Site-Selective Acylation and Subsequent Selective Glycosylation of Pyranosides

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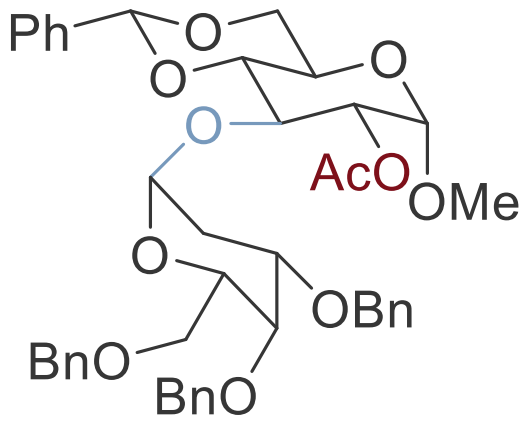
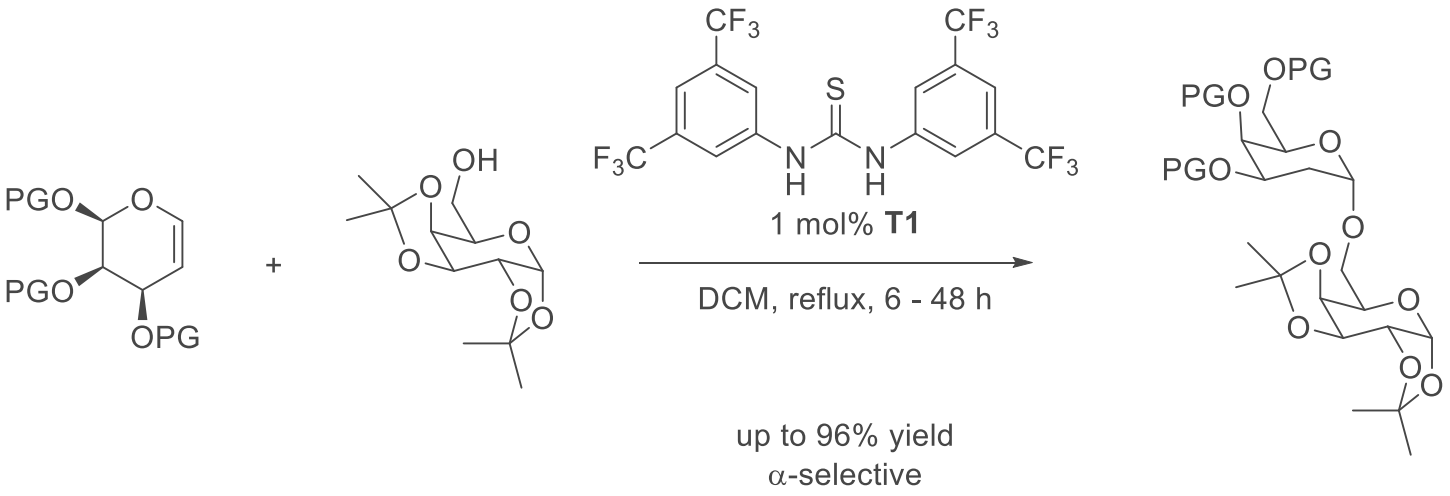


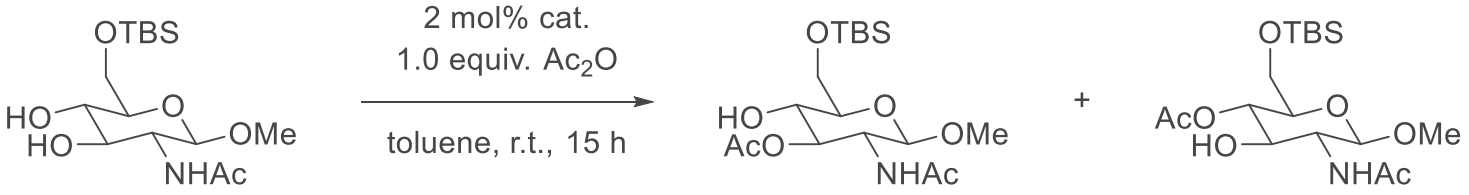
Motivation

- Develop a multicatalysis sequence with our groups catalysts
- McGarrigle showed selective glycosylation of galactals with T1



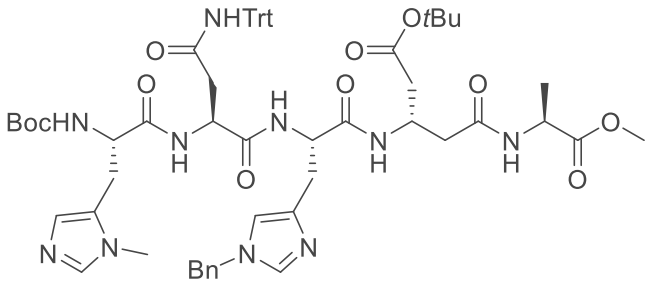
E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

- Miller *et al*. 2003: peptide catalyzed acylation



1 **2**

Catalyst	1	2	DiAc	C [%]
NMI	50	22	28	86
3	97	3	0	88
4	53	47	0	80



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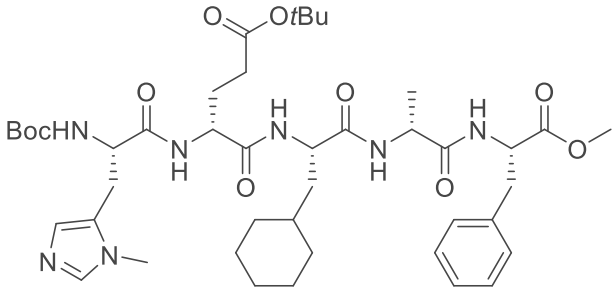
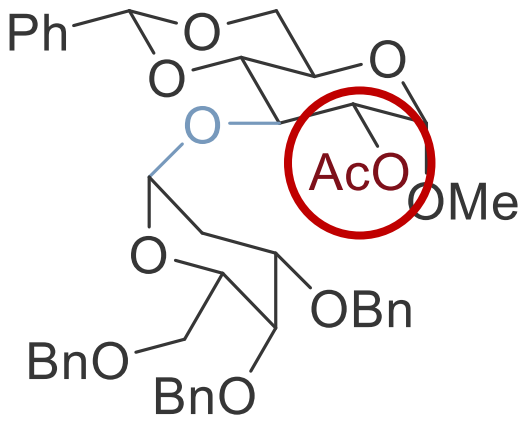


3

K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869–8875; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

Site-Selective Acylation of Pyranosides



Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

- Several reviews about carbohydrates

- Focus on acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

- Lipases catalyze acetylation with very high selectivity (up to 100%) and very high yields (up to 95%)

- Most catalysts/additives are only working with one of the pyranoses

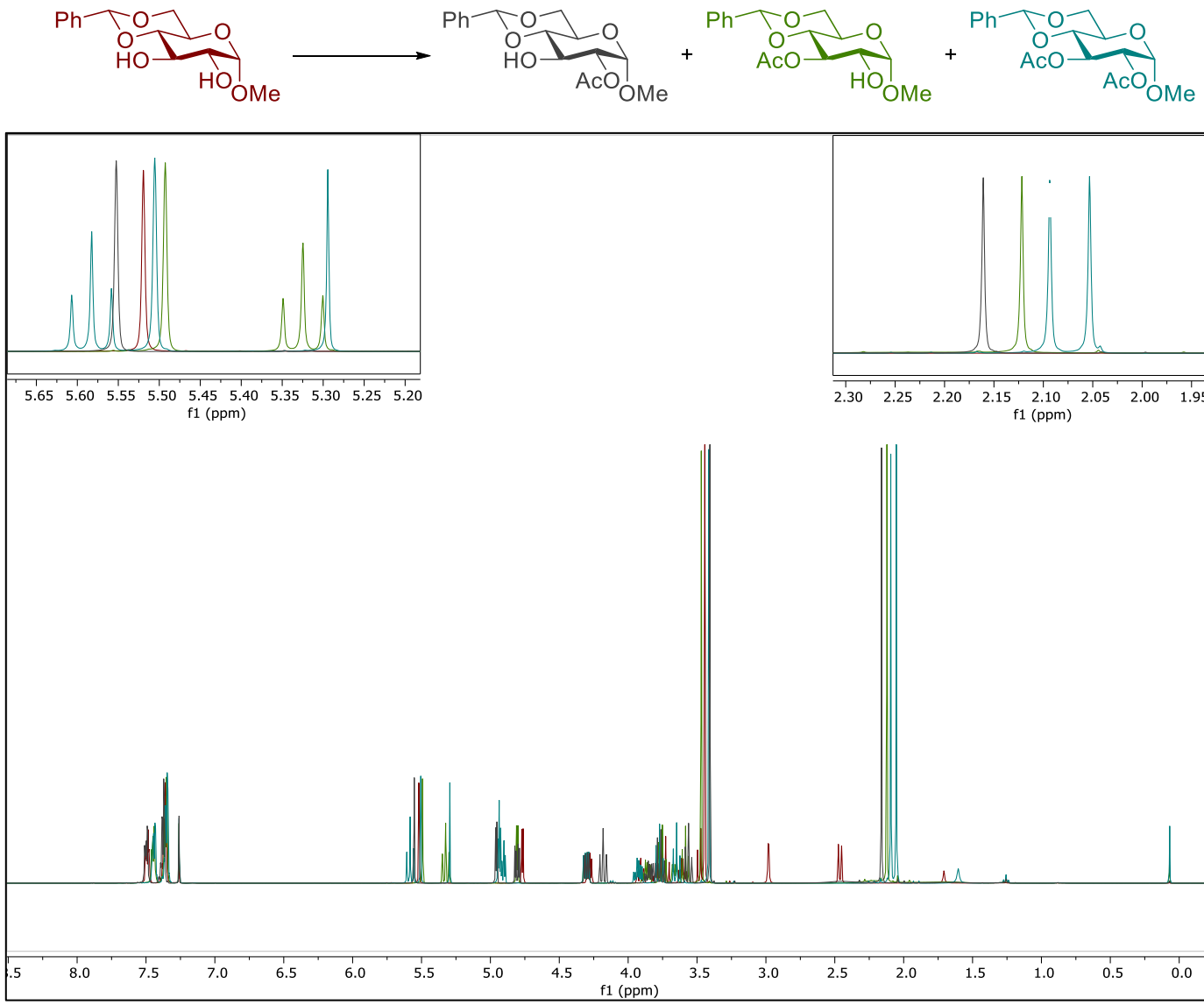
Y. Ueda, T. Kawabata, *Top. Curr. Chem.* **2016**, 372, 203-232; J. Lawandi, S. Rocheleau, N. Moitessier, *Tetrahedron* **2016**, *72*, 6283-6319; M. J. Chinn, G. Lacazio, D. G. Spackman, N. J. Turner, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1992**, 661–662; L. Panza, M. Luisetti, E. Crociati, S. Riva, *J. Carbohydr. Chem.* **1993**, *12*, 125–130.

Overview acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

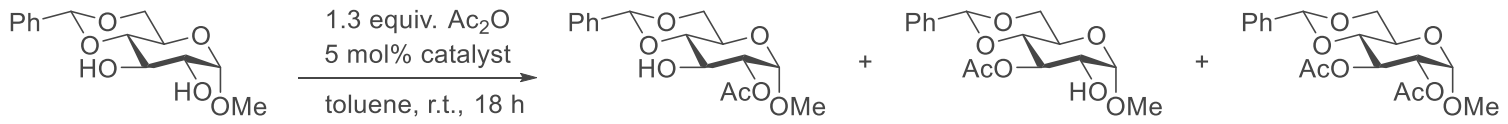
Catalyst	Product ratio			Conversion [%]
pyridine	3-29	32-42	6-26	77-93
DMAP	45-49	55-51	-	40-65
Et_3N (9 equiv.)	80	5	15	-
NaOtBu, EtOAc	48	52	-	76
$ZnCl_2$, pyridine	53	13	23	90
Ag_2O, KI, AcCl	15	81	-	-
cat. TBAOAc, $Me_2Si(OMe)_2$	65	-	-	-
lipases	up to 100	-	-	up to 95

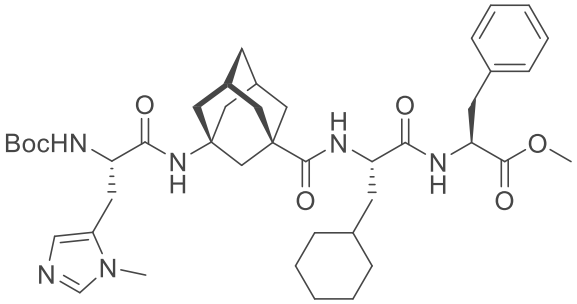
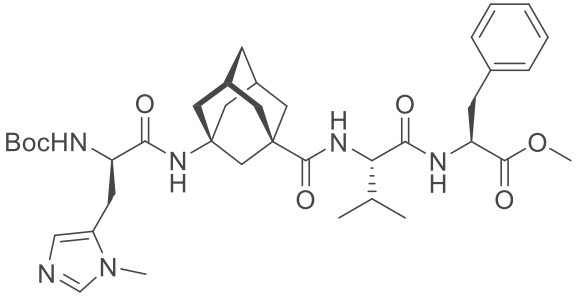
N. Moitessier, P. Englebienne, Y. Chapleur, *Tetrahedron* **2005**, *61*, 6839–6853; R. W. Jeanloz, D. A. Jeanloz, *J. Am. Chem. Soc.* **1957**, *79*, 2579–2583; S. Hanessian, M. Kagotani, *Carbohyd. Res.* **1990**, *202*, 67–79; X.-A. Lu, C.-H. Chou, C.-C. Wang, S.-C. Hung, *Synlett* **2003**, 1364–1366; X. Liu, B. Becker, M. A. Cooper, *Aust. J. Chem.* **2014**, *67*, 679–683; Y. Zhou, O. Ramström, H. Dong, *Chem. Commun.* **2012**, *48*, 5370–5372; M. J. Chinn, G. Lacazio, D. G. Spackman, N. J. Turner, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1992**, 661–662; L. Panza, M. Luisetti, E. Crociati, S. Riva, *J. Carbohydr. Chem.* **1993**, *12*, 125–130.

Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



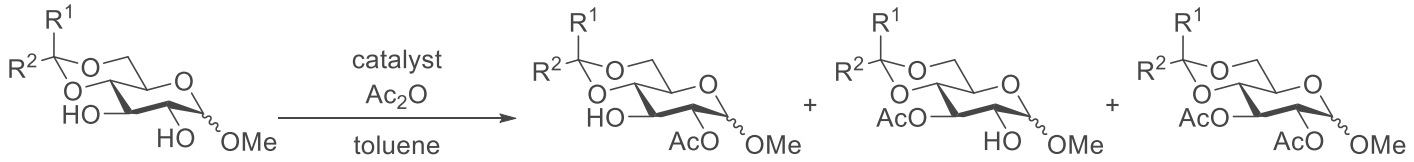
Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

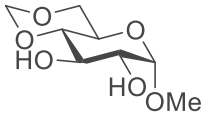


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
NMI (10mol%)	20	62	5	87	23
	55	37	8	>95	55
	70	19	3	92	76
	81	17	1	>95 (DoE)[a]	82

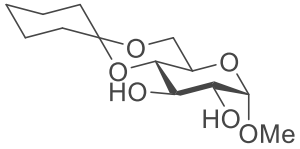
[a] conditions given by DoE: 20 mL toluene at 0 °C were used, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

Acetylation of 4,6-*O*-protected-α-D-glucopyranoside derivatives

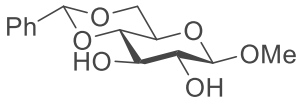




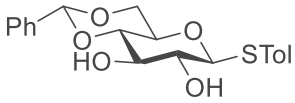
	***C* [%]**	**Selectivity[b] [%]**
NMI	58	40
Peptide	>95	76
DoE[a]	90	82



	***C* [%]**	**Selectivity[b] [%]**
NMI	36	50
Peptide	64	86
DoE[a]	69	86



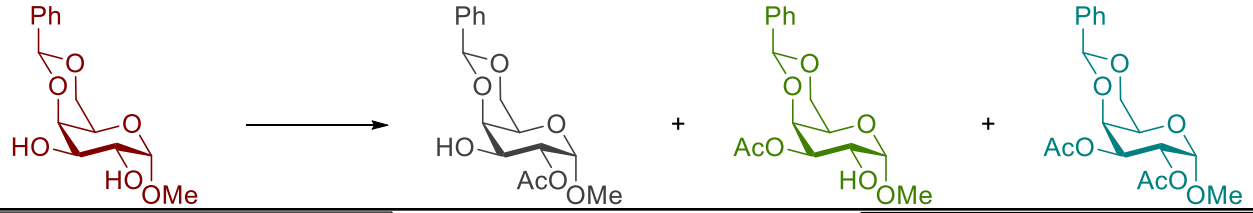
	***C* [%]**	**Selectivity[b] [%]**
NMI	32	19
Peptide	75	28
DoE[a]	15	40

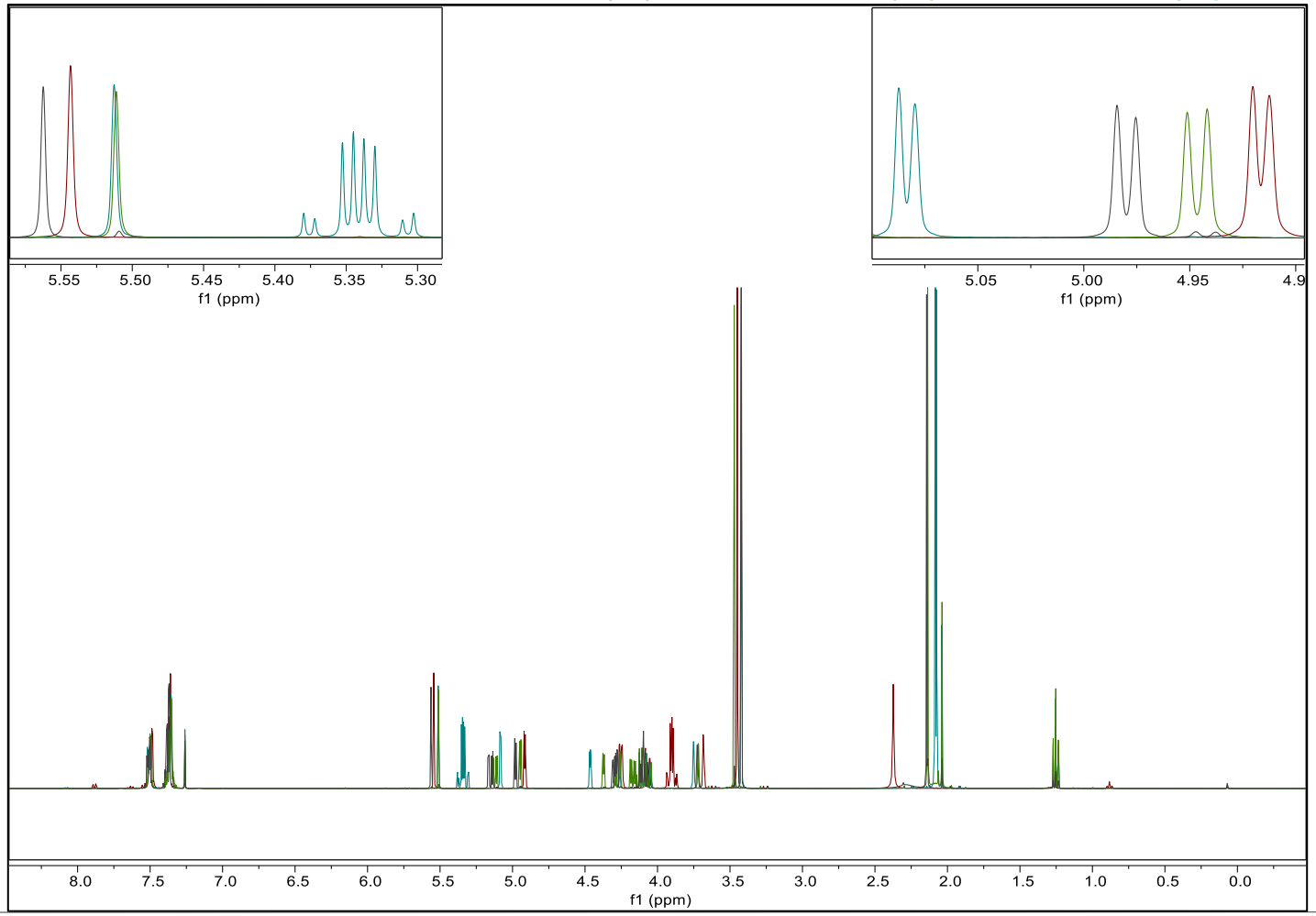


	***C* [%]**	**Selectivity[b] [%]**
NMI	62	35
Peptide	>95	53
DoE[a]	>95	58

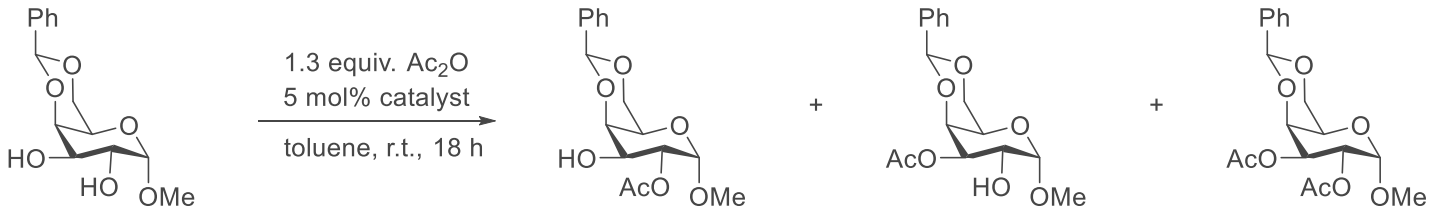
[a] conditions given by DoE: 20 mL toluene at 0 °C were used, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

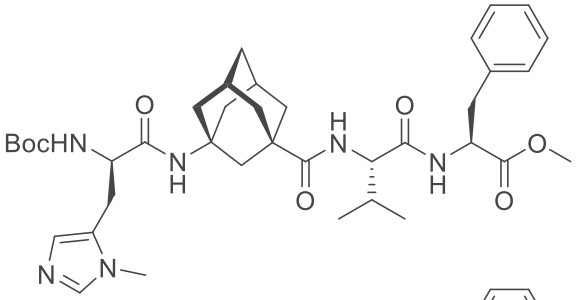
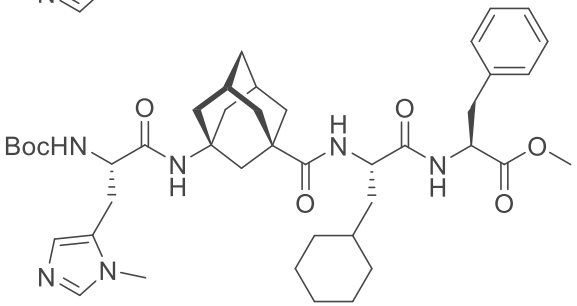
Acetylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside





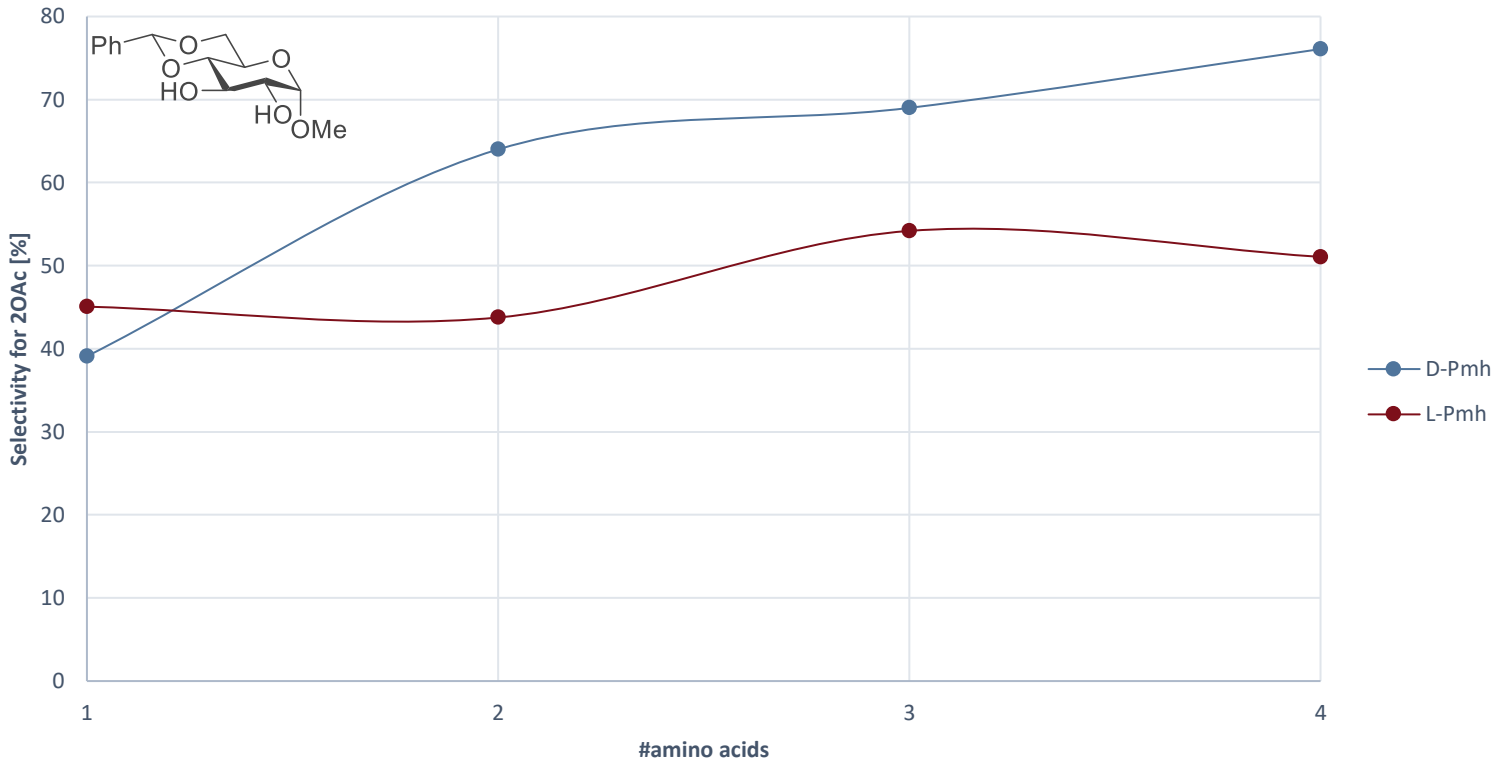
Acetylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside

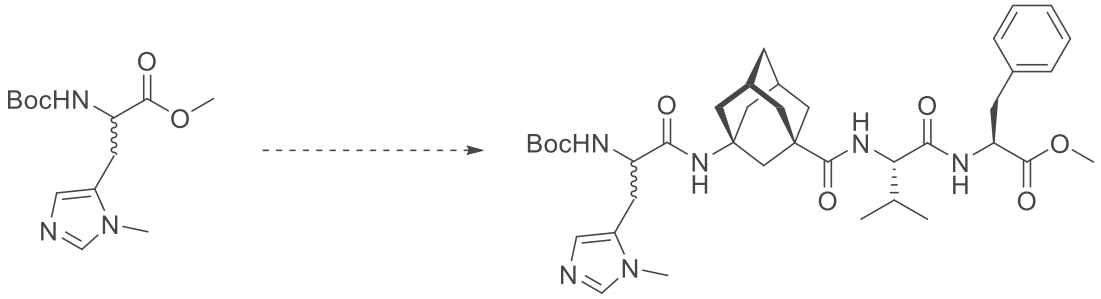


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[a] [%]
NMI (10mol%)	25	35	3	63	56
	26	69	6	>95	68
	22	65	3	90	72

[a] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside





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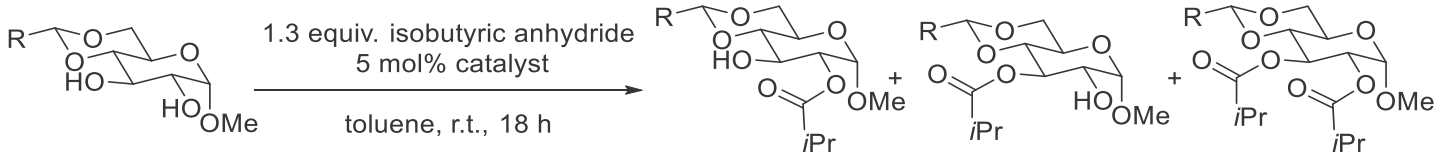
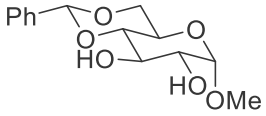
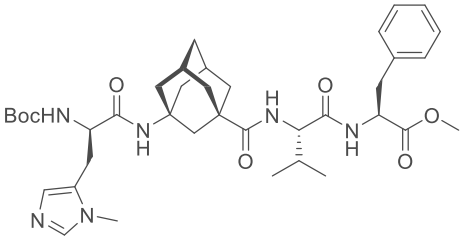
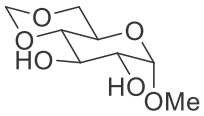
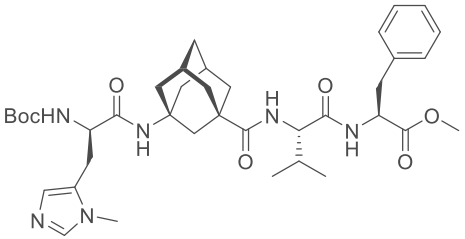
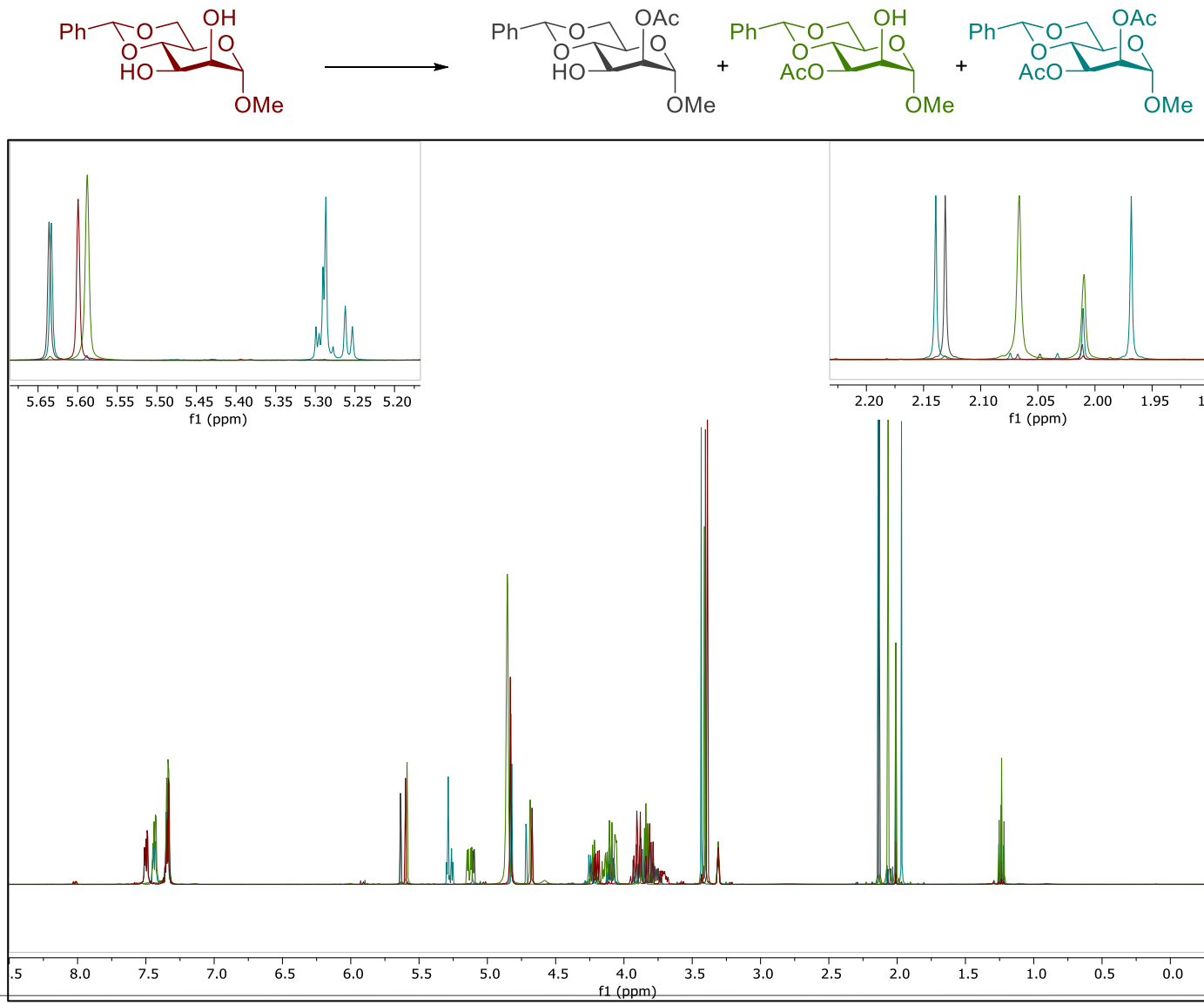
Acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



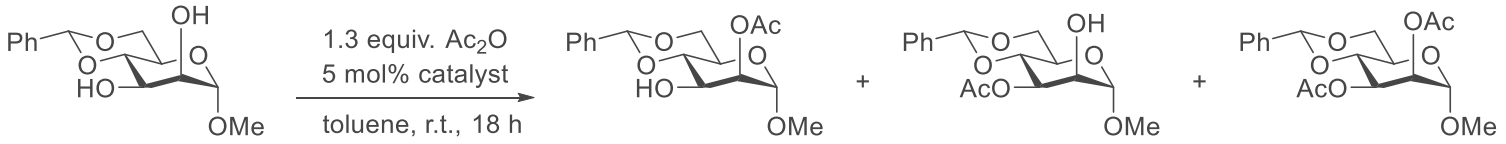
Starting Material	Catalyst	*C* [%]	Selectivity[b] [%]
	NMI	71	31
		89	85
		92[a]	83[a]
	NMI	54	48
		91	87
		81[a]	84[a]

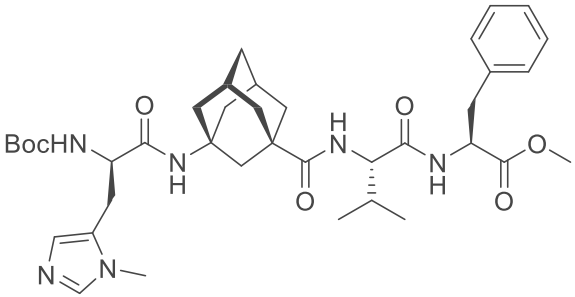
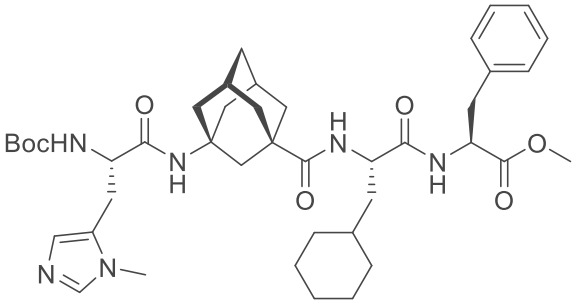
[a] conditions given by DoE: 20 mL toluene at 0 °C were used, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside



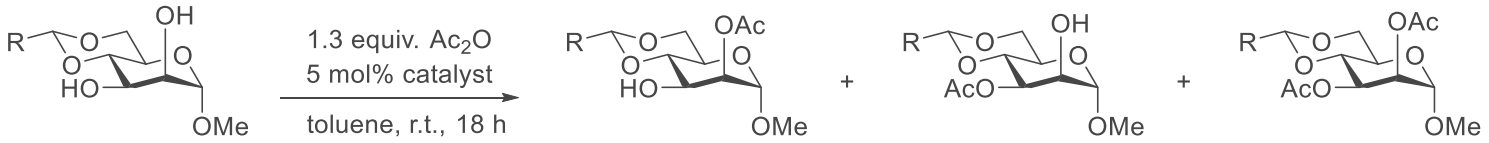
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

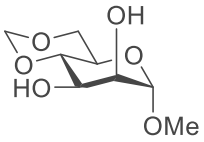
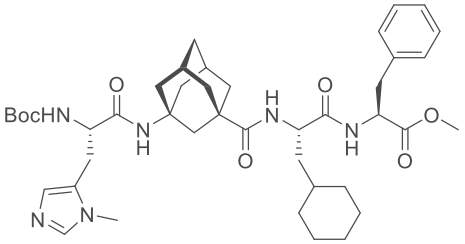
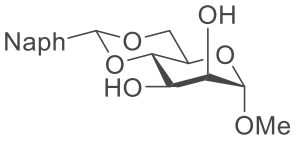
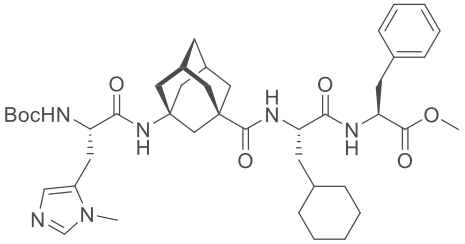


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
NMI (10mol%)	4	55	14	73	5 (75 for 3OAc)
	25	43	15	83	30
	57	5	38	>95	57
	65	5	5	75[a]	87[a]

[a] conditions given by DoE: 10 mol% cat., 1 equiv. Ac_2O, 2 h, 20 mL toluene, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

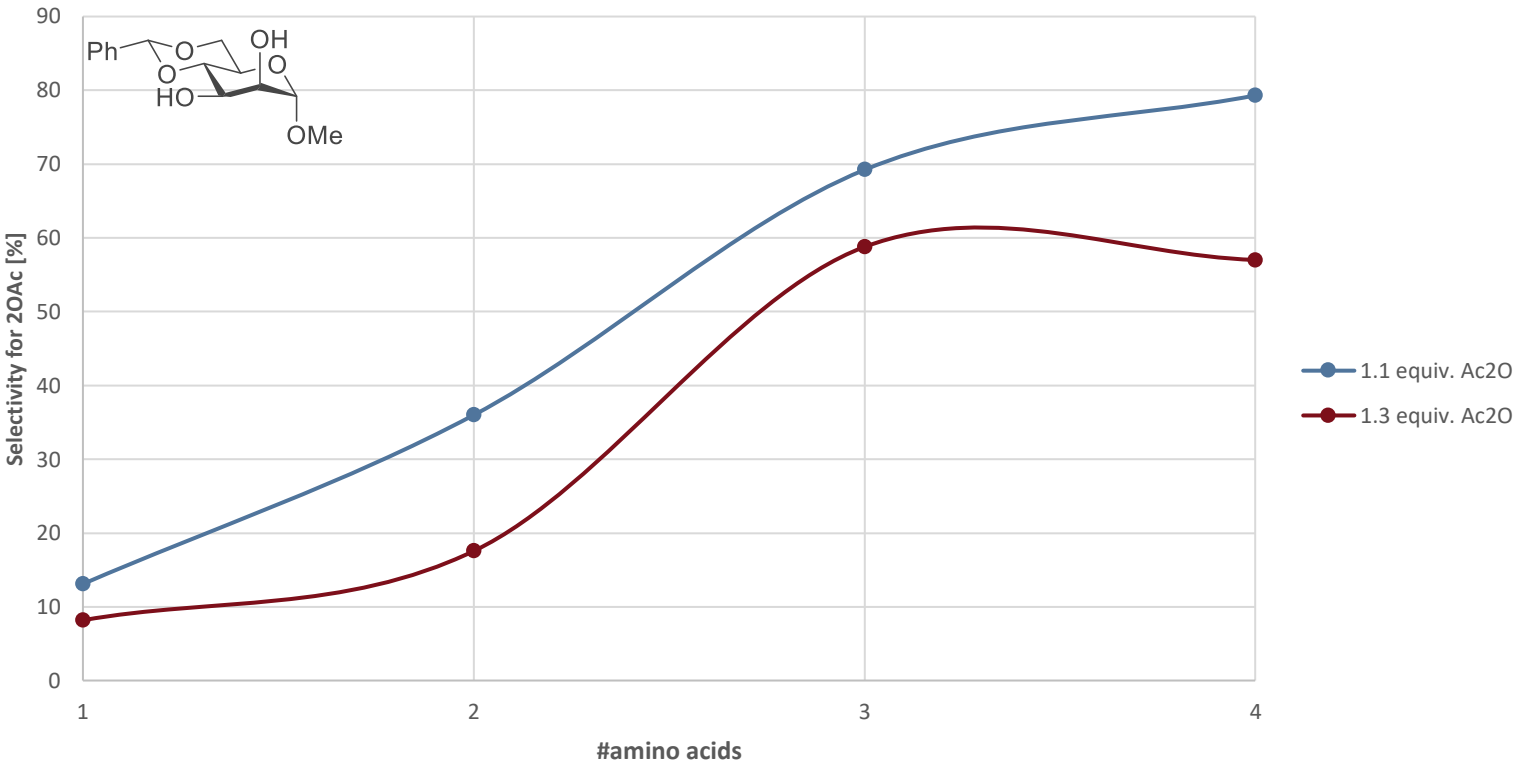
Acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

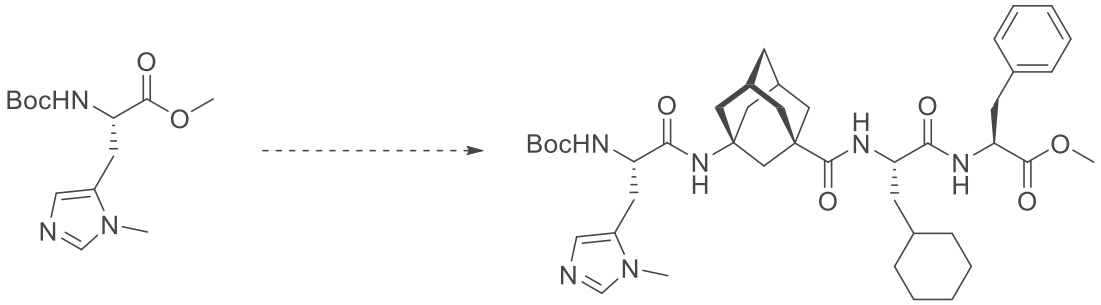


Starting Material	Catalyst	*C* [%]	Selectivity[b] [%]
	NMI	46	15
		>95	68
		55[a]	73[a]
	NMI	22	14
		88	70
		69[a]	86[a]

[a] conditions given by DoE: 10 mol% cat., 1 equiv. Ac_2O, 2 h, 20 mL toluene, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

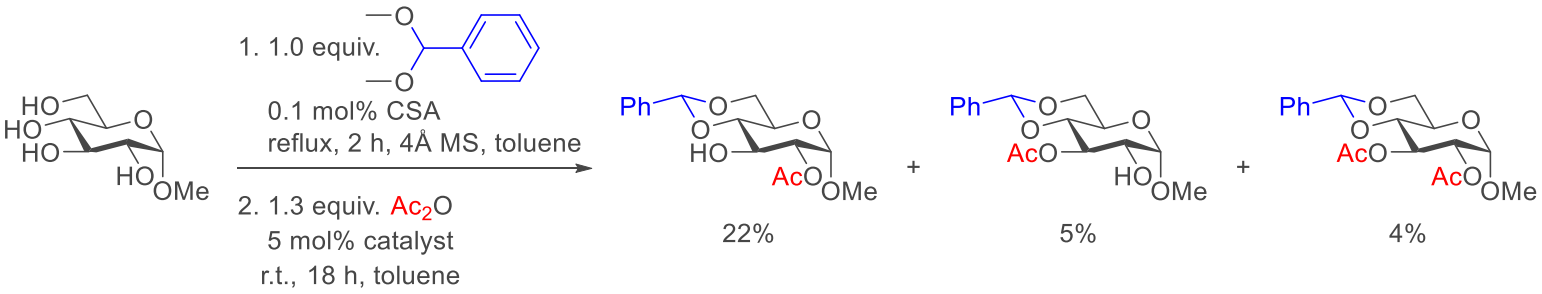
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

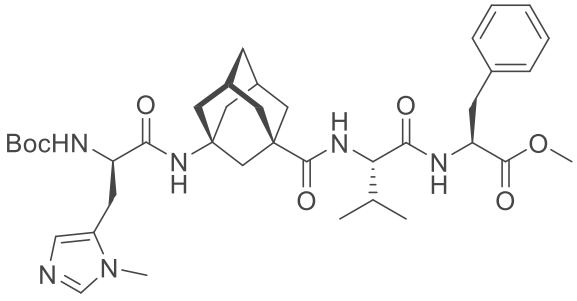




.

One-pot multiple protections





2*O*Ac [%]	3*O*Ac [%]	Diac [%]	*C* [%]	Selectivity [%]
70	19	3	92	76
71	17	12	31 (Yield)	71

- Only first reaction step: 30% isolated yield of product

Summary

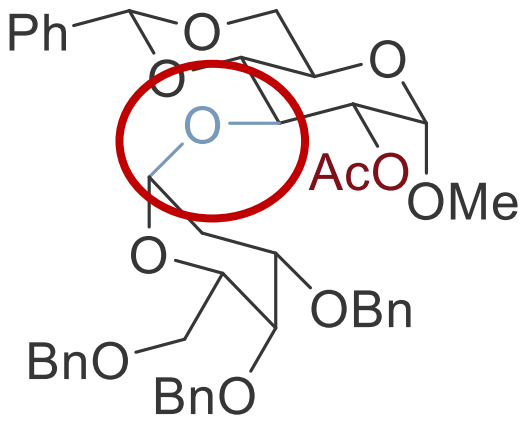
- Inversion of intrinsic reactivity for
  - methyl 4,6-*O*-protected-α-D-glucopyranosides
  - methyl 4,6-*O*-protected-α-D-mannopyranosides

- High influence of changes in 1 and 4 position onto substrate-catalyst interaction (loss of selectivity)

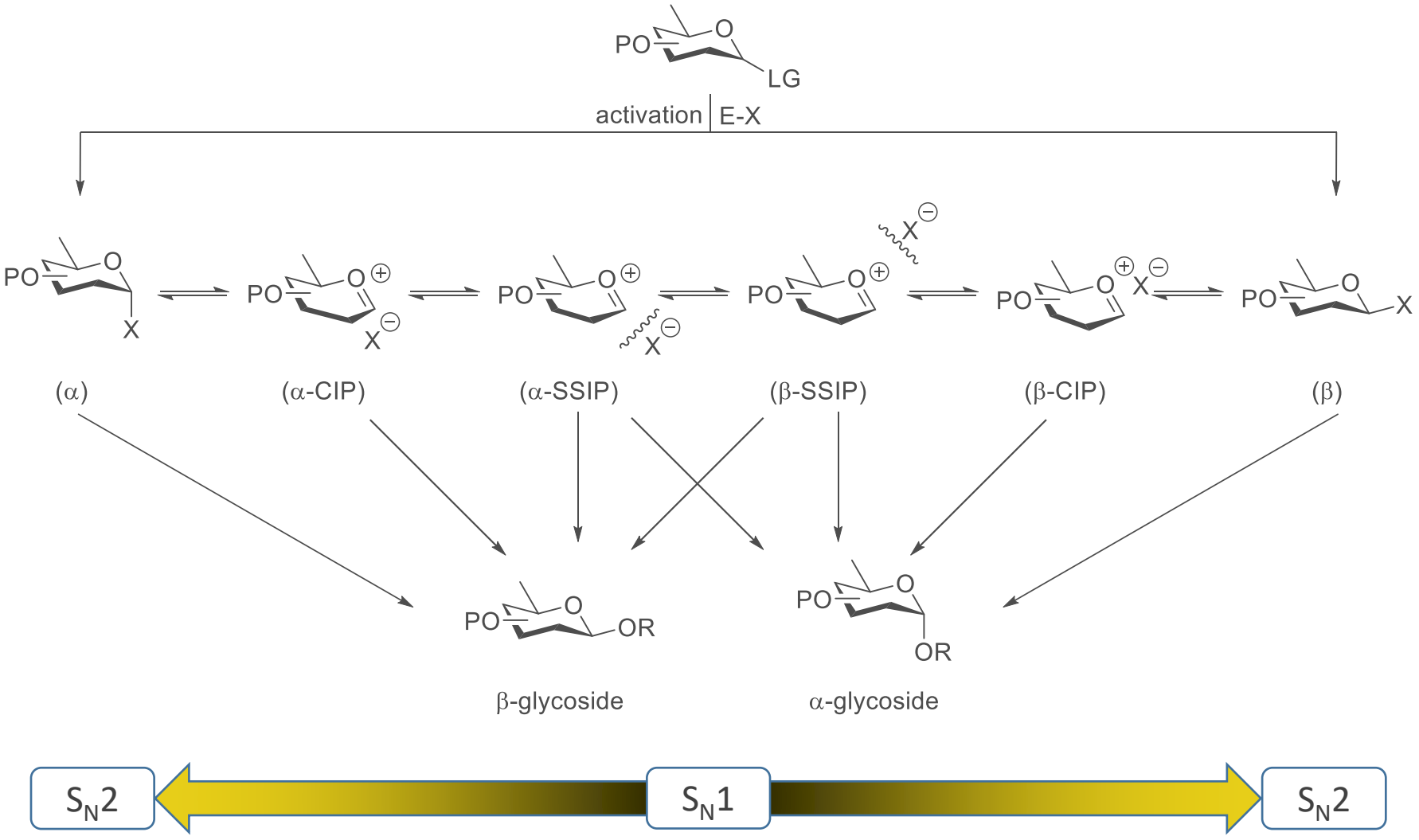
- One-pot double protection of methyl α,D-glucopyranoside possible

- Optimization of the first reaction to improve yields

Selective Glycosylation using Thiourea Catalysts



Chemical Glycosylation



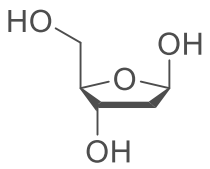
S. van der Vorm, T. Hansen, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codée, *Chem. Sci.* **2017**, *8*, 1867-1875,
L. Bohé, D. Crich, *Carbohydr. Res.* **2015**, *403*, 48-59.

- Lot of different factors effect selectivity
  - Solvent, temperature, pressure, concentration
  - Substitution of glycosyl donor/acceptor
  - etc.

- Investigations of different donors are shown in many reviews

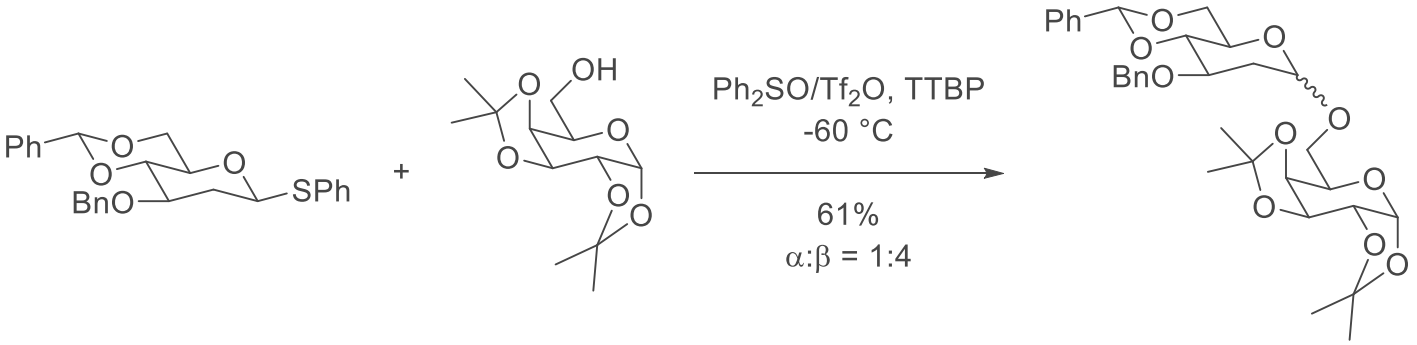
S. S. Nigudkar, A. V. Demchenko, *Chem. Sci.* **2015**, *6*, 2687-2704; R. Das, B. Mukhopadhyay, *ChemistryOpen* **2016**, *5*, 401-433, D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940, M. Bols, C. M. Pedersen, *Beilstein J. Org. Chem.* **2017**, *13*, 93-105.

- 2-Deoxy-glycosides are of special interest



- Harder to control selectivity because lack of C-2 group

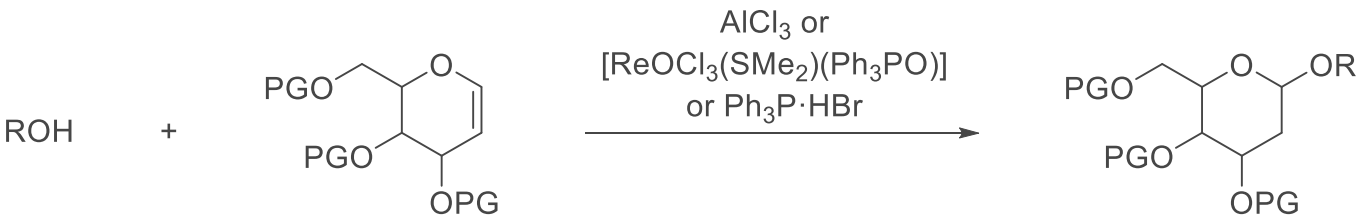
- Crich‘s group testet different acceptors with yields up to 75%



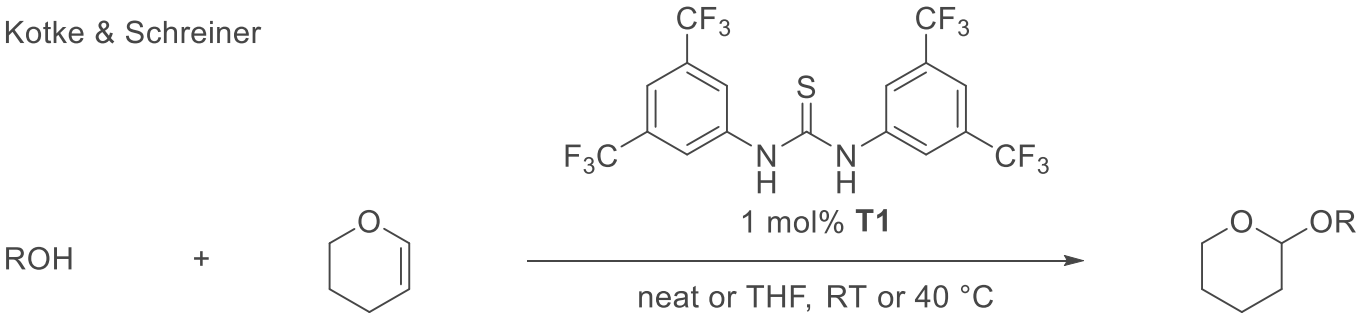
D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940, E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012,** *51*, 9152–9155, D. Crich, O. Vinogradova, *J. Org. Chem.* **2006**, *71*, 8473-8480.

- Direct glycosylation of galactals to form 2-deoxyglycosides

Glycosylation

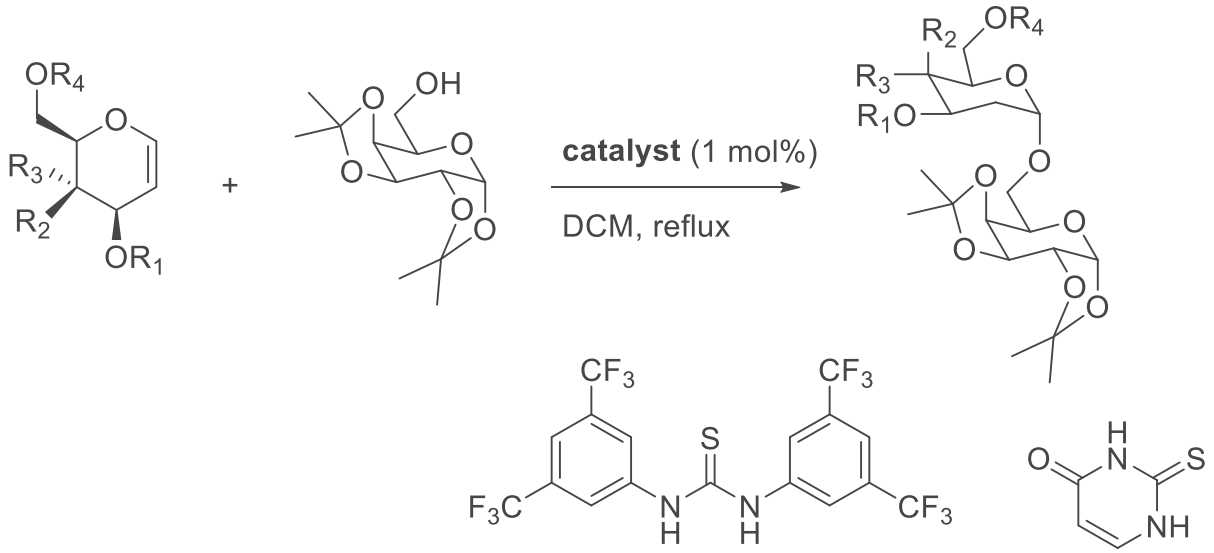


Kotke & Schreiner



E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; M. Kotke, P. R. Schreiner, *Synthesis* **2007**, *5*, 779-790; B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510-4511; V. Bollit, C. Mioskowski, S.-G. Lee, J. R. Falck, *J. Org. Chem.* **1990**, *55*, 5812-5813; H.-C. Lin, J.-F. Pan, Y.-B. Chen, Z.-P. Lin, C.-H. Lin, *Tetrahedron* **2011**, *67*, 6362-6368.

Investigation by McGarrigles Group

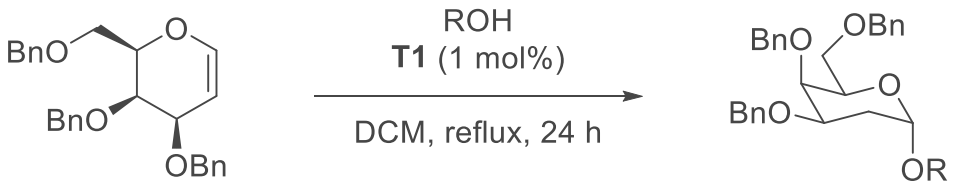


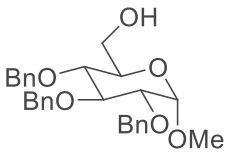
R_1	R_2	R_3	R_4	*t* [h]	Yield [%]	*t* [h]	Yield [%]
Allyl	OAllyl	H	Allyl	18	96	18	82
Bn	OBn	H	Bn	24	96	18	85
Bn	H	OBn	Bn	-	-	18	46[a]
TBS	OTBS	H	TBS	48	72	48	11
Ac	OAc	H	Ac	48	0	18	0
Bn	OBn	H	Ac	24	89	18	85

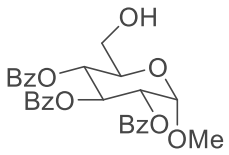
[a]Isolated with 10-20% inseparable impurities due to ferrier rearrangement.

E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; G. A. Bradshaw, A. C. Colgan, N. P. Allen, I. Pongener, M. B. Boland, Y. Ortin, E. M. McGarrigle, *Chem. Sci.* **2019**, *10*, 508.

Investigation by McGarrigles Group




98%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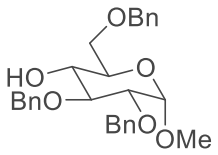
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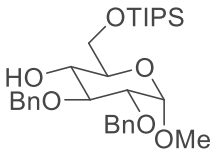
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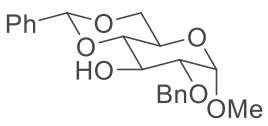
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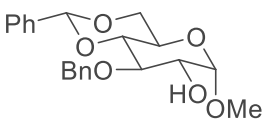
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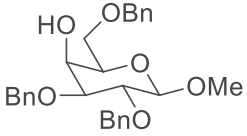
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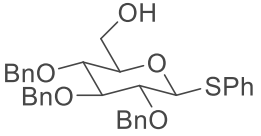
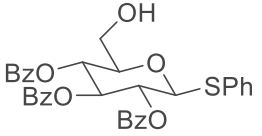
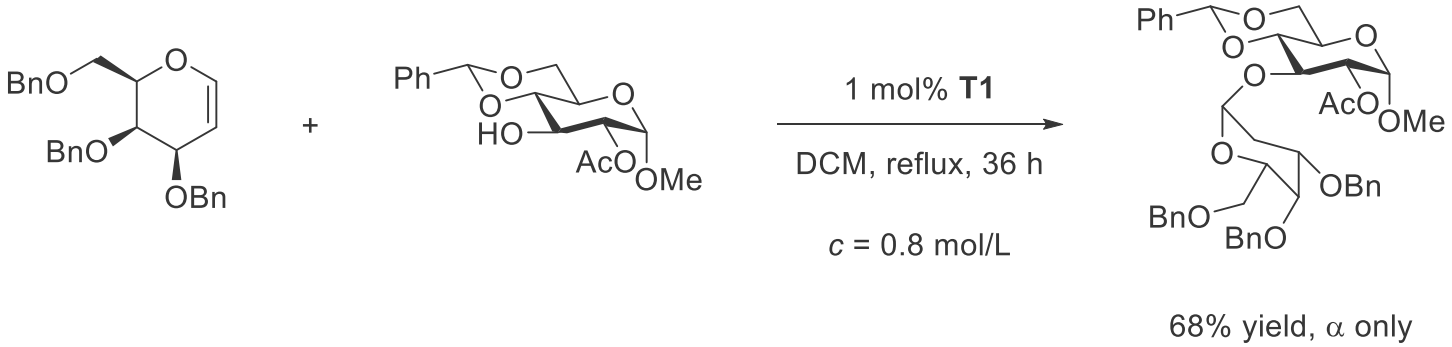
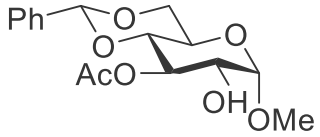

92%


87%

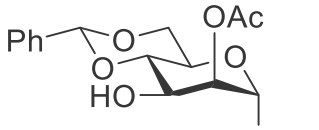
E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012.**

First Glycosylation Reactions

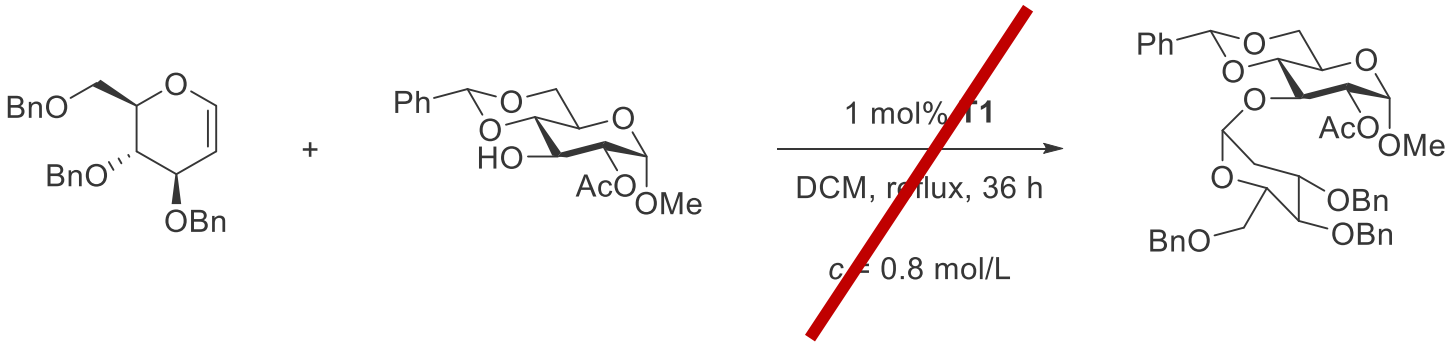




34%[a]

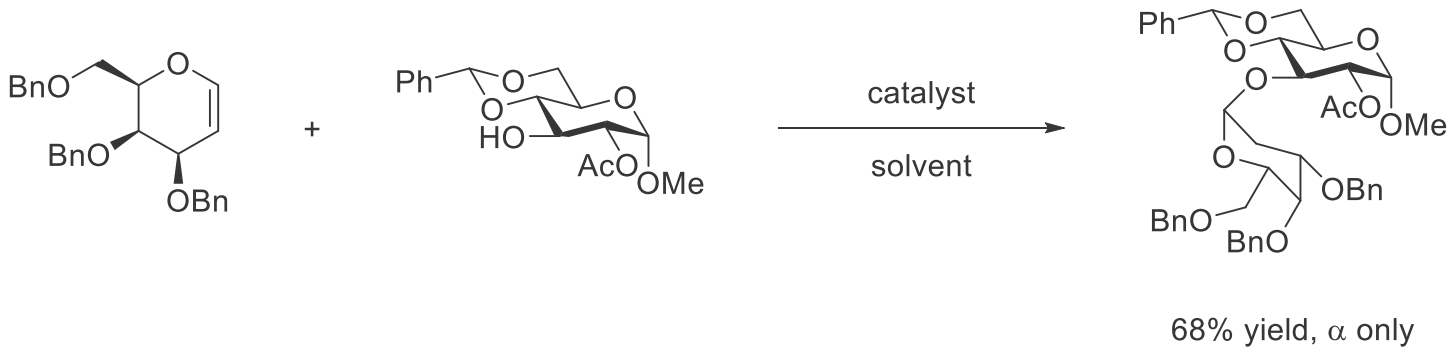


40%[a]

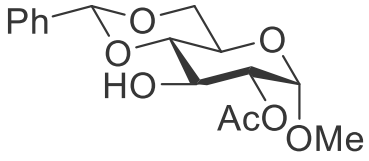
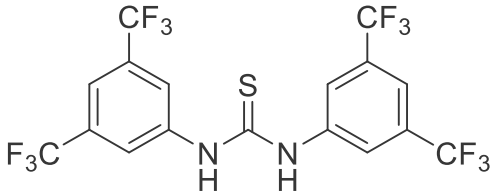
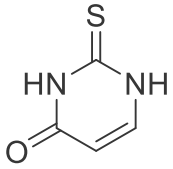


[a] Galactal is slowly decomposing, therefore the yields where lower

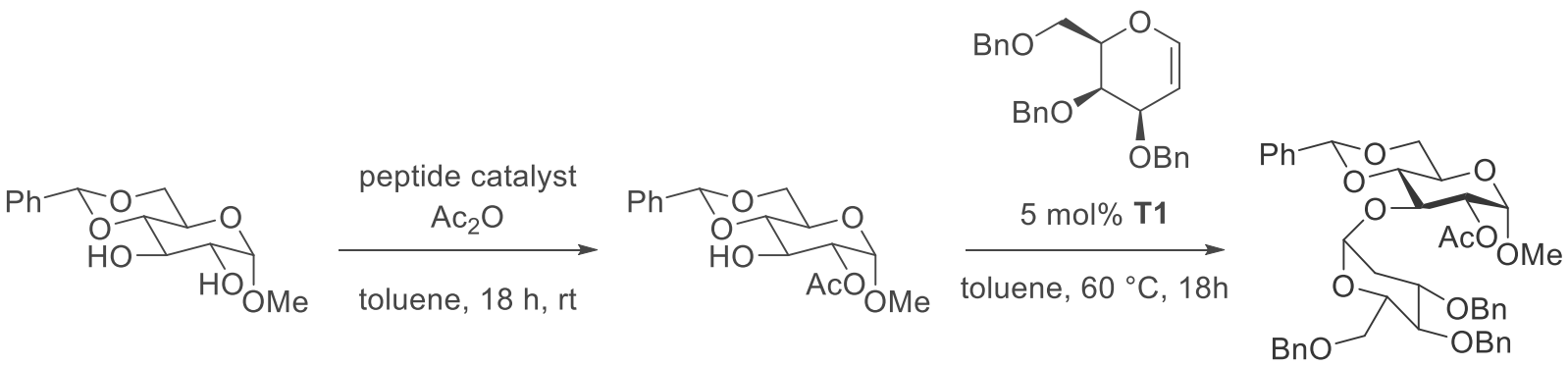
Glycosylation Reactions



68% yield, α only

Acceptor	Catalyst	Conditions	Yield
		0.5 mmol/0.6 mL DCM 1 mol%, reflux	68%
		0.1 mmol/1 mL DCM 5 mol%, reflux	75%
		0.1 mmol/5 mL toluene 5 mol%, 70 °C	70%
		0.1 mmol/1 mL DCM 5 mol%, reflux	73%
		0.1 mmol/10 mL toluene 5 mol%, 70 °C	73%

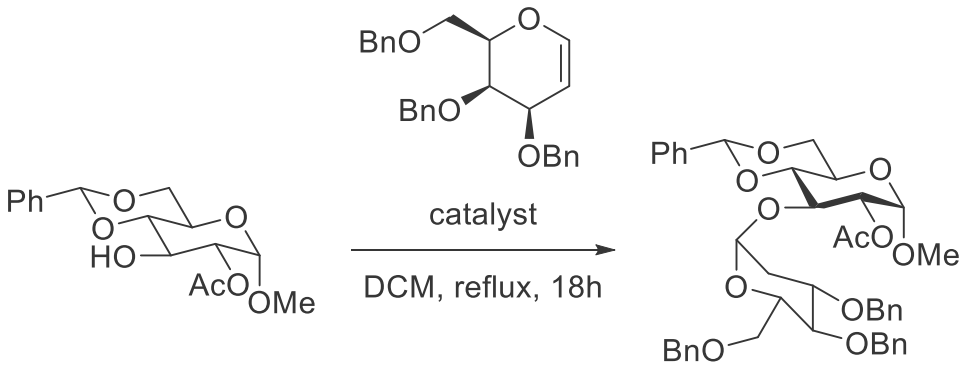
Multicatalytic Sequence

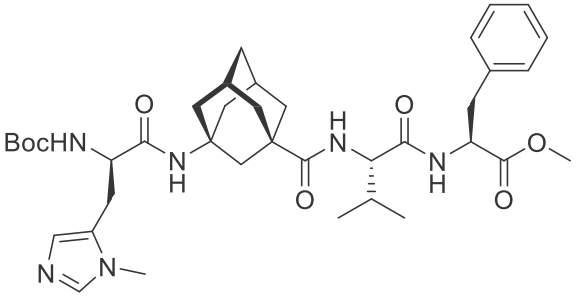


- no product formation observed

- investigation of possible interfering interactions

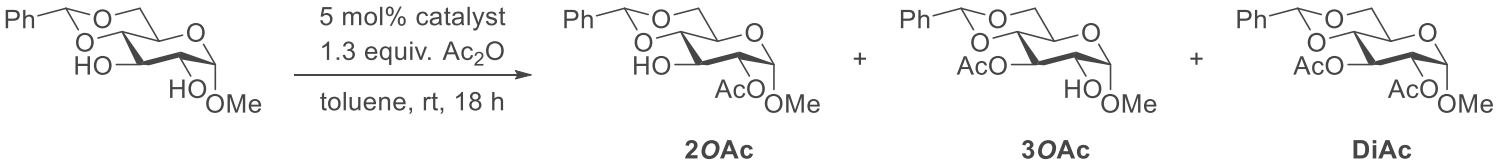
Multicatalytic Sequence





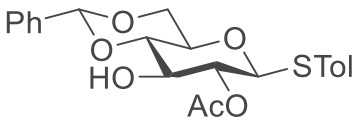
x mol% **T1:** no conversion

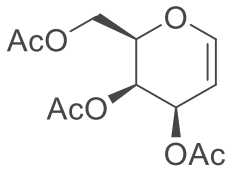
x mol% thiouracil: no conversion

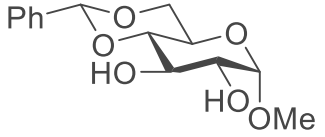


Catalyst added	2*O*Ac [%]	3*O*Ac [%]	DiAc [%]	C (%)	Selectivity (%)
none	70	19	3	92	76
5 mol% **T1**	64	25	11	> 95	64
5 mol% thiouracil	68	23	9	>95	68

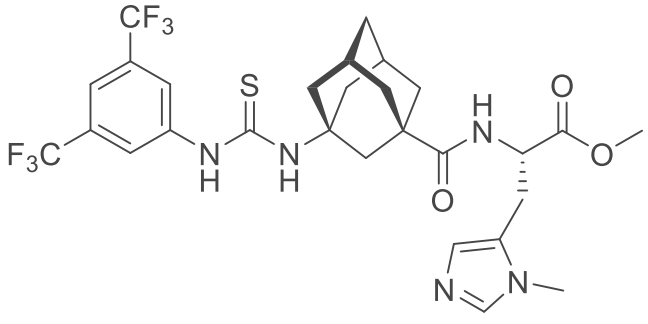
- NMR investigation to identify problems
- Test more galactals and carbohydrates

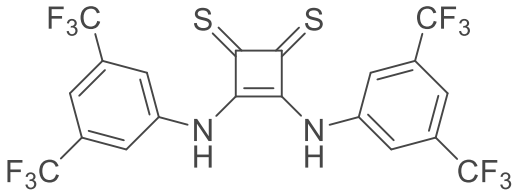






- Test more catalysts





Acknowledgment

- Prof. Peter R. Schreiner
- Markus, Ricky, Lukas, Simon and Raffi
- Eschi, JMS, Friedhelm, Toppsi
- Analytical department
- PRS-Group

Thank you for your attention!