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Jennifer J Becker, Michel R Gagne

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14. ABSTRACT
The development of new catalysts has enabled the selective activation of carbohydrates to access new potential drug precursors, or when more aggressively applied, hydrocarbons. The latter can be used as a high energy fuel. The development of flow approaches has also enabled reactions that were traditionally carried out under batch conditions to now be carried out continuously with concomitant high efficiencies and high material throughput.

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a. REPORT	b. ABSTRACT	c. THIS PAGE			Jennifer Becker
UU	UU	UU	UU		19b. TELEPHONE NUMBER: 919-549-4224

Report Title

Selective Methods for C-X Activation in Carbohydrates

ABSTRACT

The development of new catalysts has enabled the selective activation of carbohydrates to access new potential drug precursors, or when more aggressively applied, hydrocarbons. The latter can be used as a high energy fuel. The development of flow approaches has also enabled reactions that were traditionally carried out under batch conditions to now be carried out continuously with concomitant high efficiencies and high material throughput.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

Received		Paper
02/12/2013	7.00	Matthew P. McLaughlin, Laura L. Adduci, Jennifer J. Becker, Michel R. Gagné. Iridium-Catalyzed Hydrosilylative Reduction of Glucose to Hexane(s), Journal of the American Chemical Society, (01 2013): 1225. doi: 10.1021/ja3110494
02/12/2013	9.00	R. Stephen Andrews, Jennifer J. Becker, Michel R. Gagné. Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light, Angewandte Chemie International Edition, (08 2010): 7274. doi: 10.1002/anie.201004311
02/12/2013	8.00	Joseph G. Sokol, Chandra Sekhar Korapala, Peter S. White, Jennifer J. Becker, Michel R. Gagné. Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes, Angewandte Chemie International Edition, (06 2011): 5658. doi: 10.1002/anie.201100463
08/28/2012	1.00	R. Stephen Andrews, Jennifer J. Becker, Michel R. Gagné. A Photoflow Reactor for the Continuous Photoredox-Mediated Synthesis of C-Glycoamino Acids and C-Glycolipids, Angewandte Chemie International Edition, (04 2012): 0. doi: 10.1002/anie.201200593
08/28/2012	2.00	Rui-Yao Wang, Ha Nguyen, Jennifer J. Becker, Michel R. Gagné, Shu-Bin Zhao. Electrophilic fluorination of cationic Pt-aryl complexes, Chemical Communications, (2012): 0. doi: 10.1039/c1cc15006e
08/28/2012	3.00	Shu-Bin Zhao, Jennifer J. Becker, Michel R. Gagne?. Steric Crowding Makes Challenging C-F Elimination Feasible, Organometallics, (08 2011): 0. doi: 10.1021/om200515f
09/17/2012	5.00	R. Stephen Andrews, Jennifer J. Becker, Michel R. Gagne. Investigating the Rate of Photoreductive Glucosyl Radical Generation, Organic Letters, (05 2011): 2406. doi: 10.1021/ol200644w
TOTAL:	**7**	

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

Received Paper

TOTAL:

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received	Paper

TOTAL:

Number of Manuscripts:

Books

Received	Paper

TOTAL:

Patents Submitted

Patents Awarded

Awards

Gagne elected fellow of the AAAS

Graduate Students

NAME	PERCENT_SUPPORTED	Discipline
Laura Adduci	1.00	
Steve Andrews	1.00	
FTE Equivalent:	**2.00**	
Total Number:	**2**	

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Colleen Munroe-Leighton	1.00
Matthew McLaughlin	1.00
FTE Equivalent:	**2.00**
Total Number:	**2**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Michel R gagne	0.00	
FTE Equivalent:	**0.00**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT_SUPPORTED	Discipline
Madi Saltzer	1.00	Chemistry
Lourens du Pisanie	1.00	Chemistry
FTE Equivalent:	**2.00**	
Total Number:	**2**	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	1.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	1.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	1.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	1.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	1.00

Names of Personnel receiving masters degrees

NAME
Total Number:

Names of personnel receiving PHDs

NAME
Steve Andrews
Total Number: 1

Names of other research staff

NAME	PERCENT_SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

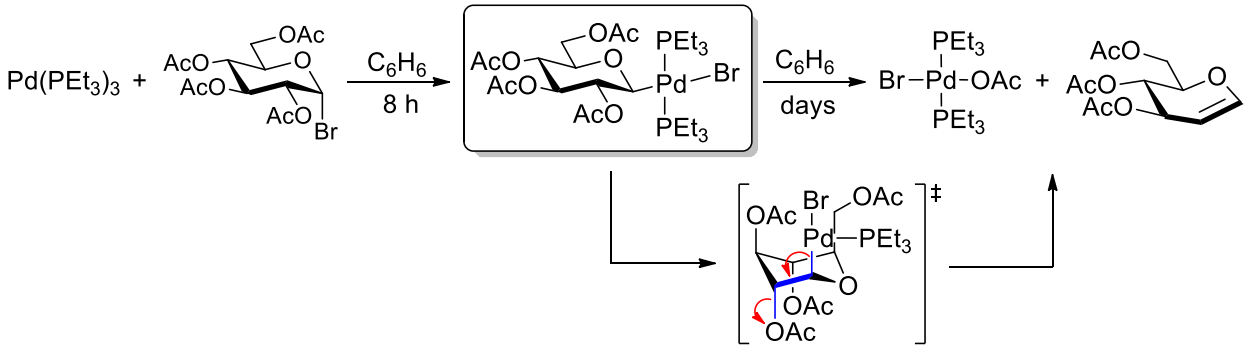
see attached

Technology Transfer

Selective Methods for C-X Activation in Carbohydrates
Dr. Jennifer J. Becker

Publication: "Oxidative Addition of Secondary C-X Bonds to Palladium(0): A Beneficial Anomeric Acceleration." Munro-Leighton, C.; Adduci, L. L.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 2646-2649.

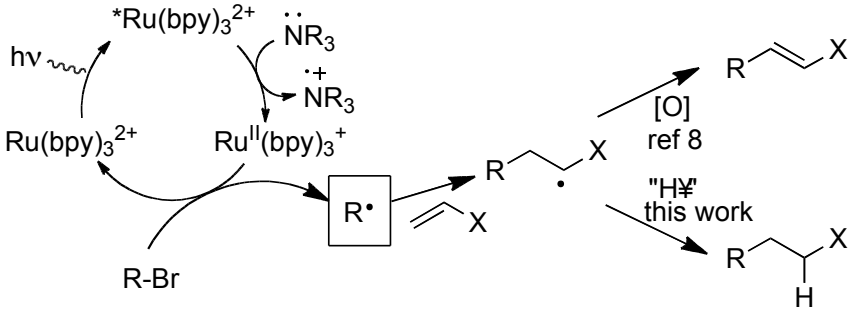
Our 2011 *Organometallics* paper reports that acetobromo-α-D-glucose reacts with $Pd(PEt_3)_3$ to give the product of invertive oxidative addition, $Pd(PEt_3)_2(Br)$(AcO-β-glucose). This organometallic product, which was characterized by NMR and X-ray crystallography, represents the first reported crystal structure of a glycosyl-palladium compound. Although the isolated compound is stable in air, dissolution in benzene initiates a β-acetoxy elimination process that generates tri-*O*-acetyl glucal and $Pd(PEt_3)_2(Br)(OAc)$. Replacement of PEt_3 with other trialkyl phosphine ligands having similar steric and electronic properties, including PBu_3, PEt_2Ph, and $PMePh_2$, also gave oxidative addition. In contrast to the observed reactivity of acetobromo-α-D-glucose, cyclohexyl bromide does not react with $Pd(PEt_3)_3$, indicating that the anomeric effect plays an important assistive role in the activation of a secondary alkyl halide by palladium(0).



To explore the reactivity of the novel glucosyl palladium complex, we investigated the mechanism of β-acetoxy elimination. Experiments in which the rate of elimination was monitored in the presence of excess Br^- and PEt_3 indicated that elimination is dissociative in PEt_3, but not in Br^-. Noting that a syn elimination pathway was unlikely because the stereochemistry of the glucosyl ring prevents the compound from accessing the necessary synperiplanar conformation, we focused our attention on anti elimination mechanisms. Since the crystal structure did not show an antiperiplanar arrangement of the palladium center and the acetate leaving group, we suggested that the ring undergoes an inversion process to adopt an antiperiplanar conformation. Both full and partial ring inversion were proposed to result in plausible elimination intermediates. To distinguish between the two, a tethering experiment was performed in which two carbon atoms on the glucosyl ring were linked by a benzylidene group, preventing complete inversion while allowing partial inversion. The failure of this modification to prevent elimination indicated that complete inversion was unnecessary; we now believe that the structure adopts a "boat" conformation to position the palladium center and acetate group in an antiperiplanar arrangement that is ideally suited for β-acetoxy elimination.

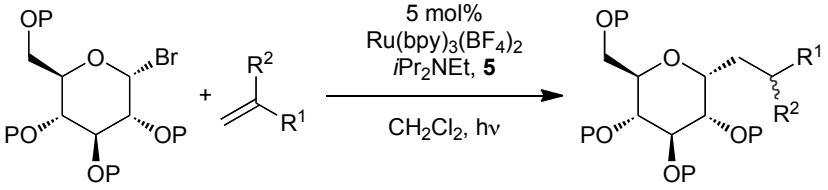
Publication: "Visible Light-Mediated Intermolecular Addition of Glycosyl Halides to Alkenes"
R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem., Int. Ed.* **2010**, *49*, 7274-7276.

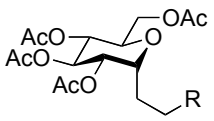
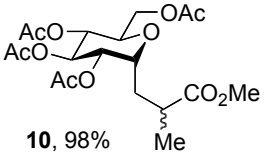
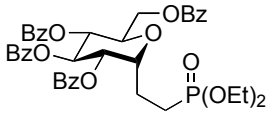
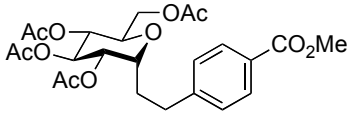
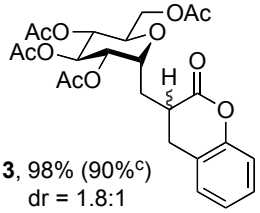
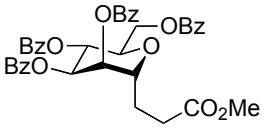
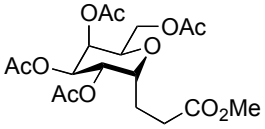
This publication represents the culmination of efforts to reductively activate C-X bonds in carbohydrates by the catching of photons from visible light with a photoredox catalyst. A photo-reductive cycle was established using $Ru(bpy)_3^{2+}$ as the photocatalyst and a tertiary amine base as the stoichiometric reductant. The methodology was demonstrated to readily reduce activated C-X bonds in carbohydrates and provide access to reactive glycosyl radicals, which selectively couple with activated alkenes to form important C-Glycosides. The developed photocycle is as shown below, and is initiated by the absorption of a photon from a compact fluorescent light bulb to promote a high lying metal-based electron into the π* band of the bpy ligand; a so called metal to ligand charge transfer (MLCT) transition. This charge separated state is thermally reduced with electron donors of matched redox character to generate an excited state species that has is electronically filled Ru center, a high lying electron in a ligand based orbital. This ligand-centered electron is highly reducing and is redox matched to quickly and efficiently react with activated carbohydrates. When the carbohydrate is a glycosyl bromide, electron transfer to the carbohydrate generates a dissociative state that quickly cleaves the C-Br bond to generate the glucose radical and bromide anion.



The synthetic scope of this methodology is highlighted in Table 1, which shows how various types of carbohydrates can be activated, which types of activated alkenes functional optimally. The optimized conditions utilize 5 mol% catalyst or less, and rely on the output of department store 14 Watt compact fluorescent light bulbs. Nearly all of the results collected in Table 1 represent high water marks in terms of reaction yields and ease of synthesis.

Table 1. Scope of the *C*-Alkylation with Activated Alkenes.

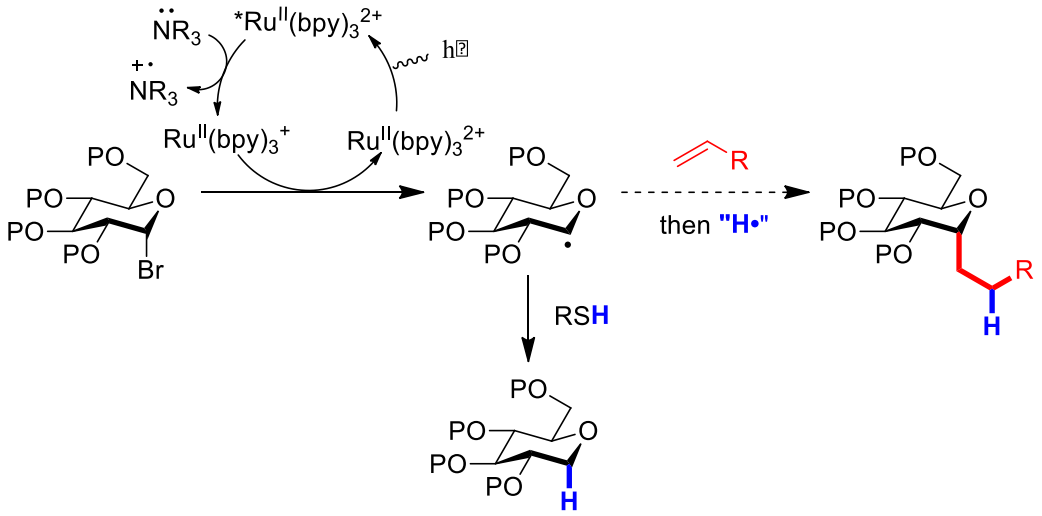


Entry	Product	Yield[a]
1 2 3 4		**6**, R = CO_2Me: 94%[b] (75%[c]) **7**, R = COMe: 86% **8**, R = CHO: 85% **9**, R = CN: 85%
5		**10**, 98% dr =1.5:1
6		**11**, 42% (63%[d])
7		**12**, 51%
8		**13**, 98% (90%[c]) dr = 1.8:1
9		**14**, 81%[b]
10		**15**, 80%

[a] Isolated yield; conditions: glycosyl bromide (0.12 mmol, 0.12 mM in CH_2Cl_2), alkene (0.24 mmol), **3** (0.36 mmol), $Ru(bpy)_3(BF_4)_2$ (0.06 mmol), **5** (0.24 mmol) at room temperature overnight irradiation with a 14W fluorescent bulb. [b] 0.134 mmol **5**. [c] 1.2 mmol glucosyl bromide. [d] 1.2 mmol alkene.

Publication: "Investigating the Rate of Photoreductive Glucosyl Radical Generation" R. S. Andrews, J. J. Becker, M. R. Gagné, *Org. Lett.* **2011**, *13,* 2406-2409.

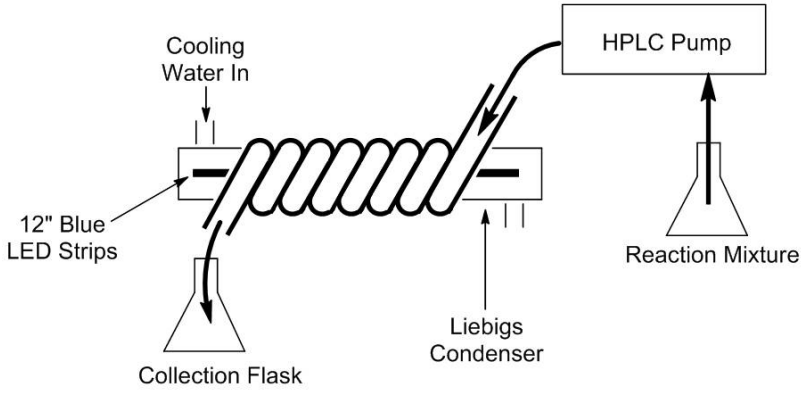
Our recent efforts are focused on the nature of the photoredox cycle and how changes in the initial concentrations of reagents affect the rate of the reaction. In order to accomplish this, we utilized thiols as an electrophilic radical source to trap the photogenerated glucosyl radical. By monitoring the reactions over a set period of time, we were able to determine that the concentration of thiol had no effect on the rate of starting material consumption, so the trapping of the radical is not the turnover limiting step in the reaction.



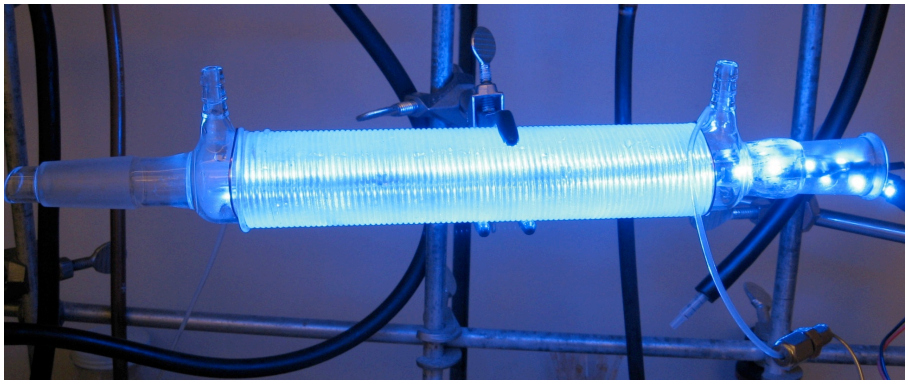
We varied the concentration of terminal reductant (i.e. *N,N*-diisopropylethylamine) and observed saturation with the rate. Similar results were observed with increasing catalyst concentrations under anhydrous conditions. However, under aqueous conditions, in addition to a significant increase in rate, the reaction rates varied directly at low catalyst concentrations (< 1 mM) and inversely at high concentrations (> 1mM). The use of hydrophobic ligands on the catalyst also resulted in increased rates of reaction. We propose this is due to the increased ability to solvate ion pairs after electron transfer to prevent energy, and time, wasting back-electron transfer.

Publication: "A Photoflow Reactor for the Continuous Photoredox-Mediated Synthesis of C-Glycoamino Acids and C-Glycolipids." Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 4140-4143.

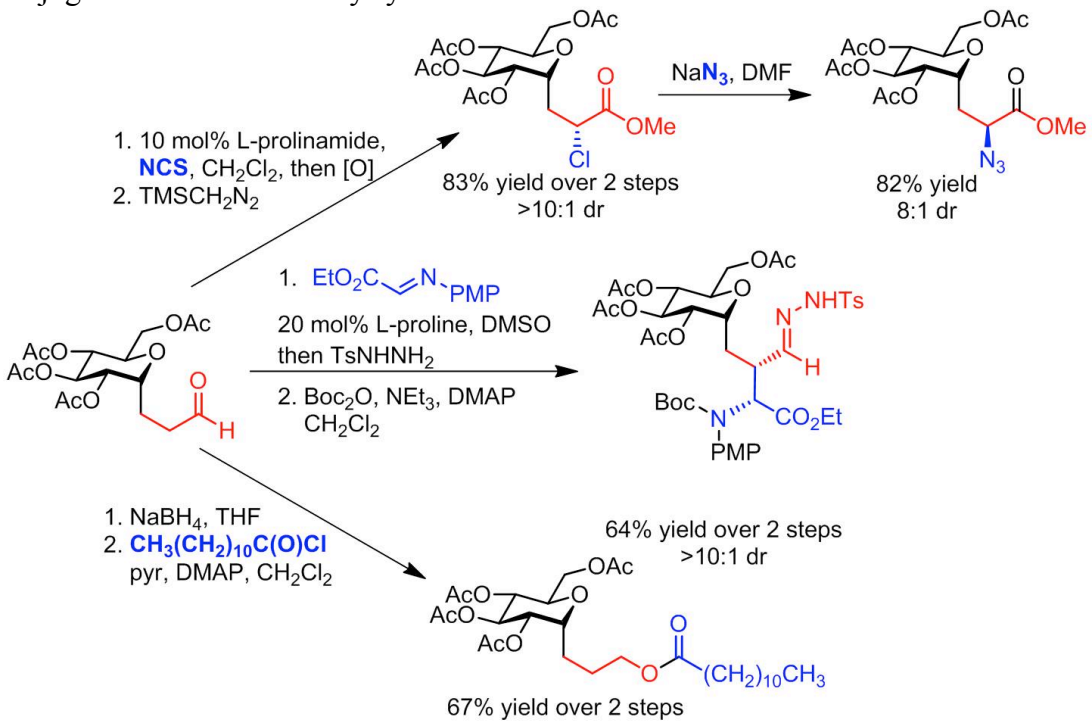
The success of our photomediated *C*-glycoside synthesis prompted a plan to elaborate the product *C*-glycosides into *C*-glycopeptides and *C*-glycolipids. The proposed divergent synthesis was plagued by difficulties in scaling up the *C*-glycoside synthesis to give a reasonable amount of starting material. It was found that efficiency of the reaction was highly dependent on vessel size, with faster reaction rates in NMR tubes than in flasks. This difference in efficiently is likely due to Beer's law, which predicts that the excellent photon absorber $Ru(bpy)_3^{2+}$, with its high molar extinction coefficient, absorbs the vast majority of incoming light within a short distance of the vessel wall, leaving the bulk of the reaction mixture essentially dark. To overcome this limitation, a simple photoredox reactor was built.



The design consists of flexible, transparent, inert tubing wrapped around a condenser. Blue LEDs, located in the center of the condenser, illuminate the tubing containing the reaction mixture. A water jacket insulates the reaction from the heat of the LEDs, and the reaction mixture is pushed through the tubing using an HPLC pump.



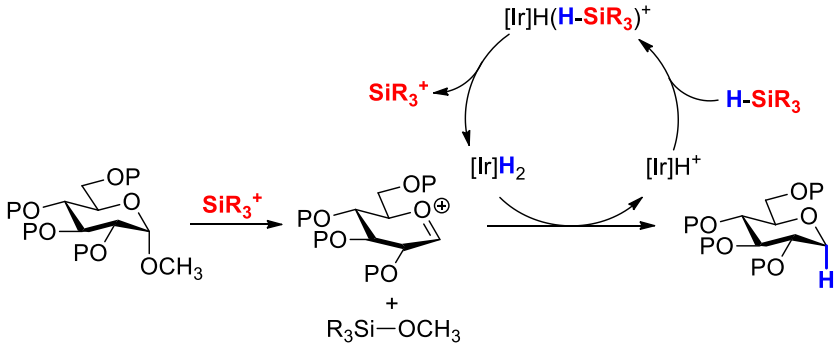
Multiple photoflow reactors were connected in series if a longer residence time was necessary to ensure complete conversion to the desired C-glycoside. This reactor allowed the synthesis of >5 grams of C-glycoside per day. With sufficient starting material in hand, a variety of glycoconjugates were successfully synthesized.



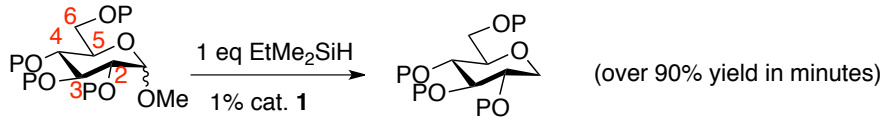
Publication: "Oxidative Addition of Secondary C-X Bonds to Palladium(0): A Beneficial Anomeric Acceleration." Munro-Leighton, C.; Adduci, L. L.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 2646-2649.

Publication: “Iridium-catalyzed hydrosilylative reduction of glucose to hexane(s).” McLaughlin, M. P.; Adduci, L. L.; Becker, J. J.; Gagné, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 1225-1227.

A previously reported iridium pincer catalyst was utilized for the hydrosilylative defunctionalization of glucose.



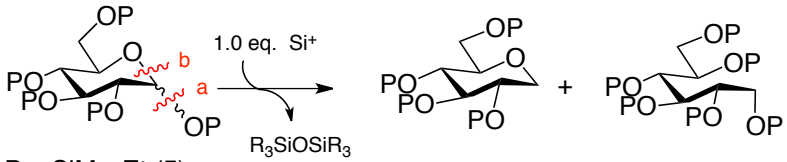
The catalyst was found to efficiently reduce both α and β methyl protected glucoses (**2** and **3**) to give the 1-deoxy sugar (**4**) with good yield in minutes.



P = $SiMe_2Et$
Axial (α) OMe , **2**
Equatorial (β) OMe, **3**

4

In contrast, the fully silylated sugar (**5**) yielded multiple products, included the 1-deoxy and ring opened producs **4** and **6**, and was much slower reacting (likely due to the reduced basicity).

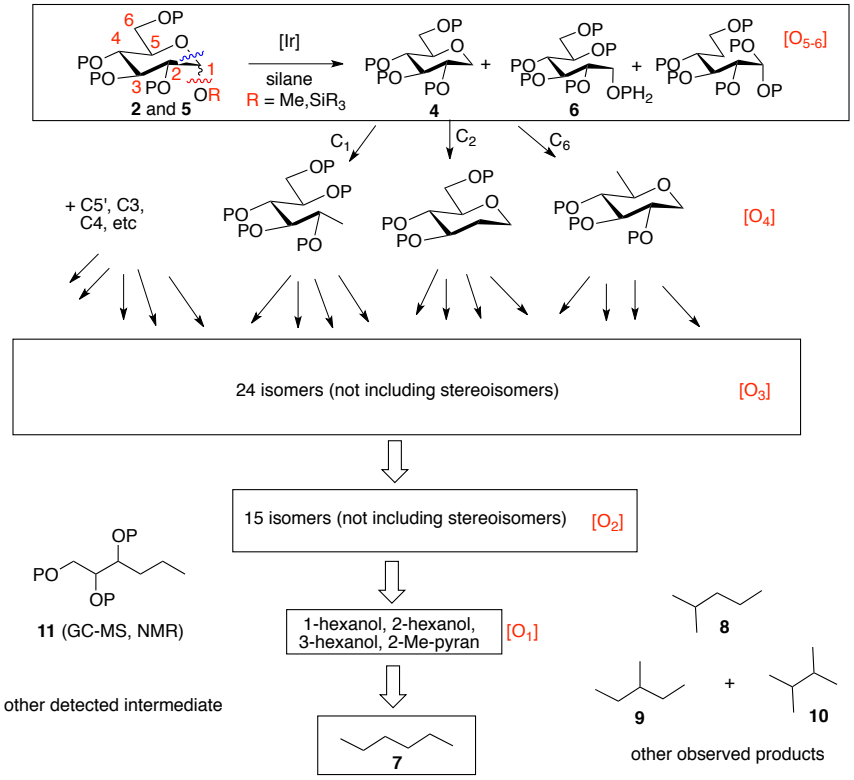


P = $SiMe_2Et$ (**5**)
α/β mix

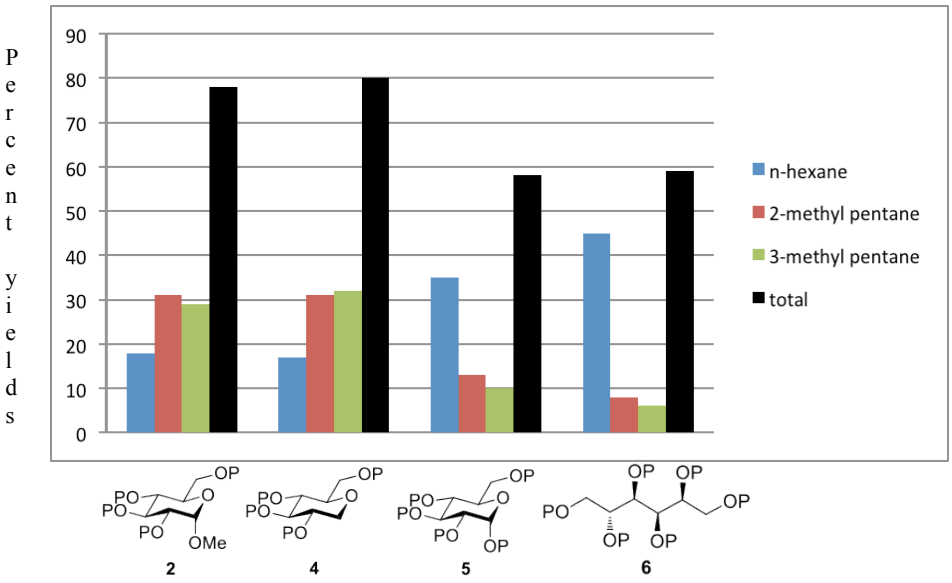
4 (≈15%)

6 (≈20%)

Increasing the catalyst loading and using the more reactive silane $SiEt_2H_2$ allowed the full hydrosilylative reduction of glucose to multiple alkane products, with the major species being n-hexane, 2- and 3-methylpentane. The initial reactivity showed selectivity for the anomeric and ethereal oxygens but those products reacted by promiscuous C-O activation yielding a plethora of reaction intermediates. Despite the large diversity of intermediates the sugar starting materials largely converged on hexane products.



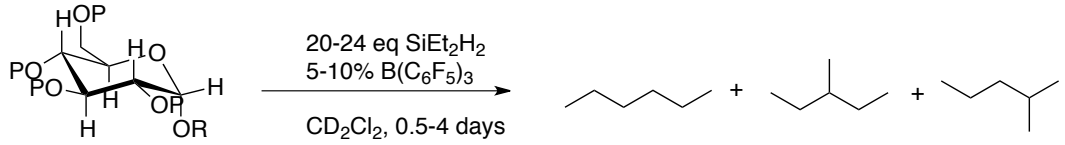
Both the α and β anomers of MeO-glu, **2** and **3**, consistently yielded a higher proportion of the rearranged products than **5**. A possible source for this surprising divergence in hexane isomer production was suggested by the comparative deoxygenation of **4** and **6** (glucitol). Like **2**, the C_1-deoxy **4** gives significant rearrangement, consistent with rapid conversion of **2** to **4** during the reaction. Reduction of **6**, however, gives predominantly n-hexane suggesting that **2** and **5** may bifurcate at the first reaction steps. It thus seems likely that pyranose **4** is the species most likely to initiate branching, presumably through carbocation(s) that may or may not involve neighboring group participation.



Unpublished preliminary results: “hydrosilylation of carbohydrates with borane catalysts” (2012-2013).

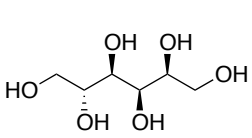
Borane lewis acids have previously been shown to be efficient catalysts for the hydrosilylation of carbon-oxygen bonds.[1] Despite their remarkable activity, the only borane reports for sugar defunctionalization utilize $BF_3(Et_2O)$ for the hydrosilylation of the activated C_1 position.[2] In order to seek new potential routes for carbohydrate defunctionalization we explored the hydrosilylation of carbohydrates by $B(C_6F_5)_3$.

Like the aforementioned iridium system, the major products observed for the hydrosilylation of monosaccharides were n-hexane, 2- and 3-methylpentane. Glucose hydrosilylation could be carried out on the methyl and silyl protected sugars to yield fully deoxygenated products within 12 hours (5% catalyst and 20-24 eq of $SiEt_2H_2$). Unprotected glucose was slower to react, requiring 4 days and twice the catalyst loading for complete reaction.

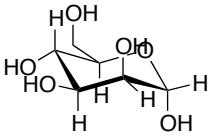


P = $SiMe_3$, R = $SiMe_3$ or Me
P = Me, R = Me
P = H, R = H or Me

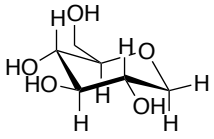
The $B(C_6F_5)_3$ catalyst showed substantially higher rates of hydrosilylation on the silyl protected glucose than the iridium catalyst (at least 10x faster). In contrast, comparing the activity for unprotected glucose showed that both catalysts took days for complete reaction (probably in part because of slow in situ protection resulting from insolubility). Expanding the substrate scope, we found that sorbitol, mannose, 1,5-anhydroglucitol, 1,6-anhydroglucose, and the disaccharide α-maltose were fully hydrosilylated under similar conditions, each yielding a different alkane product distribution.



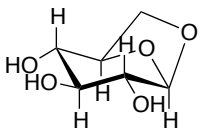
Sorbitol



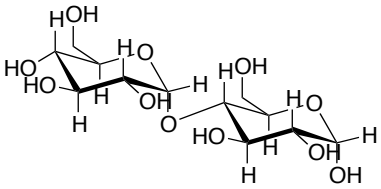
Mannose



1,5-Anhydroglucitol



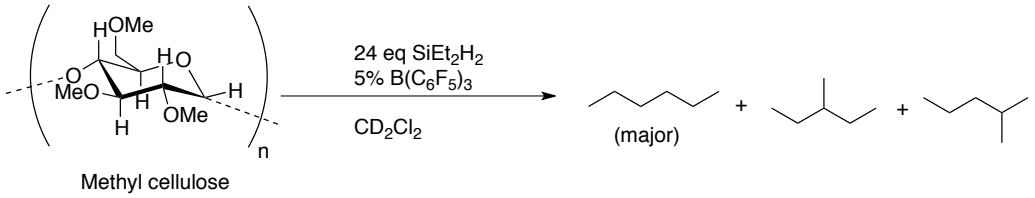
1,6-Anhydroglucose



α-Maltose

The chain length of the substrate did not dramatically affect the rate of the reaction, with the methyl protected polysaccharide cellulose reacting faster than unprotected glucose. Complete

hydrosilylation of methyl cellulose yielded a similar mixture of alkane products in under 24 hours (5% catalyst, 24 eq of $SiEt_2H_2$ per monomer).



Methyl cellulose

These preliminary studies have shown the distribution the alkane product distribution is quite sensitive to the catalyst, protecting groups, and identity of the sugar used. In contrast, preliminary competition experiments with the primary and secondary alcohols 1- and 2-hexanol showed that both catalysts have a similar selectivity for the secondary alcohol and show no significant alkyl shift products (this is in contrast to alkyl halides and ethers where the iridium system reacts preferentially with primary substrates). Studies are underway to understand the various routes for carbohydrate defunctionalization, the effects of the sugar environment and catalyst on the downstream product distribution, and this reactions potential to yield value added chemicals.

Reference:

1. (a) Mack, D. J.; Guo, B.; Njardarson, J. T. *Chem. Commun.* **2012**, *48*, 7844– 7846; (b) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 8919; (c) Parks, D. J.; Blackwell, J. M.; Piers, W. E. J. Org. Chem. **2000**, *65*, 3090– 3098; (d) Nimmagadda, R. D.; McRae, C. Tetrahedron Lett. **2006**, *47*, 5755– 5758.

2. (a) Rolf, D.; Bennek, J. A.; Gray, G. R. *Carbohydr. Res.* **1985**, *137*, 183– 196; (b) In Hwan, O.; Gray, G. R. *Carbohydr. Res.* **1995**, *278*, 329– 338; (c) Ewing, G. J.; Robins, M. *J. Org. Lett.* **1999**, *1*, 635– 636.