

Catalytic methods for the synthesis of glycosides

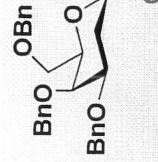


M. Carmen Galan

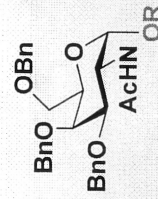
Deoxyglycosides - limitations of current methods

Heavy dependence on neighbouring group participation – issues in terms of choice of protecting groups.

No efficient methods for:



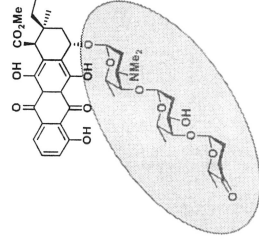
2-Deoxy sugars



Aminoglycosides

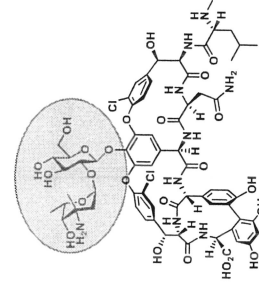
Deoxyglycosides - limitations of current methods

Anticancer

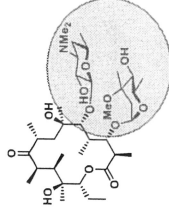


Adarubicin

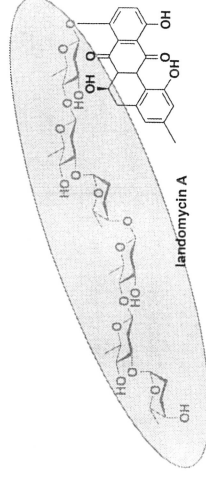
Antibacterial



Vancomycin



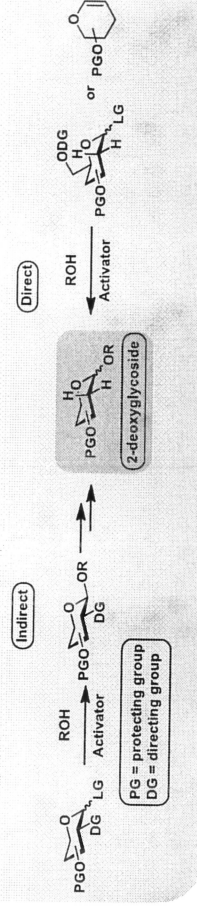
Erythromycin



Ibandronic A

Synthesis of 2-deoxyglycosides

- Mild conditions afford better selectivities



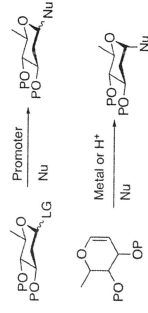
Indirect - Castiñón, S., *J. Org. Chem.* **2005**, *70*, 10297–10310

Direct - Toste, F. D., *J. Am. Chem. Soc.* **2004**, *126*, 4510–4511, Boons, G.-J. *Org. Lett.* **2008**, *10*, 4367–4370

For reviews see: Medina, S.; Galan M. C. *Carbohydr. Chem.* **2016**, *41*, 59.
William, R.; Galan, M. C. *Eur. J. Org. Chem.* **2017**, 6247
Bennett, C.; Galan, M. C. *Chem. Rev.* **2018**, *118*, 7931.

Synthesis of 2-deoxyglycosides

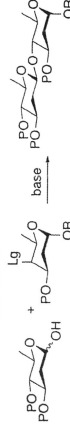
A - DIRECT GLYCOSYLATION



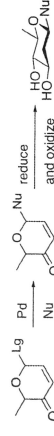
B - INDIRECT SYNTHESIS



C - ANOMERIC ALKYLATION

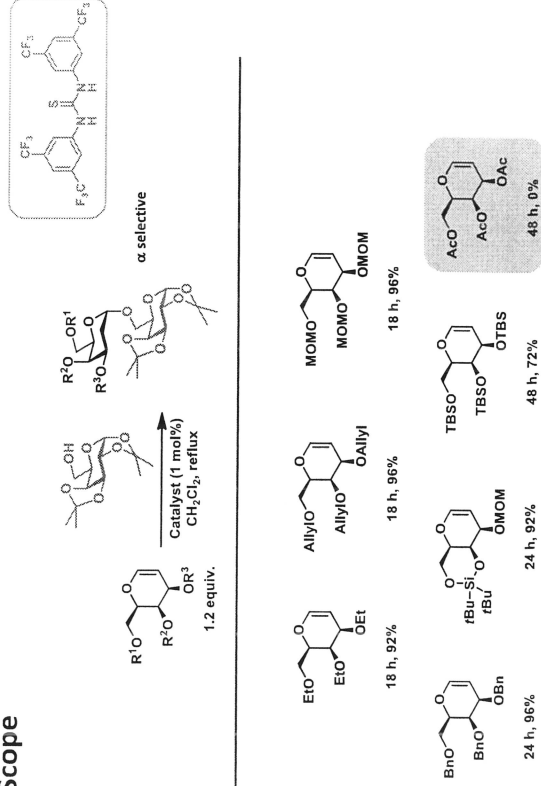


D - DE NOVO SYNTHESIS



Bennett, C; Galan, M. C. *Chem. Rev.* **2018**, *118*, 7931.

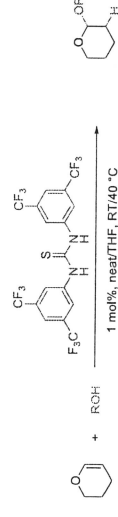
Organocatalytic Stereoselective Synthesis of Glycosides Galactal Scope



Isolated Yields

Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M., *Angew. Chem., Int. Ed.* **2012**, *51*, 9152-9155

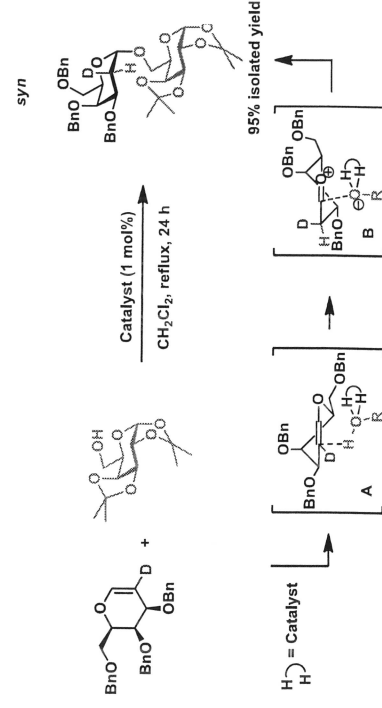
Organocatalytic Stereoselective Synthesis of Glycosides



Kotke, M.; Schreiner, P. R., *Synthesis* **2007**, 779-790.

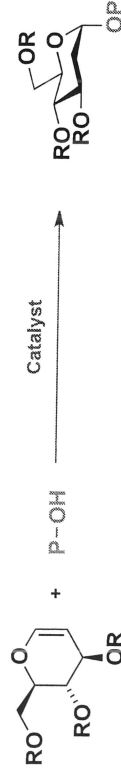


syn vs. anti Addition of Alcohol?

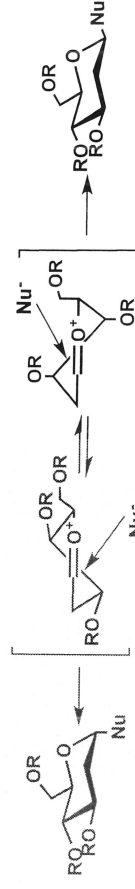


Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M., *Angew. Chem., Int. Ed.* **2012**, *51*, 9152-9155

Reactivity of Glucals



Protecting groups can influence the reactivity of a glycosyl donor and the intermediate conformer equilibrium by influencing thermodynamic factors



Woerpel et al., *J Am Chem Soc* 2003, 125, 15521-15528.

Fraser-Reid, et al. *J Am Chem Soc* 1988, 110, 5583-5584.

Wong, et. Al. *J Am Chem Soc* 1999, 121, 734-753.

Codee, Overkleef, van der Marei, et. al. *Carbohydr Res* 2007, 342, 419-429.

Demchenko. *J Org Chem* 2010, 75, 1095-1100.

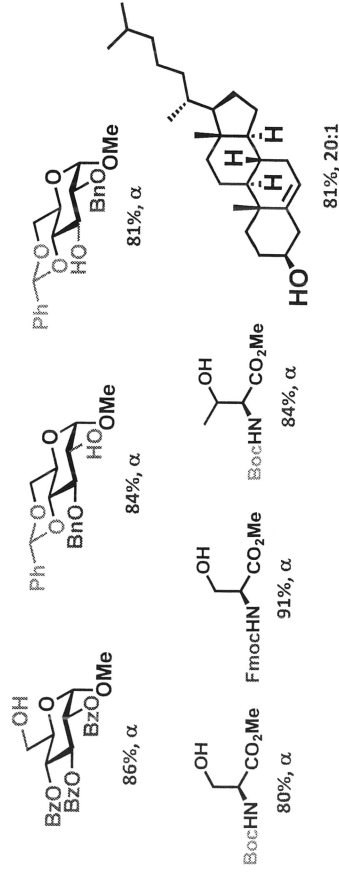
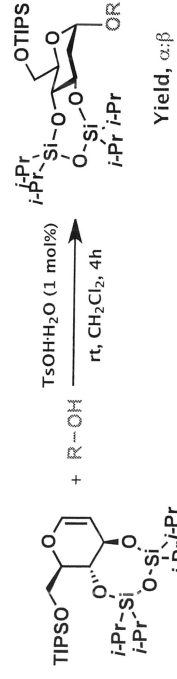
Fraser-Reid, J. C. Lopez, et. al. *Reactivity Tuning in Oligosaccharide Assembly* 2011, 301, 1-29.

Crich, *Reactivity Tuning in Oligosaccharide Assembly* 2011, 301, 141-188;

Pedersen, Bols, et. al. *Cr Chim* 2011, 14, 17-43.

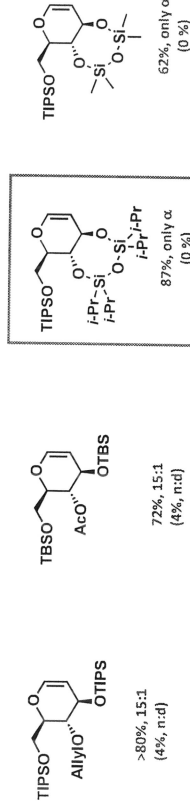
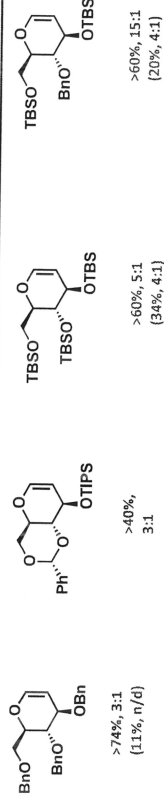
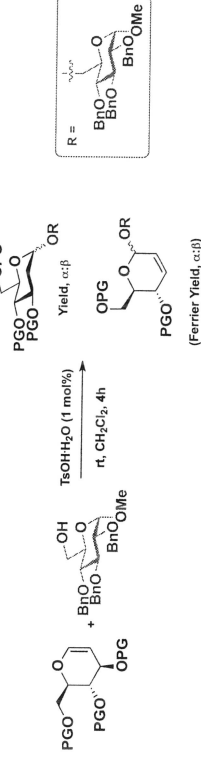
Yamada, *Trends Glycosci Glyc* 2011, 23, 122-133.

Brønsted acid catalysed glycosylation of glucals Acceptor Scope



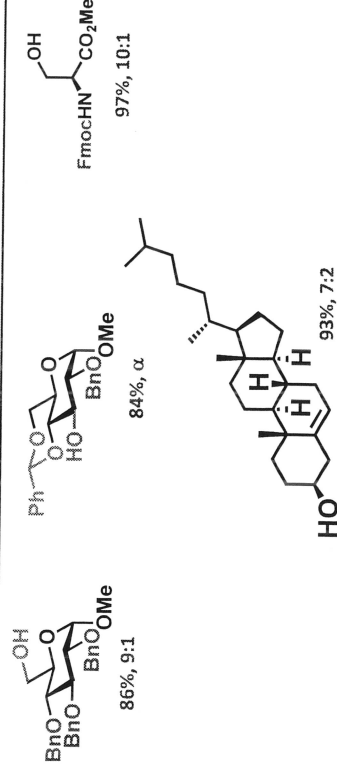
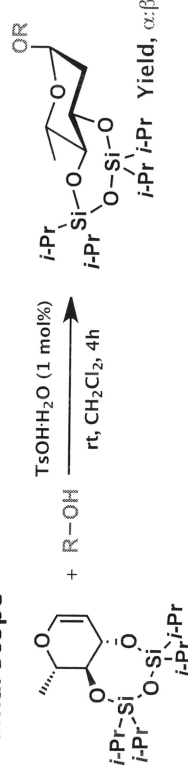
Galan, M. C. et al *Angew. Chem. Int. Ed.* (2014), 53, 8190

Brønsted acid catalysed glycosylation of glucals



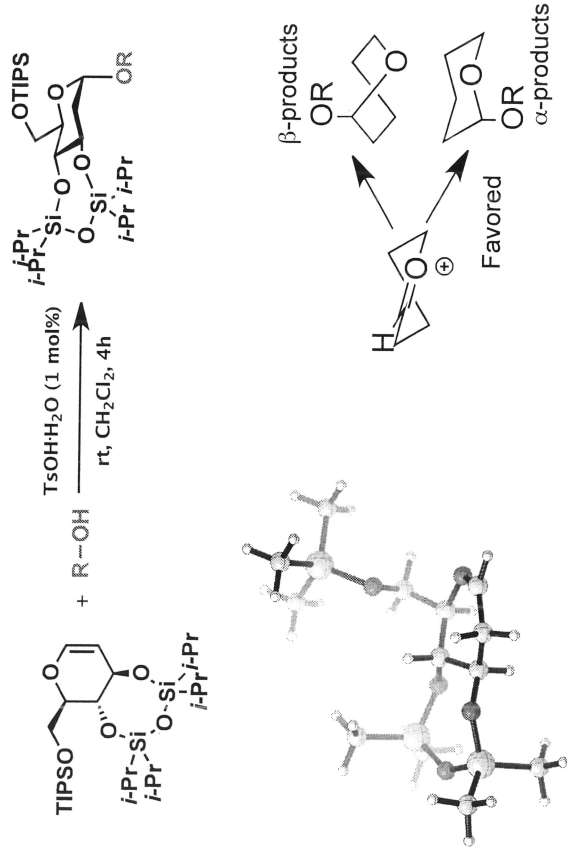
Balmond, McGarrigle, Galan, M. C. et al *Angew. Chem. Int. Ed.* (2014), 53, 8190

Brønsted acid catalysed glycosylation of glucals L-Rhamal Scope

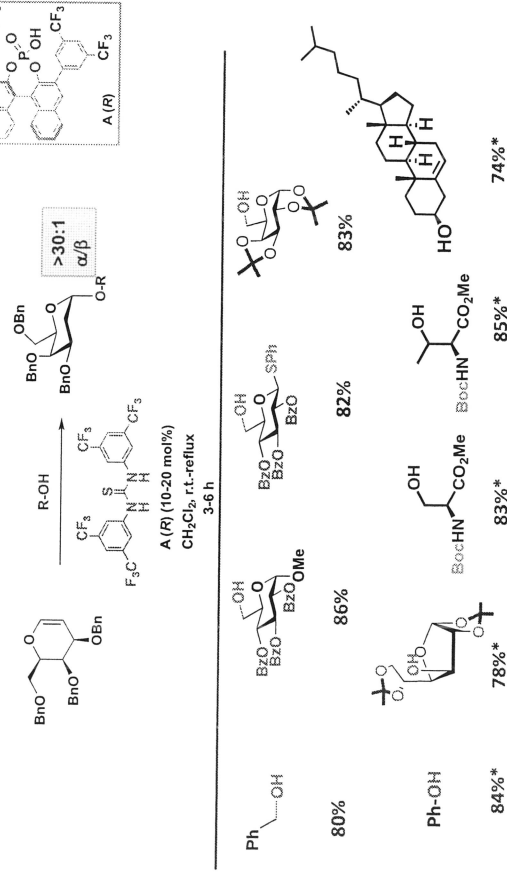


Balmond, McGarrigle, Galan, M. C. et al *Angew. Chem. Int. Ed.* (2014), 53, 8190

Brønsted acid catalysed glycosylation of glucals Reactivity of Glucals



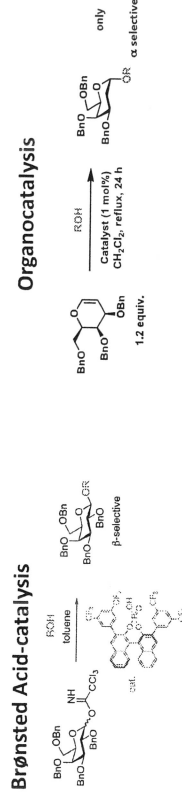
Cooperative Brønsted Acid-Type Organocatalysis Acceptor Scope



*Reactions with secondary OH nucleophiles required 20 mol% of thiourea and 45 °C

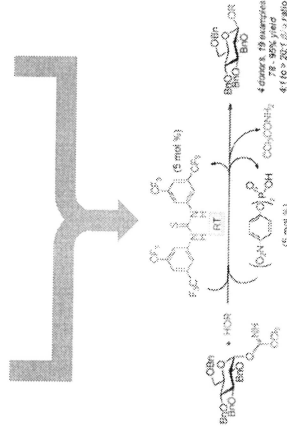
Palo Nieto, C.; Sau, A., Williams R.; Galan, M.C. *submitted 2016*

Cooperative Brønsted Acid-Type Organocatalysis for the Stereoselective Synthesis of Deoxyglycosides.



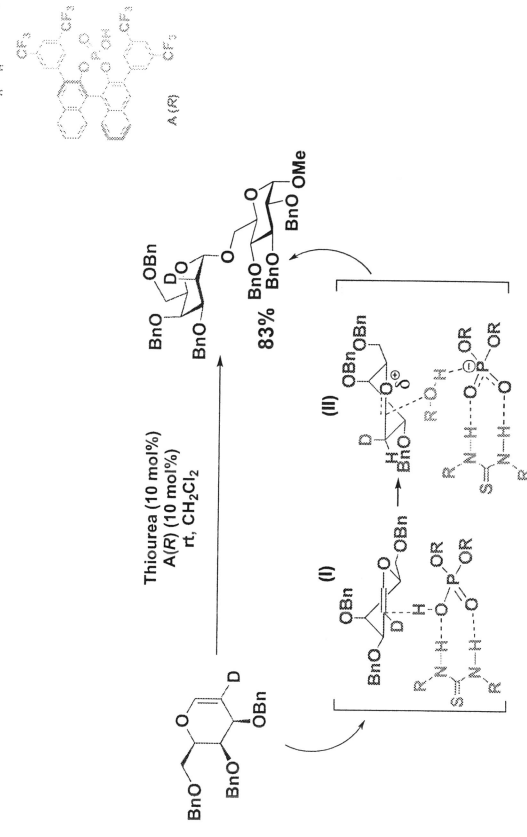
T. Akiyama, *Chem. Rev.* 2007, 107, 5744
A. J. Fairbanks, et al. *Org. Lett.* 2010, 12, 1452

Galan, M. C.; McGarrigle, E. M. et al
Angew. Chem., Int. Ed. 2014, 51, 9152

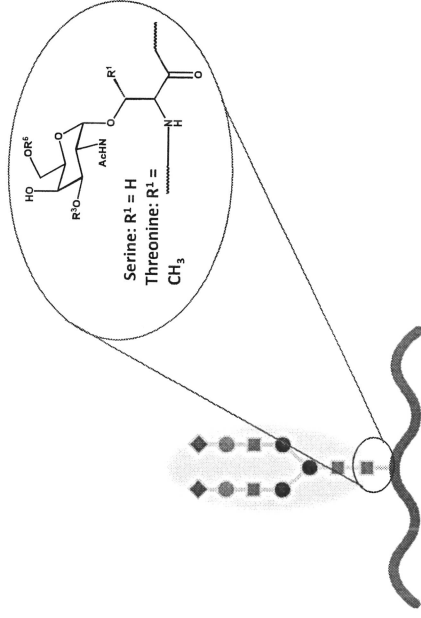


R. R. Schmidt et al., *Angew. Chem. Int. Edit.* 2013, 52, 10089

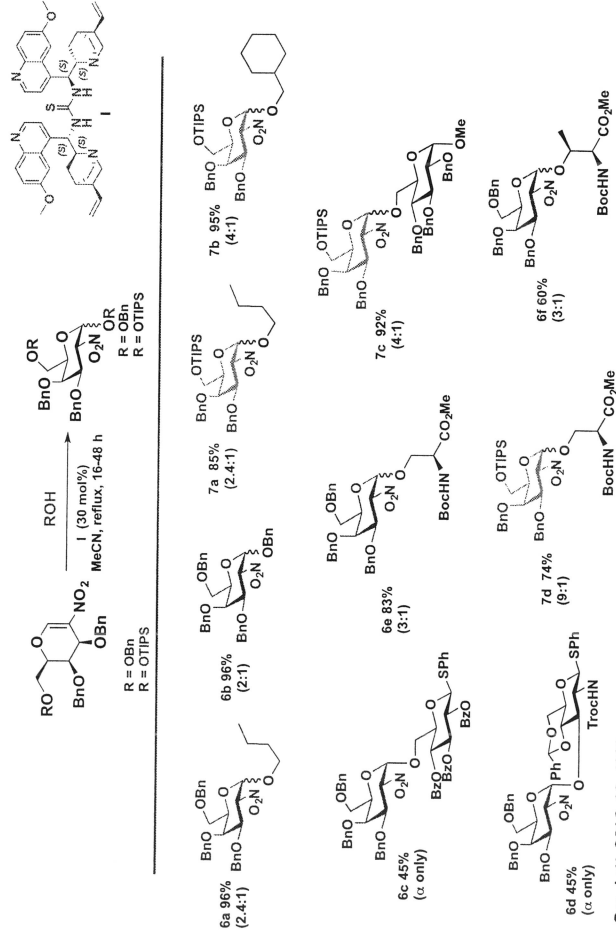
Cooperative Brønsted Acid-Type Organocatalysis Proposed Mechanism



Can we find an organocatalytic method to target the stereoselective synthesis of 2-Amino-2-deoxy glycosides?

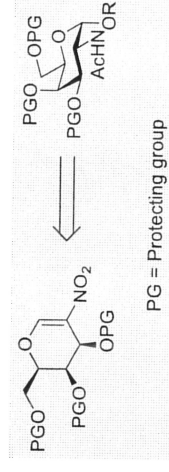


Bifunctional Organocatalyst – Donor/Acceptor Scope

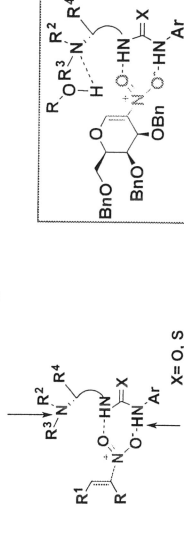


Org. Lett. 2016, 18, 4222

2-Nitro-galactals as precursors for 2-amino-2-deoxyglycosides.



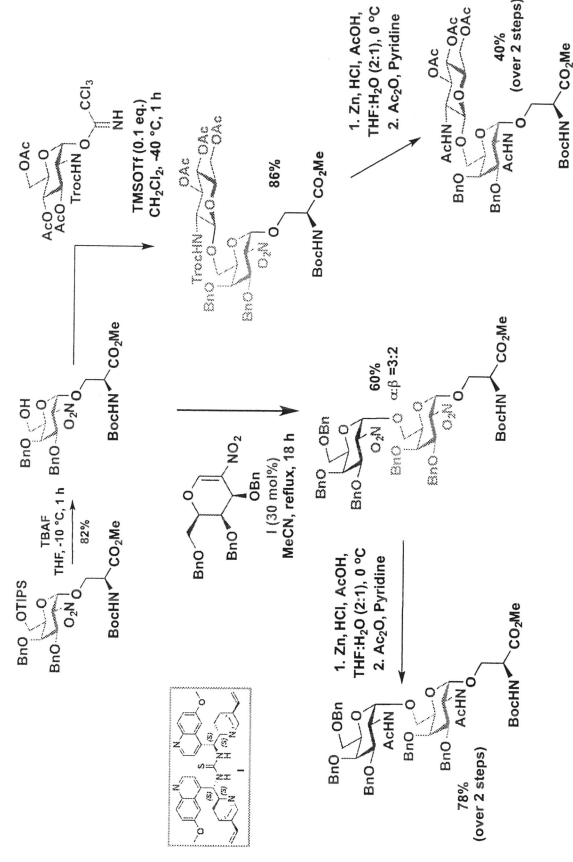
Directs facial addition of nucleophile via H-bonding



Connoni, S. et al J. Angew. Chem. Int. Ed. 2005, 44, 6367.

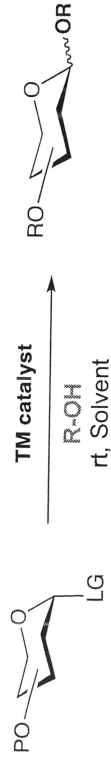
Medina, Harper, Balmond, McGarrigle and M. C. Galan et al *Org. Lett.* 2016, 18, 4222

Bifunctional Organocatalyst – Application to the synthesis mucin type Core 6 and 7 glycosides



Org. Lett. 2016, 18, 4222

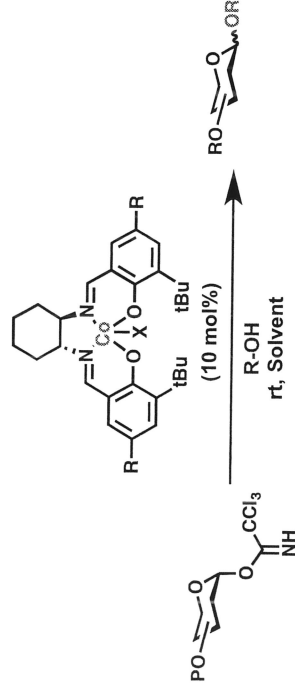
Transition metal catalysis in Oligosaccharide Synthesis



For recent reviews:

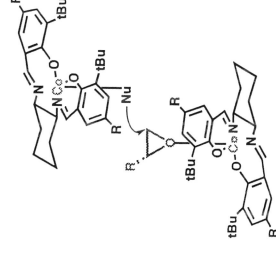
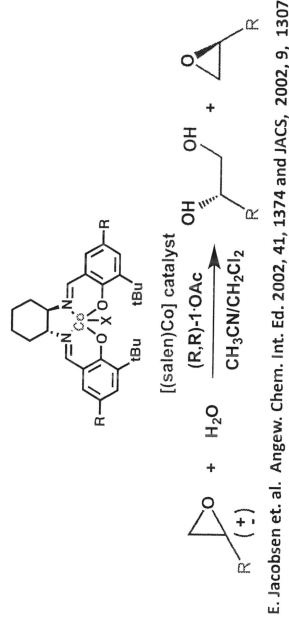
- "Selective Glycosylations - Synthetic Methods and Catalysts" Bennett C. Wiley-VCH publishers. 2017
- J. L. Zhu et al., *Eur. J. Org. Chem.* 2016, 4724.
- H. M. Nguyen et al., *ACS Catal.* 2012, 2, 1563

Can we use (salen)Co catalysts as glycosylation promoters?

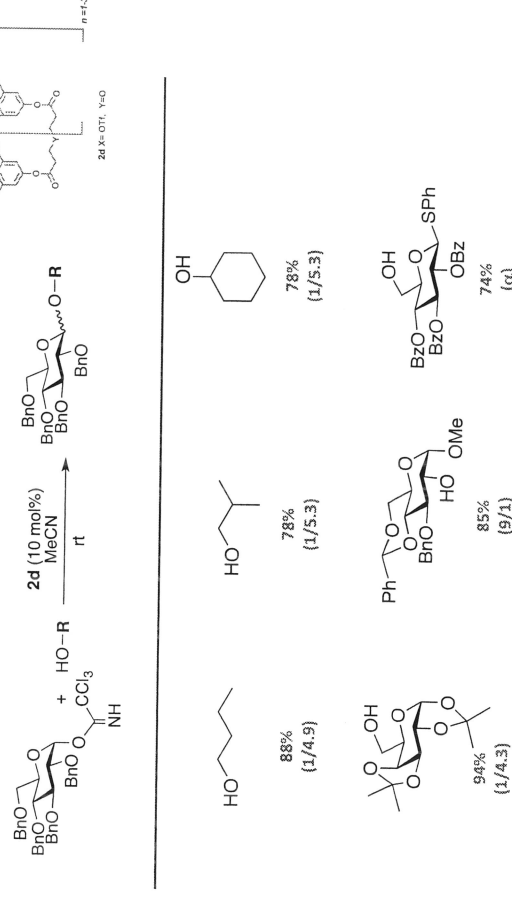


For recent review on transition metal catalyzed glycosylations : H. M. Nguyen et al. *ACS Catal.* 2012, 2, 1563–1595

Transition metals as glycosylation promoters: (salen)Co catalysts

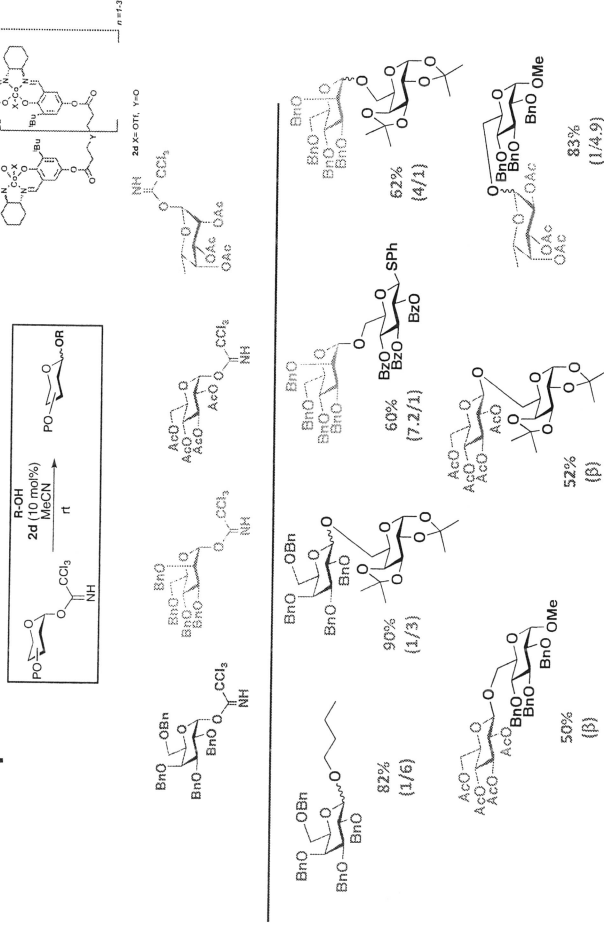


(Salen)Co catalysts as glycosylation promoters Acceptor Scope

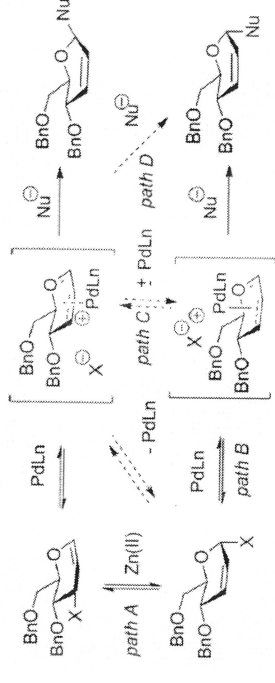
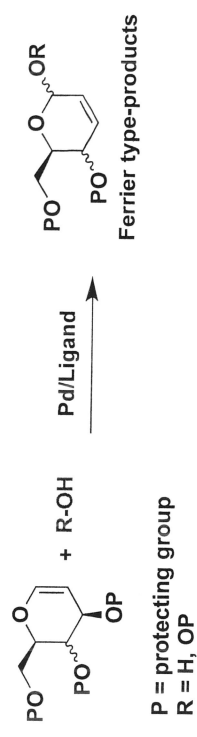


S. Medina, A. Henderson, J. Bower and M. C. Galan*. *Chem. Commun.* 2015, 51, 8939-8941

(Salen)Co catalysts as glycosylation promoters Donor Scope

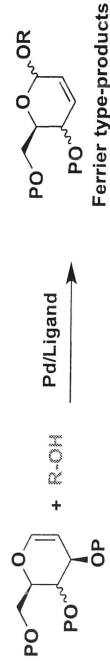


Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

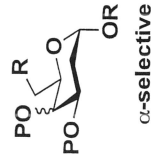


A. Gomez, J. C. Lopez, et al. Eur. J. Org. Chem. 2013, 7221–7262

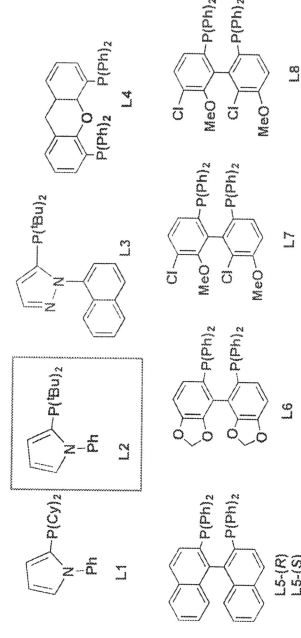
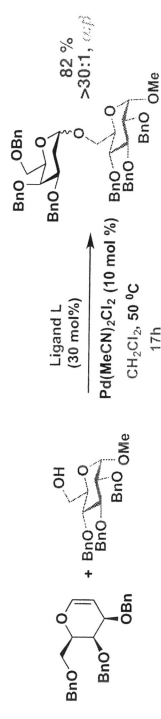
Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.



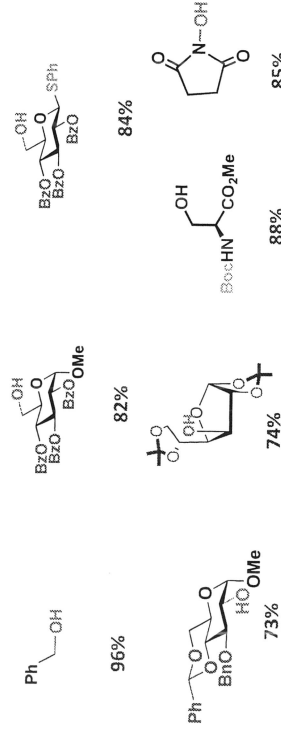
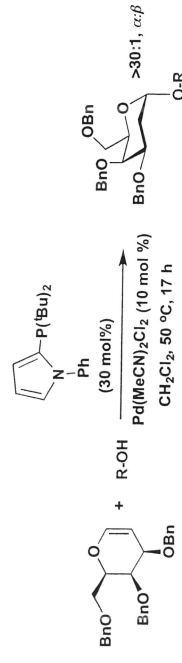
P = protecting group
R = H, OP



Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.



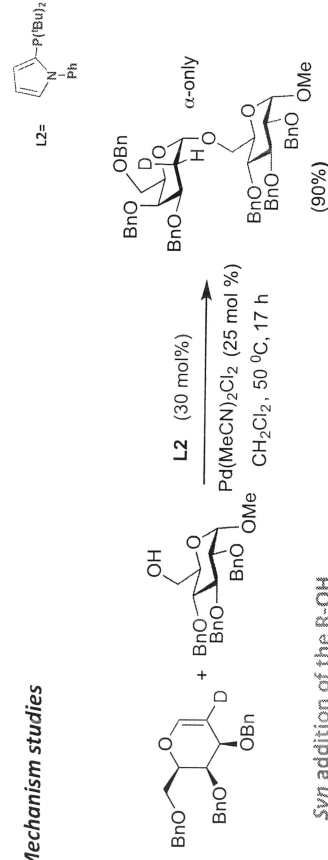
Pd-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.



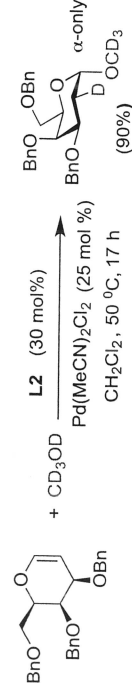
A. Sau, R. Williams, C. Palo-Nieto, A. Franconetti, S. Medina and M. C. Galan Angew. Chem. Int. Ed. 2017, 56, 640.

Pd-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

- *Mechanism studies*

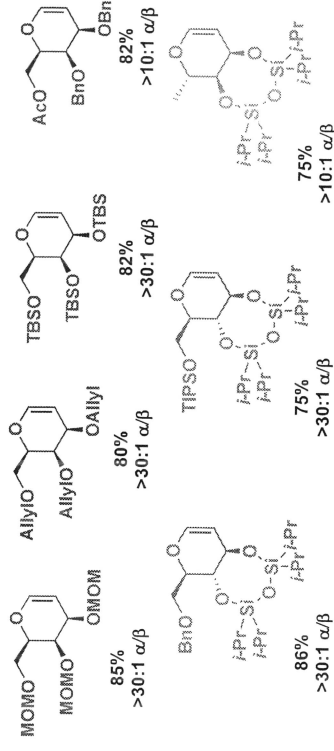
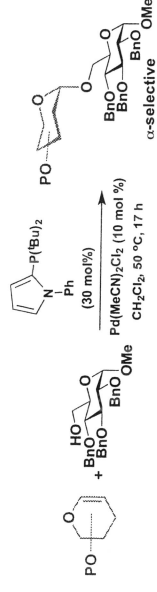


Syn addition of the R-OH



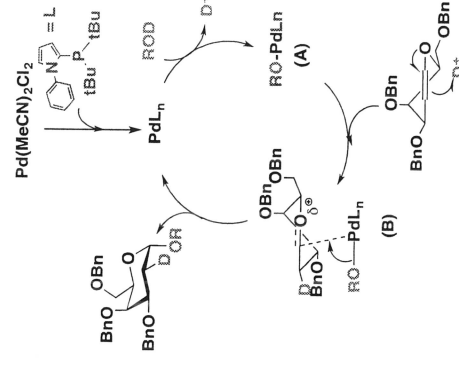
R-OH is the proton source

Pd-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycols

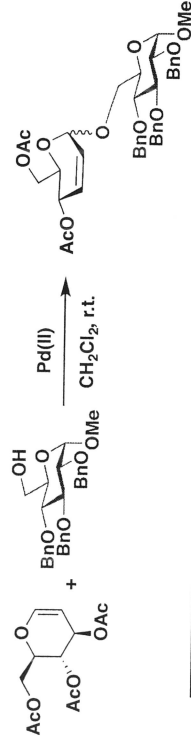


Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

- *Proposed Mechanism*



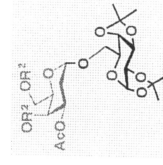
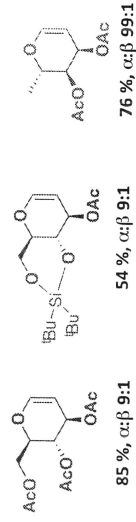
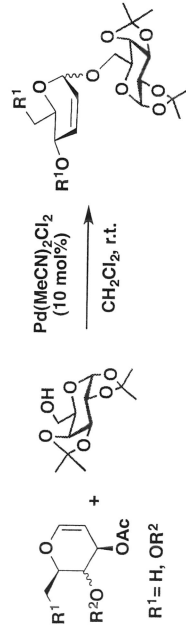
Palladium-Catalysed Stereoselective O-glycosylation of O(3)-Acylated Glycals



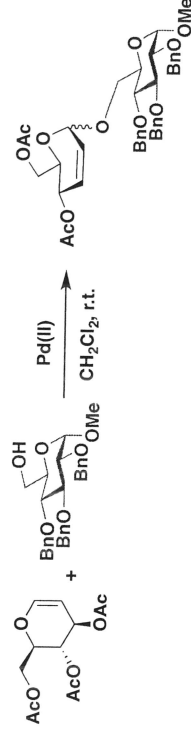
Entry	Catalyst (Loading mol%)	Solvent	Time (h)	Yield ^[a] (%)	α:β ^[a]
1	Pd(MeCN) ₂ Cl ₂ (2.5)	CH ₂ Cl ₂	24	40	5:1
2	Pd(MeCN) ₂ Cl ₂ (5)	CH ₂ Cl ₂	24	52	5:1
3	Pd(MeCN) ₂ Cl ₂ (10)	CH ₂ Cl ₂	5	88	6:1
4	Pd(CH ₃ CN) ₂ (OTf) ₂ (10)	CH ₂ Cl ₂	17	88	3:1
5	Pd(CH ₃ CN) ₄ (OTf) ₂ (10)	CH ₂ Cl ₂	5	N/A	N/A ^[b]
6	Pd(CH ₃ CN) ₄ (BF ₄) ₂ (10)	CH ₂ Cl ₂	5	90	2.3:1
7	Pd(OAc) ₂ (10)	CH ₂ Cl ₂	5	N/A	-

Palladium-Catalysed Stereoselective O-glycosylation of O(3)-Acylated Glycals

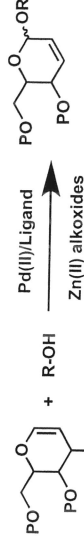
Scope



Palladium-Catalysed Stereoselective O-glycosylation of O(3)-Acylated Glycals



Previous work

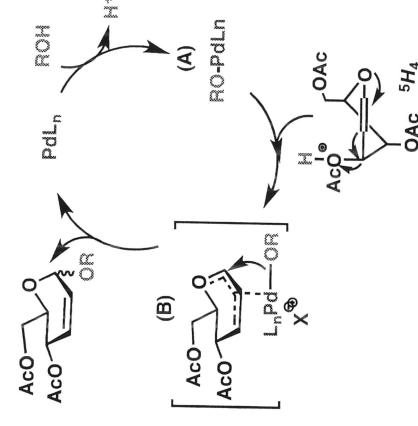


LG = OAc, Boc or OC(NH)CCl₃
P = Activating protecting groups

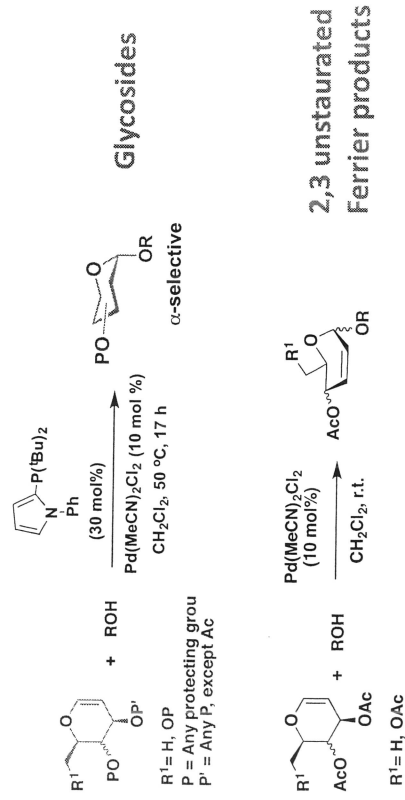
O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406.
Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714.
Lee, C. J. *Am. Chem. Soc.* **2004**, *126*, 1336.
Nguyen, H. M. *Org. Lett.* **2007**, *9*, 3173.

Palladium-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

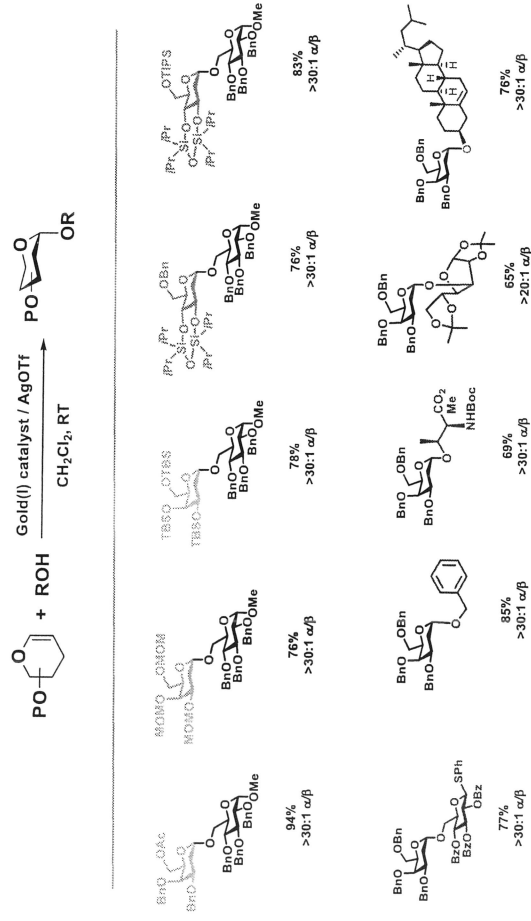
Proposed Mechanism



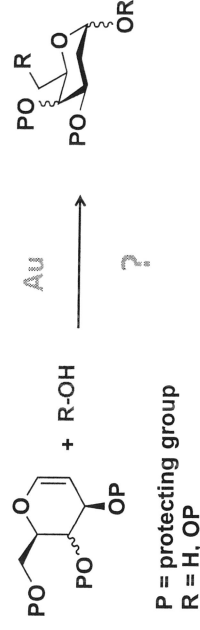
The reactivity of Pd(II) can be tuned by the choice of ligands or glycol substrates



Au-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycols.



Au-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycols.



For Au(III) of:

- alkynyl or propargyl 1,2-orthoesters:
S. Hotha, Chem. Commun. 2008, 4282–4284
- Trichloroacetimidates
R. R. Schmidt, J. Am. Chem. Soc. 2015, 137, 12653–12659

For Au(I) activation of:

- glycosyl ortho-alkynylbenzoates
B. Yu, J. Am. Chem. Soc. 2014, 136, 4157–4160.
- 2-deoxy-5-but-3-ynyl thioglycoside
J. Zhu, ACS Catal. 2013, 3, 57–60.

Au-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycols.

