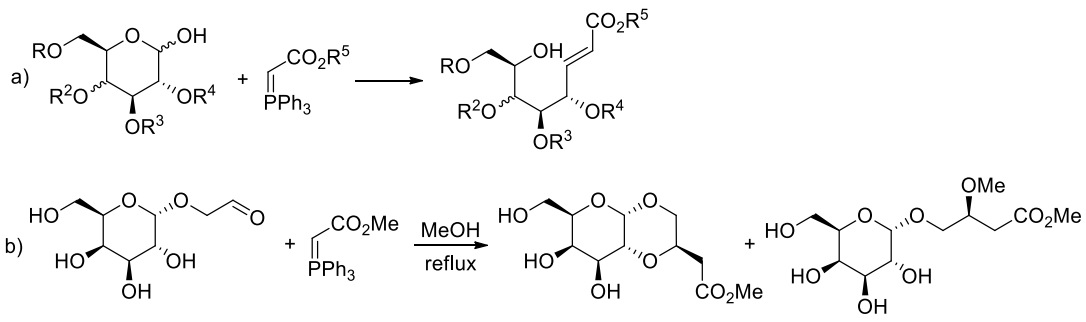


Scheme 2.15 One-pot allylation/Wittig reactions

2.1.3 One-Pot Decarboxylative Allylation/Wittig Reaction Using Glycals

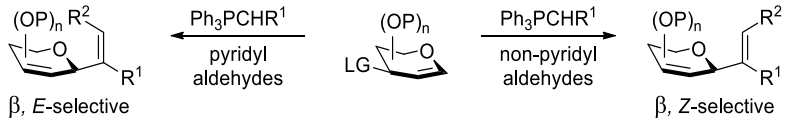
It is interesting to note that although the first work on palladium-catalysed *C*-glycosylation was reported close to forty years ago, this reaction is not extensively used.[9d, 24] One main reason is the difficult generation of π-allyl palladium species from the electron-rich enol ethers.[25] With the recent reports of Pd-catalysed decarboxylative allylation,[26] further advances on its application to *C*-glycosides have since been made.[27] Notably, the challenge of stereoselectivity for *C*-glycosylation can be addressed through this synthetic strategy despite the absence of anomeric effect.

Based on our previous works on decarboxylative allylation, the matching of nucleophilicity with π-allyl palladium system is extremely important, hence careful selection of appropriate *C*-nucleophile needs to be addressed. As shown previously, recent development demonstrated the new role of stabilised phosphorus ylides (*P*-ylides) as nucleophiles and application to tandem reactions, making them suitable candidates in these reactions. Notably, the only application of phosphorus ylide to sugar substrate was performing Wittig reactions on either the free aldehyde of the ring-opened sugar or external carbonyl group on sugar (**Scheme 2.16**).[28]



Scheme 2.16 Wittig reaction of phosphorus ylides with sugar

In addition, our recent work on reversing anomeric selectivity involving Pd-N coordination[29] motivated us to explore the effect of such coordination on one-pot sequential reactions, particularly for the downstream step. We postulate that the palladium may have dual roles in our tandem reaction, whereby it acts as a catalyst for Tsuji-Trost type reaction for the first step and coordinating agent for the second step in the presence of pyridyl group. As such, it should be able to control both the anomeric selectivity as well as olefin selectivity, achieving the desired diastereoselectivity in *C*-vinyl glycosides (**Scheme 2.17**).



Scheme 2.17 Diastereoselective formation of C-vinyl glycosides

2.2 Results and Discussion

2.2.1 Condition Optimisation

The model glucal **2.1a** was chosen as the model glycosyl donor in our glycosylation study. With the consideration of driving the allylation, we installed the carbonate moiety as the leaving group which will release carbon dioxide as a clean by-product. However, the resulting nucleophile upon decarboxylation should not be as active as the previously reported cases to avoid the intramolecular reaction. Hence, to drive the interceptive decarboxylative allylation, *tert*-butyloxycarbonyl group was selected as the leaving group on *C3*.

In our earlier attempts, *in situ* activation of non-stabilised *P*-ylides was attempted. However, the glucal starting material decomposed in the presence of strong bases which were required in the activation of the *P*-ylides. Hence, we decided upon stabilised *P*-ylide **2.2a** as our model glycosyl acceptor to avoid the usage of strong bases.

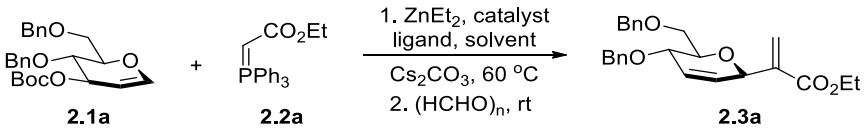
We then began our study on one-pot allylation/Wittig reaction using glucal **2.1a**, *P*-ylide **2.2a** and formalin solution in the presence of palladium(II) acetate catalyst, 1,4-bis(diphenylphosphino)butane (DPPB) ligand and cesium carbonate in dimethylformamide at 60 ^{o}C (**Table 2.1**). However, no desired product was obtained and the reaction mixture was complex on the thin layer chromatography. Hence, we proposed that the presence of water in the formalin solution could result in complex reactions, which include 1) Cannizaro reaction of the aldehyde; 2) formaldehyde

predominately existing as the hydrated methanediol form; 3) hydrolysis of phosphorus ylide.

Next, we switched the formaldehyde source from formalin solution to paraformaldehyde but unfortunately, no reaction was observed either (entry 1). This lack of reaction was possibly due to the incompatibility of the electrophilic and nucleophilic systems.

In an attempt to increase the compatibility between the soft π-allyl palladium electrophile and the *P*-ylide nucleophile, we applied $ZnEt_2$ as an additive to soften the nucleophile.[30] Gratifyingly, the desired product was obtained with 92% yield (entry 2). Solvent had a significant effect on the reaction efficiency, which was probably due to the base solubility (entries 3-5). Pd source did not have a significant effect on the reaction and the highest yield was achieved with $Pd(OAc)_2$ (entries 2, 7, 8). Of the ligands, DPPB was found to be most suited for this reaction (entries 2, 9-11). Based on these observations, entry 2 was chosen as the optimal set of reaction conditions. The assignment of β-stereochemistry was based on the strong observed correlation between *H1* and *H5* for product **2.3a** during NOE experiment.

Table 2.1 Reaction optimisation[a]



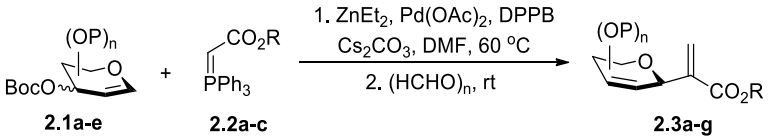
Entry	Catalyst	Ligand	Solvent	Yield[b] (%)
1[c]	$Pd(OAc)_2$	DPPB	DMF	-
2	$Pd(OAc)_2$	DPPB	DMF	92
3	$Pd(OAc)_2$	DPPB	dioxane	34
4	$Pd(OAc)_2$	DPPB	DMSO	47
5	$Pd(OAc)_2$	DPPB	CH_3CN	41
6	$Pd(TFA)_2$	DPPB	DMF	69
7	$Pd(C_6H_5CN)_2Cl_2$	DPPB	DMF	80
8	$[Pd(CH_3CN)_4](BF_4)_2$	DPPB	DMF	89
9[d]	$Pd(OAc)_2$	XPhos	DMF	71
10	$Pd(OAc)_2$	DPPF	DMF	69
11	$Pd(OAc)_2$	DPPPent	DMF	70

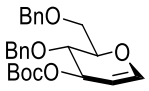
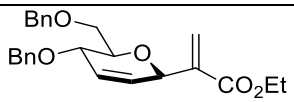
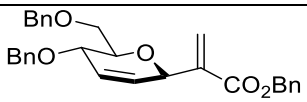
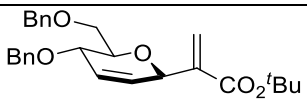
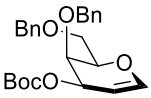
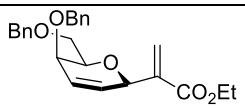
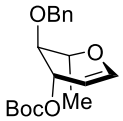
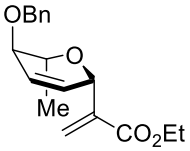
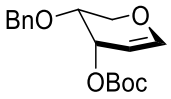
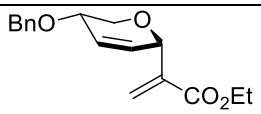
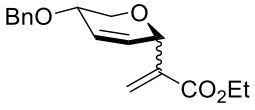
[a] Unless otherwise specified, all reactions were carried out using glucal **2.1a** (0.1 mmol, 1 equiv.), *P*-ylide **2.2a** (0.15 mmol, 1.5 equiv.), $ZnEt_2$ (0.15 mmol, 1.5 equiv.), [Pd] 20 mol %, ligand 30 mol %, Cs_2CO_3 (0.15 mmol, 1.5 equiv.) in 1.6 mL of solvent. [b] Isolated yields. [c] Without the addition of $ZnEt_2$. [d] 60 mol % of ligand used.

2.2.2 Substrate Scope

With the optimal conditions in hand, the scope of this one-pot allylation/Wittig reaction was investigated, using various *P*-ylide glycosyl donors and glycosyl acceptors (**Table 2.2**). The reaction efficiency remained unchanged when the ester functionality of *P*-ylide was switched from ethyl to benzyl and *tert*-butyl groups (**2.3a**–**c**). Glycals with varying substituents on each position were then screened to investigate the substituent effect. Interestingly, regardless of the substituents, *C*-vinyl glycosides were formed with preferred *β*-selectivity. Due to steric factors, **2.3d** was obtained with diminished yield. The formation of a side product also resulted in lowered yield of **2.3e**. We made the observation that when the *C3* and *C4* substituents of glycosyl donor were *cis* to each other, the control of stereoselectivity was independent of the *C6* substitutent, as in the case of arabinal (**2.3f**), where *β*-anomer was obtained exclusively. Conversely, when the substituents were *trans* to each other, *C6* substituent had a significant effect on the stereochemical control, as in the case of xylal (**2.3g**) with decreased stereoselectivity. Mechanistically, we proposed that the palladium-complex preferred to coordinate to the opposite face of the leaving group. This resulted in conflicting stereo-directing effects when *C3* and *C4* were *trans* to each other, as steric effect between the bulky *C4* substituent and the palladium complex existed. Hence, a reduction in anomeric selectivity was observed, which was significant especially in the absence of the *C6* substituent.

Table 2.2 Scope of glycosyl donors and acceptors



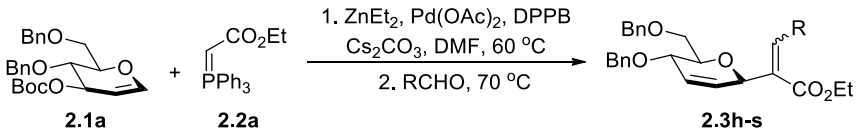
Entry	Glycal	Product	Yield[a] (%)
1	 **2.1a**	 **2.3a**	92
2[b]	**2.1a**	 **2.3b**	92
3[c]	**2.1a**	 **2.3c**	94
4	 **2.1b**	 **2.3d**	58
5	 **2.1c**	 **2.3e**	56
6	 **2.1d**	 **2.3f**	95
7	 **2.1e**	 **2.3g**	60 (β:α = 2:1)

[a] Isolated yields. [b] Using benzyl(triphenylphosphoranylidene) acetate. [c] Using (*tert*-butoxycarbonylmethylene) triphenylphosphorane.

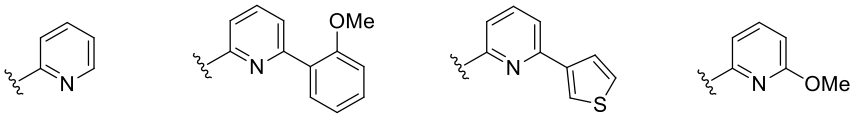
Next, aldehydes with aromatic and heterocyclic substituents were subjected to the reaction conditions to prove the synthetic application of our methodology in the formation of trisubstituted *C*-vinyl glycosides as well as investigate the effect of Pd-N coordination in the one-pot reaction (**Table 2.3**). Surprisingly, sterically unfavoured (*E)*-olefins were successfully obtained using pyridine-containing carboxaldehydes (**2.3h**–**k**). When electron-donating substituents were present at the *ortho*-position to the pyridyl N atom (**2.3i**–**k**), high reaction efficiency was observed, with a exceptionally high yield of 84% for the 6-(3-thienyl)-2-pyridyl group (**2.3j**). This suggested the presence of another factor that dominated over steric effect. To the best of our knowledge, the reaction efficiency for the formation of trisubstituted alkenes using Wittig reaction often ranged from low to moderate due to steric factors and such highly efficient cases were rare.[31]

On the other hand, in the absence of pyridyl groups, aldehydes with 5-membered heterocycles (**2.3l**–**n**) and benzaldehydes, required the electron-withdrawing substituents (**2.3o**–**s**) to enhance their electrophilicity and promote the intermolecular Wittig reaction. In these examples, (*Z*)-isomer was preferred due to the absence of coordinating effects. Interestingly, Wittig selectivity was often reported to be directed by steric effects and such examples of obtaining opposite olefin selectivity from aldehydes beaing substituents of similar sizes have not been investigated. Notably, the resultant *C*-vinyl glycosides were obtained with exclusive *β*-selectivity regardless of the aldehyde substituents.

Table 2.3 Scope of aldehydes[a]



2.1a **2.2a** **2.3h-s**



2.3h 34% (*E*) **2.3i** 49% (*E*) **2.3j** 84% (*E*) **2.3k** 61% (*E*)

2.3l 53% (*Z*) **2.3m** 32% (*Z*) **2.3n** 51% (*Z*) **2.3o** 32% (*Z*)

2.3p 44% (*Z*) **2.3q** 40% (*Z*) **2.3r** 48% (*Z*) **2.3s** 57% (*Z*)

[a] Isolated yields over two steps.

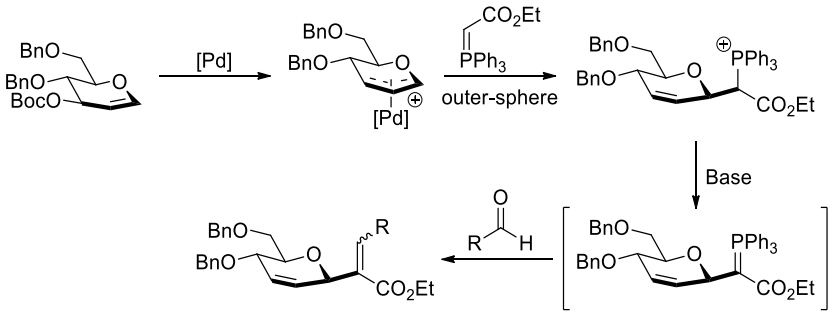
2.2.3 Plausible Mechanism

Based on the observed stereoselectivity for disubstituted alkenes and diastereoselectivity for trisubstituted alkenes, the following mechanistic pathways are proposed. Tsuji-Trost allylation proceeds *via* an outer sphere mechanism, as the softened *P*-ylide nucleophile prefers to attack the soft π-allyllic species, accounting for β-selectivity (**Scheme 2.18**). The stereochemical outcome for the subsequent Wittig reaction is dictated by the substitutents on the aldehydes (**Scheme 2.19**). Apart from the differing (*E*)- and (*Z*)-selectivities, the reaction efficiency is improved in the presence of electron-donating groups as in case of pyridyl aldehydes while the reversed case for non-pyridyl aldehydes is true with enhanced efficiency with electron-withdrawing groups, thereby indicating that two different pathways should be proposed for the subsequent Wittig reaction in this one-pot reaction.

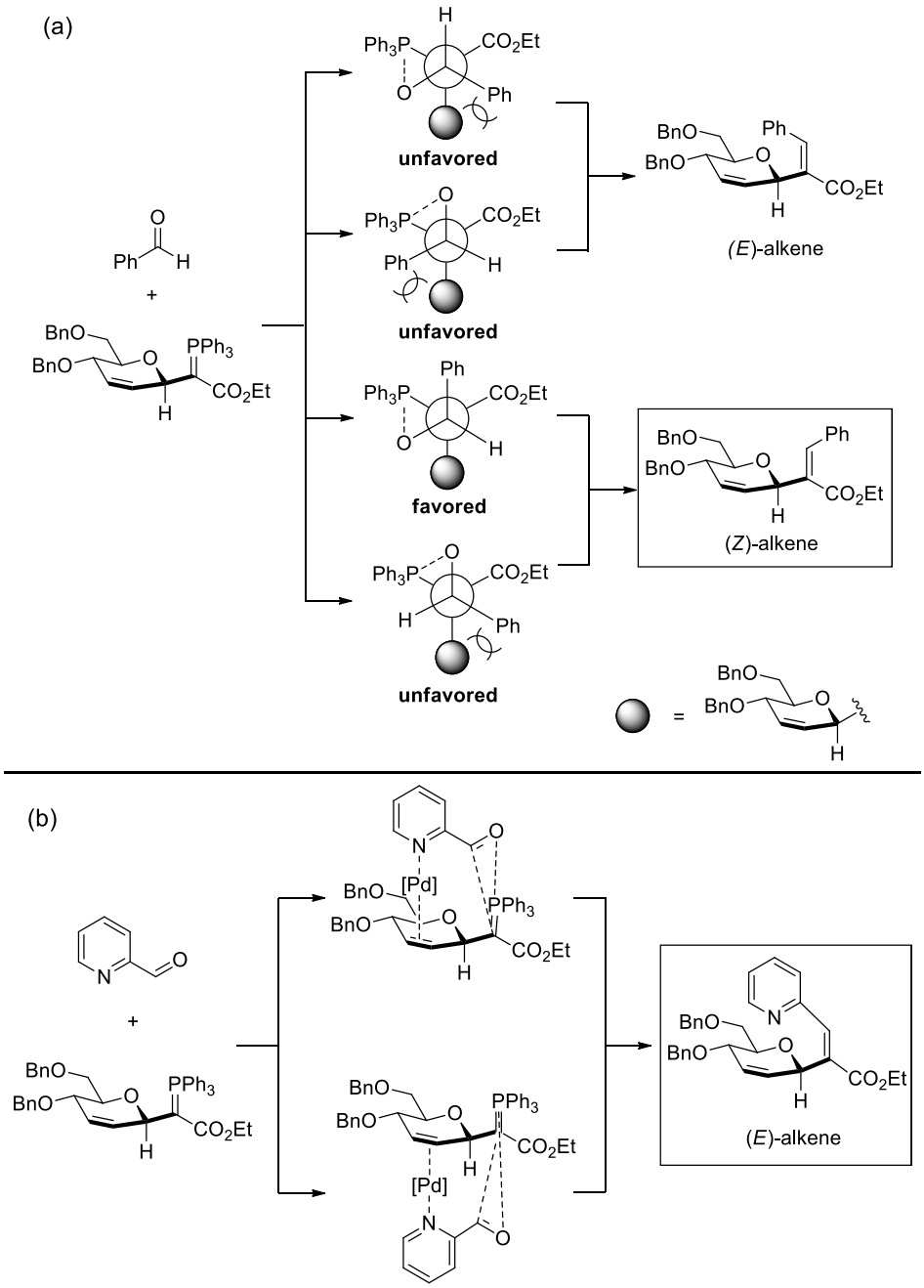
In the absence of pyridyl group, aldehydes with phenyl, furyl and thienyl moieties undergo *via* the typical intermolecular Wittig reaction to give (*Z*)-alkenes. Using the Newman projection of the puckered 4-membered oxaphosphetane intermediate formed from the [2+2] cycloaddition, the preference for (*Z*)-selectivity can be explained. Oxaphosphetane with the aldehyde substituent *anti* to the sugar group is preferentially formed, in order to minimise *gauche* interactions between the bulky sugar ring and aldehyde substituent, accounting for the favoured (*Z*)-stereoselectivity (**Scheme 2.19a**).

On the other hand, we propose that some degree of Pd-N coordination exists,[32] when aldehydes with pyridyl groups are utilised, leading to a reversal in olefin

stereoselectivity. This is supported by the experimental observations of surprising formation of sterically unfavourable (*E*)-selective glycosides and increased yields with enhanced nucleophilicity of pyridyl ring when electron-donating groups are installed. Through the Pd-N coordination, Wittig reaction can proceed *via* a *pseudo*-intramolecular manner as the *P*-ylide and aldehyde are brought in close proximity for [2+2] cycloaddition, thereby overcoming the steric hindrance in a typical Wittig reaction and achieving breakthrough in the low efficiency for trisubstituted alkenes in most reported cases (**Scheme 2.19b**).



Scheme 2.18 Proposed mechanism



Scheme 2.19 Proposed key oxaphosphetane intermediates accounting for (*Z*)-/(*E*)-selectivity

2.3 Conclusion

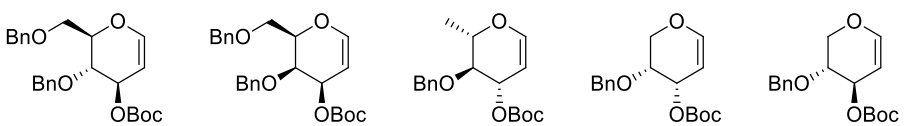
In summary, we have described a diastereoselective palladium-catalysed one-pot decarboxylative allylation/Wittig reaction to obtain *C*-vinyl glycosides. The diastereoselectivity from glycosylation and subsequent Wittig reaction was directed by palladium catalyst and dependent on the coordinating ability of the aldehydes: *β*,(*E)*-Selective and *β*,(*Z)*-selective *C*-vinyl glycosides could be obtained when pyridyl and non-pyridyl aldehydes were employed respectively. Based on the observed results, we have proposed two separate pathways for coordinating and non-coordinating aldehydes: *pseudo*-intramolecular pathway in the presence of Pd-N coordination and the classic intermolecular pathway in the absence of such coordination. As a result, *C*-vinyl glycosides can be synthsised in moderate to high efficiency with controlled diastereoselectivity.

Looking forward, these *C*-vinyl glycosides can be employed as useful synthetic precursors for pharmaceutical and natural products as they can be subjected to downstream modifications. Apart from it, the discovery of aldehydes' coordinating ability affecting alkene stereoselectivity serves as an alternative approach to selectively form (*E*) and (*Z*)-alkenes during Wittig reaction.

2.4 Experimental Section

General: All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Merck, Strem and Alfa Asear) and used without further purification unless stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensdch polarimeter with a 1 cm cell (c given in g/100 mL). NMR spectra were recorded at room temperature on 400 MHz Bruker DPX 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). 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. HRMS (ESI) spectra were recorded on a Waters Q-Tof premier^{TM} mass spectrometer.

Preparation of glycosyl acceptors (2.1a-e):



2.1a **2.1b** **2.1c** **2.1d** **2.1e**

1,5-Anhydro-2-deoxy-4,6-bis-*O*-(phenylmethyl)-3-*O*-(*tert*-butyloxycarbonyl)-D-*arabino*-hex-1-enitol (2.1a)

Glycosyl acceptor **2.1a** was prepared according to literature procedures.[33]

2,6-Anhydro-5-deoxy-1,3-bis-*O*-(phenylmethyl)-4-*O*-(*tert*-butyloxycarbonyl)-D-*arabino*-hex-5-enitol (2.1b)

Glycosyl acceptor **2.1b** was prepared according to literature procedures.[33]

1,5-Anhydro-2,6-dideoxy-4-*O*-(phenylmethyl)-3-*O*-(*tert*-butyloxycarbonyl)-L-*arabino*-hex-1-enitol (2.1c)

To 1,5-anhydro-2,6-dideoxy-4-*O*-(phenylmethyl)-L-arabino-hex-1-enitol (66.0 mg, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (5.0 mL), Boc_2O (0.28 mL, 1.20 mmol, 4 equiv.), Et_3N (0.05 mL, 0.39 mmol, 1.3 equiv.) and DMAP (3.67 mg, 0.03 mmol, 0.1 equiv.) was added. Completion of reaction was confirmed by TLC. Water (10.0 mL) was added and the product was extracted with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated. **2.1c** was obtained (47.1 mg, 49%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -102.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.22 (m, 5H), 6.38 (dd, *J* = 6.0, 1.4 Hz, 1H), 5.26 (ddd, *J* = 6.4, 2.9, 1.5 Hz, 1H), 4.83 – 4.75 (m, 2H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.02 (dq, *J* = 8.7, 6.5 Hz, 1H), 3.53 (dd, *J* = 8.6, 6.3 Hz, 1H), 1.49 (s, 9H), 1.37 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.04, 145.84, 137.86, 128.32, 127.85, 127.74, 99.08, 82.22, 78.20, 73.83, 73.73, 73.63, 27.75, 17.23; HRMS (ESI) calcd. for $[C_{18}H_{25}O_5]^+$ 321.1702; found 321.1701.

1,5-Anhydro-2-deoxy-4-*O*-(phenylmethyl)-3-*O*-(*tert*-butyloxycarbonyl)-D-*erythro*-pent-1-enitol (2.1d)

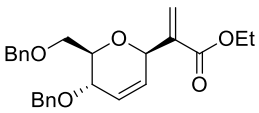
To 1,5-anhydro-2-deoxy-4-*O*-(phenylmethyl)-D-*erythro*-pent-1-enitol (61.8 mg, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (5.0 mL), Boc_2O (0.28 mL, 1.20 mmol, 4 equiv.), Et_3N (0.05 mL, 0.39 mmol, 1.3 equiv.) and DMAP (3.67 mg, 0.03 mmol, 0.1 equiv.) was added. Completion of reaction was confirmed by TLC. Water (10.0 mL) was added and the product was extracted with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated. **2.1d** was obtained (48.7 mg, 53%) as colorless oil after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 21.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 5H), 6.46 (d, *J* = 5.9 Hz, 1H), 5.34 – 5.25 (m, 1H), 4.88 (t, *J* = 5.8 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 3.99 (ddd, *J* = 10.2, 4.4, 1.6 Hz, 1H), 3.90 (t, *J* = 10.6 Hz, 1H), 3.80 (dt, *J* = 11.0, 4.1 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.29, 148.38, 137.65, 128.33, 127.76, 127.68, 96.75, 81.99, 71.73, 71.46, 64.77, 63.19, 27.73; HRMS (ESI) calcd. for $[C_{17}H_{22}O_5Na]^+$ 329.1545; found 329.1550.

1,5-Anhydro-2-deoxy-4-*O*-(phenylmethyl)-3-*O*-(*tert*-butyloxycarbonyl)-D-*threo*-pent-1-enitol (2.1e)

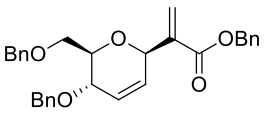
To 1,5-anhydro-2-deoxy-4-*O*-(phenylmethyl)-D-*threo*-pent-1-enitol (61.8 mg, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (5.0 mL), Boc_2O (0.28 mL, 1.20 mmol, 4 equiv.), Et_3N (0.05 mL, 0.39 mmol, 1.3 equiv.) and DMAP (3.67 mg, 0.03 mmol, 0.1 equiv.) was added. Completion of reaction was confirmed by TLC. Water (10.0 mL) was added and the product was extracted with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and

concentrated. **2.1e** was obtained (37.7 mg, 41%) as colorless oil after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -32.6 (*c* = 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.23 (m, 5H), 6.60 (d, *J* = 5.1 Hz, 1H), 5.00 – 4.88 (m, 2H), 4.70 (q, *J* = 12.1 Hz, 2H), 4.13 (ddd, *J* = 12.0, 3.4, 1.4 Hz, 1H), 3.91 (dd, *J* = 11.9, 2.0 Hz, 1H), 3.66 (dq, *J* = 4.4, 2.1 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.57, 148.17, 137.62, 128.38, 128.35, 127.80, 97.02, 82.43, 71.86, 71.22, 66.28, 64.24, 27.73; HRMS (ESI) calcd. for $[C_{17}H_{22}O_5Na]^+$ 329.1365; found 329.1363.

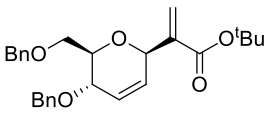
Preparation of *C*-vinyl glycosides (2.3a-g):



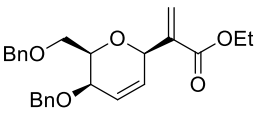
2.3a



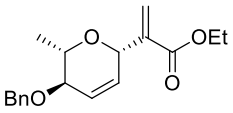
2.3b



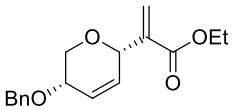
2.3c



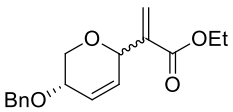
2.3d



2.3e



2.3f



2.3g (mixture)

Ethyl 2-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3a)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2

equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3a** was obtained (37.5 mg, 92%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 33.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 10H), 6.32 (t, *J* = 1.3 Hz, 1H), 5.99 (t, *J* = 1.6 Hz, 1H), 5.91 (s, 2H), 5.08 (dd, *J* = 3.1, 1.5 Hz, 1H), 4.66 – 4.56 (m, 3H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.23 (qd, *J* = 7.1, 2.2 Hz, 2H), 4.06 (dd, *J* = 8.6, 3.1 Hz, 1H), 3.82 – 3.68 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.42, 139.64, 138.36, 138.00, 130.01, 128.33, 128.25, 127.84, 127.70, 127.65, 127.46, 125.91, 125.84, 77.54, 73.28, 73.04, 71.09, 70.19, 69.70, 60.71, 14.13; HRMS (ESI) calcd. for $[C_{25}H_{29}O_5]^+$409.2015; found 409.2021.

Benzyl 2-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3b)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, benzyl(triphenylphosphoranylidene)acetate **2.2b** (61.5 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room

temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3b** was obtained (43.3 mg, 92%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 102.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 4.7 Hz, 4H), 7.34 – 7.22 (m, 11H), 6.38 (t, *J* = 1.3 Hz, 1H), 6.02 (t, *J* = 1.5 Hz, 1H), 5.96 – 5.85 (m, 2H), 5.22 (d, *J* = 2.3 Hz, 2H), 5.10 (dq, *J* = 2.6, 1.2 Hz, 1H), 4.69 – 4.51 (m, 3H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.04 (ddd, *J* = 8.7, 2.7, 1.6 Hz, 1H), 3.82 – 3.66 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.28, 139.43, 138.38, 138.01, 135.75, 129.89, 128.55, 128.37, 128.30, 128.21, 128.04, 127.88, 127.75, 127.70, 127.51, 126.62, 126.10, 77.58, 73.33, 73.10, 71.16, 70.22, 69.71, 66.50; HRMS (ESI) calcd. for $[C_{30}H_{31}O_5]^+$471.2171; found 471.2173.

tert-Butyl 2-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3c)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, (*tert*-butoxycarbonylmethylene)triphenylphosphorane **2.2c** (56.4 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction

mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3c** was obtained (41.0 mg, 94%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 122.9 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 10H), 6.23 (s, 1H), 5.91 (s, 3H), 5.06 – 4.99 (m, 1H), 4.69 – 4.55 (m, 3H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.05 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.83 – 3.66 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.70, 141.03, 138.43, 138.06, 130.34, 128.37, 128.29, 127.89, 127.74, 127.69, 127.48, 125.69, 124.94, 81.11, 77.62, 73.32, 73.22, 71.17, 70.31, 69.79, 28.07; HRMS (ESI) calcd. for $[C_{27}H_{32}O_5Na]^+$459.2147; found 459.2148.

Ethyl 2-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*threo*-hex-2-enopyranosyl) acrylate (2.3d)

To a solution of glycal **2.1b** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried

over anhydrous Na_2SO_4 and concentrated. **2.3d** was obtained (23.7 mg, 58%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -2.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 10H), 6.39 – 6.33 (m, 1H), 6.15 – 6.06 (m, 2H), 6.02 – 5.96 (m, 1H), 5.08 – 5.03 (m, 1H), 4.68 – 4.50 (m, 4H), 4.29 – 4.19 (m, 2H), 3.96 – 3.91 (m, 1H), 3.90 – 3.85 (m, 1H), 3.86 – 3.75 (m, 2H), 1.31 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.54, 139.06, 138.86, 138.33, 133.59, 128.35, 128.29, 127.76, 127.68, 127.57, 127.50, 126.33, 123.56, 77.20, 73.51, 73.25, 70.34, 69.91, 68.12, 60.78, 14.19; HRMS (ESI) calcd. for $[C_{25}H_{29}O_5]^+$409.2015; found 409.2012.

Ethyl 2-(2,3,6-dideoxy-4-*O*-(phenylmethyl)-*β*-L-*erythro*-hex-2-enopyranosyl) acrylate (2.3e)

To a solution of glycal **2.1c** (32.0 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3e** was obtained (16.9 mg, 56%) as pale yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 2.7

(*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H), 6.33 (s, 1H), 6.01 – 5.84 (m, 3H), 5.07 – 5.05 (m, 1H), 4.72 – 4.56 (m, 2H), 4.26 (qd, *J* = 7.2, 1.9 Hz, 2H), 3.78 – 3.74 (m, 1H), 3.73 – 3.66 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.54, 140.01, 138.19, 130.03, 128.42, 127.90, 127.77, 126.17, 125.89, 76.12, 73.94, 72.90, 71.14, 60.77, 18.75, 14.17; HRMS (ESI) calcd. for $[C_{18}H_{23}O_4]^+$303.1596; found 303.1599.

Ethyl 2-(2,3-dideoxy-4-*O*-(phenylmethyl)-*β*-D-*erythro*-pent-2-enopyranosyl) acrylate (2.3f)

To a solution of glycal **2.1d** (30.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3f** was obtained (27.4 mg, 95%) as colorless oil after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 71.6 (*c* = 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 6.37 – 6.30 (m, 1H), 6.07 – 5.98 (m, 1H), 5.98 – 5.89 (m, 1H), 5.84 – 5.79 (m, 1H), 5.12 – 5.07 (m, 1H), 4.63 (d, *J* = 1.5 Hz, 2H), 4.25 (qd, *J* = 7.1, 2.9 Hz, 2H), 4.08 – 3.96 (m,

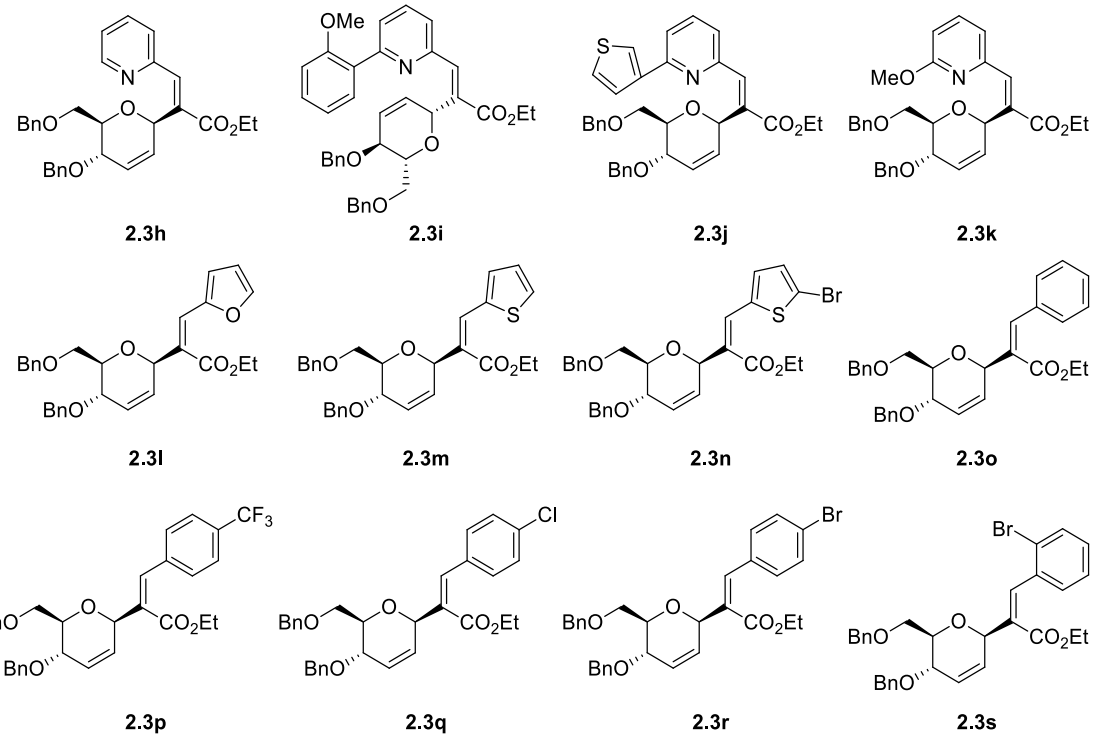
2H), 3.75 – 3.64 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.71, 138.94, 138.33, 130.35, 128.44, 127.73, 126.69, 126.48, 71.51, 70.75, 68.87, 65.95, 60.95, 14.17; HRMS (ESI) calcd. for $[C_{17}H_{21}O_4]^+$289.1440; found 289.1443.

Ethyl 2-(2,3-dideoxy-4-*O*-(phenylmethyl)-*β*-D-*threo*-pent-2-enopyranosyl) acrylate (2.3g)

To a solution of glycal **2.1e** (30.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, paraformaldehyde (16 mg) was added and the reaction mixture was stirred for another 24 h at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3g** was obtained (17.3 mg, 60%) as colorless oil after flash chromatography on silica (8:1, *n*-Hexane/EtOAc). Obtained as a 2:1 mixture of diastereomers about the anomeric position. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 – 7.27 (m, 5H, both isomers), 6.38 (d, J = 2.7 Hz, 1H, minor isomer), 6.34 (d, J = 2.8 Hz, 1H, major isomer), 6.05 – 6.03 (m, 1H, minor isomer), 6.03 – 6.00 (m, 2H, major isomer), 5.97 – 5.92 (m, 2H, minor isomer), 5.82 (dd, J = 2.9, 1.4 Hz, 1H, major isomer), 5.12 – 5.08 (m, 1H, major isomer), 5.04 – 4.99 (m, 1H, minor isomer), 4.68 – 4.59 (m, 2H, both isomers), 4.30 – 4.18 (m, 2H, both isomers), 4.07 –

4.04 (m, 1H, minor isomer), 4.03 – 3.98 (m, 2H, major isomer), 3.93 – 3.88 (m, 1H, minor isomer), 3.81 (dt, *J* = 12.0, 3.2 Hz, 1H, minor isomer), 3.74 – 3.66 (m, 1H, major isomer), 1.30 – 1.34 (m, 3H, both isomers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.74, 165.70, 138.94, 138.72, 138.49, 138.33, 131.72, 130.35, 128.43, 128.41, 127.73, 127.66, 126.78, 126.69, 126.47, 125.42, 71.50, 71.49, 70.74, 70.36, 68.87, 68.49, 66.25, 65.94, 60.94, 60.90, 14.19, 14.17; HRMS (ESI) calcd. for $[C_{17}H_{20}O_4Na]^+$311.1259; found 311.1261.

Preparation of *C*-vinyl glycosides (2.3h-s):



(*E*)-Ethyl 3-(2-pyridinyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3h)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added

dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 2-pyridinecarboxaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3h** was obtained (16.5 mg, 34%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 9.6$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 – 8.58 (m, 1H), 7.62 – 7.48 (m, 3H), 7.38 – 7.22 (m, 9H), 7.17 (ddd, *J* = 7.4, 4.8, 1.3 Hz, 1H), 6.02 – 5.91 (m, 3H), 4.69 – 4.49 (m, 4H), 4.29 – 4.14 (m, 2H), 4.14 – 4.06 (m, 1H), 3.81 – 3.71 (m, 2H), 3.66 (dd, *J* = 10.8, 5.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.84, 153.97, 149.40, 139.08, 138.56, 138.21, 136.11, 135.39, 130.29, 128.36, 128.22, 127.87, 127.69, 127.39, 125.99, 125.44, 122.89, 77.46, 73.28, 71.29, 71.02, 70.26, 70.06, 60.86, 14.14; HRMS (ESI) calcd. for $[C_{30}H_{31}NO_5Na]^+$508.2100; found 508.2109.

(*E*)-Ethyl 3-[6-(2-methoxyphenyl)-2-pyridinyl]-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3i)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room

temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 6-(2-methoxyphenyl)-2-pyridinecarboxaldehyde (42.6 mg, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3i** was obtained (29.0 mg, 49%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 26.6 (*c* = 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.77 (m, 2H), 7.68 – 7.59 (m, 2H), 7.43 – 7.28 (m, 7H), 7.09 – 7.03 (m, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 5.98 (s, 2H), 4.67 – 4.48 (m, 4H), 4.26 – 4.16 (m, 2H), 4.12 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.86 (s, 3H), 3.83 – 3.66 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.03, 157.13, 155.66, 153.40, 139.12, 138.65, 138.30, 135.86, 135.23, 131.25, 130.27, 130.09, 128.35, 128.20, 127.89, 127.67, 127.33, 125.55, 124.52, 124.03, 121.13, 111.42, 77.45, 73.31, 71.40, 71.03, 70.49, 70.12, 60.75, 55.58, 14.16; HRMS (ESI) calcd. for $[C_{37}H_{37}NO_6Na]^+$614.2519; found 614.2522.

(*E*)-Ethyl 3-[6-(3-thienyl)-2-pyridinyl]-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3j)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room

temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.). and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 6-(3-thienyl)pyridine-2-carboxaldehyde (37.8 mg, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3j** was obtained (47.6 mg, 84%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 68.6$ (*c* = 0.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.77 (m, 2H), 7.68 – 7.59 (m, 2H), 7.42 – 7.23 (m, 12H), 7.09 – 7.03 (m, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 5.98 (s, 2H), 4.67 – 4.48 (m, 4H), 4.26 – 4.16 (m, 2H), 4.12 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.86 (s, 3H), 3.83 – 3.66 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.07, 153.59, 153.02, 141.86, 138.54, 138.14, 137.68, 137.05, 136.06, 129.95, 128.39, 128.21, 127.95, 127.73, 127.68, 127.36, 126.45, 126.16, 126.15, 124.33, 124.00, 119.38, 77.41, 73.28, 71.32, 71.23, 70.45, 70.01, 60.81, 14.15; HRMS (ESI) calcd. for $[C_{34}H_{33}NO_5SNa]^+$590.1977; found 590.1984.

(*E*)-Ethyl 3-(6-methoxy-2-pyridinyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3k)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room

temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 6-methoxy-2-pyridinecarboxaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3k** was obtained (31.4 mg, 61%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 105.0 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.36 – 7.27 (m, 10H), 7.05 – 6.98 (m, 1H), 6.69 (dd, *J* = 8.4, 0.7 Hz, 1H), 6.51 – 6.44 (m, 1H), 6.07 – 5.95 (m, 2H), 4.72 – 4.47 (m, 5H), 4.25 – 4.15 (m, 2H), 4.14 – 4.10 (m, 1H), 3.89 (s, 3H), 3.80 – 3.68 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.20, 163.36, 151.16, 138.79, 138.58, 138.14, 137.03, 135.48, 130.11, 128.41, 128.23, 127.98, 127.77, 127.69, 127.39, 125.79, 120.07, 111.27, 77.61, 73.31, 71.42, 71.35, 70.44, 70.04, 60.75, 53.74, 14.16; HRMS (ESI) calcd. for $[C_{31}H_{33}NO_6Na]^+$538.2206; found 538.2205.

(*Z*)-Ethyl 3-(2-furyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3l)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was

added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, furan-2-carboxaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3l** was obtained (25.1 mg, 53%) as orange oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 42.3$ (*c* = 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.44 (m, 2H), 7.30 (m, 10H), 6.85 – 6.77 (m, 1H), 6.41 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.02 (dt, *J* = 10.3, 2.2 Hz, 1H), 5.82 (dt, *J* = 10.3, 1.8 Hz, 1H), 5.75 (q, *J* = 2.7 Hz, 1H), 4.69 – 4.50 (m, 4H), 4.19 (qd, *J* = 7.1, 2.8 Hz, 3H), 3.87 – 3.78 (m, 2H), 3.76 – 3.70 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.64, 150.15, 144.89, 138.51, 138.18, 129.95, 128.39, 128.36, 128.19, 127.87, 127.70, 127.67, 127.40, 127.36, 125.54, 117.29, 112.28, 77.83, 73.28, 71.72, 71.10, 70.32, 70.04, 60.70, 14.16; HRMS (ESI) calcd. for $[C_{29}H_{30}O_6Na]^+$497.1940; found 497.1940.

(*Z*)-Ethyl 3-(2-thienyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3m)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2

equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 2-thiophenecarboxaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3m** was obtained (15.7 mg, 32%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 48.2 (*c* = 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.86 (m, 1H), 7.47 – 7.43 (m, 1H), 7.38 (dt, *J* = 3.6, 1.0 Hz, 1H), 7.36 – 7.26 (m, 10H), 7.01 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.02 (ddd, *J* = 10.4, 2.8, 1.8 Hz, 1H), 5.82 (dt, *J* = 10.4, 1.7 Hz, 1H), 5.59 – 5.52 (m, 1H), 4.74 – 4.48 (m, 4H), 4.31 – 4.17 (m, 3H), 3.91 – 3.81 (m, 2H), 3.80 – 3.73 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.65, 138.55, 138.20, 136.87, 135.27, 133.42, 130.64, 129.69, 128.38, 128.19, 127.86, 127.80, 127.72, 127.66, 127.49, 127.36, 125.70, 78.17, 73.31, 71.76, 71.16, 70.48, 70.06, 60.81, 14.21; HRMS (ESI) calcd. for $[C_{29}H_{30}O_5SNa]^+$513.1712; found 513.1713.

(*Z*)-Ethyl 3-(5-bromo-2-thienyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3n)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2

equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 5-bromo-2-thiophenecarboxaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3n** was obtained (29.0 mg, 51%) as yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 23.0 (*c* = 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 0.7 Hz, 1H), 7.35 – 7.27 (m, 10H), 7.11 (dd, *J* = 3.9, 0.8 Hz, 1H), 6.95 (d, *J* = 3.9 Hz, 1H), 6.01 (ddd, *J* = 10.3, 2.8, 1.8 Hz, 1H), 5.78 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.45 (td, *J* = 2.9, 1.6 Hz, 1H), 4.70 – 4.49 (m, 4H), 4.27 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.90 – 3.83 (m, 1H), 3.82 – 3.74 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.52, 138.36, 138.31, 138.03, 134.53, 134.14, 130.14, 129.28, 128.39, 128.24, 127.90, 127.75, 127.69, 127.52, 127.41, 125.94, 118.79, 78.32, 73.29, 71.94, 71.14, 70.19, 69.77, 61.02, 14.21; HRMS (ESI) calcd. for $[C_{29}H_{29}BrO_5SNa]^+$591.0817; found 591.0823.

(*Z*)-Ethyl 3-phenyl-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3o)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2

equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, benzaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3o** was obtained (15.5 mg, 32%) as colorless oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 3.0$; (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.85 (m, 1H), 7.47 (dd, *J* = 6.9, 2.9 Hz, 2H), 7.32 (m, 13H), 5.94 (dt, *J* = 10.3, 2.3 Hz, 1H), 5.79 (dt, *J* = 10.3, 1.7 Hz, 1H), 5.27 – 5.20 (m, 1H), 4.68 – 4.46 (m, 4H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.16 – 4.07 (m, 1H), 3.83 – 3.75 (m, 2H), 3.72 – 3.66 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.60, 143.96, 138.57, 138.14, 134.66, 131.33, 130.24, 129.68, 129.68, 128.92, 128.37, 128.23, 127.86, 127.71, 127.65, 127.40, 125.44, 77.74, 73.30, 71.32, 71.04, 70.44, 70.15, 60.78, 14.17; HRMS (ESI) calcd. for $[C_{31}H_{33}O_5]^+$485.2328; found 485.2323.

(*Z*)-Ethyl 3-(4-trifluoromethylphenyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3p)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was

stirred at 60 °C for 42 h. After cooling to room temperature, 4-(trifluoromethyl)benzaldehyde (0.03 mL, 0.20 mmol, 2 equiv) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3p** was obtained (24.3 mg, 44%) as yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 3.9 (*c* = 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 1H), 7.62 – 7.55 (m, 2H), 7.50 – 7.43 (m, 2H), 7.35 – 7.26 (m, 10H), 5.90 (dt, *J* = 10.4, 2.2 Hz, 1H), 5.74 (dt, *J* = 10.3, 1.8 Hz, 1H), 5.19 – 5.13 (m, 1H), 4.66 – 4.44 (m, 4H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.09 – 4.00 (m, 1H), 3.83 – 3.71 (m, 2H), 3.62 (dd, *J* = 10.4, 6.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.20, 142.44, 138.35, 138.26, 137.97, 133.11, 130.70, 130.38, 129.89, 129.71, 128.40, 128.27, 127.90, 127.81, 127.73, 127.58, 125.72 (q, $J_{(C-F)}$ = 3.7 Hz), 125.04, 125.00, 124.96, 124.93, 77.77, 77.20, 73.38, 71.28, 71.04, 70.12, 70.01, 61.11, 14.16; HRMS (ESI) calcd. for $[C_{32}H_{31}O_5F_3Na]^+$575.2021; found 575.2021.

(*Z*)-Ethyl 3-(4-chlorophenyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3q)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was

stirred at 60 °C for 42 h. After cooling to room temperature, 4-chlorobenzaldehyde (28.1 mg, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3q** was obtained (20.7 mg, 40%) as yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 46.9 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.79 (m, 1H), 7.47 – 7.40 (m, 2H), 7.37 – 7.26 (m, 10H), 7.24 – 7.17 (m, 2H), 5.92 (dt, *J* = 10.4, 2.2 Hz, 1H), 5.74 (dt, *J* = 10.3, 1.8 Hz, 1H), 5.21 – 5.15 (m, 1H), 4.67 – 4.45 (m, 4H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.16 – 4.05 (m, 1H), 3.85 – 3.73 (m, 2H), 3.67 (dd, *J* = 10.3, 5.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.42, 142.95, 138.43, 138.03, 135.04, 133.02, 131.65, 131.17, 129.96, 128.39, 128.28, 127.90, 127.78, 127.73, 127.54, 125.57, 77.83, 73.35, 71.30, 71.06, 70.26, 70.03, 60.95, 14.16; HRMS (ESI) calcd. for $[C_{31}H_{31}O_5ClNa]^+$541.1759; found 541.1748.

(*Z*)-Ethyl 3-(4-bromophenyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3r)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 4-bromobenzaldehyde

(37.0 mg, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3r** was obtained (27.0 mg, 48%) as yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 34.5$ (*c* = 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.46 – 7.24 (m, 13H), 5.91 (dt, *J* = 10.4, 2.2 Hz, 1H), 5.74 (dt, *J* = 10.3, 1.8 Hz, 1H), 5.21 – 5.14 (m, 1H), 4.67 – 4.45 (m, 4H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.16 – 4.05 (m, 1H), 3.84 – 3.74 (m, 2H), 3.66 (dd, *J* = 10.3, 5.9 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.43, 143.01, 138.44, 138.04, 133.50, 131.75, 131.41, 131.37, 129.94, 128.42, 128.31, 127.92, 127.80, 127.76, 127.58, 125.61, 123.40, 77.84, 73.38, 71.32, 71.07, 70.27, 70.05, 60.98, 14.18; HRMS (ESI) calcd. for $[C_{31}H_{31}O_5BrNa]^+$585.1253; found 585.1262.

(*Z*)-Ethyl 3-(2-bromophenyl)-(2,3-dideoxy-4,6-bis-*O*-(phenylmethyl)-*β*-D-*erythro*-hex-2-enopyranosyl) acrylate (2.3s)

To a solution of glycal **2.1a** (42.6 mg, 0.10 mmol, 1 equiv.) in DMF (0.8 mL), a solution of Et_2Zn (1.0 M in Hexanes, 0.15 mL, 0.15 mmol, 1.5 equiv.) was added dropwise over 1 min at 25 °C under nitrogen. After stirring for 4 h at room temperature, *P*-ylide **2.2a** (52.2 mg, 0.15 mmol, 1.5 equiv.) in DMF (0.8 mL) was added to the mixture dropwise, followed by $Pd(OAc)_2$ (4.49 mg, 0.02 mmol, 0.2 equiv.) and DPPB ligand (12.8 mg, 0.03 mmol, 0.3 equiv.). The reaction mixture was stirred at 60 °C for 42 h. After cooling to room temperature, 2-bromobenzaldehyde (0.02 mL, 0.20 mmol, 2 equiv.) was added and the reaction mixture was stirred for

another 24 h at 70 °C. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **2.3s** was obtained (32.0 mg, 57%) as yellow oil after flash chromatography on silica (10:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22} = 44.5$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 2.4 Hz, 1H), 7.57 – 7.42 (m, 3H), 7.41 – 7.27 (m, 10H), 6.05 – 5.93 (m, 1H), 5.92 – 5.82 (m, 2H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.58 – 4.47 (m, 3H), 4.28 – 4.15 (m, 2H), 4.08 – 4.11 (m, 1H), 3.79 – 3.71 (m, 2H), 3.65 (dd, *J* = 10.8, 5.8 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.64, 151.97, 148.26, 138.46, 138.12, 137.93, 135.85, 135.81, 131.48, 129.89, 128.36, 128.30, 128.25, 127.88, 127.72, 127.64, 127.47, 126.76, 125.68, 77.50, 73.31, 71.26, 71.03, 70.08, 69.94, 60.99, 14.11; HRMS (ESI) calcd. for $[C_{31}H_{31}O_5BrNa]^+$585.1253; found 585.1255.

2.5 References

1. Leng, W.-L.; Liao, H.; Yao, H.; Ang, Z.-E.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2017,** *19*, 416-419.
2. (a) Barnes, J. A.; Coore, H. G.; Mohammed, A. H.; Sharma, R. K., *Signal transduction mechanisms*. Springer Science & Business Media: 2013; Vol. 15; (b) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981,** *103*, 2469-2471.
3. (a) Härle, J.; Günther, S.; Lauinger, B.; Weber, M.; Kammerer, B.; Zechel, D. L.; Luzhetskyy, A.; Bechthold, A. *Chem. Biol.* **2011,** *18*, 520-530; (b) Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem. Int. Ed.* **2004,** *43*, 3818-3822; (c) Weatherman, R. V.; Kiessling, L. L. *J. Org. Chem.* **1996,** *61*, 534-538.
4. (a) Colombo, M. I.; Zinczuk, J.; Ruveda, E. A. *Tetrahedron* **1992,** *48*, 963-1037; (b) Ookura, R.; Kito, K.; Saito, Y.; Kusumi, T.; Ooi, T. *Chem. Lett.* **2009,** *38*, 384-384.
5. (a) Bai, Y.; Leow, M.; Zeng, J.; Liu, X.-W. *Org. Lett.* **2011,** *13*, 5648-5651; (b) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990,** *55*, 2572-2574.
6. (a) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2012,** *51*, 11101-11104; (b) Cheng, G.; Fan, R.; Hernández-Torres, J. M.; Boulineau, F. P.; Wei, A. *Org. Lett.* **2007,** *9*, 4849-4852; (c) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000,** *2*, 2707-2709; (d) Takahashi, T.; Ebata, S.; Yamada, H. *Synlett* **1998**, 381-382.
7. (a) Tatina, M. B.; Kusunuru, A. K.; Yousuf, S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2014,** *12*, 7900-7903; (b) Tatina, M.; Kusunuru, A. K.; Yousuf, S. K.; Mukherjee, D. *Chem. Commun.* **2013,** *49*, 11409-11411.
8. (a) Pasetto, P.; Walczak, M. C. *Tetrahedron* **2009,** *65*, 8468-8477; (b) Giguère, D.; Cloutier, P.; Roy, R. *J. Org. Chem.* **2009,** *74*, 8480-8483; (c) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron* **2005,** *61*, 7184-7192.
9. (a) McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012,** *2*, 1563-1595; (b) Nishikawa, T.; Adachi, M.; Isobe, M., C-Glycosylation. In *Glycoscience*, Springer: 2008; pp 755-811; (c) Somsák, L. *Chem. Rev.* **2001,** *101*, 81-136; (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998,** *54*, 9913-9959; (e) Postema, M. H. *Tetrahedron* **1992,** *48*, 8545-8599.
10. (a) Vieira, A. S.; Fiorante, P. F.; Hough, T. L.; Ferreira, F. P.; Ludtke, D. S.; Stefani, H. A. *Org. Lett.* **2008,** *10*, 5215-5218; (b) Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002,** *4*, 293-295; (c) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180-1181.
11. Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954,** *87*, 1318-1330.
12. Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013,** *42*, 6670-6696.
13. Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Recl.* **1997**, 1283-1301.
14. Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 0579-0594.
15. Barnhardt, R. G.; McEwen, W. E. *J. Am. Chem. Soc.* **1967,** *89*, 7009-7014.
16. Tomilov, Y. V.; Platonov, D. N.; Dorokhov, D. V.; Nefedov, O. M. *Tetrahedron Lett.* **2007,** *48*, 883-886.

17. Ykman, P.; L'abbé, G.; Smets, G. *Tetrahedron* **1971,** *27*, 845-849.
18. Ohshiro, Y.; Mori, Y.; Minami, T.; Agawa, T. *J. Org. Chem.* **1970,** *35*, 2076-2077.
19. Abdou, W. M.; Fahmy, A. F.; Kamel, A. A. *Heteroat. Chem.* **2002,** *13*, 357-365.
20. Gonsalves, A. M. A. R.; Cabral, A. M.; e Melo, T. M. P.; Gilchrist, T. L. *Synthesis* **1997**, 673-676.
21. Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008,** *130*, 2456-2457.
22. (a) Lin, A.; Wang, J.; Mao, H.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Org. Lett.* **2011,** *13*, 4176-4179; (b) Allu, S.; Selvakumar, S.; Singh, V. K. *Tetrahedron Lett.* **2010,** *51*, 446-448.
23. (a) Xu, S.; Zhu, S.; Shang, J.; Zhang, J.; Tang, Y.; Dou, J. *J. Org. Chem.* **2014,** *79*, 3696-3703; (b) Ma, X.-T.; Wang, Y.; Dai, R.-H.; Liu, C.-R.; Tian, S.-K. *J. Org. Chem.* **2013,** *78*, 11071-11075; (c) Lin, A.; Wang, J.; Mao, H.; Shi, Y.; Mao, Z.; Zhu, C. *Eur. J. Org. Chem.* **2013**, 6241-6245; (d) Liu, W. B.; He, H.; Dai, L. X.; You, S. L. *Chem. Eur. J.* **2010,** *16*, 7376-7379.
24. (a) Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001,** *3*, 2013-2015; (b) Daves Jr, G. D. *Acc. Chem. Res.* **1990,** *23*, 201-206; (c) Czernecki, S.; Gruy, F. *Tetrahedron Lett.* **1981,** *22*, 437-440; (d) Arai, I.; Daves Jr, G. D. *J. Am. Chem. Soc.* **1981,** *103*, 7683-7683.
25. (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003,** *125*, 12406-12407; (b) RajanBabu, T. V. *J. Org. Chem.* **1985,** *50*, 3642-3644; (c) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982,** *47*, 2812-2814.
26. (a) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012,** *4*, 130-133; (b) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011,** *111*, 1846-1913; (c) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009,** *131*, 18343-18357; (d) Kan, S. J.; Matsubara, R.; Berthiol, F.; Kobayashi, S. *Chem. Commun.* **2008**, 6354-6356; (e) You, S. L.; Dai, L. X. *Angew. Chem. Int. Ed.* **2006,** *45*, 5246-5248.
27. (a) Bai, Y.; Leng, W.-L.; Li, Y.; Liu, X.-W. *Chem. Commun.* **2014,** *50*, 13391-13393; (b) Zeng, J.; Ma, J.; Xiang, S.; Cai, S.; Liu, X. W. *Angew. Chem. Int. Ed.* **2013,** *52*, 5134-5137.
28. (a) Kochetkov, N. K.; Chernyak, A. Y. *Adv. Macromol. Carb. Res.* **1997,** *1*, 93-175; (b) Postema, M. H.; Calimente, D. *Tetrahedron Lett.* **1999,** *40*, 4755-4759; (c) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1987,** *171*, 49-57.
29. Xiang, S.; Hoang, K. L. M.; He, J.; Tan, Y. J.; Liu, X. W. *Angew. Chem. Int. Ed.* **2015,** *54*, 604-607.
30. Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004,** *126*, 1336-1337.
31. (a) Xu, S.; Zhu, S.; Shang, J.; Zhang, J.; Tang, Y.; Dou, J. *J. Org. Chem.* **2014,** *79*, 3696-3703; (b) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Chem. Eur. J.* **2010,** *16*, 7376-7379.
32. (a) Kayastha, A. K.; Jia, X. G.; Yasomanee, J. P.; Demchenko, A. V. *Org. Lett.* **2015,** *17*, 4448-4451; (b) Albano, V. G.; Natile, G.; Panunzi, A. *Coord. Chem. Rev.* **1994,** *133*, 67-114; (c) Maresca, L.; Natile, G. *Comments Inorg. Chem.* **1993,** *14*, 349-366.

33. Lin, H.-C.; Pan, J.-F.; Chen, Y.-B.; Lin, Z.-P.; Lin, C.-H. *Tetrahedron* **2011,** *67*, 6362-6368.

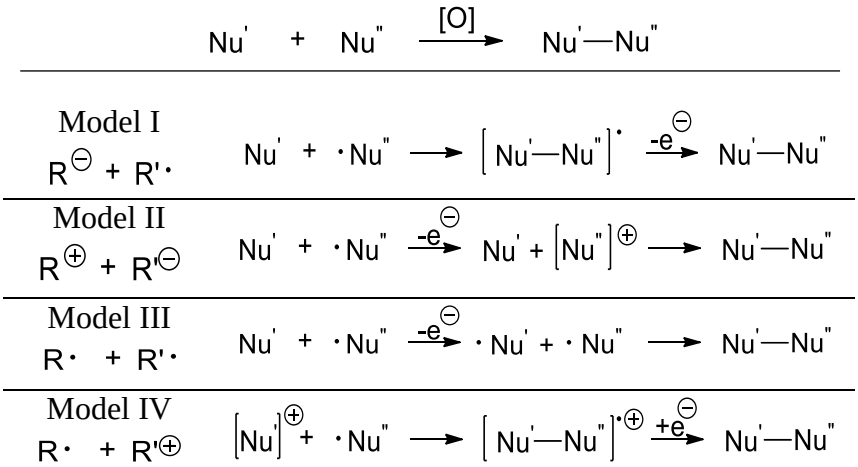
Chapter 3:

Palladium and Iridium Dual Catalysed Radical-Radical Cross-Coupling: New Insights to Stereoselective *C*-Glycosylation

3.1 Introduction

3.1.1 Radical Oxidative Cross-Coupling

Nucleophiles can participate in oxidative cross-coupling in three forms: neutral radical, cation or anion. There are generally four kinds of radical oxidative cross-coupling models (**Scheme 3.1**).[1]

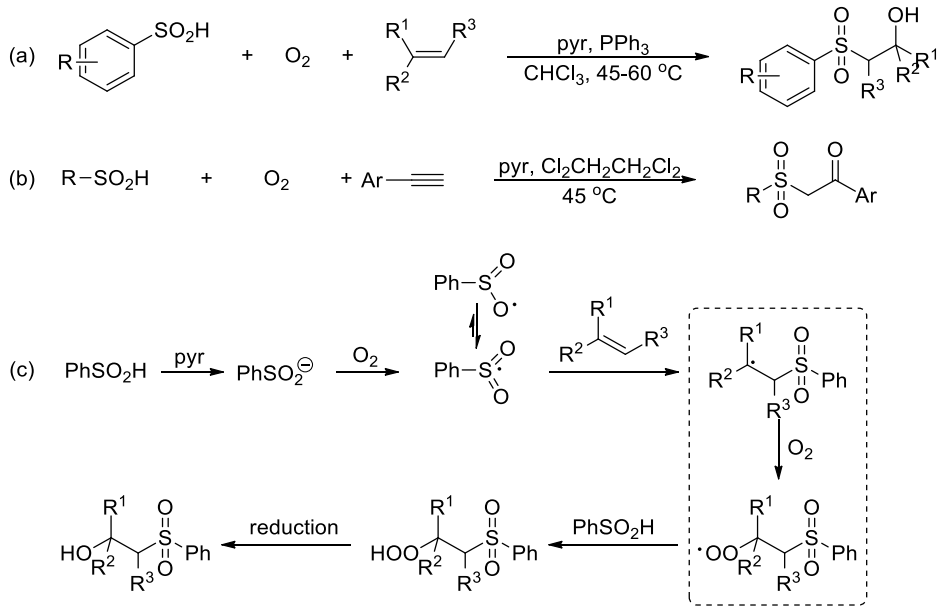


Scheme 3.1 Radical oxidative cross-coupling models

In model I involving neutral radicals, radical oxidation first occurs, resulting in bond formation. Another radical oxidation occurs to give the cross-coupled product. In model II, a two-step radical oxidation occurs to generate a cation, which then reacts with the nucleophile to give the product. In anionic model III, both nucleophiles lose an electron each and the radical-radical cross-coupling occurs. In model IV, a cation and radical react to yield a cationic radical which is reduced to obtain the product. Notably, while radical-radical couplings are very efficient, one of the main challenges of model III type radical coupling is the selective cross-coupling. In addressing this challenge, there is a need to understand the concept of persistent radical effect.[2]

The persistent radical effect helps to account for the selective formation of cross-coupled product between two radicals, in which one is a persistent radical and the other is a transient radical and both have equal rates of formation. Initial self-termination or dimerisation of the transient radical leads to an accumulation of the persistent radical over time. This increased concentration helps to accelerate the cross-coupling and suppress the self-termination of transient radicals. Five factors that can influence the persistence of radical include steric effects, stereoelectronic effects, resonance stabilisation, presence of electron-withdrawing groups and unpaired-spin delocalisation with heteroatom.[3] It is noted that benzyl radicals are classified as stabilised but transient radicals that usually undergo self-termination quickly.

An example of persistent radical is the dioxygen. Lei and co-workers demonstrated the radical-radical cross-coupling, using dioxygen and sulfinic acid with a *C2* linker, which can be alkene (**Scheme 3.2a**)[4] or alkyne (**Scheme 3.2b**)[5]. In **Scheme 3.2c**, the proposed coupling of dioxygen and the tertiary radical was shown to produce the peroxyl radical.

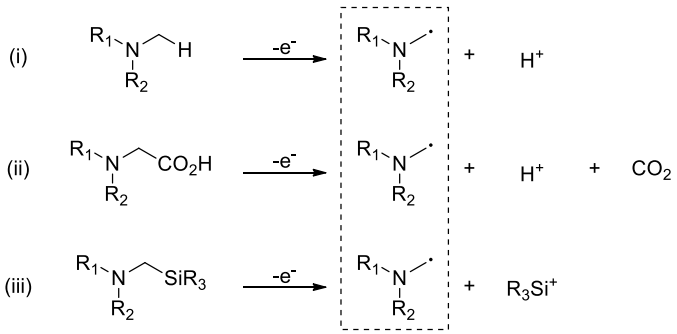


Scheme 3.2 Radical-radical cross-coupling with dioxygen and sulfinic acid

Due to the uncommon occurrence of persistent radicals, we will focus on transient radicals, particularly those that are stabilised and can be generated easily.

3.1.2 Generation of *α*-Aminoalkyl Radicals

One representative example of such radicals is the *α*-aminoalkyl radical species, in which single electron oxidation results in the generation of a radical.[6] However, due to the ease of oxidation, further oxidation could occur much easier than the initial amines, resulting in formation of imine cation. In such case, photoinduced single electron transfer (SET) is preferred in order to obtain precise control of the reaction. The electron-rich amine first undergoes SET to generate the radical cation, which then undergoes fragmentation to form a cation and neutral radical through dissociation of C-H or C-C bonds. In general, there are three common methods to generate the *α*-aminoalkyl radical species: (i) oxidative deprotonation electron transfer of amines; (ii) decarboxylation of *α*-amino acids and (iii) desilylation of *α*-silylamines (**Scheme 3.3**).[6]

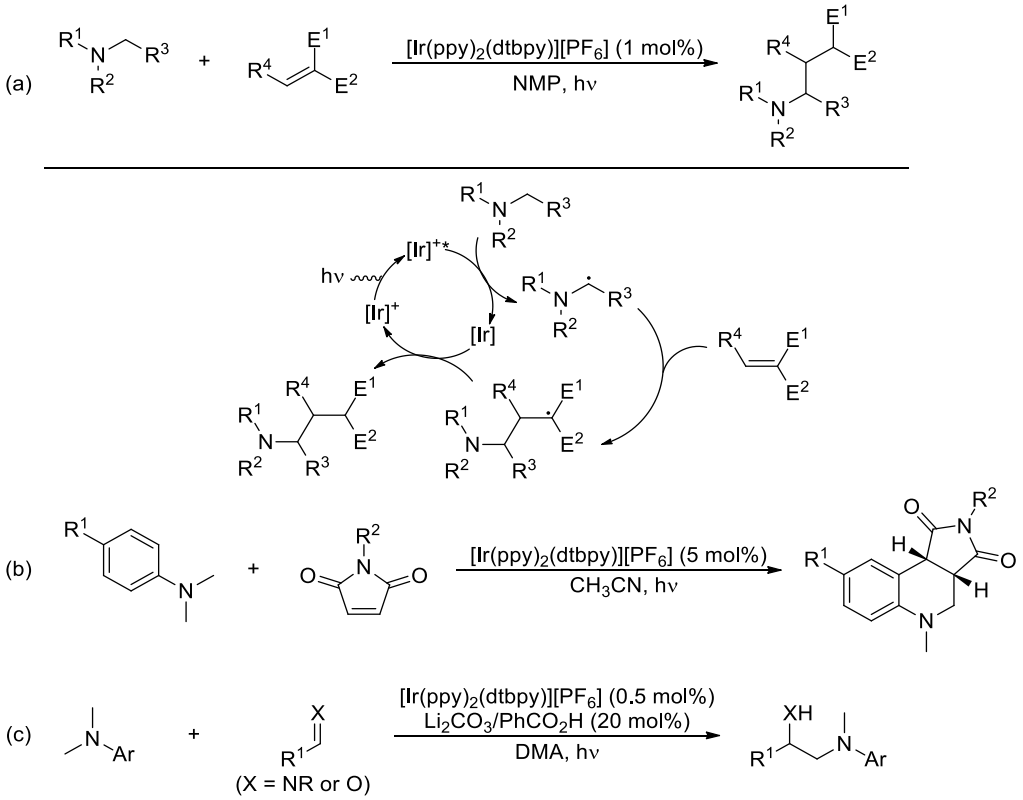


Scheme 3.3 Methods to generate *α*-aminoalkyl radical species

In the oxidative deprotonation electron transfer of amines, oxidation to form radical cation results in the increased acidity of C-H *α* position to the amine (pKa ~8), hence allowing ease of deprotonation to form neutral radical species. As mentioned earlier, further oxidation can occur and judicious design of substituents has to be

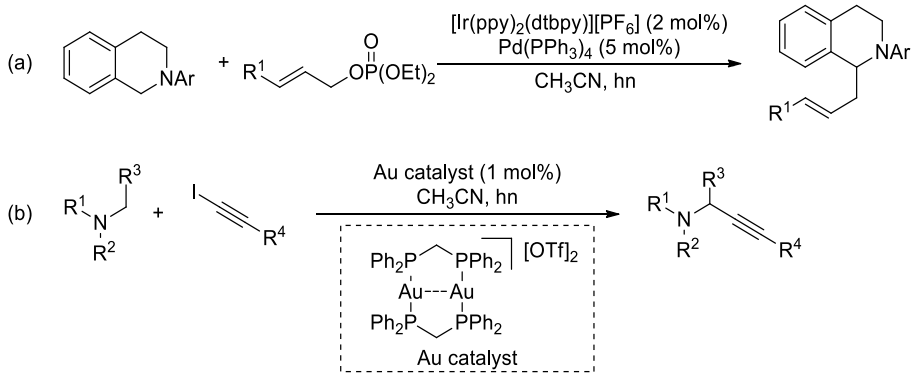
considered to circumvent the issue. The resultant α-aminoalkyl radical species can then react with various unsaturated bonds such as alkene,[7] arenes,[8] azodicarboxylate ester,[9] isocyanate,[10] imine,[11] aldehyde,[12] alkyne,[13] as well as undergo substitution with arenes,[14] halides,[15] vinylic[16] and allylic systems.[7c, 17] Through measuring the quantum yield, involvement of a radical chain mechanism can be determined if the quantum yield is above unity (Φ>1).[18]

In view of the abundance of reported works in this field, we have chosen significant findings and interesting results to be highlighted. Nishibayashi reported a photoredox catalysed addition reaction to electron deficient alkene with the quantum yield of 0.32, eliminating the possibility of radical chain from their mechanism (**Scheme 3.4a**).[7f] In a work by Yu and Bian, the addition of α-aminoalkyl radical to maleimide, which was then trapped by neighbouring arene, followed by subsequent oxidation and deprotonation to furnish the 1,2,3,4-tetrahydroquinolines (**Scheme 3.4b**).[8d] Rueping was able to apply both *N*-arylimines and aryl aldehydes successfully to the photoredox catalysed addition reaction in the presence of lithium carbonate and benzoic acid respectively (**Scheme 3.4c**).[12]



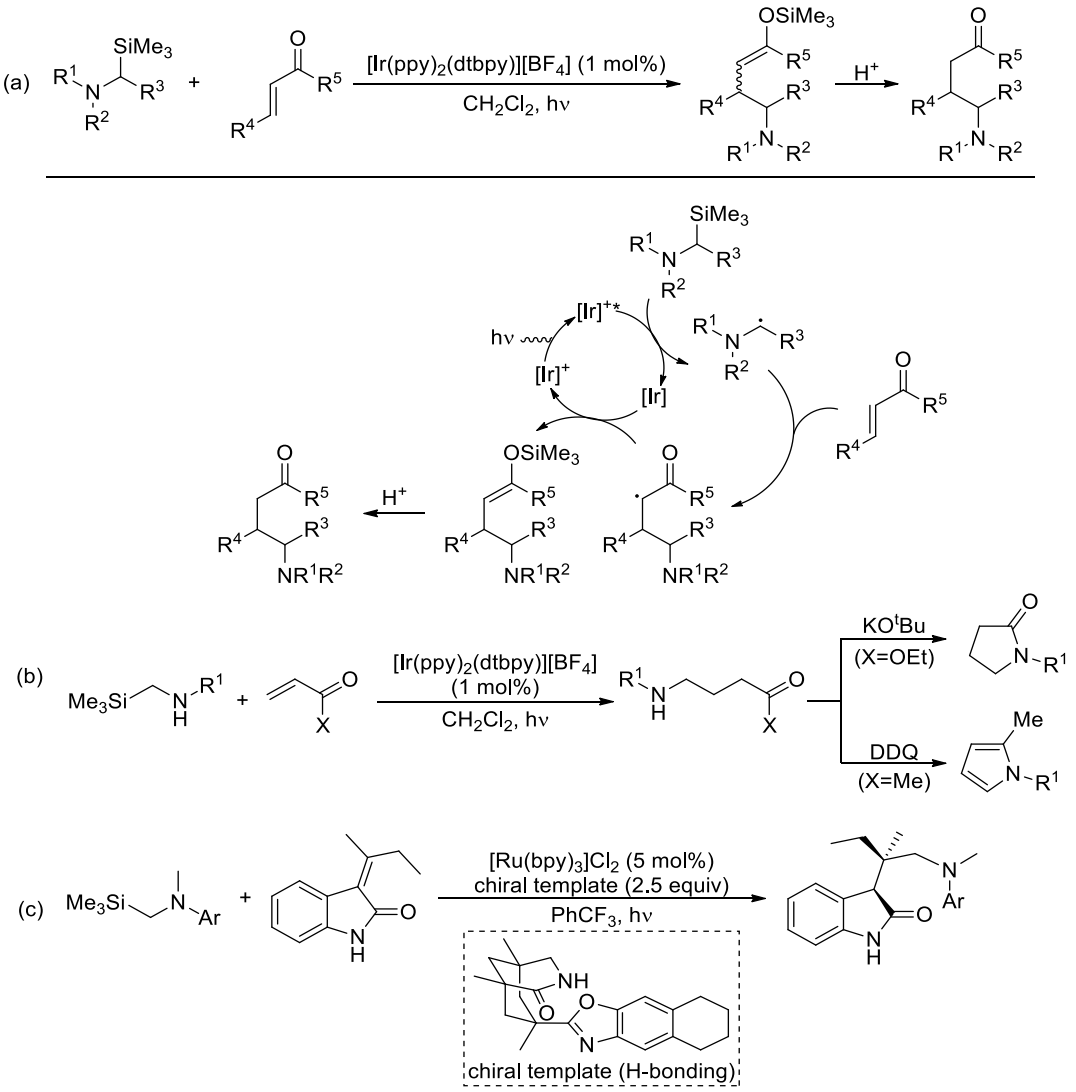
Scheme 3.4 Photocatalysed addition reactions of amines to unsaturated compounds

Notably, the combination of dual catalysts, like photoredox and transition metal catalysts can also be utilised in substitution reactions. Lu and Xiao used iridium photocatalyst with palladium catalyst for allylic substitution (**Scheme 3.5a**).[17] On the other hand, Hashmi used a bimetallic gold complex to undergo substitution of alkynyl halides (**Scheme 3.5b**).[14a] Interestingly, this gold complex was able to undergo photocatalysed reaction in the presence of sunlight.



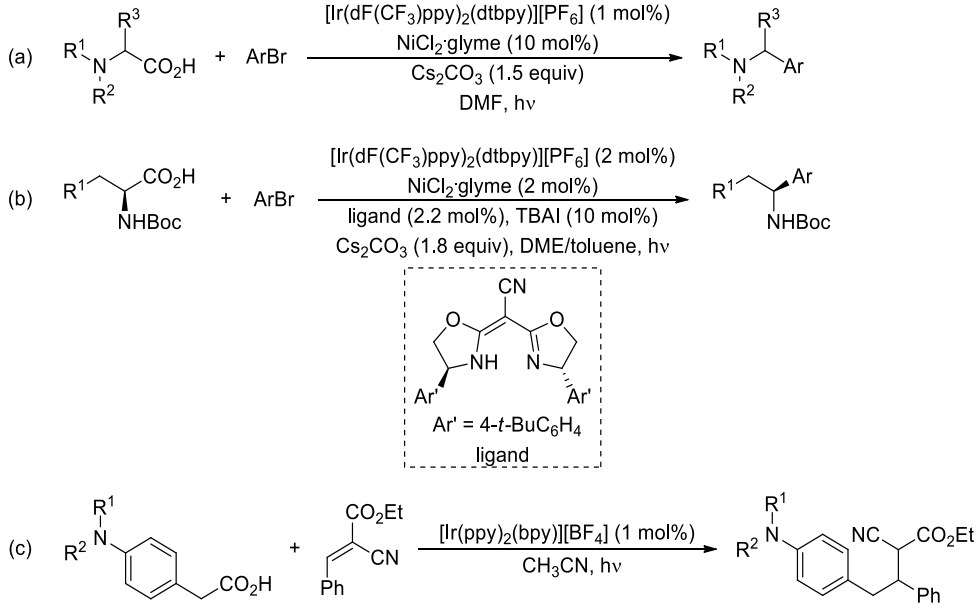
Scheme 3.5 Photocatalysed substitution reactions with amines

In a similar fashion, *α*-silylamines can be applied in these reactions, as the same *α*-aminoalkyl radical species can be generated *via* C-Si bond dissociation.[19] Nishibayashi reported the reaction of *α*-silylamines with *α,β*-unsaturated carbonyl compounds, with the quantum yield of 0.68. The mechanism was proposed to proceed by the cleavage of C-Si bond, followed by addition to the olefin, oxidation and subsequent protonation (**Scheme 3.6a**).[19d] Interestingly, when *α*-silyl secondary amines were utilised, cyclisation could proceed in one-reaction to yield *γ*-lactam and pyrrole, with addition of potassium *tert*-butoxide and 2,3-dichloro-5,6-dicyanobenzoquinone respectively (**Scheme 3.6b**).[19c] Bach later developed an enantioselective variant of the reaction, through the use of a chiral template (**Scheme 3.6c**).[19a]



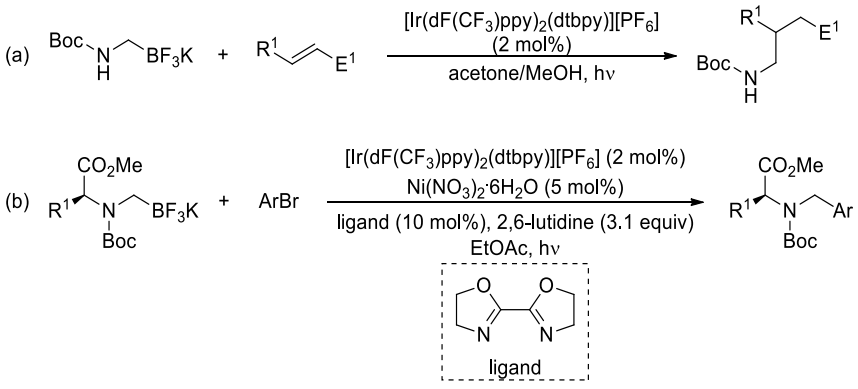
Scheme 3.6 Oxidative desilylation of α-silylamines

Another method to generate α-aminoalkyl radical species is through the decarboxylation of α-amino acids. Notably, the release of carbon dioxide drives the formation of the α-aminoalkyl radical species. Addition reactions onto unsaturated bonds as well as substitutions with aryl halides and allylic system have been developed by Macmillan, Nishibayashi and Tunge respectively (**Scheme 3.7**).[20] Notably, an enantioselective variant was successfully carried out using a chiral nickel catalyst complex.[20a]



Scheme 3.7 Oxidative decarboxylation of α-amino acids

Apart from the above-mentioned methods, single electron transmetallation is another interesting access to the radical species through using trifluoroborate salts. Molander, Koike and Akita have managed to perform single electron oxidation to achieve alkyl radicals (**Scheme 3.8**).[21]



Scheme 3.8 Single electron transmetallation of trifluoroborate salts

3.1.3 Generation of Glycosyl Radicals

As compared to the activation of glycosyl groups into polar species, such as Lewis acids, transition metals-catalysed transformation into cationic species and conversion to acyl anion equivalent by organocatalysts, the use of glycosyl functionality as a neutral radical source remains to be further explored.[22] While the radical-mediated glycosylation offers the advantages of wide functional group tolerance and good anomeric stereoselectivity, the requirements of toxic chemicals, harsh heating conditions and large excess of radical acceptor are factors that discourage the application of radical chemistry in glycosylation.

α-Selectivity is favoured when the radical is formed at the anomeric position. In tetraacetyl-substituted glycosyl substrate, the generated radical is in a boat conformation with *C2* and *C3* in the axial positions.[22b, 22c] This anomeric radical stabilisation occurs through an overlap with the adjacent *σ** orbital of C-O at *C2* position, which is further enhanced with the interaction with pyranose oxygen lone pair (**Figure 3.1**).[22b, 22c]

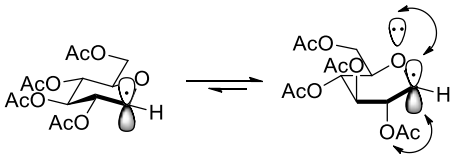
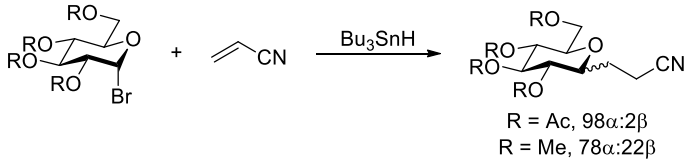


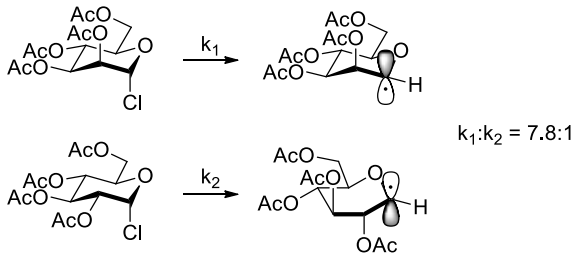
Figure 3.1 Conformations of glycosyl radical

In tin-catalysed glycosylation, Giese and co-workers were able to achieve excellent anomeric selectivity with the tetraacetyl-substituted glycosyl substrates, but when the acetyl groups were replaced by methyl groups, the selectivity decreased, which can be

attributed to the decreased stabilisation in boat conformation with poor electron-withdrawing groups (**Scheme 3.9**).[22a, 22b] In a comparative study, it was found that the mannosyl radical underwent chlorine atom abstraction much faster than glycosyl radical, forming the mannosyl radical in chair conformation (**Scheme 3.10**).[22b]

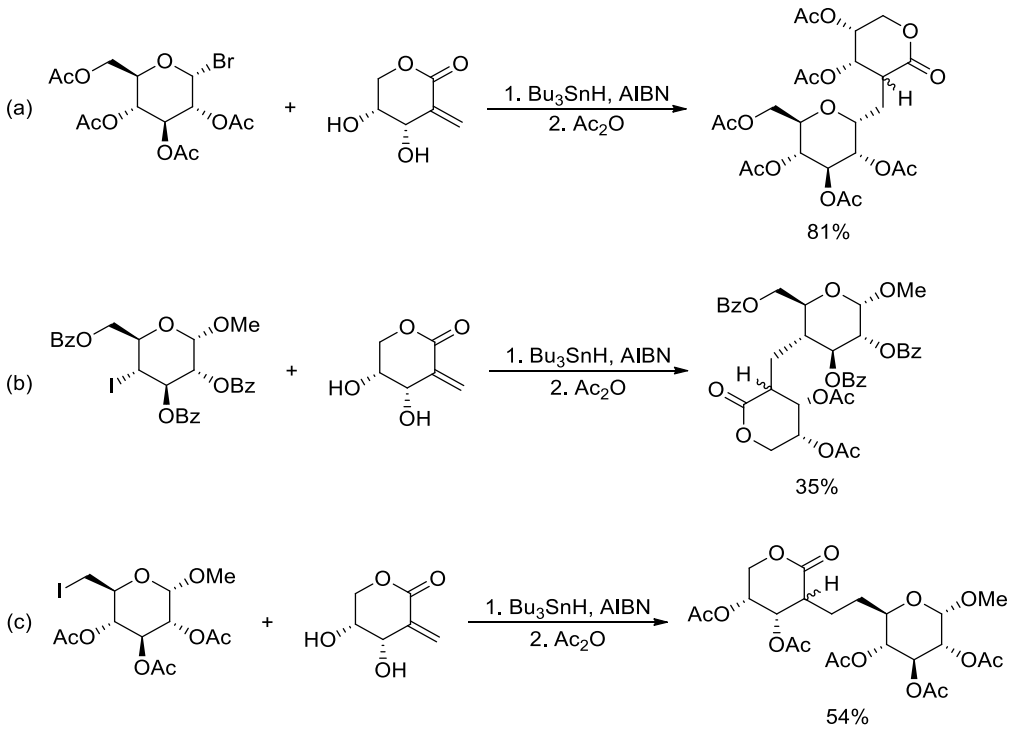


Scheme 3.9 Comparative study of acetyl and methyl protected glycosyl radicals

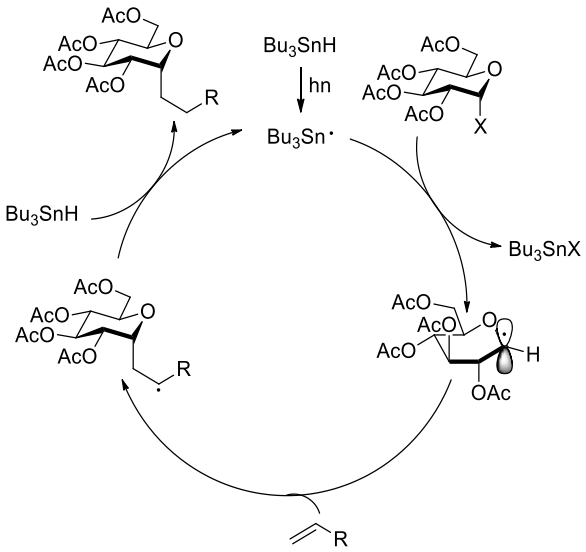


Scheme 3.10 Reactivity rates of mannosyl and glycosyl radicals

Giese then coupled this glycosyl radical to a variety of alkenes to achieve *C*-glycosides (**Scheme 3.11**).[23] Radicals were generated at different positions (*C1*, *C4* and *C6*) of glucose to explore the effect of radical position on stereoselectivity. All of them proceeded by the same mechanism (**Scheme 3.12**)[23]: tributyltin hydride undergoes photolysis to give rise to tin radical, which abstracts the halide atom to form the glycosyl radical. The addition of glycosyl radical to alkene results in a new alkyl radical, which abstracts a hydrogen atom from tributyltin hydride to regenerate the tin radical, allowing the cycle to continue.



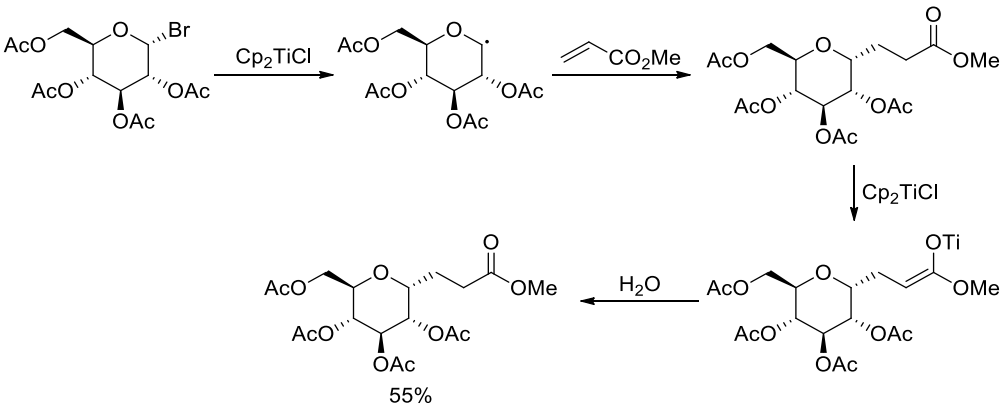
Scheme 3.11 Coupling of glycosyl radicals at different positions to alkenes



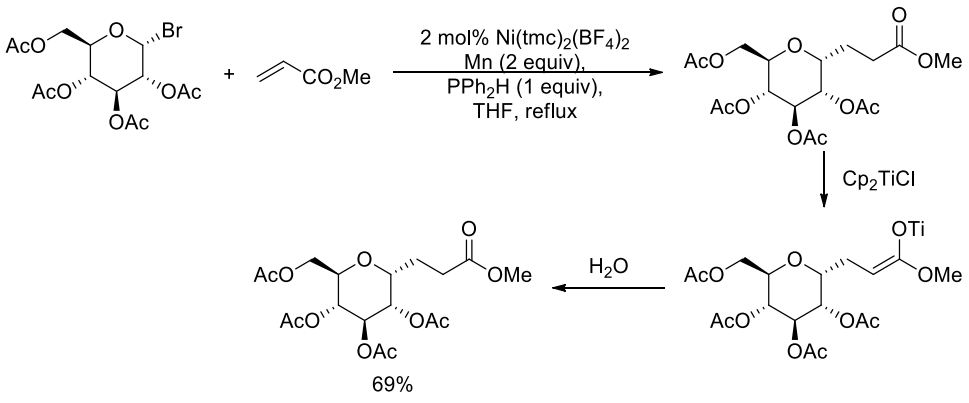
Scheme 3.12 Tin-mediated *C*-glycosylation by radical mechanism

Other metals have been developed for the radical glycosylation to avoid the toxic and harsh conditions in tin-mediated reactions. In a similar fashion, Spencer and

Schwartz utilised titanocene(III) chloride to form glycosyl radical for addition to *α,β*-unsaturated ester (**Scheme 3.13**).[24] The corresponding alkyl radical is then reduced to titanium enolate by another titanocene(III) chloride, which tautomerises to the ester upon workup. Marsden's group also reported the generation of the glycosyl radical using nickel catalyst, manganese as a reductant and phosphine to reduce the alkyl radical (**Scheme 3.14**).[25]



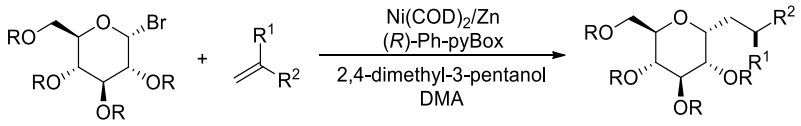
Scheme 3.13 Titanocene(III) chloride catalysed *C*-glycosylation



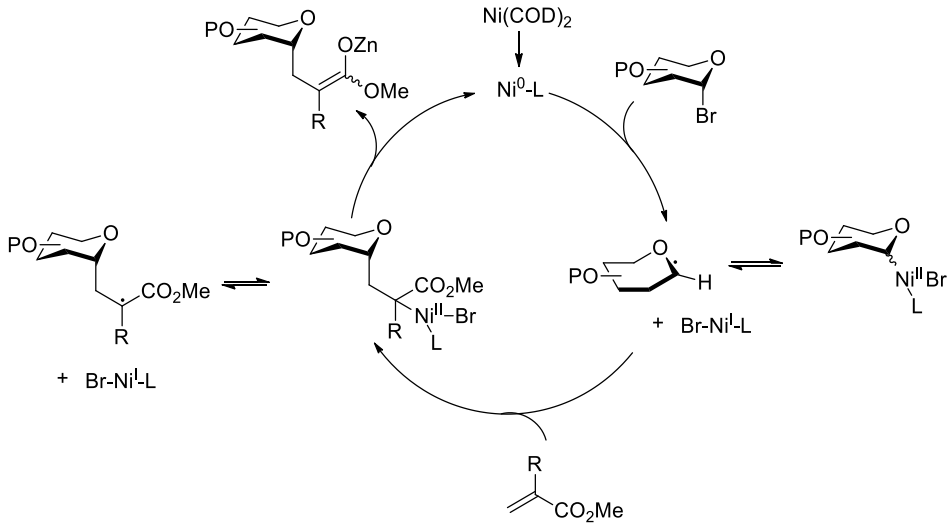
Scheme 3.14 Nickel catalysed *C*-glycosylation

Gagné's group further explored the possibility of carrying out these *C*-glycosylations under mild conditions and reducing the equivalence of alkenes

required. In his first generation of *C*-glycosylation, Ni and Zn were utilised as reductants, with 2,4-dimethyl-3-pentanol as proton source. In this reaction, glycosyl bromides and alkenes could be coupled at room temperature (**Scheme 3.15**).[26] Glycosyl radical was first generated and added to alkene to form α-radical, which was reduced by zinc to form zinc enolate (**Scheme 3.16**). Finally, protonation yielded the product. Notably, alkenes with electron-withdrawing substituents react faster and α-selectivity was observed. Geminally disubstituted alkenes were later applied and diastereoselective coupling could be achieved.



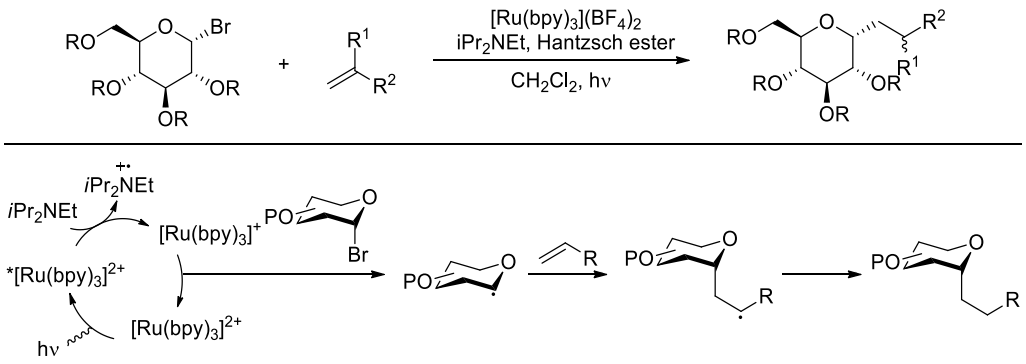
Scheme 3.15 Nickel catalysed *C*-glycosylation by Gagné



Scheme 3.16 Mechanism for nickel catalysed *C*-glycosylation by Gagné

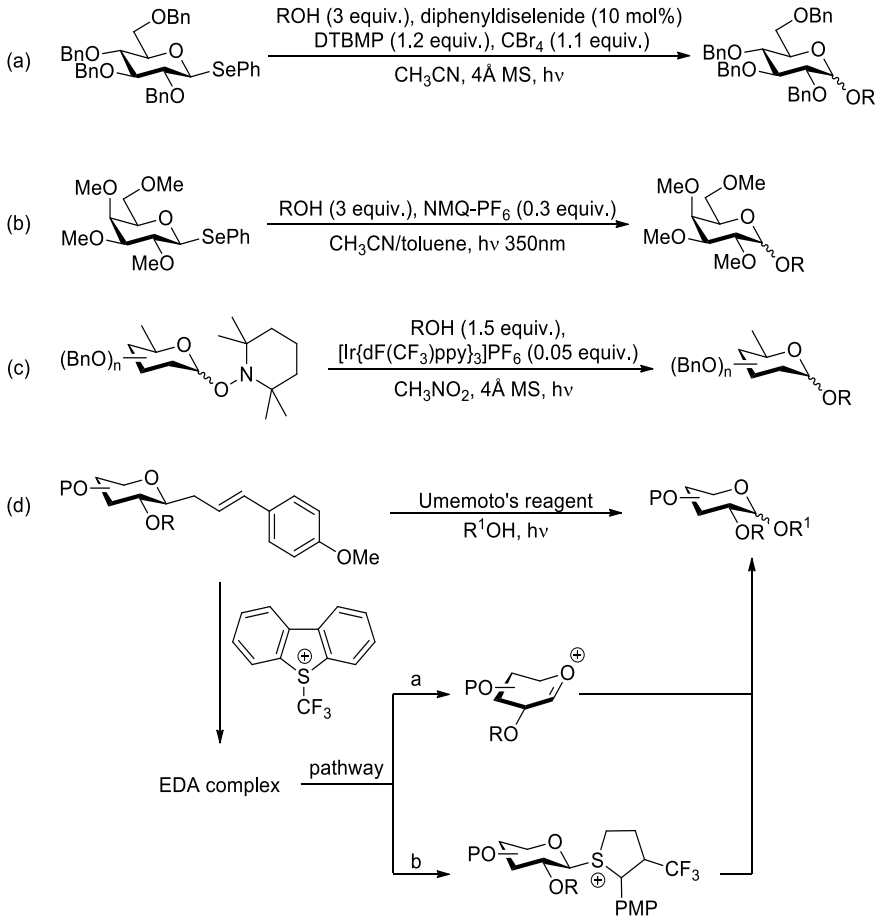
In his later work, Gagné utilised ruthenium photoredox catalyst, with *N*,*N*-diisopropylethylamine as the reductant and Hantzsch ester as the hydrogen atom

transfer source to achieve stereoselective *C*-glycosylation *via* an oxidative quenching mechanism (**Scheme 3.17**).[27] This is the one of the few reports using photoredox catalysis in glycosylations and it proceeds *via* model I cross-coupling.[27] The group also explored the factors affecting the rate of photoredox cycle and found it to be largely affected by the presence of polar cosolvents and hydrophobicity of the catalyst. Catalyst and reductant concentrations could affect the rate at low concentrations but had no significant effect at high concentrations.[28]



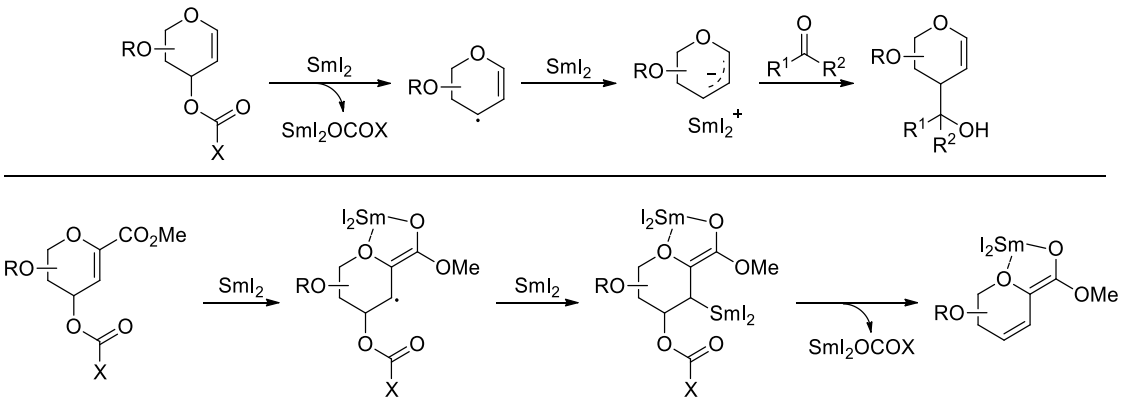
Scheme 3.17 Photoredox catalysed *C*-glycoyslation by Gagné

Photocatalysed *O*-glycosylations have been reported separately by Ragains and Crich using selenoglycosides by single-electron transfer activation (**Scheme 3.18a** and **b**).[29] Crich then used *O*-glycosyl 2,2,6,6-tetramethylpiperidinoxides in his photoinduced glycosylation (**Scheme 3.18c**).[30] Another interesting study is by Ragains where he developed an electron donor-acceptor (EDA) complex to eliminate the need for visible light photosensitisers (**Scheme 3.18d**).[31] However, in most of the cases, the stereoselectivities were moderate.



Scheme 3.18 Photoinduced glycosylations

As mentioned above, glycosyl halides are the most commonly used reagent to generate the glycosyl radical and other reagents like selenoglycosides and *O*-glycosyl 2,2,6,6-tetramethylpiperidinoxides have been used as well.[29-31] To date, the allylic glycosyl radical has yet to be utilised as a radical coupling partner. Notably, Jean-Marie's group has proposed that using samarium diiodide, they were able to obtain the allylic glycosyl radical as an intermediate, which then underwent further reduction by another molecule of samarium diiodide to become allylic anion and react with ketones, demonstrating the umpolung of glycals (**Scheme 3.19**).[32]



Scheme 3.19 Samarium diiodide mediated umpolung of glycals *via* an allylic glycosyl radical intermediate

In view of the preceding works on radical glycosylation, we envisage that the transient but stable allylic radical could potentially be applied for cross-coupling with other stabilised *C*-radicals, resulting in *C*-glycosylation. This would open up opportunities for coupling seemingly unreactive reaction partners through dual activation of the starting materials.

3.2 Results and Discussion

3.2.1 Condition Optimisation

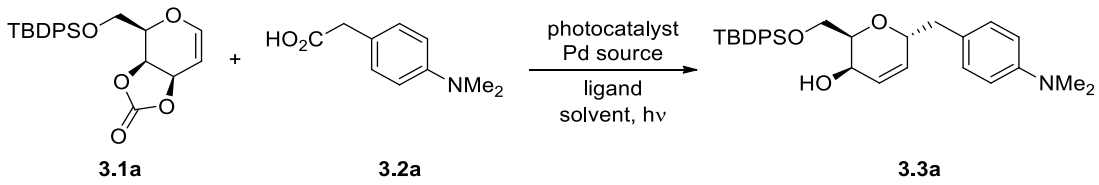
A key factor to note for dual catalysis is that the employment of dual catalysts requires the compatibility of each catalyst with the reaction conditions. A quick review of the reported photoredox catalysed examples showed that for most cases, reactions were conducted at ambient temperature.[33] However, the activation of the glycal systems typically required elevated temperatures, as seen in the previous chapter. Hence, we selected the galactal with a cyclic carbonate moiety **3.1a** as our model glycosyl donor based on our recent report of conducting glycosylation at room temperature.[34]

Next, in order to effect the electron transfer to our allylic cation generated, an appropriate electron donor should be chosen. Initial attempts of utilising potassium allyltrifluoroborate and potassium benzyltrifluoroborate salts failed to yield the desired product. We then turned our attention to amino alkanoic acid **3.2a** as the single electron oxidation should proceed with more ease in the presence of electron rich amino group.

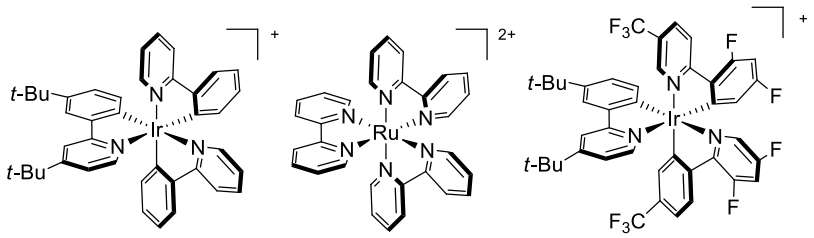
We initiated our study of this Pd/Ir dual-catalysed glycosylation by using glycal **3.1a** and amino alkanoic acid **3.2a**, [Ir(dtbbpy)$(ppy)_2$], $Pd(OAc)_2$, PPh_3 and CH_3CN. To our delight, the reaction proceeded to yield the ideal product successfully, albeit low yield. We proceeded to screen the various photocatalysts, palladium sources and solvents (**Table 3.1**). The Pd source did not have a significant effect on the efficiency of the reaction. Xphos was the best ligand for the reaction and increasing the amount

of ligand added led to an increase in yield, probably due to the competition of oxidation of the ligand and decrease in side reaction involving over-oxidation of amino group present in the product. Interestingly, solvent could affect the reaction adversely, probably due to the solubility of the deprotonated amino alkanoic acid. The optimised conditions were found to be $[Ir(dtbbpy)(ppy)_2]PF_6$, $Pd(PPh_3)_4$, XPhos and DMF solvent.

Table 3.1 Reaction optimisation



3.1a **3.2a** **3.3a**



A **B** **C**

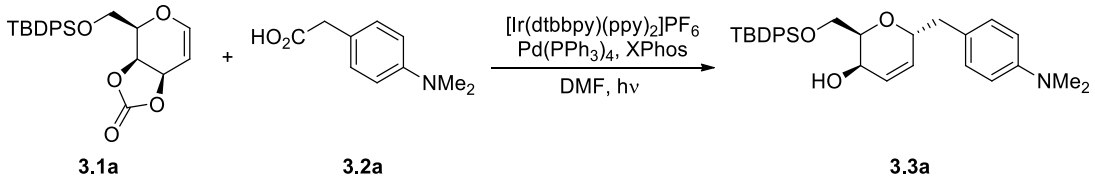
Entry[a]	Photocatalyst	Pd source	Ligand	Solvent	Yield[b] (%)
1	A	$Pd(OAc)_2$	PPh_3	CH_3CN	35
2	A	$Pd(OAc)_2$	PCy_3	CH_3CN	48
3[c]	A	$Pd(OAc)_2$	XantPhos	CH_3CN	46
4	A	$Pd(OAc)_2$	Xphos	CH_3CN	54
5	C	$Pd(OAc)_2$	Xphos	CH_3CN	32
6	B	$Pd(OAc)_2$	XPhos	CH_3CN	52
7	A	$Pd(acac)_2$	XPhos	CH_3CN	59

8	A	$Pd(PPh_3)_4$	XPhos	CH_3CN	65
9	A	$Pd(PPh_3)_4$	XPhos	dioxane/ DMA	23
10	A	$Pd(PPh_3)_4$	XPhos	DMF	73
11[d]	A	$Pd(PPh_3)_4$	XPhos	DMF	83

[a] Unless otherwise specified, all reactions were carried out using galactal **3.1a** (0.05 mmol, 1 equiv.), amino alkanoic acid **3.2a** (0.05 mmol, 1 equiv.), [photocatalyst] (0.00005 mmol, 0.01 equiv.), [Pd] 5 mol%, ligand 20 mol%, in 1.0 mL of solvent. [b] Isolated yields. [c] Ligand 10 mol%. [d] Ligand 50 mol%.

To better understand the reaction mechanism, control experiments were conducted to find out if each of the conditions was necessary (**Table 3.2**). In the presence of white light with a wide spectrum of colored lights instead of just blue light, only 15% of product was obtained. In the absence of light, palladium, iridium catalyst, or both catalysts, the reaction could not proceed. When the ligand was absent, the yield was decreased, suggesting some role of the ligand in this reaction. It is probable that some degree of oxidation of the ligand helps to drive the reaction by preventing the over-oxidation of the product. The increased pressure upon decarboxylation was believed to have an effect in driving the efficiency of the reaction. The addition of base did not facilitate the decarboxylative allylation but resulted in the decomposition of the starting material cyclic carbonate instead. Overall, it is likely that the photoredox catalyst requires blue light excitation to accept the electron from the amino group and transfer the electron to the allylic cation, which is formed by palladium-catalysed Tsuji-Trost reaction.

Table 3.2 Control experiments



3.1a **3.2a** **3.3a**

Entry[a]	**Modifications**	**Yield**[b] **(%)**
1	CFL light in place of blue light	15
2	Absence of light	N.R.
3	Absence of Pd	N.R.
4	Absence of ligand	46
5	Absence of Ir	N.R.
6	Absence of Pd & ligand	N.R.
7	Non-sealed (Ar Balloon attached)	N.R.
8	KOAc base added	31%

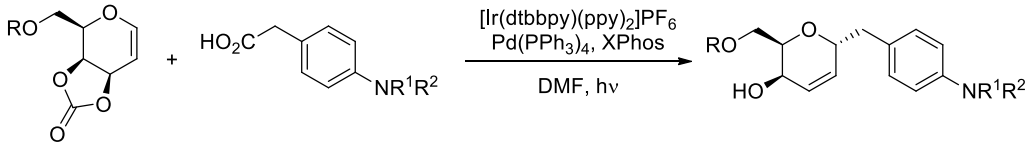
[a] Unless otherwise specified, all reactions were carried out using galactal **3.1a** (0.05 mmol, 1 equiv.), amino alkanoic acid **3.2a** (0.05 mmol, 1 equiv.), [photocatalyst A] (0.00005 mmol, 0.01 equiv.), $Pd(PPh_3)_4$ 5 mol%, XPhos 50 mol%, in 1.0 mL of DMF. [b] Isolated yields.

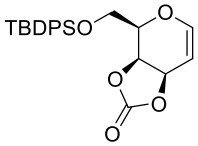
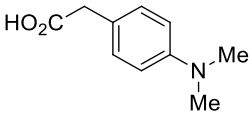
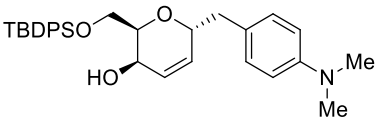
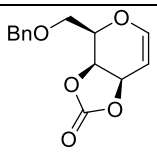
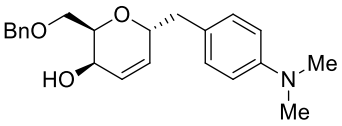
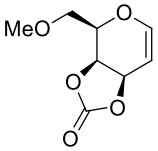
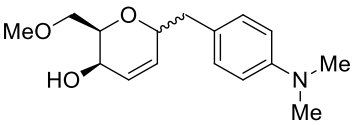
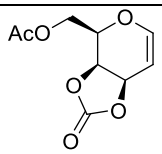
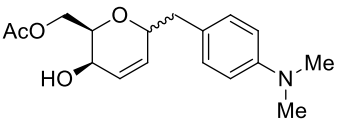
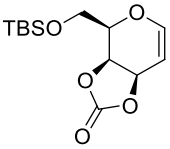
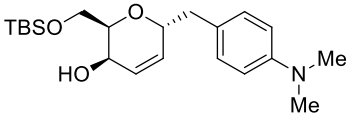
3.2.2 Substrate Scope

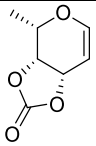
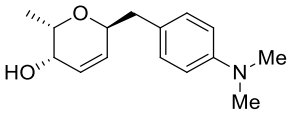
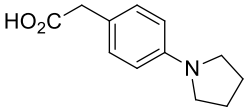
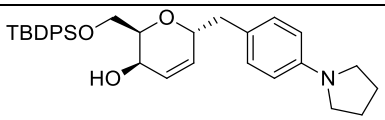
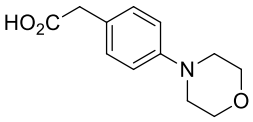
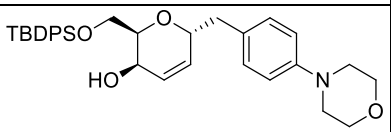
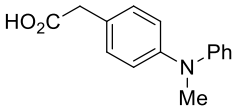
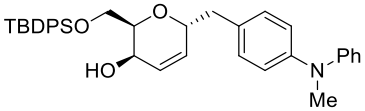
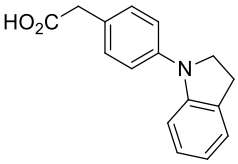
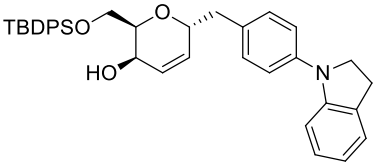
With the optimised conditions in hand, the scope of the reaction was tested by changing the glycals as well as amino alkanoic acids. Interestingly, this reaction could tolerate a variety of protecting groups, such as benzyl, methyl, acetyl and *tert*-butyldimethylsilyl group (**3.3a**-**e**). However, when the size of the protecting group decreased from benzyl to methyl group (**3.3b** and **3.3c**), the α-selectivity dropped. The α-selectivity decreased further when an electron-withdrawing acetyl group was attached (**3.3d**), probably due to the destabilisation of the allylic cation which is generated *in situ*. Silyl protecting groups were optimal for this reaction (**3.3a** and **3.3e**). This is due to the observation that the presence of bulkier group on the glycosyl donor not only directed the stereoselectivity of approach of glycosyl acceptor but also helped to prevent the occurrence of side reactions through sterics. In the case of **3.3f**, the yield of the desired product decreased to 46%.

Next, the scope of the amino alkanoic acids was also expanded (**3.3g**-**j**) using silyl protected galactal **3.1a**. Amino alkanoic acids bearing cyclic amines (**3.3g**, **3.3h** and **3.3j**) resulted in lower yields as compared to non-cyclic amines (**3.3a** and **3.3i**) and bulkier amino groups resulted in decreased efficiency (**3.3a** and **3.3i**). For all compounds, α-selectivity was preferred due to the steric hindrance from substituents on the pyranose ring as well as anomeric radical stabilisation described earlier.

Table 3.3 Substrate scope

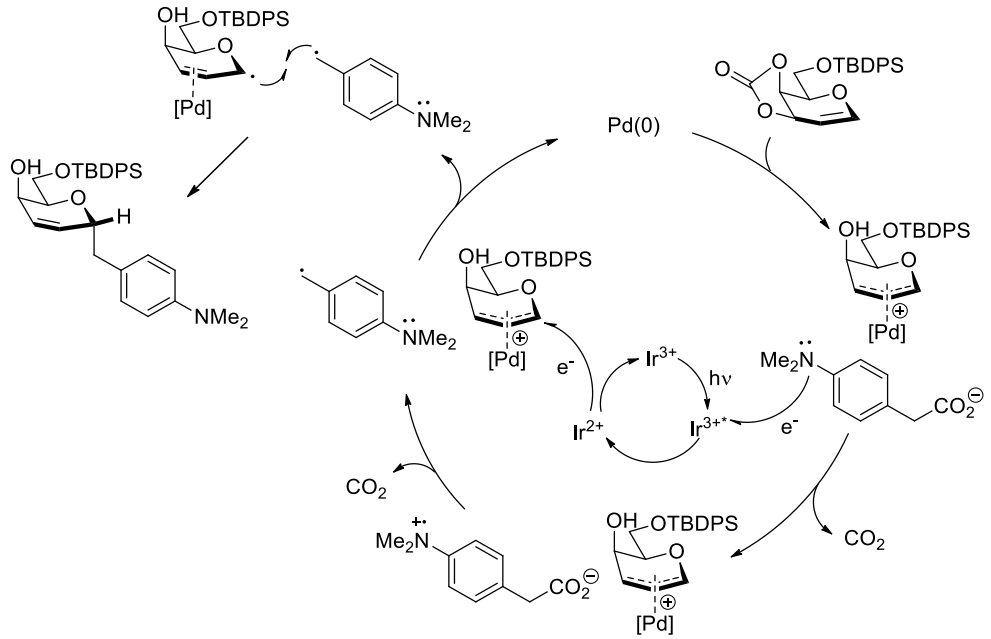


Entry	Glycal	Amino alkanoic acid	Product	Yield [a] (%)
1	 **3.1a**	 **3.2a**	 **3.3a**	83
2	 **3.1b**	**3.2a**	 **3.3b**	63
3	 **3.1c**	**3.2a**	 **3.3c**	71 (α:β = 3:1)
4	 **3.1d**	**3.2a**	 **3.3d**	40 (α:β = 1.5:1)
5	 **3.1e**	**3.2a**	 **3.3e**	85

6	 **3.1f**	**3.2a**	 **3.3f**	46
7	**3.1a**	 **3.2b**	 **3.3g**	59
8	**3.1a**	 **3.2c**	 **3.3h**	64
9	**3.1a**	 **3.2d**	 **3.3i**	71
10	**3.1a**	 **3.2e**	 **3.3j**	45

3.2.3 Plausible Mechanism

From the observed results and control experiments, we propose the following mechanism (**Scheme 3.20**). Palladium catalysed Tsuji-Trost allylation first occurs to form π-allyl palladium complex, which then receives an electron from the reduced photocatalyst (formed *via* reduction through reacting with the amino alkanoic acid). The amino alkanoic acid undergoes decarboxylation to generate alkyl radical, which then attacks the sugar allylic radical, forming *C*-aryl glycoside. Due to anomeric stabilisation of α-radical, formation of α-glycoside is favoured.



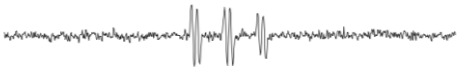
Scheme 3.20 Proposed mechanism for the Pd/Ir dual catalysed glycosylation

In an attempt to prove the formation of allylic glycosyl radical *in situ*, electron paramagnetic resonance (EPR) studies were conducted but to no success. Under the optimised reaction conditions, no signal was detected. In consideration that the half-life of the radical might be too short for EPR detection, especially in our radical-

radical coupling reaction, we decided to add spin trap to form stable adduct, which can also produce paramagnetic resonance spectrum in EPR spectroscopy. PBN was chosen and added as the spin trap to stabilise our radical species. Although a signal was detected, it was later proved to be from the reaction of PBN and photocatalyst (**Figure 3.2**). Further investigation into the mechanism is currently undergoing.

Under optimised conditions: No signal

Addition of PBN spin trap into mixture



Only PBN + Ir catalyst

Figure 3.2 EPR study results

3.3 Conclusion

Dual catalysis has been useful in achieving unprecedented transformations between seemingly unreactive starting material pairs. In the particular case of benzyl allylation, palladium or iridium catalytic system alone were unable to achieve the coupled product under mild conditions, but the combination of both was able to furnish the desired allylated product easily.

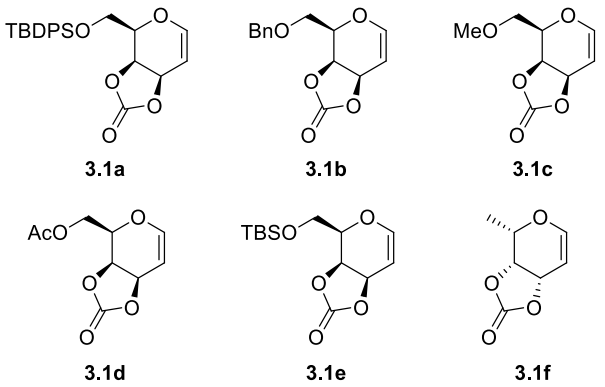
We have described an efficient and α-stereoselective method of constructing *C*-benzyl glycoside using glycal and amino alkanoic acid under irradiation of blue light. We proposed that the mechanism proceeds *via* radical-radical coupling between the allylic sugar radical (formed from reduction of palladium-catalysed decarboxylative product) and benzyl radical (from radical decarboxylation after oxidation of amino alkanoic acid). This easily generated allylic sugar radical holds great potential in the application to other glycosylations. Currently, we are still working on the expansion of substrate scope as well as the investigation into the reaction mechanism.

Overall, this work has demonstrated the potential of radical-radical coupling through formation of transient sugar radical. This unique strategy of utilizing radical chemistry in sugars could be further tapped on later, such as radical addition and radical polymerization.

3.4 Experimental Section

General: All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Merck, Strem and Alfa Asear) and used without further purification unless stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensdch polarimeter with a 1 cm cell (c given in g/100 mL). NMR spectra were recorded at room temperature on 300, 400, 500 MHz Bruker DPX 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in CDCl3). 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. HRMS (ESI) spectra were recorded on a Waters Q-Tof premier^{TM} mass spectrometer.

Preparation of glycosyl acceptors (3.1a-f):



3.1a **3.1b** **3.1c** **3.1d** **3.1e** **3.1f**

1,5-Anhydro-2-deoxy-6-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*arabino*-hex-1-enitol cyclic 3,4-carbonate (3.1a)

Glycosyl acceptor **3.1a** was prepared according to literature procedures.[34]

1,5-Anhydro-2-deoxy-6-*O*-(phenylmethyl)-D-*arabino*-hex-1-enitol cyclic 3,4-carbonate (3.1b)

Glycosyl acceptor **3.1b** was prepared according to literature procedures.[35]

1,5-Anhydro-2-deoxy-6-*O*-(methyl)-D-*arabino*-hex-1-enitol cyclic 3,4-carbonate (3.1c)

To galactal cyclic carbonate (86.0 mg, 0.50 mmol, 1 equiv.) in DMF (0.8 mL) cooled to 0 ^{o}C, MeI (0.10 mL, 1.50 mmol, 3 equiv.) was added. After stirring for 5 min, NaH (22 mg, 0.55 mmol, 1.1 equiv.) was added. The resultant solution was stirred for 1h, after which chloroform was added, treated with sodium chloride solution and stir for 5min. **3.1c** was achieved (51.0 mg, 55%) as colorless oil after flash chromatography on silica (1:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -25.2 (*c* = 0.30, $CHCl_3$); ^{1}H NMR (500

MHz, $CDCl_3$): δ 6.68 (d, J = 6.2 Hz, 1H), 5.17 (dd, J = 7.7, 3.2 Hz, 1H), 4.98 – 4.92 (m, 1H), 4.89 (d, J = 7.7 Hz, 1H), 4.05 (td, J = 6.6, 1.5 Hz, 1H), 3.76 – 3.63 (m, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.94, 149.18, 98.02, 73.13, 72.39, 70.45, 68.77, 59.47; HRMS (ESI) calcd. for $[C_8H_{11}O_5]^+$ 187.0606; found 187.0609.

1,5-Anhydro-2-deoxy-6-*O*-(acetyl)-D-*arabino*-hex-1-enitol cyclic 3,4-carbonate (3.1d)

To galactal cyclic carbonate (172 mg, 1.0 mmol, 1.2 equiv.) in pyridine (2.0 mL) cooled to 0 ^{o}C, Ac_2O (0.08 mL, 0.80 mmol, 1 equiv.) and DMAP (5.74 mg, 0.05 mmol, 0.06 equiv.) was added. After stirring for 1 h at rt, the solvent was removed by co-evaporating with toluene twice. **3.1d** was achieved (92.0 mg, 43%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -17.3 (c = 0.29, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (d, J = 6.2 Hz, 1H), 5.19 (dd, J = 7.7, 3.3 Hz, 1H), 4.97 (ddd, J = 6.2, 3.2, 1.2 Hz, 1H), 4.89 (d, J = 7.8 Hz, 1H), 4.39 (ddd, J = 11.8, 7.3, 1.3 Hz, 1H), 4.33 (ddd, J = 11.8, 5.3, 1.5 Hz, 1H), 4.12 (ddd, J = 7.1, 5.3, 1.5 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.34, 153.68, 148.92, 98.11, 72.98, 71.42, 68.70, 62.27, 20.56; HRMS (ESI) calcd. for $[C_9H_{11}O_6]^+$ 215.0556; found 215.0558.

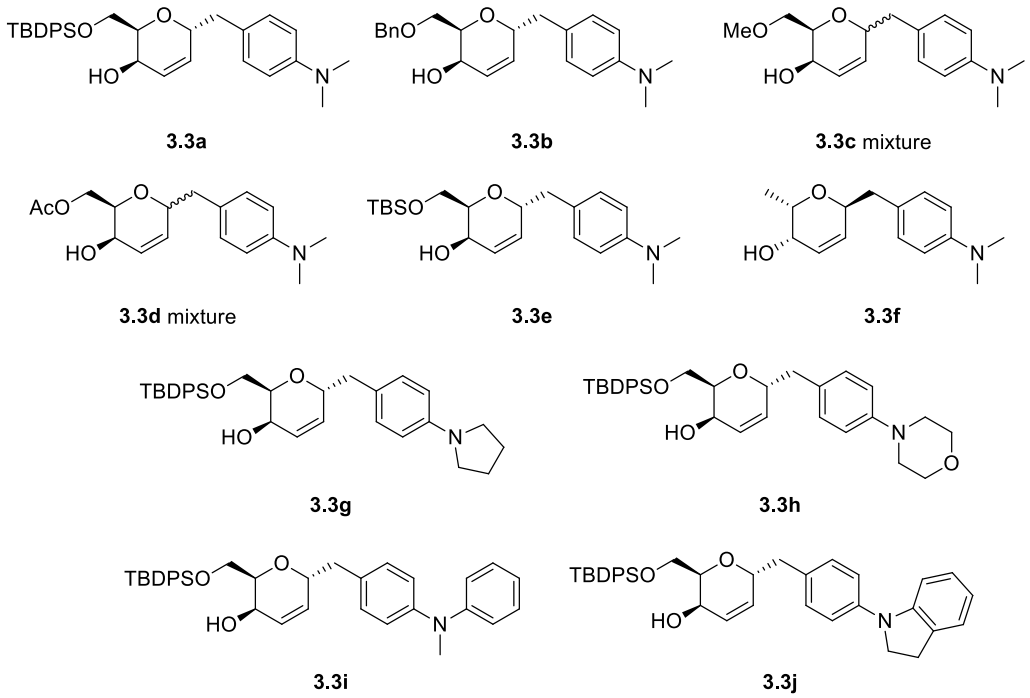
1,5-Anhydro-2-deoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-*arabino*-hex-1-enitol cyclic 3,4-carbonate (3.1e)

Glycosyl acceptor **3.1e** was prepared according to literature procedures.[34]

1,5-Anhydro-2,6-dideoxy-L-arabino-hex-1-enitol 3,4-carbonate (3.1f)

Glycosyl acceptor **3.1h** was prepared according to literature procedures.[34]

Preparation of *C*-aryl glycosides (3.3a-j):



4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-α-D-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (3.3a)

A solution of cyclic carbonate **3.1a** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4

and concentrated. **3.3a** was obtained (20.8 mg, 83%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -28.2 (*c* = 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.70 (m, 4H), 7.45 – 7.36 (m, 6H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.06 (ddd, *J* = 10.2, 5.5, 2.0 Hz, 1H), 5.87 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.35 – 4.28 (m, 1H), 4.04 – 3.98 (m, 1H), 3.95 – 3.87 (m, 2H), 3.81 (dd, *J* = 8.2, 3.9 Hz, 1H), 2.89 (s, 6H), 2.88 – 2.77 (m, 1H), 2.64 (dd, *J* = 13.7, 6.7 Hz, 1H), 1.83 (d, *J* = 8.9 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.28, 135.64, 133.03, 129.89, 129.83, 129.70, 129.49, 127.70, 126.20, 112.90, 74.85, 71.86, 63.44, 62.16, 40.78, 37.09, 29.69, 26.89; HRMS (ESI) calcd. for $[C_8H_{11}O_5]^+$ 502.2777; found 502.2770.

4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(phenylmethyl)-*α*-D-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (3.3b)

A solution of cyclic carbonate **3.1b** (13.1 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3b** was obtained (11.1 mg, 63%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -41.6 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.25 (m, 5H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* =

8.6 Hz, 2H), 6.04 (ddd, *J* = 10.2, 5.5, 2.0 Hz, 1H), 5.90 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.59 (d, *J* = 4.6 Hz, 2H), 4.40 – 4.36 (m, 1H), 4.10 – 4.03 (m, 1H), 3.94 – 3.88 (m, 1H), 3.82 – 3.66 (m, 2H), 2.96 – 2.90 (m, 1H), 2.90 (s, 6H), 2.69 (dd, *J* = 13.7, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.88, 138.27, 133.07, 129.99, 128.40, 128.35, 127.72, 127.59, 126.18, 113.06, 77.20, 74.87, 73.61, 70.82, 70.26, 62.69, 37.64; HRMS (ESI) calcd. for $[C_{22}H_{28}NO_3]^+$ 354.2069; found 354.2062.

4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(methyl)-*α*/*β*-D-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (3.3c)

A solution of cyclic carbonate **3.1c** (9.30 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3c** was obtained (9.9 mg, 71%, *α*:*β* = 3:1) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc).

***α*-anomer** (7.4 mg, 53%): $[\alpha]_D^{22}$ = -36.2 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.03 (ddd, *J* = 10.3, 5.5, 2.0 Hz, 1H), 5.88 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.41 – 4.36 (m, 1H), 4.04 – 3.97 (m, 1H), 3.92 – 3.87 (m, 1H), 3.71 – 3.57 (m, 2H), 3.43 (s, 3H), 2.98 – 2.92 (m, 1H), 2.92 (s,

6H), 2.85 – 2.68 (m, 1H), 1.89 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.43, 129.92, 128.43, 126.07, 125.71, 112.92, 74.89, 72.64, 70.61, 62.73, 59.42, 40.80, 37.95; HRMS (ESI) calcd. for $[C_{16}H_{23}NO_3Na]^+$ 300.1576; found 300.1570.

***β*-anomer** (2.5 mg, 18%): $[\alpha]_D^{22}$ = -2.5 (*c* = 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.96 (ddd, *J* = 10.2, 5.6, 2.1 Hz, 1H), 5.83 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.39 – 4.34 (m, 1H), 3.83 – 3.76 (m, 1H), 3.76 – 3.67 (m, 1H), 3.67 – 3.55 (m, 2H), 3.43 (s, 3H), 2.91 (s, 9H), 2.99 – 2.93 (m, 1H), 2.75 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.36 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.42, 133.35, 130.44, 126.83, 124.84, 112.56, 76.55, 76.02, 73.04, 63.04, 59.45, 40.71, 40.19; HRMS (ESI) calcd. for $[C_{16}H_{24}NO_3]^+$ 278.1756; found 278.1755.

4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(acetyl)-*α*/*β*-D-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (3.3d)

A solution of cyclic carbonate **3.1d** (10.7 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3d** was obtained (6.1 mg, 40%, *α*:*β* = 1.5:1) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc).

***α*-anomer** (3.7mg , 24%): $[\alpha]_D^{22}$ = -29.4 (*c* = 0.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.05 (ddd, *J* = 10.3, 5.5, 2.0 Hz, 1H), 5.93 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.45 – 4.39 (m, 2H), 4.36 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.25 (dd, *J* = 11.6, 7.4 Hz, 1H), 4.08 –4.00 (m, 1H), 3.88 – 3.83 (m, 1H), 2.92 (s, 6H), 2.70 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.05, 149.46, 133.33, 129.86, 125.87, 125.61, 112.88, 74.88, 69.84, 64.16, 62.23, 40.78, 37.50, 20.98; HRMS (ESI) calcd. for $[C_{17}H_{23}NO_4Na]^+$ 328.1525; found 328.1519.

***β*-anomer** (2.4 mg, 16%): $[\alpha]_D^{22}$ = -35.9 (*c* = 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.97 (ddd, *J* = 10.1, 6.0, 2.2 Hz, 1H), 5.84 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.37 –4.21 (m, 3H), 3.83 – 3.75 (m, 1H), 3.75 –3.70 (m, 1H), 3.00 – 2.84 (m, 7H), 2.76 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.38, 147.90, 133.52, 130.41, 126.70, 124.77, 112.52, 75.34, 72.42, 67.91, 64.12, 40.69, 40.13, 20.96; HRMS (ESI) calcd. for $[C_{17}H_{23}NO_4Na]^+$ 328.1525; found 328.1520.

4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-*α*-D-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (**3.3e**)

A solution of cyclic carbonate **3.1e** (14.3 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water

(5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3e** was obtained (16.0 mg, 85%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = 22.3 (*c* = 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.10 – 6.01 (m, 1H), 5.88 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.39 – 4.32 (m, 1H), 3.98 – 3.93 (m, 1H), 3.92 – 3.73 (m, 3H), 2.95 – 2.87 (m, 7H), 2.72 (q, *J* = 7.6, 6.8 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.38, 132.91, 129.87, 126.27, 125.99, 112.94, 74.79, 71.96, 62.86, 62.21, 40.82, 37.84, 25.92, -5.33; HRMS (ESI) calcd. for $[C_{21}H_{36}NO_3Si]^+$ 378.2464; found 378.2470.

4-Methyl-(2,3,6-dideoxy-4-hydroxyl-*α*-L-*arabino*-hex-2-enopyranosyl) *N*,*N*-dimethylaniline (**3.3f**)

A solution of cyclic carbonate **3.1f** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2a** (9.0 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3f** was obtained (5.7 mg, 46%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -10.0 (*c* = 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.01

– 5.97 (m, 1H), 5.83 – 5.80 (m, 1H), 4.64 – 4.61 (m, 1H), 4.31 – 4.28 (m, 1H), 3.98 – 3.88 (m, 1H), 2.95 – 2.86 (m, 7H), 2.75 – 2.67 (m, 1H), 0.95 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.67, 133.06, 130.38, 127.63, 120.22, 112.59, 76.18, 73.35, 65.02, 40.73, 40.45, 16.90; HRMS (ESI) calcd. for $[C_{15}H_{22}NO_2]^+$ 248.1651; found 248.1646.

1-[4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-*α*-D-*arabino*-hex-2-enopyranosyl)] phenyl pyrrolidine (3.3g)

A solution of cyclic carbonate **3.1a** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2b** (10.3 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3g** was obtained (15.6 mg, 59%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -31.6 (c = 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.67 (m, 4H), 7.44 – 7.37 (m, 6H), 6.98 (d, J = 8.4 Hz, 2H), 6.47 – 6.40 (m, 2H), 6.05 (ddd, J = 10.2, 5.5, 2.0 Hz, 1H), 5.87 (dd, J = 10.2, 3.1 Hz, 1H), 4.33 – 4.28 (m, 1H), 4.02 – 3.96 (m, 1H), 3.96 – 3.85 (m, 2H), 3.85 – 3.78 (m, 1H), 3.23 (t, J = 8.1 Hz, 4H), 2.82 (dd, J = 13.6, 7.6 Hz, 1H), 2.64 (dd, J = 13.6, 7.0 Hz, 1H), 1.98 (t, J = 8.1 Hz, 4H), 1.83 (d, J = 9.0 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.65, 135.61, 133.09, 129.90, 129.74, 129.68, 129.62,

127.69, 126.14, 111.68, 74.95, 71.88, 63.48, 62.17, 47.65, 37.85, 31.57, 26.90, 25.43; HRMS (ESI) calcd. for $[C_{33}H_{42}NO_3Si]^+$ 528.2934; found 528.2939.

1-[4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-*α*-D-*arabino*-hex-2-enopyranosyl)] phenyl morpholine (3.3h)

A solution of cyclic carbonate **3.1a** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2c** (11.1 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3h** was obtained (17.4 mg, 64%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -16.8 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.69 (m, 4H), 7.47 – 7.38 (m, 6H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.09 (ddd, *J* = 10.2, 5.6, 2.0 Hz, 1H), 5.89 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.40 – 4.30 (m, 2H), 4.08 – 3.89 (m, 2H), 3.89 –3.84 (m, 4H), 3.10 (dd, *J* = 5.7, 3.9 Hz, 4H), 2.93 – 2.81 (m, 1H), 2.67 (dd, *J* = 13.7, 6.2 Hz, 1H), 1.84 (d, *J* = 9.0 Hz, 1H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.77, 135.59, 132.84, 129.94, 129.71, 129.57, 127.78, 127.69, 126.39, 115.83, 74.67, 71.89, 66.92, 63.50, 62.16, 49.55, 37.61, 29.68, 26.84; HRMS (ESI) calcd. for $[C_{33}H_{41}NO_3SiNa]^+$ 566.2703; found 566.2710.

4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-*α*-D-*arabino*-hex-2-enopyranosyl)] *N*-methyl-*N*-phenylaniline (3.3i)

A solution of cyclic carbonate **3.1a** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2d** (12.1 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3i** was obtained (20.0 mg, 71%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -53.3 (*c* = 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 – 7.68 (m, 4H), 7.42 – 7.35 (m, 6H), 7.24 – 7.22 (m, 3H), 7.05 – 7.05 (m, 2H), 6.96 – 6.87 (m, 4H), 6.08 (ddd, *J* = 10.1, 5.6, 2.1 Hz, 1H), 5.90 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.39 – 4.34 (m, 1H), 4.05 – 3.98 (m, 1H), 3.97 – 3.84 (m, 2H), 3.81 (dd, *J* = 8.2, 3.9 Hz, 1H), 3.25 (s, 3H), 2.87 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.66 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.82 (d, *J* = 9.0 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.09, 147.37, 135.64, 135.59, 132.85, 131.30, 130.01, 129.73, 129.07, 127.71, 126.48, 121.15, 120.65, 119.58, 74.64, 71.95, 63.51, 62.19, 40.21, 37.79, 29.69, 26.91; HRMS (ESI) calcd. for $[C_{36}H_{41}NO_3NaSi]^+$ 586.2753; found 586.2760.

1-[4-Methyl-(2,3-dideoxy-4-hydroxyl-6-*O*-(*tert*-butyldiphenylsilyl)-*α*-D-*arabino*-hex-2-enopyranosyl)] phenyl indoline (3.3j)

A solution of cyclic carbonate **3.1a** (20.5 mg, 0.05 mmol, 1 equiv.) in DMF (1.0 mL), was degassed and refilled with Ar. To a vial containing aniline **3.2e** (12.7 mg, 0.05 mmol, 1 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.46 mg, 0.00005 mmol, 0.01 equiv.) $Pd(PPh_3)_4$ (2.89 mg, 0.00025 mmol, 0.05 equiv.), XPhos (11.9 mg, 0.025 mmol, 0.5 equiv.), the cyclic carbonate solution was added in dropwise under Ar. This solution was allowed to stir overnight, under blue LED irradation at room temperature. Water (5.0 mL) was added and the product was extracted with ethyl acetate (5.0 mL X 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. **3.3j** was obtained (12.9 mg, 45%) as colorless oil after flash chromatography on silica (2:1, *n*-Hexane/EtOAc). $[\alpha]_D^{22}$ = -61.7 (*c* = 0.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.67 (m, 4H), 7.45 – 7.35 (m, 6H), 7.16 – 7.03 (m, 7H), 6.74 – 6.70 (m, 1H), 6.09 (ddd, *J* = 10.1, 5.5, 2.1 Hz, 1H), 5.91 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.40 – 4.36 (m, 1H), 4.03 – 3.99 (m, 1H), 3.93 (t, *J* = 8.4 Hz, 2H), 3.89 – 3.85 (m, 1H), 3.84 – 3.80 (m, 1H), 3.10 (t, *J* = 8.4 Hz, 2H), 2.88 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.68 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.83 (d, *J* = 9.0 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.06, 147.35, 135.63, 135.58, 133.50, 132.86, 131.29, 130.01, 129.73, 129.07, 126.46, 121.15, 120.63, 119.55, 74.64, 71.92, 63.49, 62.18, 40.21, 37.76, 29.69, 26.89, 26.75; HRMS (ESI) calcd. for $[C_{37}H_{41}O_3NaSi]^+$ 598.2753; found 598.2741.

3.5 References

1. Liu, C.; Liu, D.; Lei, A. *Acc. Chem. Res.* **2014,** *47*, 3459-3470.
2. (a) Tebben, L.; Studer, A. *Angew. Chem. Int. Ed.* **2011,** *50*, 5034-5068; (b) Fischer, H. *Chem. Rev.* **2001,** *101*, 3581-3610.
3. Focsaneanu, K.-S.; Scaiano, J. C. *Helv. Chim. Acta* **2006,** *89*, 2473-2482.
4. Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. *Angew. Chem. Int. Ed.* **2013,** *52*, 7156-7159.
5. Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. *J. Am. Chem. Soc.* **2013,** *135*, 11481-11484.
6. Nakajima, K.; Miyake, Y.; Nishibayashi, Y. *Acc. Chem. Res.* **2016,** *49*, 1946-1956.
7. (a) Dai, X.; Mao, R.; Guan, B.; Xu, X.; Li, X. *RSC Adv.* **2015,** *5*, 55290-55294; (b) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014,** *6*, 57-64; (c) Dai, X.; Cheng, D.; Guan, B.; Mao, W.; Xu, X.; Li, X. *J. Org. Chem.* **2014,** *79*, 7212-7219; (d) Ruiz Espelt, L.; Wiensch, E. M.; Yoon, T. P. *J. Org. Chem.* **2013,** *78*, 4107-4114; (e) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. *J. Am. Chem. Soc.* **2013,** *135*, 1823-1829; (f) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012,** *134*, 3338-3341; (g) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012,** *14*, 672-675.
8. (a) Liang, Z.; Xu, S.; Tian, W.; Zhang, R. *Beilstein J. Org. Chem.* **2015,** *11*, 425; (b) Lenhart, D.; Bach, T. *Beilstein J. Org. Chem.* **2014,** *10*, 890; (c) Chen, L.; Chao, C. S.; Pan, Y.; Dong, S.; Teo, Y. C.; Wang, J.; Tan, C.-H. *Org. Biomol. Chem.* **2013,** *11*, 5922-5925; (d) Ju, X.; Li, D.; Li, W.; Yu, W.; Bian, F. *Adv. Synth. Catal.* **2012,** *354*, 3561-3567.
9. Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J.* **2012,** *18*, 16473-16477.
10. Zhou, H.; Lu, P.; Gu, X.; Li, P. *Org. Lett.* **2013,** *15*, 5646-5649.
11. Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015,** *137*, 13768-13771.
12. Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. *Angew. Chem. Int. Ed.* **2016,** *55*, 6776-6779.
13. Zhang, P.; Xiao, T.; Xiong, S.; Dong, X.; Zhou, L. *Org. Lett.* **2014,** *16*, 3264-3267.
14. (a) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2015,** *54*, 6046-6050; (b) Zuo, Z.; MacMillan, D. W. *J. Am. Chem. Soc.* **2014,** *136*, 5257-5260; (c) McNally, A.; Prier, C. K.; MacMillan, D. W. *Science* **2011,** *334*, 1114-1117.
15. (a) Prier, C. K.; MacMillan, D. W. *Chem. Sci.* **2014,** *5*, 4173-4178; (b) Singh, A.; Arora, A.; Weaver, J. D. *Org. Lett.* **2013,** *15*, 5390-5393.
16. (a) Noble, A.; McCarver, S. J.; MacMillan, D. W. *J. Am. Chem. Soc.* **2015,** *137*, 624-627; (b) Noble, A.; MacMillan, D. W. *J. Am. Chem. Soc.* **2014,** *136*, 11602-11605.
17. Xuan, J.; Zeng, T. T.; Feng, Z. J.; Deng, Q. H.; Chen, J. R.; Lu, L. Q.; Xiao, W. J.; Alper, H. *Angew. Chem. Int. Ed.* **2015,** *54*, 1625-1628.

18. (a) Hoffmann, N. *J. Phys. Org. Chem.* **2015,** *28*, 121-136; (b) Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999,** *40*, 3169-3172.
19. (a) Lenhart, D.; Bauer, A.; Pöthig, A.; Bach, T. *Chem. Eur. J.* **2016,** *22*, 6519-6523; (b) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015,** *137*, 2452-2455; (c) Nakajima, K.; Kitagawa, M.; Ashida, Y.; Miyake, Y.; Nishibayashi, Y. *Chem. Commun.* **2014,** *50*, 8900-8903; (d) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2012,** *48*, 6966-6968.
20. (a) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. *J. Am. Chem. Soc.* **2016,** *138*, 1832-1835; (b) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014,** *136*, 13606-13609; (c) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. *Science* **2014,** *345*, 437-440; (d) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. *J. Am. Chem. Soc.* **2014,** *136*, 10886-10889; (e) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013,** *49*, 7854-7856.
21. (a) El Khatib, M.; Serafim, R. A. M.; Molander, G. A. *Angew. Chem. Int. Ed.* **2016,** *55*, 254-258; (b) Miyazawa, K.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2014,** *356*, 2749-2755; (c) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, 1253647.
22. (a) Korth, H.-G.; Sustmann, R.; Gröninger, K. S.; Witzel, T.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461-1464; (b) Dupuis, J.; Giese, B.; Rüegge, D.; Fischer, H.; Korth, H. G.; Sustmann, R. *Angew. Chem. Int. Ed.* **1984,** *23*, 896-898; (c) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984,** *25*, 1349-1352.
23. (a) Giese, B. *Angew. Chem. Int. Ed.* **1989,** *28*, 969-980; (b) Giese, B.; Witzel, T. *Angew. Chem. Int. Ed.* **1986,** *25*, 450-451; (c) Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem. Int. Ed.* **1984,** *23*, 69-70; (d) Giese, B.; Dupuis, J. *Angew. Chem. Int. Ed.* **1983,** *22*, 622-623.
24. (a) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000,** *56*, 2103-2112; (b) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997,** *62*, 4204-4205.
25. Readman, S. K.; Marsden, S. P.; Hodgson, A. *Synlett* **2000**, 1628-1630.
26. Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009,** *11*, 879-882.
27. Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2010,** *49*, 7274-7276.
28. Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Org. Lett.* **2011,** *13*, 2406-2409.
29. (a) Spell, M.; Wang, X.; Wahba, A. E.; Conner, E.; Ragains, J. *Carbohydr. Res.* **2013,** *369*, 42-47; (b) Cumpstey, I.; Crich, D. *J. Carbohydr. Chem.* **2011,** *30*, 469-485.
30. Wen, P.; Crich, D. *Org. Lett.* **2017,** *19*, 2402-2405.
31. Spell, M. L.; Deveaux, K.; Bresnahan, C. G.; Bernard, B. L.; Sheffield, W.; Kumar, R.; Ragains, J. R. *Angew. Chem. Int. Ed.* **2016,** *55*, 6515-6519.
32. Le, T. X.; Papin, C.; Doisneau, G.; Beau, J. M. *Angew. Chem. Int. Ed.* **2014,** *53*, 6184-6187.
33. (a) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016,** *81*, 6898-6926; (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013,**

113, 5322-5363; (c) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017,** *1*, 0052.
34. Yao, H.; Zhang, S.; Leng, W.-L.; Leow, M.-L.; Xiang, S.; He, J.; Liao, H.; Le Mai Hoang, K.; Liu, X.-W. *ACS Catal.* **2017**, 5456-5460.
35. Deshpande, P. P.; Kim, H. M.; Zatorski, A.; Park, T.-K.; Ragupathi, G.; Livingston, P. O.; Live, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998,** *120*, 1600-1614.

Chapter 4:

Synthesis of Indolizines: Intramolecular C-N Bond Formation under Metal-Free Conditions

**This chapter has been published in "Intramolecular C-N Bond Formation under Metal-Free Conditions: Synthesis of Indolizines", Chem. Asian J., 2015, 10, 853-856.[1] Reproduced with permission from ref 1.

4.1 Introduction

4.1.1 *N*-Containing Heterocycles in Nature

As part of our long-standing interest in medicinal chemistry as well as allylic systems, we decided to extend our study of allylic chemistry to non-sugar system for pharmaceutical applications.

Most of the top marketed drugs contain *N*-containing heterocycles.[2] Besides their biological and pharmaceutical activities, they are also found in agrochemicals, making them desirable compounds and driving interest in their synthetic developments. Of the *N*-heterocycles, one core structure is the indolizine structure, which is a 10π electron, conjugated system. This core structure exists in some natural products with fused rings and the reduced derivatives could be found in nature too (**Figure 4.1**).[3]

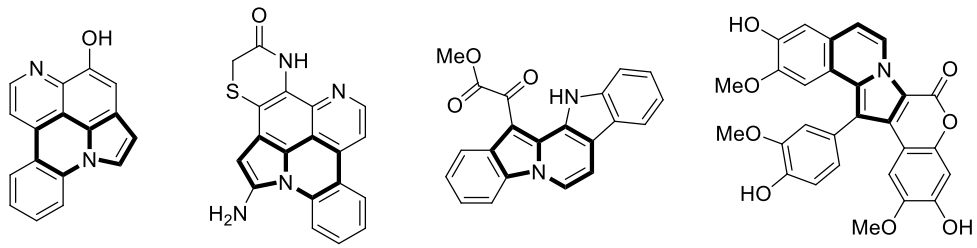


Figure 4.1 Indolizine-bearing natural products

Being bioisosteres of indoles, they exhibit numerous bioactivities, for example antibacterial, anticancer, anti-cholinergic, anti-fungal, anti-histaminic, anti-inflammatory, anti-tubercular, cytotoxic, CNS depressant and herbicidal activities, as well as acting as aromatase and phosphodiesterase inhibitors (**Figure 4.2**).[3-4]

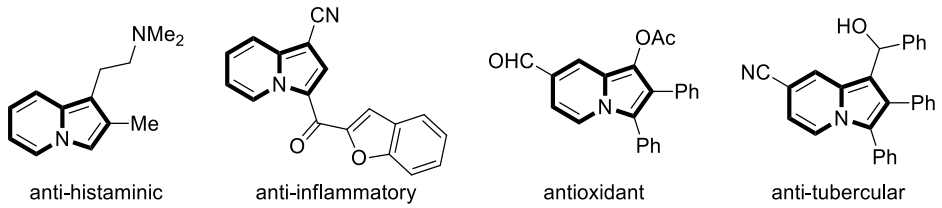


Figure 4.2 Indolizine compounds and their bioactivities

The discovery of indolizines dates back to 1890 by an Italian chemist, Angeli.[4b] Scholtz later reported the first synthesis, with the product reported to possess both characteristics of pyrroles and indoles, while being a chemical and structural isomer of indole and isoindole.[5] This was validated by Diels and Alder through reduction and subsequent reaction with cyanogen bromide.[4b] The fused heterocycle is made up of an electron-rich pyrrole and an electron-poor pyridine with a bridging C-N bond (**Figure 4.3**).[6]

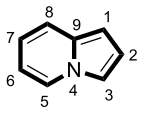
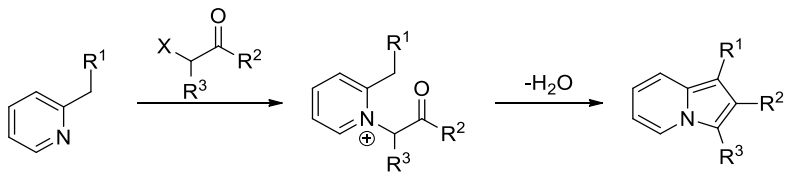


Figure 4.3: Structural numbering of atoms on indolizines

4.1.2 Strategies to Obtain Indolizines

The first synthesis was carried out by Scholtz by heating 2-methylpyridine and acetic anhydride at high temperatures to give 1,3-diacetylindolizine, which upon hydrolysis yielded indolizine.[5] To date, strategies to obtain indolizines can be generalised under four major categories: Tschitschibabin reaction, condensation, 1,3-dipolar cycloaddition and 1,5-dipolar cycloaddition, all of which proceeding *via* pyridine annulation.[3] There is also another less common but feasible method, which is *via* pyrrole annulation.[3]

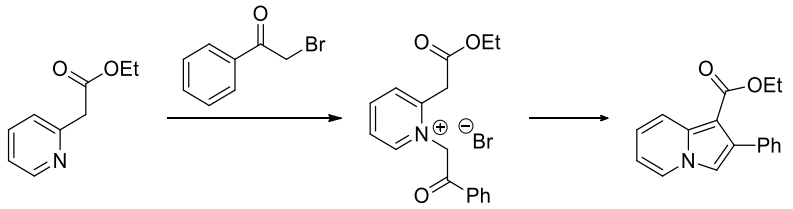
Tschitschibabin first discovered the named reaction and it has been later developed as one of the most general synthetic method to synthesise indolizines.[7] He first formed the quaternary pyridinium salts using α-halocarbonyl compounds, followed by intramolecular Aldol-type condensation under basic conditions (**Scheme 4.1**). Base might not be necessary depending on the properties of the pyridinium salt. This method is efficient in preparing 2-substituted indolizines but the incorporation of bulky substituents at *C1* and *C3* retards the reaction.



Scheme 4.1 Tschitschibabin reaction

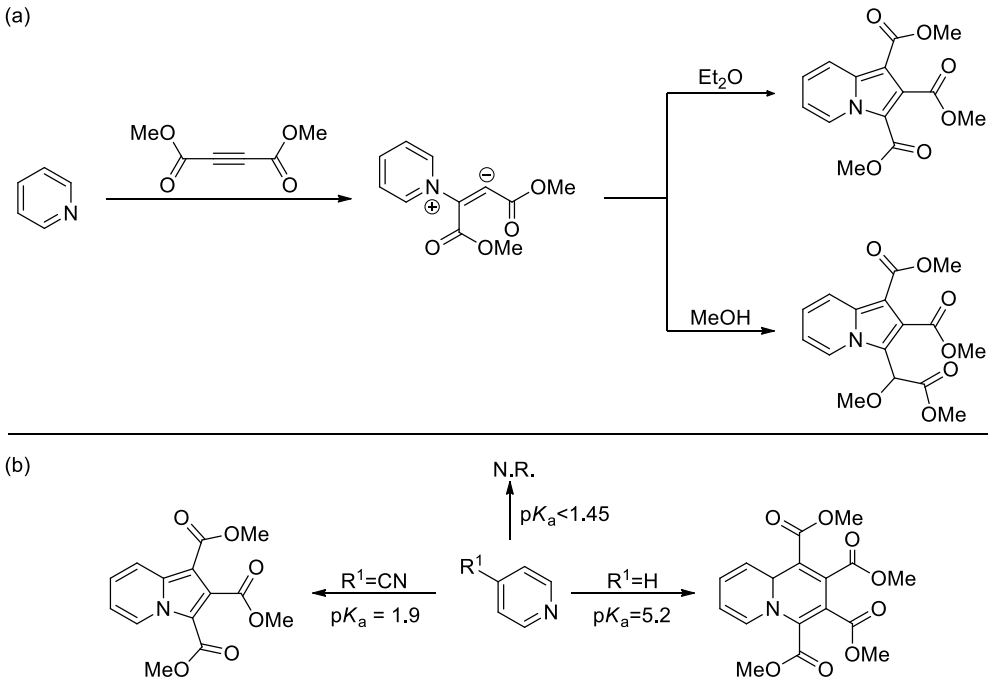
Borrows later applied the Tshitchibabin reaction using α-halodiketones and α-haloketoesters to yield acyl and alkoxy carbonyl substituted indolizines.[8] Bragg and

Wibberley then synthesised a series of indolizines and the formation of the quaternary salt could be done *in situ* without isolation (**Scheme 4.2**).[9]



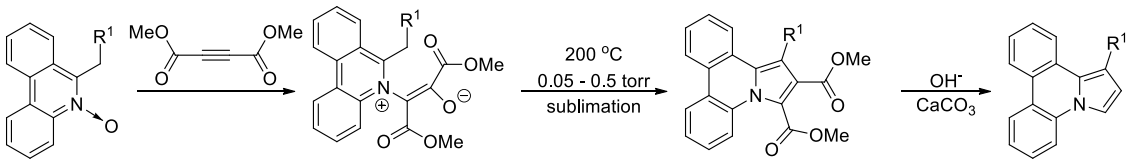
Scheme 4.2 Indolizine synthesis without isolation of quaternary salt intermediate

Diels later on used pyridine and acetylene dicarboxylate, which underwent intermolecular condensation to obtain the substituted indolizines (**Scheme 4.3a**).[10] Interestingly, an investigation by Acheson and Robinson revealed that the pyridine basicity was related to their reactivity towards acetylene dicarboxylate, whereby low pK_a (1.90) drove the indolizine formation. However, any further decrease in pK_a value led to no reaction while higher pK_a (5.2), on the other hand, resulted in quinolizine (**Scheme 4.3b**).[11]

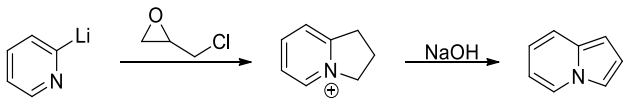


Scheme 4.3 Reaction of pyridine with acetylene: formation of pyridinium ylide and subsequent condensation

Acheson then utilised pyridine *N*-oxide and acetylene dicarboxylate and the intermediate condensed upon sublimation (**Scheme 4.4**).[12] Further treatment with base led to ester hydrolysis and decarboxylation, forming the 1-substituted indolizine. 2-Pyridyllithium and 2-chloromethyloxirane was later applied by Melton and Wibberley to furnish indoliziniumchloride intermediate, which gave the unsubstituted indolizine after subjecting to treatment with base (**Scheme 4.5**).[13]



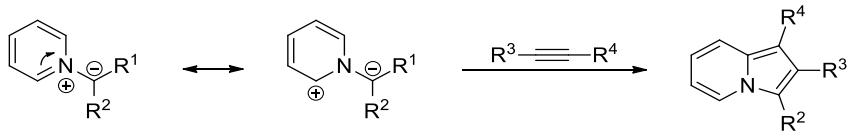
Scheme 4.4 Reaction of pyridine *N*-oxide and acetylene dicarboxylate



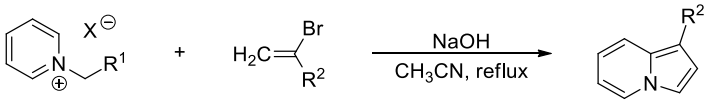
Scheme 4.5 Formation of unsubstituted indolizine

Apart from condensation, 1,3-dipolar cycloaddition is also a common method to access the pyrrole ring.[14] This is achieved by applying pyridinium ylides to a variety of dipolarophiles. The advantage of this method lies in its simplicity with only two steps: addition and rearomatisation. The first application of this approach was conducted by Boekelheide and Fahrenholtz using alkyne substrate, whereby a subsequent dehydrogenation occurred in the presence of Pd/C to give the indolizine.[15]

Other applications include using azomethine and dimethyl fumarate[16] and diphenylthiirene-*S*,*S*-dioxide.[13] By utilising alkynes, or pyridinium salts with carboxylate or ester functionalities, dehydrogenation catalyst was not required for rearomatisation (**Scheme 4.6**).[15, 17] With the installation of nitro, halo or alkoxy leaving group for alkenes substrates, elimination would occur in place of dehydrogenation (**Scheme 4.7**).[18] Without these leaving groups, an oxidant was required for the rearomatisation, such as MnO_2,[19] tetrakis(pyridine)cobalt(II) dichromate[20] and chloranil.[21]

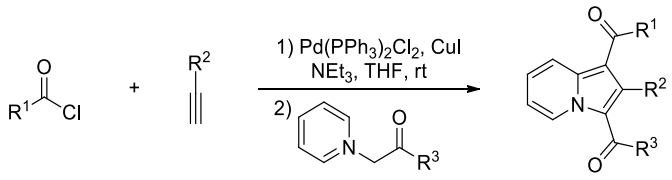


Scheme 4.6 1,3-Dipolar cycloaddition using alkynes as dipolarophiles

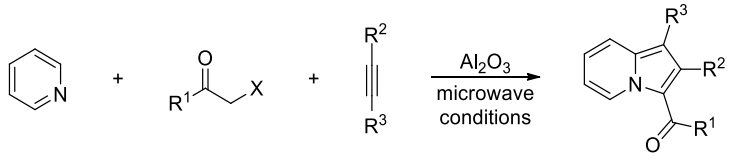


Scheme 4.7 1,3-Dipolar cycloaddition and subsequent eliminations

Müller demonstrated the multicomponent synthesis by having a one-pot Sonogashira coupling/1,3-dipolar cycloaddition through a ynone intermediate (**Scheme 4.8**).[22] In another example by Boruah, the isolation of ylide or usage of salt is not necessary in the application of multicomponent synthesis.[23] The ylide intermediate was formed *in situ* by applying pyridine, alkyne and *α*-haloketone, which then underwent the 1,3-dipolar cycloaddition under microwave conditions (**Scheme 4.9**).

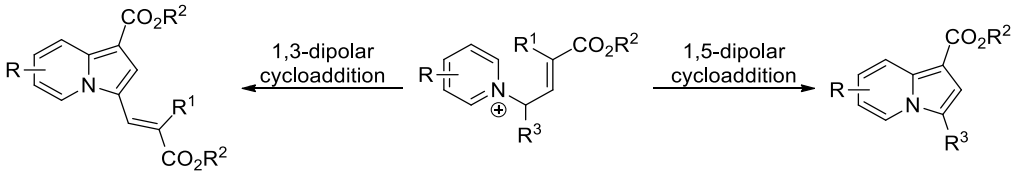


Scheme 4.8 One-pot Sonogashira coupling/1,3-dipolar cycloaddition



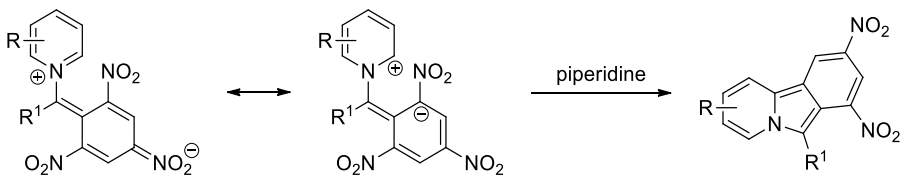
Scheme 4.9 Multicomponent synthesis

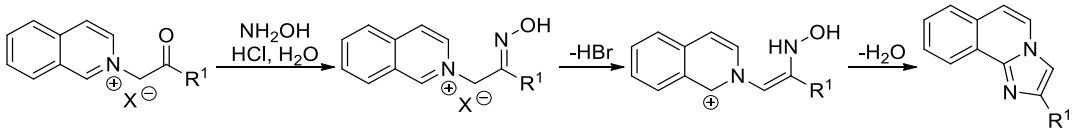
During the investigation of this type of cycloaddition, it was found that *N*-allylpyridinium ylide could act as 1,3-dipoles and 1,5-dipoles, yielding 1,3-dipolar cycloaddition and 1,5-dipolar cycloaddition indolizine products (**Scheme 4.10**), paving the road for further investigation into other types of cycloadditions.[24]



Scheme 4.10 *N*-Allylpyridinium ylide reaction

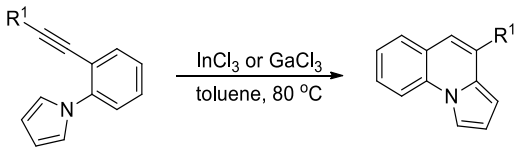
The 1,5-cycloaddition approach was later adopted in the synthesis of benzindolizines and azaindolizines (**Scheme 4.11**).[25]





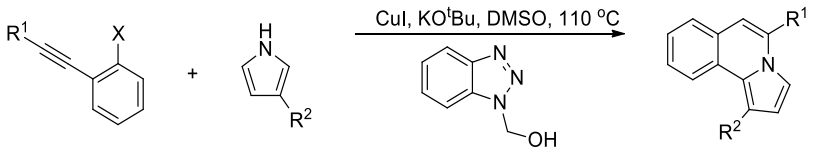
Scheme 4.11 1,5-Cycloadditions

The retrosynthesis of indolizine ring could also be disconnected at the pyridine ring, leaving the pyrrole ring intact. One way to form the pyridine ring is by cycloisomerisation (**Scheme 4.12**).[26] Typically, the substituted pyrrole undergoes a 6-*endo-dig* cycloisomerisation.



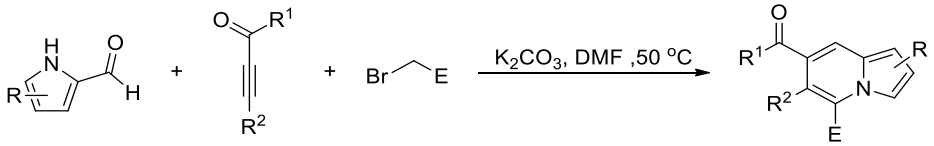
Scheme 4.12 Cycloisomerisation

Larock explored the addition of pyrrole to alkyne and subsequent intramolecular arylation, proceeding *via* an alkenylpyrrole intermediate (**Scheme 4.13**).[26a]



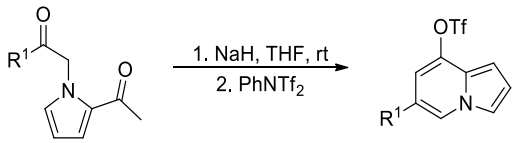
Scheme 4.13 Addition/intramolecular arylation

Zou reacted pyrrole with alkyne and bromoalkane to obtain the trisubstituted indolizine ring in a multicomponent one-pot reaction (**Scheme 4.14**).[27]

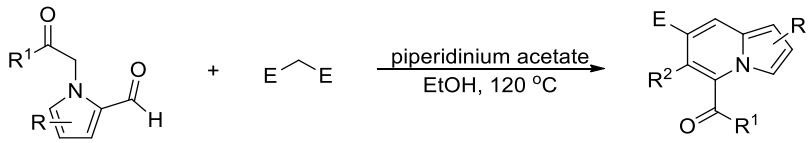


Scheme 4.14 Multicomponent one-pot reaction

Kim's group investigated the Aldol condensation to obtain indolizine ring (**Scheme 4.15**).[28] They also further explored the cascade reaction, Knoevenagel condensation and subsequent intramolecular aldol cyclisation (**Scheme 4.16**).[29]



Scheme 4.15 Aldol condensation



Scheme 4.16 Knoevenagel condensation/intramolecular aldol cyclisation

In spite of these methodologies, an efficient and simpler method to synthesise multisubstituted indolizines is still highly sought after. The generation of multisubstituted indolizines would allow for in-depth studies of structural activity relationship. Hence, more in-depth research into C-H bond activation for formation of indolizines was conducted.

4.2 Results and Discussion

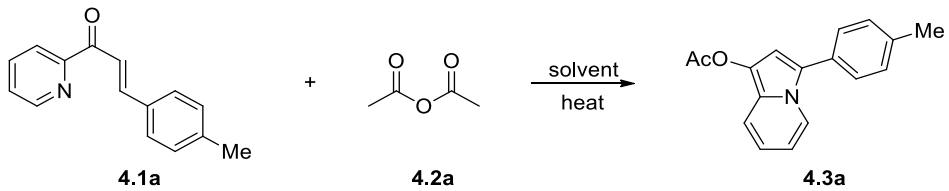
4.2.1 Condition Optimisation

Founded on our previous understanding of allylic cations, we believe that a metal catalyst is required to activate the Michael acceptor to drive the cyclisation. However, contrary to our belief, a serendipitous discovery on that such metal activation was unnecessary was made. When applying (*E*)-3-(4”-methylphenyl)-1-(pyrid-2’-yl)prop-2-enone (**4.1a**) in the absence of metal catalyst, the desired product could be furnished. In this reaction, acetic anhydride was utilised as our electrophilic reagent and indolizine **4.3a** was obtained in a high yield.

This result was very encouraging as the typical harsh reagents and metal catalysts for C-H activation were not necessary, making this approach a green and economical option. Toxicity from trace amounts of reagents could be avoided, hence making it a suitable method for synthesising drug analogues. We then initiated our investigation into this reaction by a careful examination of the reaction conditions (**Table 4.1**). It appeared that reaction temperature had a significant impact on the reaction. At 80 ^{o}C, there was low conversion of starting material **4.1a** and only trace amount of the product **4.3a** was formed, even at prolonged reaction time of 24 h (entry 1). As we increased the temperature to 110 ^{o}C, the yields also improved and the starting material was consumed in 10 h (entries 2 and 3). However, when the temperature was increased beyond 110 ^{o}C, the reaction efficiency decreased due to decomposition (entry 4).

Next, we screened a variety of solvents. When using polar solvents (entries 3 and 9-11), the yields increased. The highest efficiency was observed with 1, 2-dichloroethane, in which the reaction went to completion and product **4.3a** had an isolated yield of 92% (entry 11). Other solvents, such as ethereal, acidic and non-polar solvents, resulted in lower yields (entries 7, 8, 12 and13).

Table 4.1 Reaction optimisation[a]



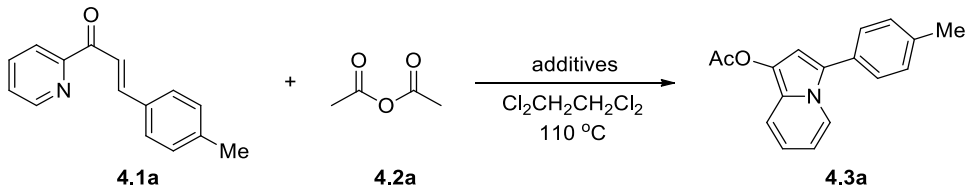
4.1a **4.2a** **4.3a**

Entry	Solvent	Temp. (°C)	Yield[b] (%)
1	CH_3CN	80	trace
2	CH_3CN	100	56
3	CH_3CN	110	93
4	CH_3CN	120	89
5	CH_2Cl_2	110	70
6	Hexane	110	30
7	THF	110	25
8	Toluene	110	75
9	$CHCl_3$	110	95
10	DMF	110	90
11	$Cl_2CH_2CH_2Cl_2$	110	97(92)
12	1,4-dioxane	110	10
13	acetic acid	110	70

[a] Unless otherwise specified, all reactions were carried out using substituted pyridine **4.1a** (0.5 mmol, 1 equiv.), acetic anhydride **4.2a** (1.0 mL) in 5.0 mL of solvent. [b] ^{1}H NMR yields obtained using 1,3,5-trimethoxybenzene as reference; isolated yield in parentheses.

To confirm that the additives such as metal catalysts are not necessary in the reaction, we then screened the additives (**Table 4.2**). When transition metal, Lewis acid or base was introduced, there was no improvement in the reaction and the yield decreased instead (entries 1-6). Hence, the optimised reaction was fixed to be using CH_3CN as the solvent and heating at 110 ^oC.

Table 4.2 Screening reaction additives[a]



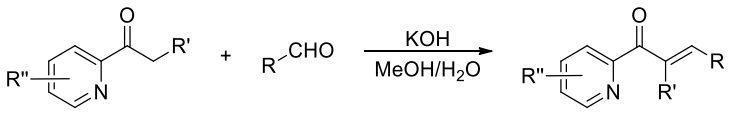
4.1a **4.2a** **4.3a**

Entry	Additives	Yield[b] (%)
1	$Pd(OAc)_2$ (5 mol %)	60
2	$PdCl_2$ (5 mol %)	68
3	$FeCl_3$ (10 mol %)	31
4	Et_3N (1 equiv.)	N.R.
5	TsOH (0.5 equiv.)	85
6	$BF_3{\cdot}Et_2O$ (0.5 equiv.)	32

[a] Unless otherwise specified, all reactions were carried out using substituted pyridine **4.1a** (0.5 mmol, 1 equiv.), acetic anhydride **4.2a** (1.0 mL) in 5.0 mL of $Cl_2CH_2CH_2Cl_2$. [b] ^{1}H NMR yields using 1,3,5-trimethoxybenzene as reference.

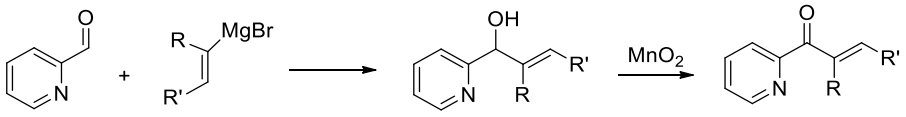
4.2.2 Substrate Scope

We proceeded to synthesise a variety of chalcones for the substrate screening using Singh's procedure.[30] Aldol condensation was conducted by subjecting 2-acetylpyridine to substituted aldehydes, under basic conditions, achieving the desired chalcones (**Scheme 4.17**). Through reacting 2-pyridinecarboxaldehyde with the corresponding Grignard reagents and subsequent oxidation by MnO_2, α,β-unsaturated compounds **4.1k** and **4.1m** could be obtained (**Scheme 4.18**).



1a R = 4-methylphenyl, R' = H, R'' = H
1b R = phenyl, R' = H, R'' = H
1c R = 4-bromophenyl, R' = H, R'' = H
1d R = 2-trifluoromethylphenyl, R' = H, R'' = H
1e R = 1-naphthalenyl, R' = H, R'' = H
1f R = 2-naphthalenyl, R' = H, R'' = H
1g R = phenyl, R' = methyl, R'' = H
1h R = naphthalen-1-yl, R' = methyl, R'' = H
1i R = 2-pyridinyl, R' = H, R'' = H
1j R = 2-phenylvinyl, R' = H, R'' = H
1l R = phenyl, R' = H, R'' = 5-methyl

Scheme 4.17 Syntheses of chalcones using Singh's method



1k R = H, R' = Me
1m R = R' = Ph

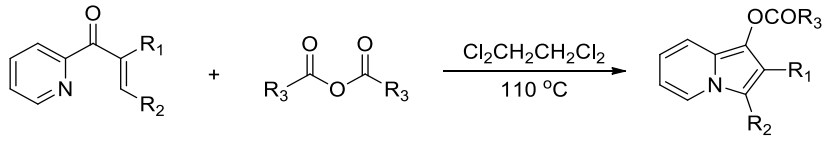
Scheme 4.18 Grignard reaction and subsequent oxidation

The chalcones were subjected to the optimised reaction conditions to test the functional group tolerance of the reaction (**Table 4.3**). The results showed that electron-donating and electron-withdrawing substituents were tolerated on the phenyl

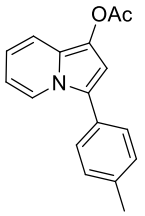
ring (**4.3a**–**f**). However, electron-donating group on the phenyl ring resulted in higher yields (**4.3a**) as compared to unsubstituted phenyl ring (**4.3b**). In contrast, the efficiency of reaction was lowered in the presence of electron-withdrawing group (**4.3d**). An advantage of this reaction is that halogen-containing aryl substrate could be tolerated, which is advantageous as the bromoaryl substituted indolizine can later serve as a precursor in Pd-catalysed cross-coupling reactions for further functionalisations (**4.3c**). Chalcones with increased substituents can be synthesised in excellent yields as well (**4.3g**–**i**). As this reaction did not require a transition metal catalyst, reactions with chalcones bearing heteroatoms can proceed smoothly without the concern of deactivating the catalyst by chelation (**4.3j** and **4.3m**). Alkyl substituted chalcones can also be applied successfully (**4.3k** and **4.3l**), with the notable example of 5-phenyl-1-(2-pyridinyl)-penta-2,4-diene-1-one having excellent regioselectivity. Substituents on the pyridine ring did not have an adverse effect on the reaction as well (**4.3q**).

Other electrophilic reagents (such as trimethylacetic anhydride, isovaleric anhydride and propionic anhydride) could also yield the corresponding indolizines (**4.3n**–**p**). However, in the presence of other electrophilic reagents like iodomethane, acetic chloride, 4-methylbenzenesulfonic anhydride, TMSOTf, benzoic anhydride and triflic anhydride, the starting material decomposed or there was no observable reaction.

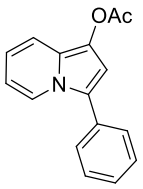
Table 4.3 Substrate scope of indolizines[a]



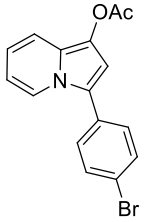
4.1a-m **4.2a-d** **4.3a-q**



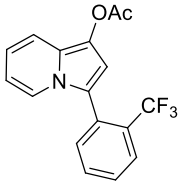
4.3a
92%



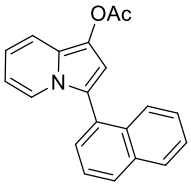
4.3b
81%



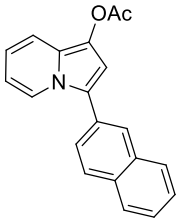
4.3c
73%



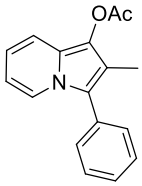
4.3d
48%



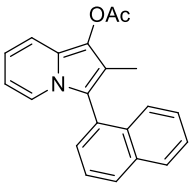
4.3e
95%



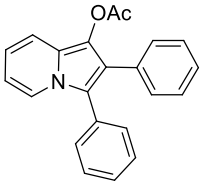
4.3f
95%



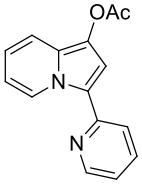
4.3g
98%



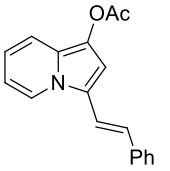
4.3h
98%



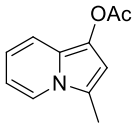
4.3i
99%



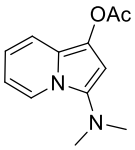
4.3j
82%



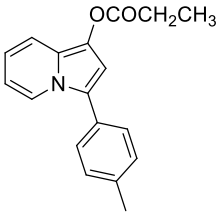
4.3k
75%



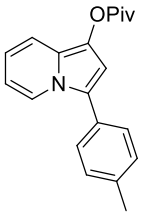
4.3l
70%



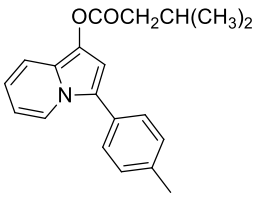
4.3m
72%



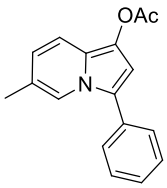
4.3n
95%



4.3o
55%



4.3p
60%

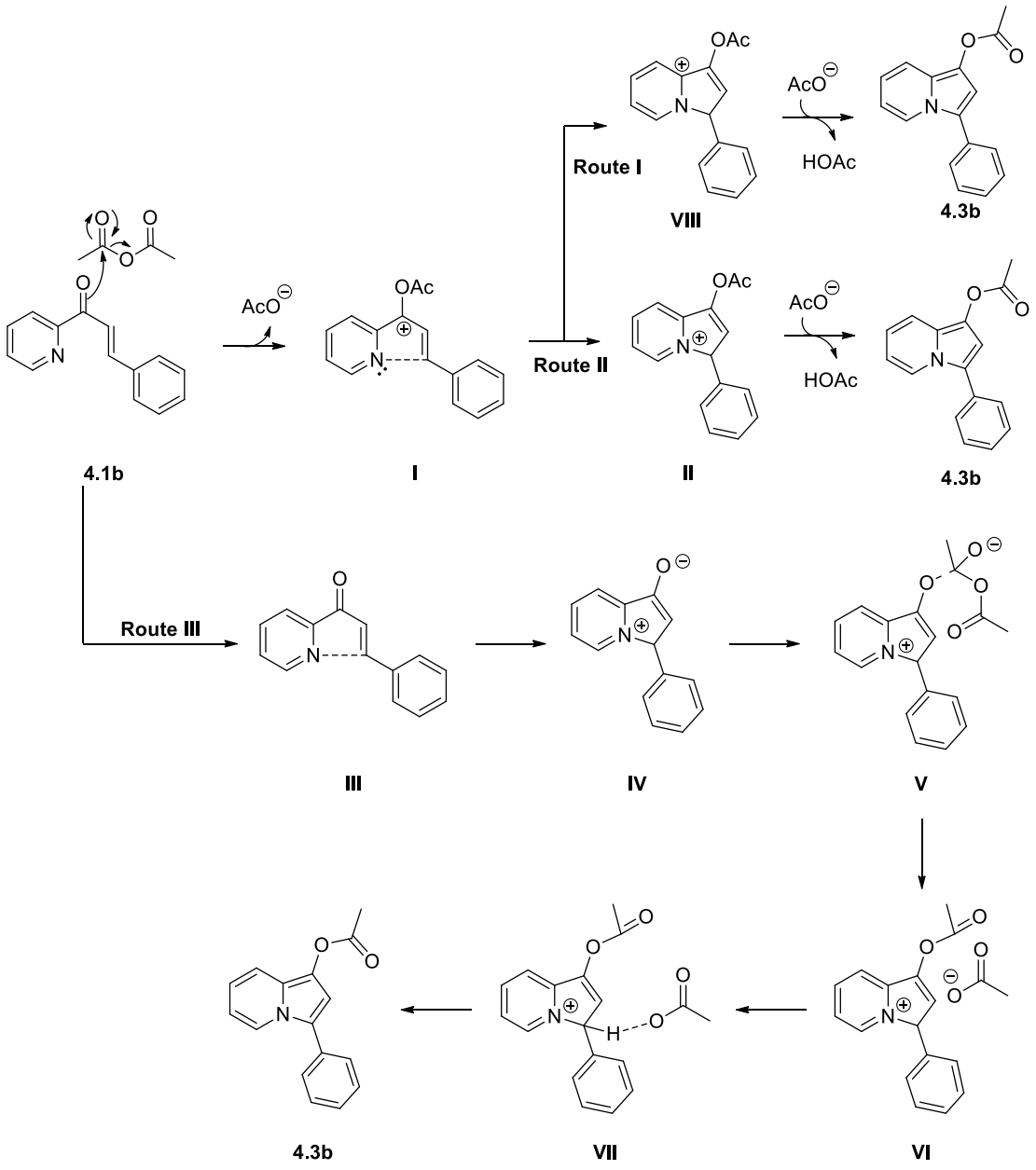


4.3q
88%

[a] Isolated yields.

4.2.3 Plausible Mechanism

The following reaction pathways are proposed to explain the formation of indolizines (**Scheme 4.19**). There are three possible pathways: the first two proceeds *via* the activation of chalcone through coordination of the electrophilic reagent to the carbonyl group to generate π-allylic cationic intermediate **I**. One of them would then proceed *via* electrocyclisation to give intermediate **VIII** while the other proceeds by nucleophilic attack of the pyridyl *N*, resulting in quaternary pyridinium intermediate **II**. Deprotonation is then driven by the regeneration of aromaticity to form indolizine **4.3b**. The third proposed mechanism proceeds *via* Michael addition to form enolate **IV**, the alkoxide ion then attacks the acetic anhydride and subsequent deprotonation occurs to achieve **4.3b**. However, based on the experimental results, **Route II** is likely to be the preferred route. Firstly, in the absence of acetic anhydride, no product formation was observed, indicating that acetic anhydride plays a crucial role in driving the reaction forward, hinting that **Routes I** or **II** are more probable. Furthermore, 5-*endo*-*trig* ring closure in **Route III** is Baldwin disfavoured. It is likely that the cationic species formed provides a driving force for the ring closure, making it an exception for Baldwin's rule. Another piece of supporting information is from the screening of additives, in which the addition of Pd catalysts has led to slight decrease in yields. In the case of **Route I**, the addition of Pd catalyst would not have any effect on the electrocyclic reaction while for the case of **Route II**, the coordination of Pd to N would retard the nucleophilic attack of pyridyl *N* to allylic cation, hence leading to decrease in reaction efficiency. Hence, **Route II** is likely to be the plausible mechanism based on the observed experimental results.



Scheme 4.19 Proposed mechanisms for cyclisation reaction

4.3 Conclusion

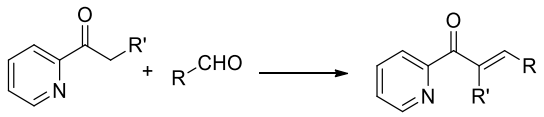
In summary, we have reported a metal-free method to achieve intramolecular C-N bond formation *via* C-H bond activation and successfully applied it to synthesise indolizines in moderate to excellent yields. This method offers the advantages of being mild, green and simple to carry out, with easily accessible starting materials. In addition, indolizines with substituents at different ring-positions, electron-withdrawing and electron-donating can also be achieved, which would greatly aid the structure-activity relationship studies of these bioactive compounds. This serves as precedent for the synthesis of this group of biologically active compounds, particularly when considering their manufacturing strategies in pharmaceutical companies, eliminating the possibility of trace metal contents and making them safe for consumption.

4.4 Experimental Section

General: All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Merck, Strem and Alfa Asear) and used without further purification unless stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Chromatograms were visualised by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. NMR spectra were recorded at room temperature on 400 MHz Bruker DPX 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). 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. HRMS (ESI) spectra were recorded on a Waters Q-Tof premier^{TM} mass spectrometer.

Preparation of chalcones (4.1a-j):

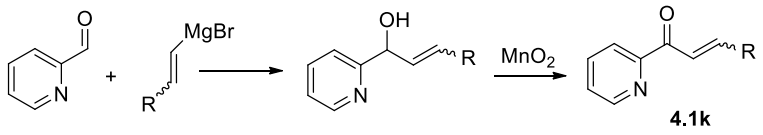
Chalcones **4.1a-j** were prepared in accordance with literature reported by Singh and co-workers with minor modifications.[30]



4.1a R = 4-methylphenyl, R' = H
4.1b R = phenyl, R' = H
4.1c R = 4-bromophenyl, R' = H
4.1d R = 2-trifluoromethylphenyl, R' = H
4.1e R = 1-naphthalenyl, R' = H
4.1f R = 2-naphthalenyl, R' = H
4.1g R = phenyl, R' = methyl
4.1h R = naphthalen-1-yl, R' = methyl
4.1i R = 2-pyridinyl, R' = H
4.1j R = 2-phenylvinyl, R' = H

Potassium hydroxide (0.1 M solution, 0.7 mL, 0.7 mmol, 0.19 equiv.) was added to a solution of 2-acetylpyridine (2-propionylpyridine) (3.65 mmol, 1 equiv.) and aldehyde (7.3 mmol, 2 equiv.) in methanol (17 mL) at 0 ºC. The reaction mixture was warmed to room temperature and stirred at this temperature until completion of the reaction (TLC). Methanol was evaporated and the residue was suspended in water (15 mL). The mixture was extracted with CH_2Cl_2 thrice. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was isolated by column chromatography.

General procedure to prepare chalcones (4.1k and 4.1m):



4.1k

Preparation of 3-substituted-1-(pyridin-2-yl)prop-2-en-1-ols:

To a flame-dried 50-mL round bottom flask was added 2-pyridinecarboxaldehyde (0.19 mL, 2 mmol, 1 equiv.) to THF (10 mL). The solution was cooled to 0 ^{o}C and a 0.5 M 1-propenyl magnesium bromide or *cis*-1,2-diphenylvinyl magnesium bromide solution in THF (5 mL, 2.5 mmol, 1.25 equiv.) was added *via* syringe. The reaction

mixture was warmed to 25 ^{o}C over two hours. The reaction mixture was then diluted in diethyl ether and quenched with saturated aqueous NH_4Cl. The organic layer was washed twice with water (10 mL) and dried over magnesium sulfate. The solution was filtered and concentrated by rotary evaporation to afford the desired product as clear oil which is directly applied to the next step.

1-(2-Pyridinyl)-2-buten-1-one (4.1k)

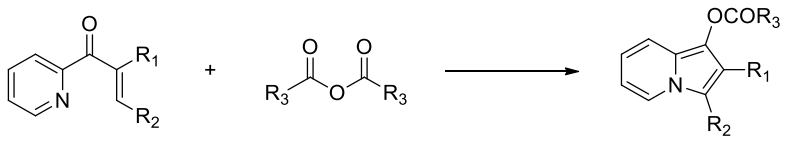
MnO_2 (869.4 mg, 10 mmol, 5 equiv.) was added into the flask charged with 1-(2-pyridinyl)-2-buten-1-ol (298.2 mg, 2 mmol, 1 equiv.) and dichloromethane (20 mL). The mixture was stirred at room temperature overnight and filtered. After evaporation of the solvents, chalcone **4.1k** was obtained (120.6 mg, 82%) after purification by silica gel chromatography (5:1, *n*-hexane/EtOAc), mixture of *E*/*Z* = 6:1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 – 8.64 (m, 1H, both isomers), 8.08 – 8.06 (m, 1H, both isomers), 7.89 – 7.78 (m, 1H, both isomers), 7.59 – 7.51 (m, 1H, both isomers), 7.44 – 7.41 (m, 1H, both isomers), 7.25 – 7.16 (m, 1H, major isomer), 6.58 – 6.50 (m, 1H, minor isomer) 2.23 (d, *J* = 7.2 Hz, 3H, minor isomer), 1.99 (d, J = 7.2 Hz, 3H, major isomer); ^{13}C NMR (100 MHz, CDCl3): δ 191.13, 189.31, 154.69, 154.05, 148.70, 146.12, 145.4, 136.88, 126.66, 126.52, 126.05, 123.69, 122.79, 122.37, 18.67, 16.29; HRMS (ESI) calcd. for $[C_9H_{10}NO]^+$ 148.0762; found 148.0760.

3-Phenyl-1-(pyridin-2-yl)prop-2-en-1-one (4.1m)

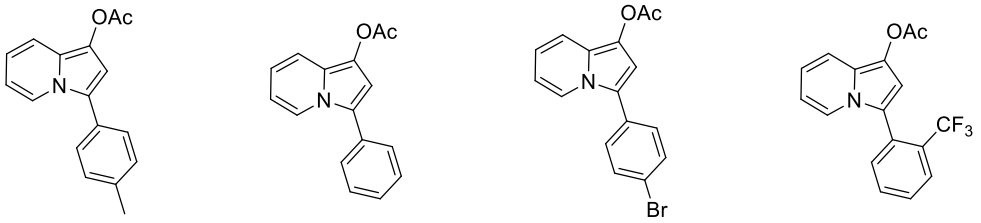
MnO_2 (869.4 mg, 10 mmol, 5 equiv.) was added into the flask charged with 3-phenyl-1-(pyridin-2-yl)prop-2-en-1-ol (422.2 mg, 2 mmol, 1 equiv.) and dichloromethane (20 mL). The mixture was stirred at room temperature overnight and filtered. After

evaporation of the solvents, chalcone **4.1m** was obtained (330.3 mg, 79%) after purification by silica gel chromatography (6:1, *n*-hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, J = 4.8 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.77 – 7.72 (dt, J = 7.6, 1.2 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.28 – 7.24 (m, 7H),7.17 – 7.09 (m, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 199.58, 153.65, 149.69, 141.31, 138.08, 136.81, 135.75, 131.16, 128.73, 128.66, 128.25, 128.01, 127.82, 126.85, 126.61, 123.66; HRMS (ESI) calcd. for $[C_{14}H_{12}NO]^+$ 210.0919; found 210.0922.

General cyclisation procedure (4.3a–q):



4.1a-m **4.2a-d** **4.3a-q**

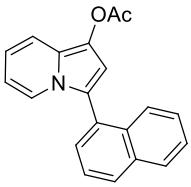


4.3a

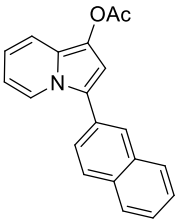
4.3b

4.3c

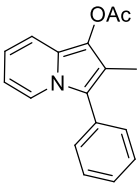
4.3d



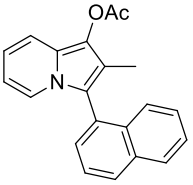
4.3e



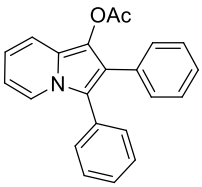
4.3f



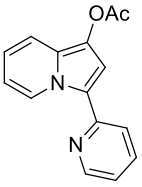
4.3g



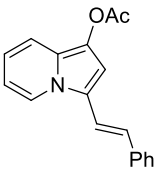
4.3h



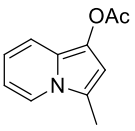
4.3i



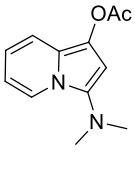
4.3j



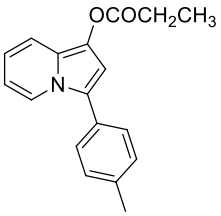
4.3k



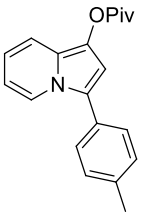
4.3l



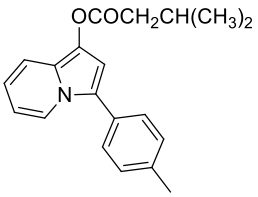
4.3m



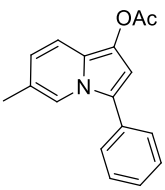
4.3n



4.3o



4.3p



4.3q

Anhydride **4.2** (1 mL) and $Cl_2CH_2CH_2Cl_2$ (5 mL) were added into a Schlenk tuble charged with chalcone **4.1** (0.5 mmol). The mixture was stirred at 110 ^oC for 10 h,

then cooled down to room temperature, diluted with ether (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted twice with ether (20 mL) and the combined organic phase was dried over Na_2SO_4. After evaporation of the solvents the residue was purified by silica gel chromatography or thin layer chromatography (TLC) (*n*-hexane/EtOAc).

1-(Acetyloxy)-3-(4-methylphenyl)indolizine (4.3a)

Following general procedure, **4.3a** was obtained as pale yellow oil (122.0 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.20 Hz, 1H), 7.46 (d, J = 8.00 Hz, 2H), 7.28 (m, 3H), 6.81 (s, 1H), 6.35 (dd, J = 6.40 Hz, 9.20Hz, 1H), 6.43 (dt, J = 1.20 Hz, 7.20Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.35, 137.11, 129.56, 128.84, 128.07, 127.08, 122.74, 122.03, 121.60, 116.21, 116.19, 110.70, 106.27, 21.20, 20.84; HRMS (ESI) calcd. for $[C_{17}H_{16}NO_2]^+$ 266.1180; found 266.1180.

1-(Acetyloxy)-3-(phenyl)indolizine (4.3b)

Following general procedure, **4.3b** was obtained as pale yellow oil (101.7 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 7.20 Hz, 1H), 7.56 (d, J = 7.20 Hz, 2H), 7.47 (t, J = 8.00 Hz, 2H), 7.35 (t, J = 7.70 Hz, 1H), 7.29 (d, J = 9.20 Hz, 1H), 6.84 (s, 1H), 6.65 (m, 1H), 6.44 (dt, J = 1.60 Hz, 7.60 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.43, 131.87, 128.97, 128.19, 127.33, 127.28, 123.08, 122.07, 121.66, 116.54, 116.34, 110.95, 106.63, 20.95; HRMS (ESI) calcd. for $\{C_{16}H_{14}NO_2]^+$ 252.1025; found 252.1023.

1-(Acetyloxy)-3-(4-bromophenyl)indolizine (4.3c)

Following general procedure, **4.3c** was obtained as pale yellow oil (120.5 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.20 Hz, 1H), 7.57 (d, J = 8.80 Hz, 2H), 7.40 (d, J = 8.40 Hz, 2H), 7.30 (d, J = 8.80 Hz, 1H), 6.83 (s, 1H), 6.66 (m, 1H), 6.45 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.24, 132.03, 130.63, 129.41, 127.32, 123.34, 121.31, 120.91, 120.63, 116.71, 116.32, 111.21, 106.72, 20.82; HRMS (ESI) calcd. for $[C_{16}H_{13}BrNO_2]^+$ 330.0130; found 330.0130.

1-(Acetyloxy)-3-(2-trifluoromethylphenyl)indolizine (4.3d)

Following general procedure, **4.3d** was obtained as pale yellow oil (76.6 mg, 48%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.00 Hz, 1H), 7.63 (t, J = 7.60 Hz, 1H), 7.55 (t, J = 7.60 Hz, 2H), 7.47 (d, J = 7.20 Hz, 1H), 7.30 (d, J = 9.20 Hz, 1H), 6.82 (s, 1H), 6.65 (m, 1H), 6.38 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.23, 133.39, 131.88, 131.17, 130.87, 130.27, 128.81, 126.82, 125.06, 122.46, 121.88, 116.75, 116.50, 116.09, 110.69, 108.36, 20.90; HRMS (ESI) calcd. for $[C_{17}H_{13}F_3NO_2]^+$ 320.0898; found 320.0898.

1-(Acetyloxy)-3-(naphthalen-1-yl)indolizine (4.3e)

Following general procedure, **4.3e** was obtained as pale yellow oil (143.0 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.00 Hz, 2H), 7.65-7.37 (m, 7H), 6.96 (s, 1H), 6.68 (m, 1H), 6.34 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.37, 133.95, 132.23, 129.08, 128.93, 128.61, 126.96, 126.75, 126.21, 125.81, 125.63, 122.63, 122.46, 119.75, 116.42, 116.19, 110.52, 108.21, 21.01; HRMS (ESI) calcd. for $[C_{20}H_{16}NO_2]^+$ 302.1181; found 302.1181.

1-(Acetyloxy)-3-(naphthalen-2-yl)indolizine (4.3f)

Following general procedure, **4.3f** was obtained as pale yellow oil (143.0 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 7.20 Hz, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.93 (d, J = 8.40 Hz, 1H), 7.87 (m, 2H), 7.68 (dd, J = 2.00 Hz, 8.40Hz, 1H), 7.51 (m, 2H), 7.33 (d, J = 9.20 Hz, 1H), 6.96 (s, 1H), 6.68 (m, 1H), 6.48 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.40, 133.68, 132.51, 129.25, 128.64, 127.94, 127.79, 127.52, 126.55, 126.54, 126.32, 126.12, 123.34, 122.05, 121.70, 116.73, 116.42, 111.15, 107.04, 20.96; HRMS (ESI) calcd. for $[C_{20}H_{16}NO_2]^+$ 302.1181; found 302.1181.

1-(Acetyloxy)-2-methyl-3-(phenyl)indolizine (4.3g)

Following general procedure, **4.3g** was obtained as pale yellow oil (129.9 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 7.20 Hz, 1H), 7.45 (m, 4H), 7.34 (m, 1H), 7.18 (d, J = 9.20 Hz, 1H), 6.60 (m, 1H), 6.30 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.39 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.52, 130.79, 129.62, 128.66, 127.25, 125.75, 122.00, 121.27, 119.55, 116.38, 115.02, 114.82, 109.73, 20.34, 8.69; HRMS (ESI) calcd. for $[C_{17}H_{16}NO_2]^+$ 266.1181; found 266.1183.

1-(Acetyloxy)-2-methyl-3-(naphthalen-1-yl)indolizine (4.3h)

Following general procedure, **4.3h** was obtained as pale yellow oil (154.4 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (m, 2H), 7.60 (m, 2H), 7.51 (m, 1H), 7.41 (m, 2H), 7.32 (d, J = 7.20 Hz, 1H), 7.26 (d, J = 8.80 Hz, 1H), 6.64 (m, 1H), 6.26 (dt, J = 1.20 Hz, 7.60 Hz, 1H), 2.45 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.75, 134.03, 132.66, 129.91, 129.03, 128.60, 128.44, 126.74, 126.19, 125.82,

125.73, 122.34, 122.30, 117.85, 116.43, 116.40, 115.20, 109.70, 20.70, 8.96; HRMS (ESI) calcd. for $[C_{21}H_{18}NO_2]^+$ 316.1338; found 316.1339.

1-(Acetyloxy) -2,3diphenylindolizine (4.3i)

Following general procedure, **4.3i** was obtained as green solid (161.9 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J*=7.20 Hz, 1H), 7.34-7.13 (m, 11H), 6.63-6.59 (m, 1H), 6.35-6.31 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 132.6, 130.59. 130.57, 129.7, 128.8, 128.1, 127.6, 126.4, 124.4, 122.8, 121.6, 119.9, 117.1, 115.8, 110.7, 20.5; HRMS (ESI) calcd.for $[C_{22}H_{18}NO_2]^+$ 328.1338; found 328.1338.

1-(Acetyloxy) -3-(2-pyridyl)indolizine (4.3j)

Following general procedure, **4.3j** was obtained as yellow solid (103.4 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (d, *J* = 7.20 Hz, 1H), 8.56 (m, 1H), 7.65 (td, *J* = 2.00 Hz, 8.4Hz, 1H), 7.59 (d, *J* = 8.00 Hz, 1H), 7.35 (d, *J* = 9.20 Hz, 1H), 7.29 (s, 1H), 7.04 (m, 1H), 6.80 (m, 1H), 6.64 (dt, *J* = 1.20 Hz, 7.60 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.22, 152.30, 148.28, 136.26, 127.66, 126.30, 125.46, 120.41, 119.71, 119.18, 118.37, 115.45, 111.66, 107.41, 20.98; HRMS (ESI) calcd. for $[C_{15}H_{13}N_2O_2]^+$ 253.0977; found 253.0978.

(*E*)-Acetic acid 3-styryl-indolizin-1-yl ester (4.3k)

Following general procedure, **4.3k** was obtained as yellow solid (103.9 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.20 Hz, 1H), 7.49 (d, *J* = 7.20 Hz, 2H), 7.35 (t, *J* = 7.60 Hz, 2H), 7.25 (m, 3H), 7.09 (s, 1H), 6.97 (d, *J* = 16.00 Hz, 1H), 6.66 (m, 1H), 6.56 (dt, *J* = 1.20 Hz, 7.60 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

169.19, 137.70, 128.74, 128.16, 127.12, 125.98, 125.82, 123.73, 121.37, 120.43, 116.63, 116.38, 114.87, 111.56, 104.15, 20.95; HRMS (ESI) calcd. for $[C_{18}H_{16}NO_2]^+$ 278.1181; found 278.1185.

1-(Acetyloxy) -3-(methyl)indolizine (4.3l)

Following general procedure, **4.3l** was obtained as yellow oil (66.2 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.20 Hz, 1H), 7.27 (d, J = 8.80 Hz, 1H), 6.60 (m, 1H), 6.57 (s, 1H), 6.50 (td, J = 1.20 Hz, 7.20 Hz, 1H), 2.45 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.59, 125.55, 121.30, 120.86, 116.45, 115.75, 114.67, 110.06, 105.52, 20.75, 11.38; HRMS (ESI) calcd. for $[C_{11}H_{12}NO_2]^+$ 190.0868; found 190.0869.

1-(Acetyloxy) -3-(*N*,*N*-dimethylamino)indolizine (4.3m)

Following general procedure, **4.3m** was obtained as yellow oil (78.5 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.20 Hz, 1H), 7.18 (d, J = 8.80 Hz, 1H), 6.51 (m, 1H), 6.42 (td, J = 1.20 Hz, 7.20 Hz, 1H), 6.40 (s, 1H), 2.73 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.50, 132.37, 124.80, 120.25, 117.46, 115.79, 114.77, 109.71, 94.87, 43.98, 20.91; HRMS (ESI) calcd. for $[C_{12}H_{15}N_2O_2]^+$ 219.1134; found 219.1136.

Propionic acid 3-(4-methylphenyl)indolizin-1-yl ester (4.3n)

Following general procedure, **4.3n** was obtained as yellow oil (132.6 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.20 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 7.27 (m, 3H), 6.82 (s, 1H), 6.63 (m, 1H),6.41 (td, J = 1.20 Hz, 7.20 Hz, 1H), 2.67 (q, J = 7.60 Hz, 2H), 2.42 (s, 3H), 1.33 (t, J = 7.60 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

172.88, 137.17, 129.65, 129.00, 128.17, 127.26, 122.82, 122.09, 121.68, 116.33, 116.18, 110.76, 106.39, 27.62, 21.29, 9.35; HRMS (ESI) calcd. for $[C_{18}H_{18}NO_2]^+$ 280.1338; found 280.1339.

Trimethylacetic acid 3-(4-methylphenyl)indolizin-1-yl ester (4.3o)

Following general procedure, **4.3o** was obtained as yellow oil (84.5 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 7.20 Hz, 1H), 7.45 (d, J = 8.40 Hz, 2H), 7.27 (m, 3H), 6.83 (s, 1H), 6.63 (m, 1H),6.41 (td, J = 1.20 Hz, 7.20 Hz, 1H), 2.42 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.80, 137.07, 129.58, 128.98, 128.08, 127.41, 122.72, 122.01, 121.60, 116.19, 116.03, 110.68, 106.32, 39.20, 27.33, 21.23; HRMS (ESI) calcd. for $[C_{20}H_{22}NO_2]^+$ 308.1651; found 308.1650.

Isovaleric acid 3-(4-methylphenyl)indolizin-1-yl ester (4.3p)

Following general procedure, **4.3p** was obtained as yellow oil (92.1 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 7.20 Hz, 1H), 7.44 (d, J = 8.40 Hz, 2H), 7.26 (m, 3H), 6.80 (s, 1H), 6.60 (m, 1H), 6.42 (td, J = 1.20 Hz, 7.20 Hz, 1H), 2.51 (d, J = 7.20 Hz, 2H), 2.41 (s, 3H), 2.31 (m, 1H), 1.10 (d, J = 6.80 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.48, 137.17, 129.63, 128.97, 128.17, 127.16, 122.84, 122.11, 121.68, 116.34, 116.21, 110.74, 106.42, 43.31, 26.02, 22.51, 21.28; HRMS (ESI) calcd. for $[C_{20}H_{22}NO_2]^+$ 308.1651; found 308.1653.

1-(Acetyloxy)-3-phenyl-5-methylindolizine (4.3q)

Following general procedure, **4.3q** was obtained as yellow oil (116.7 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 0.8 Hz, 1H), 7.58 (dd, J = 8.4, 1.2 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.24 (dd, J = 9.2, 0.4 Hz, 1H), 6.80

(s, 1H), 6.53 (dd, J = 8.4, 1.2 Hz, 1H), 2.38 (s, 3H), 2.19 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 132.0, 128.8, 128.1, 127.2, 127.0, 122.0, 121.5, 120.1, 119.8, 118.8, 115.7, 106.0, 20.8, 18.5; HRMS (ESI) calcd.for $[C_{20}H_{22}NO_2]^+$ 266.1181; found 266.1183.

4.5 References

1. Wu, J.; Leng, W.-L.; Liao, H.; Mai Hoang, K. L.; Liu, X.-W. *Chem. Asian J.* **2015,** *10*, 853-856.
2. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57*, 10257-10274.
3. Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011,** *46*, 5237-5257.
4. (a) Vemula, V.; Vurukonda, S.; Bairi, C. *Int. J. Pharm. Sci. Rev. Res.* **2011,** *11*, 159-163; (b) Borrows, E.; Holland, D. *Chem. Rev.* **1948,** *42*, 611-643.
5. Scholtz, M. *Eur. J. Inorg. Chem.* **1912,** *45*, 734-746.
6. Katritzky, A. R.; Ramsden, C. A.; Joule, J. A.; Zhdankin, V. V., *Handbook of heterocyclic chemistry*. Elsevier: 2010.
7. Uchida, T.; MATSUMOTO, K. *Synthesis* **1976**, 209-236.
8. (a) Borrows, E.; Holland, D.; Kenyon, J. *J. Chem. Soc.* **1946**, 1075-1077; (b) Borrows, E.; Holland, D.; Kenyon, J. *J. Chem. Soc.* **1946**, 1069-1075.
9. Bragg, D.; Wibberley, D. *J. Chem. Soc.* **1962**, 2627-2629.
10. Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1931,** *486*, 211-225.
11. Acheson, R.; Robinson, D. *J. Chem. Soc. C* **1968**, 1629-1633.
12. Acheson, R.; Bailey, A.; Selby, I. *Chem. Commun.* **1966**, 835a-835a.
13. Hurst, J.; Melton, T.; Wibberly, D. G. *J. Chem. Soc.* **1965,** *46*, 2948-55.
14. Venugopala, K. N.; Khedr, M. A.; Attimarad, M.; Padmashali, B.; Kulkarni, R. S.; Venugopala, R.; Odhav, B. *J. Basic. Clin. Pharm.* **2017,** *8*, 49-61.
15. Boekelheide, V.; Fahrenholtz, K. *J. Am. Chem. Soc.* **1961,** *83*, 458-462.
16. Huisgen, R.; Grashey, R.; Steingruber, E. *Tetrahedron Lett.* **1963,** *4*, 1441-1445.
17. (a) Basketter, N.; Plunkett, A. *J. Chem. Soc. D* **1971**, 1578-1578; (b) Sasaki, T.; Kanematsu, K.; Yukimoto, Y.; Ochiai, S. *J. Org. Chem.* **1971,** *36*, 813-818; (c) Farnum, D. G.; Alaimo, R. J.; Dunston, J. M. *J. Org. Chem.* **1967,** *32*, 1130-1134; (d) Henrick, C.; Ritchie, E.; Taylor, W. *Aust. J. Chem.* **1967,** *20*, 2467-2477; (e) Linn, W.; Webster, O.; Benson, R. *J. Am. Chem. Soc.* **1965,** *87*, 3651-3656.
18. Katritzky, A. R.; Qiu, G.; Yang, B.; He, H.-Y. *J. Org. Chem.* **1999,** *64*, 7618-7621.
19. Zhang, L.; Liang, F.; Sun, L.; Hu, Y.; Hu, H. *Synthesis* **2000**, 1733-1737.
20. Wei, X.; Hu, Y.; Li, T.; Hu, H. *Synth. Commun.* **1992,** *22*, 2103-2109.
21. Allgäuer, D. S.; Mayr, H. *Eur. J. Org. Chem.* **2014**, 2956-2963.
22. Rotaru, A. V.; Druta, I. D.; Oeser, T.; Müller, T. J. *Helv. Chim. Acta* **2005,** *88*, 1798-1812.
23. Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003,** *5*, 435-438.
24. (a) Tamura, Y.; Sumida, Y.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2091-2095; (b) Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G.-i. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2089-2091; (c) Sasaki, T.; Kanematsu, K.; Kakehi, A.; Ito, G. *Tetrahedron* **1972,** *28*, 4947-4958.
25. Kröhnke, F.; Zecher, W.; Curtze, J.; Drechsler, D.; Pfleghar, K.; Schnalke, K. E.; Weis, W. *Angew. Chem. Int. Ed.* **1962,** *1*, 626-632.
26. (a) Verma, A. K.; Shukla, S. P.; Singh, J.; Rustagi, V. *J. Org. Chem.* **2011,** *76*, 5670-5684; (b) Petuškova, J.; Bruns, H.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2011,** *50*, 3799-3802; (c) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. Eur. J.*

2004, *10*, 4556-4575; (d) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002,** *67*, 6264-6267.
27. Zhu, H.; Stöckigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011,** *13*, 2792-2794.
28. Lee, J. H.; Kim, I. *J. Org. Chem.* **2013,** *78*, 1283-1288.
29. Kim, M.; Jung, Y.; Kim, I. *J. Org. Chem.* **2013,** *78*, 10395-10404.
30. Singh, P. K.; Singh, V. K. *Org. Lett.* **2008,** *10*, 4121-4124.

Publications

1. **Wei-Lin Leng**, Jingxi He, Hui Yao and Xue-Wei Liu, Methodologies in Chemical Synthesis of Carbohydrates. Synthetic Glycomes, First Edition. Edited by Peng George Wang. 2018 Royal Society of Chemistry.
2. Hongze Liao, **Wei-Lin Leng**, Kim Le Mai Hoang, Hui Yao, Jingxi He, Amanda Ying Hui Voo and Xue-Wei Liu, Asymmetric Syntheses of 8-Oxabicyclo[3,2,1]octane and 11-Oxatricyclo[5.3.1.0]undecane from Glycal, *Chem. Sci*. **2017**, doi: 10.1039/C7SC01232f.
3. Hui Yao, Shasha Zhang, **Wei-Lin Leng**, Min-Li Leow, Shaohua Xiang, Jingxi He, Hongze Liao, Kim Le Mai Hoang, and Xue-Wei Liu, Catalyst-Controlled Stereoselective *O*-Glycosylation: Pd(0) vs Pd(II), *ACS Catal*. **2017**, *7*, 5456–5460.
4. Kim Le Mai Hoang, **Wei-Lin Leng**, Yu-Jia Tan, and Xue-Wei Liu, Stereoselective *C*-Glycosylation from Glycal Scaffolds. Selective Glycosylations: Synthetic Methods and Catalysts, First Edition. Edited by Clay S. Bennett. 2017 Wiley-VCH Verlag GmbH & Co.
5. **Wei-Lin Leng**, Hongze Liao, Hui Yao, Zi-En Ang, Shaohua Xiang and Xue-Wei Liu, Palladium-Catalyzed Decarboxylative Allylation/Wittig Reaction: Substrate-Controlled Synthesis of *C*-Vinyl Glycosides, *Org. Lett.* **2017**, *19*, 416–419.
6. Ronny William, **Wei-Lin Leng**, Siming Wang and Xue-Wei Liu, The First Intermolecular Interrupted Imino-Nazarov Reaction: Expeditious Access to Carbocyclic Nucleoside Analogues, *Chem. Sci.* **2016**, *7*, 1100-1103.

7. Li Ji, Shao-Hua Xiang, **Wei-Lin Leng**, Kim Le Mai Hoang and Xue-Wei Liu, Palladium-Catalyzed Glycosylation: Novel Synthetic Approach to Diverse *N*-Heterocyclic Glycosides, *Org. Lett.* **2015**, *17*, 1357-1360.
8. Junliang Wu, **Wei-Lin Leng**, Hongze Liao, Kim Le Mai Hoang and Xue-Wei Liu, Intramolecular C-N Bond Formation under Metal-Free Conditions: Synthesis of Indolizines, *Chem. Asian J.* **2015**, *10*, 853-856.
9. Yaguang Bai, **Wei-Lin Leng**, Yongxin Li and Xue-Wei Liu, A Highly Efficient Dual Catalysis Approach for *C*-glycosylation: Addition of (*o*-Azaaryl)carboxaldehyde to Glycals, *Chem. Commun.* **2014**, *50*, 13391-13393.
10. Hong Yee Tan, Shaohua Xiang, **Wei-Lin Leng** and Xue-Wei Liu, Regio and Stereoselective Synthesis of *β*-Keto Functionalized *C*-Glycosides via Iron Catalyzed Ferrier Rearrangement Reactions, *RSC Adv.* **2014**, *4*, 34816-34822.

Conferences Attended

1. Stereoselective construction of *C*-vinyl glycosides *via* tandem decarboxylative allylation/Wittig reaction. **Wei-Lin Leng**, Xue-Wei Liu. 16th Tetrahedron Symposium: Challenges in Bioorganic and Organic Chemistry. Berlin, Germany. (Poster Presentation)
2. Stereoselective *C*-Glycosylation: Pd-/Ir-catalyzed Decarboxylative Allylation of Glycals and Amino Alkanoic Acids. **Wei-Lin Leng**, Xue-Wei Liu. 23rd IUPAC Conference on Physical Organic Chemistry. Sydney, Australia. (Poster Presentation)
3. Tandem Native Chemical Ligation/Butelase-mediated Ligation: Application towards Cyclic *N*-Glycopeptide Synthesis. **Wei-Lin Leng**, Giang Kien Truc Nguyen, Aoxin Guo, James, P. Tam, Xue-Wei Liu, 2nd Peptides and Proteins Symposium. Singapore. (Poster Presentation)