Consecutive Acylation and Glycosylation of Pyranosides

28th May 2021

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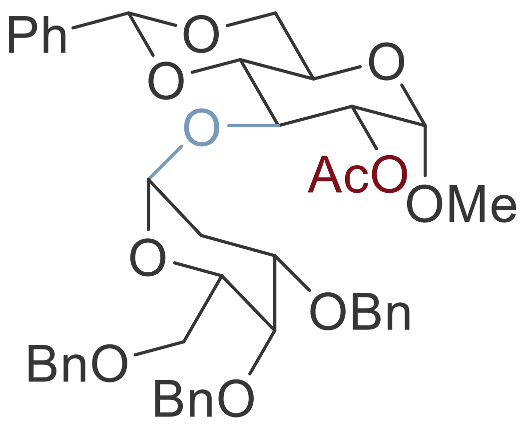
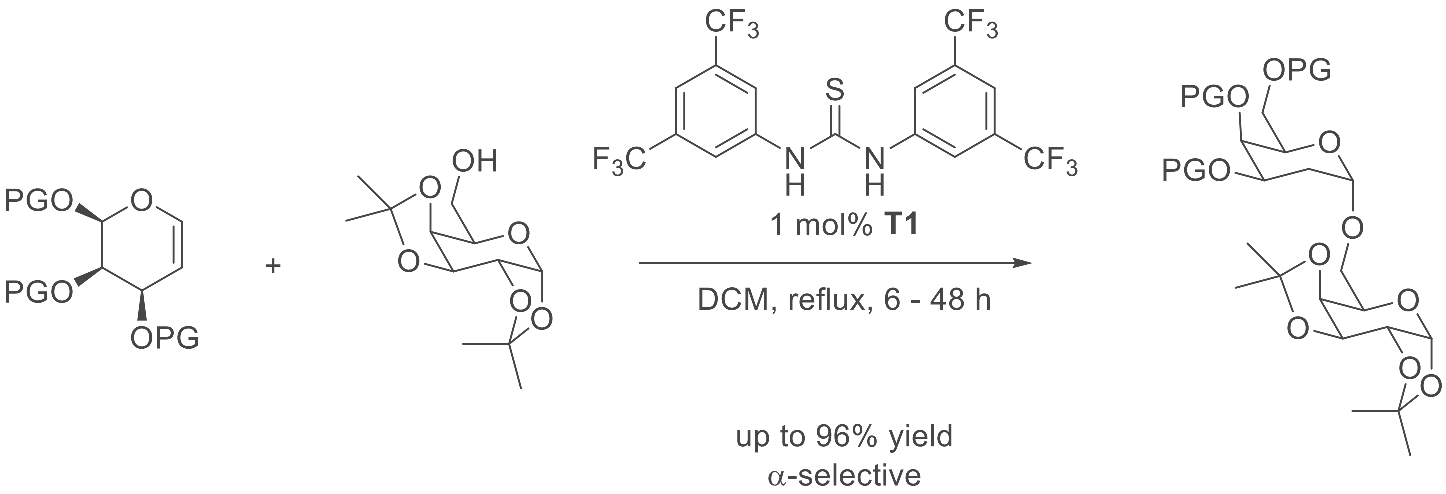


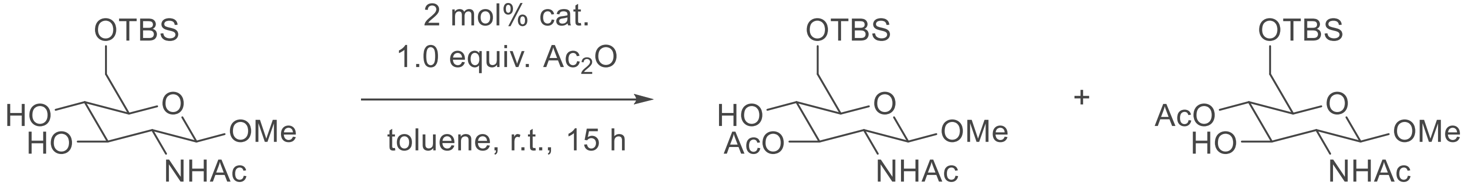
Motivation

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



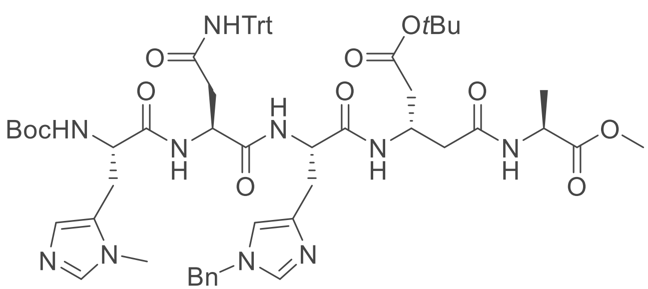
E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

- 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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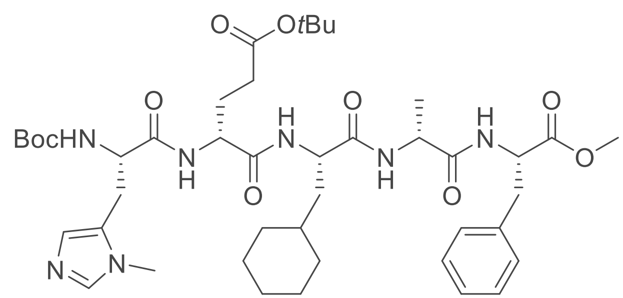

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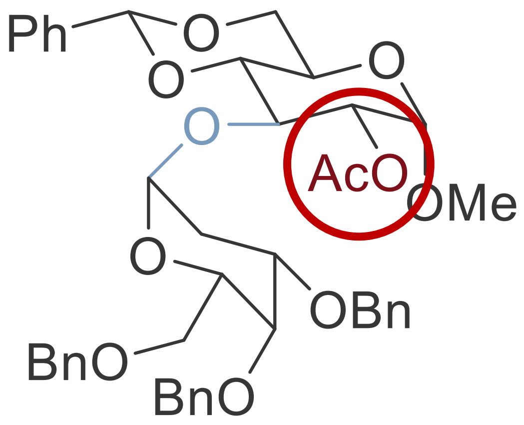
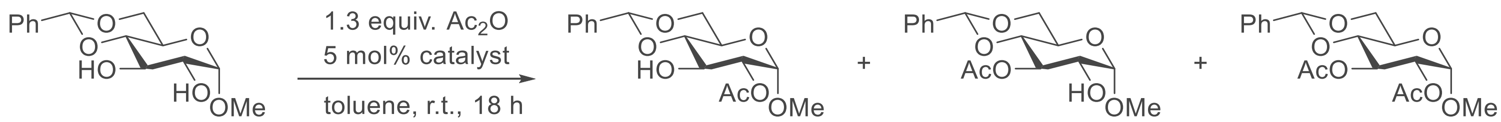
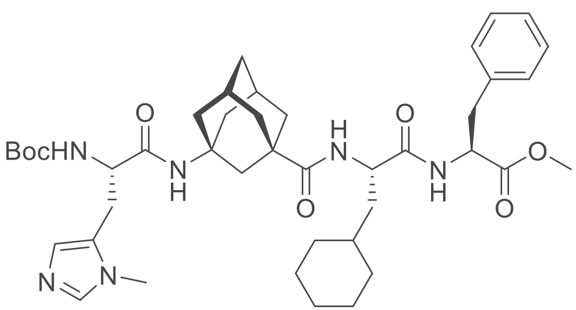
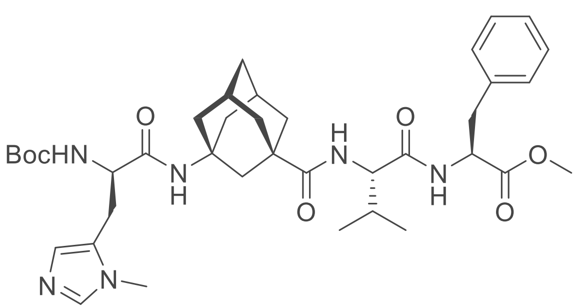
K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869–8875; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

Site-Selective Acylation of Pyranosides



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

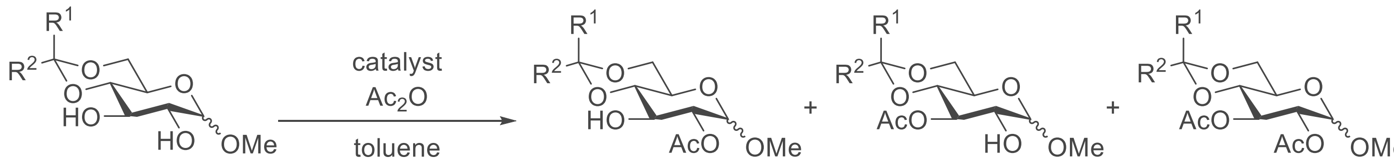


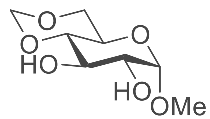
Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
NMI (10mol%)	20	62	5	87	23
	55	37	8	>95	55
	70	19	3	92	76
	81	17	1	>95 (DoE)[a]	82

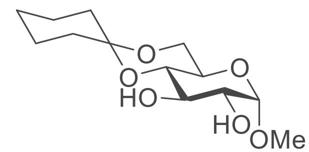
[a] conditions given by DoE: 20 mL toluene at 0 °C were used, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

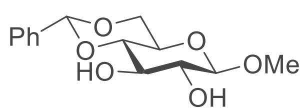
Acetylation of 4,6-*O*-protected-α-D-glucopyranoside derivatives

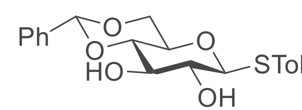






	C [%]	Selectivity[b] [%]	*C* [%]	Selectivity[b] [%]
NMI	58	40	36	50
Peptide	>95	76	64	86
DoE[a]	90	82	69	86



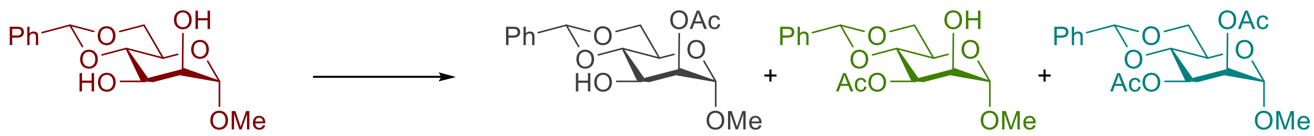


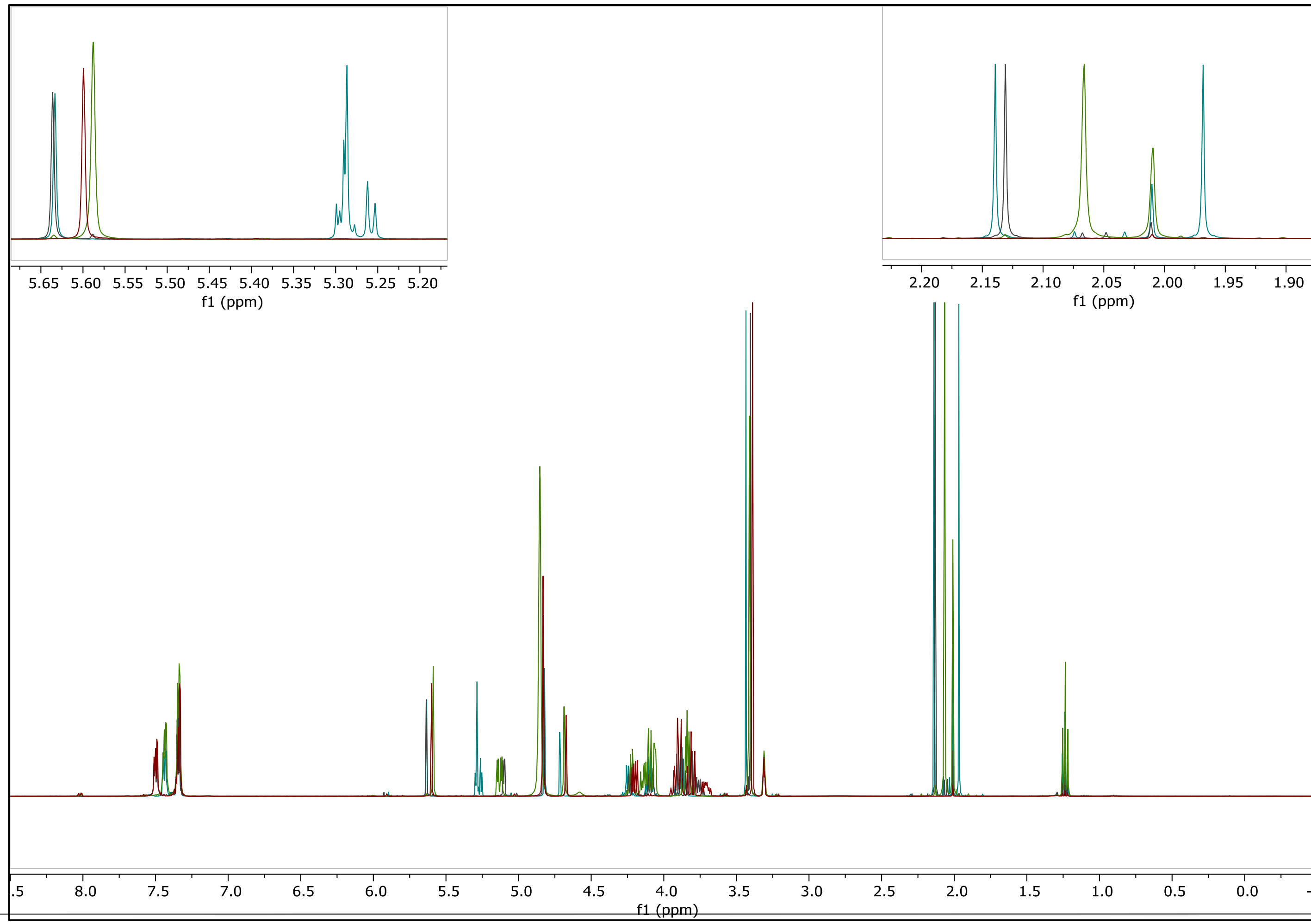
	C [%]	Selectivity[b] [%]	*C* [%]	Selectivity[b] [%]
NMI	32	19	62	35
Peptide	75	28	>95	53
DoE[a]	15	40	>95	58

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

A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

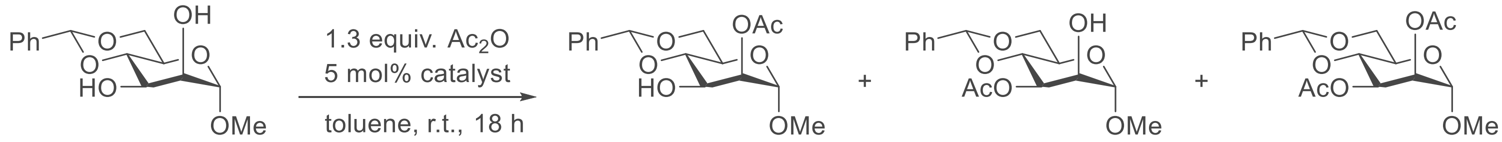
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

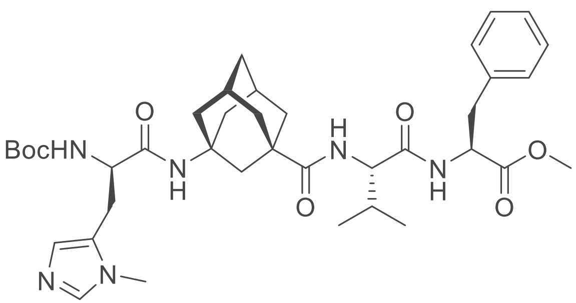
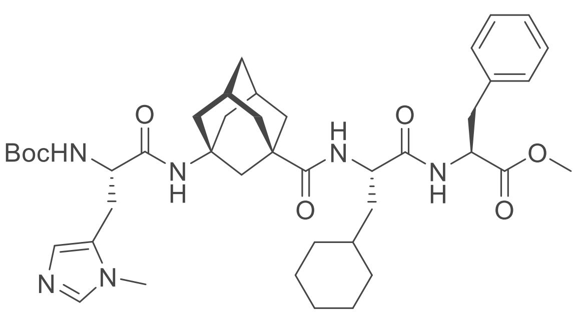




A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

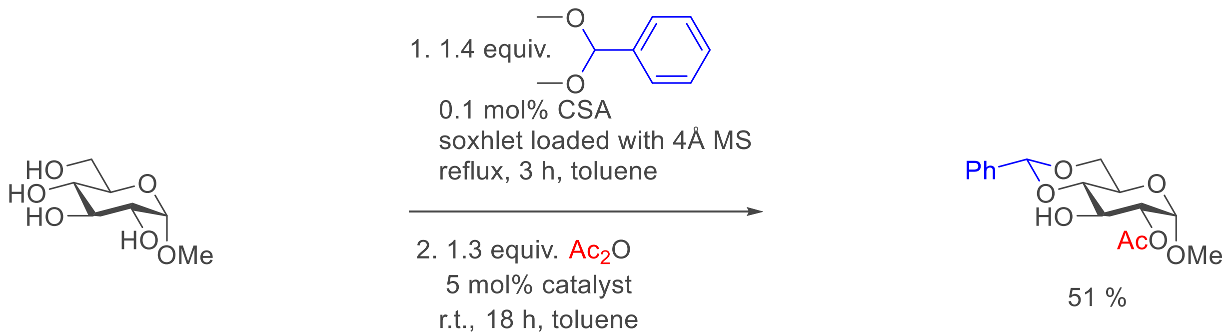
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

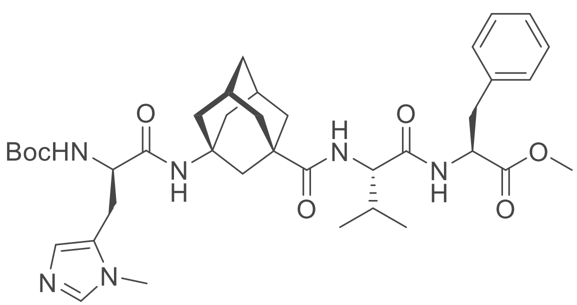


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
NMI (10mol%)	4	55	14	73	5 (75 for 3OAc)
	25	43	15	83	30
	57	5	38	>95	57
	65	5	5	75[a]	87[a]

[a] conditions given by DoE: 10 mol% cat., 1 equiv. Ac_2O, 2 h, 20 mL toluene, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.
A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

One-pot double protection

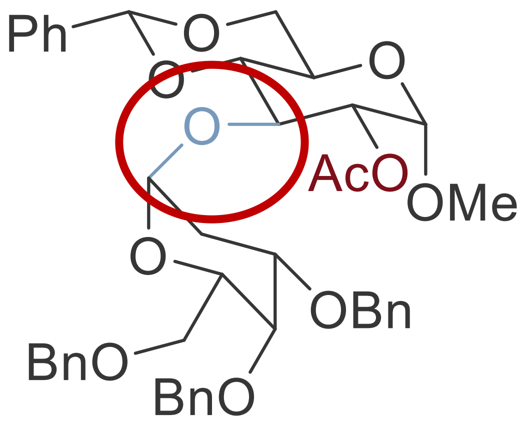




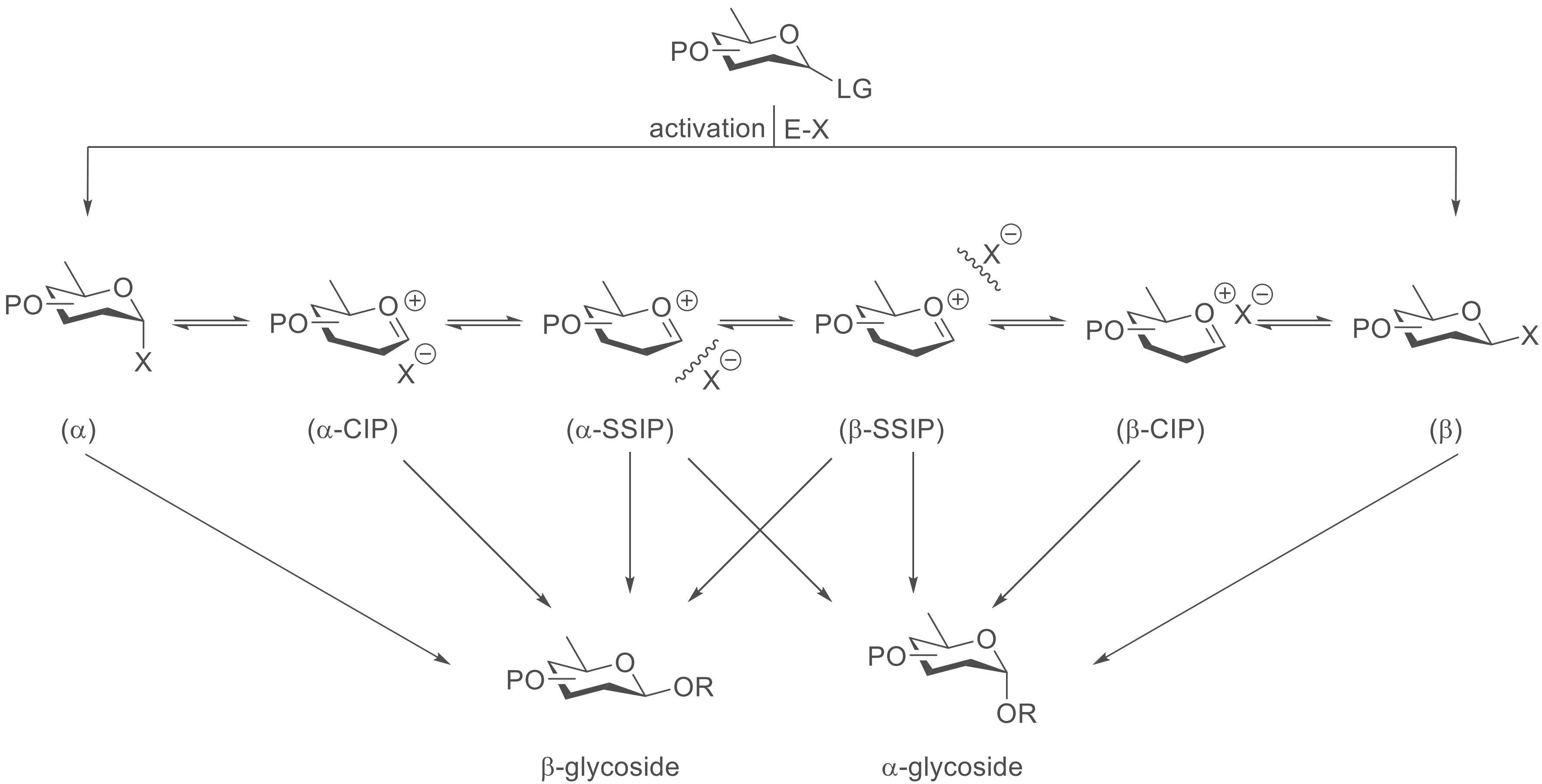
2*O*Ac [%]	3*O*Ac [%]	Diac [%]	*C* [%]	Selectivity [%]
70	19	3	92	76
51	15	7	73 (Yield)	70

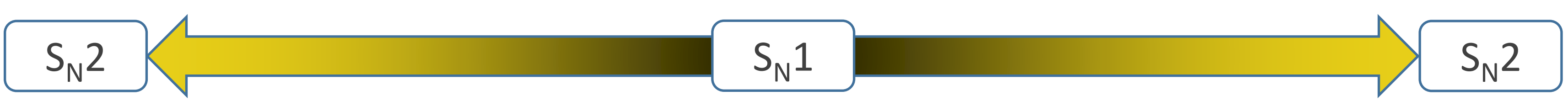
- Benzylidene-Protection: 74% yield

Selective Glycosylation using Thiourea Catalysts



Chemical Glycosylation



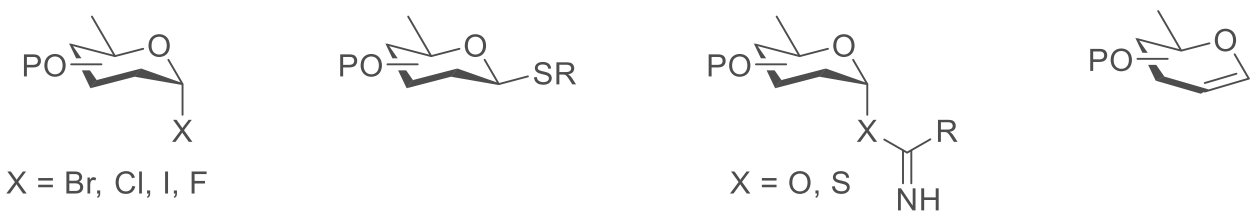


S. van der Vorm, T. Hansen, H. S. Overkleeft, G. A. van der Marel, J. D. C. Codée, *Chem. Sci.* **2017**, *8*, 1867-1875,
L. Bohé, D. Crich, *Carbohydr. Res.* **2015**, *403*, 48-59.

Chemical Glycosylation

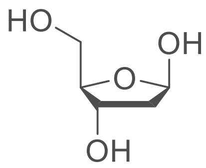
- Lot of different factors effect selectivity
  - Solvent, temperature, pressure, concentration
  - Substitution of glycosyl donor/acceptor
  - etc.

- Investigations of different donors are shown in many reviews



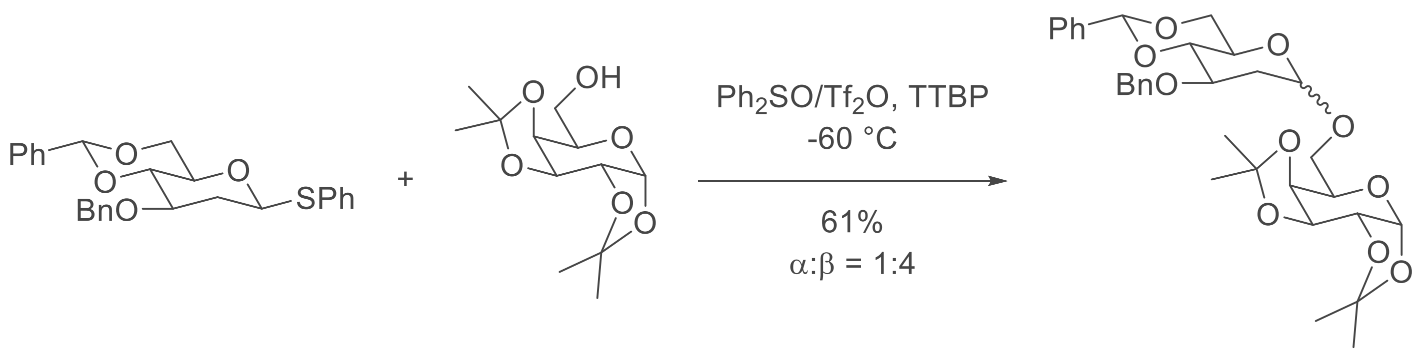
S. S. Nigudkar, A. V. Demchenko, *Chem. Sci.* **2015**, *6*, 2687-2704; R. Das, B. Mukhopadhyay, *ChemistryOpen* **2016**, *5*, 401-433, D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940, M. Bols, C. M. Pedersen, *Beilstein J. Org. Chem.* **2017**, *13*, 93-105.

- 2-Deoxy-glycosides are of special interest



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

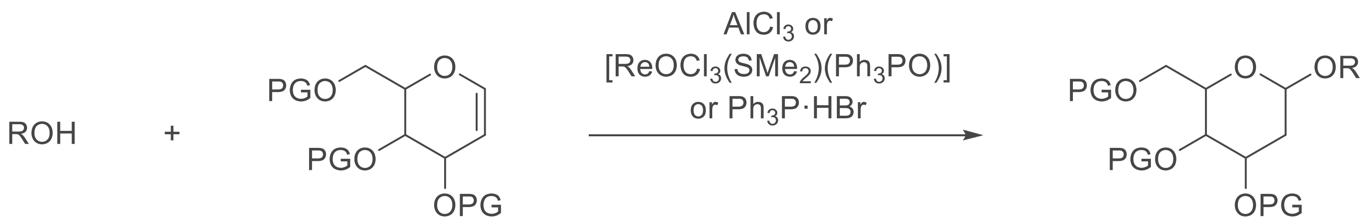
- Crich's group testet different acceptors with yields up to 75%



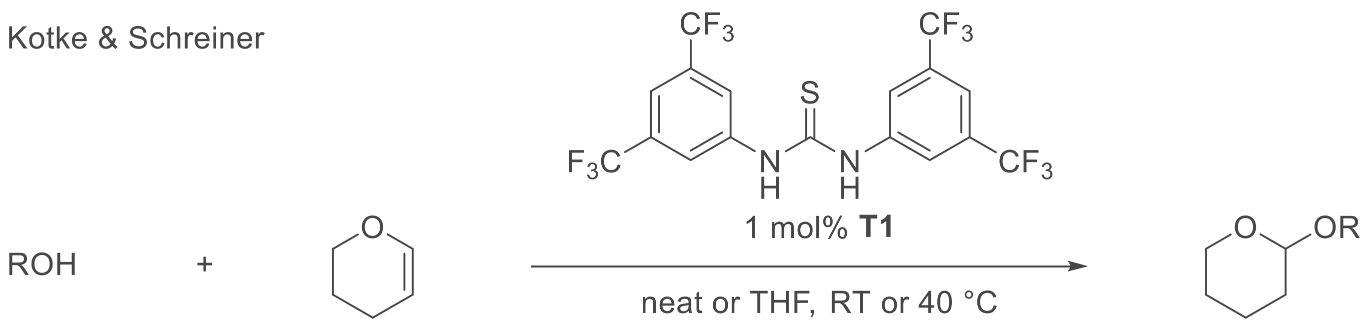
D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940, E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012,** *51*, 9152–9155, D. Crich, O. Vinogradova, *J. Org. Chem.* **2006**, *71*, 8473-8480.

- Direct glycosylation of galactals to form 2-deoxyglycosides

Glycosylation

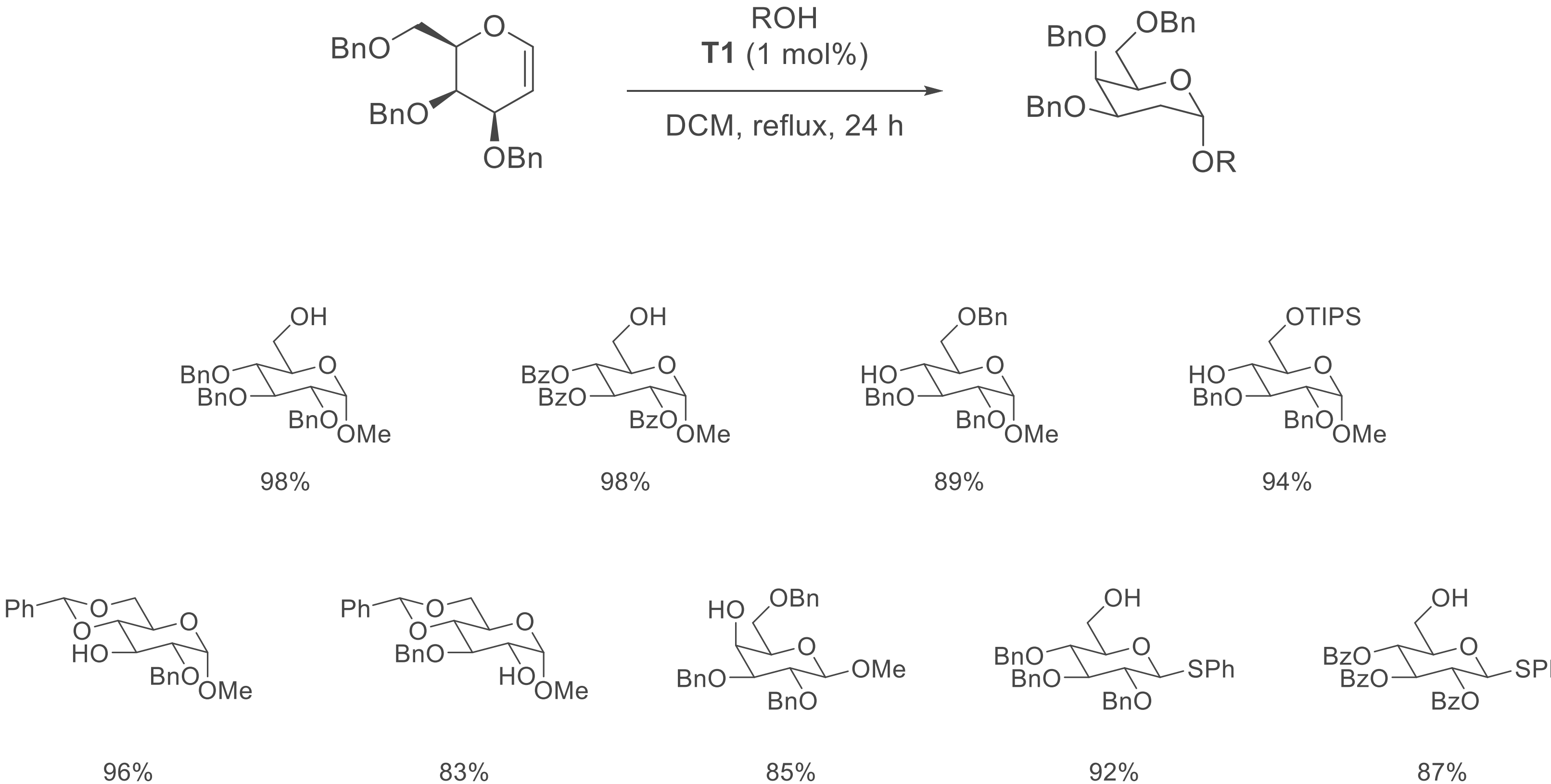


Kotke & Schreiner



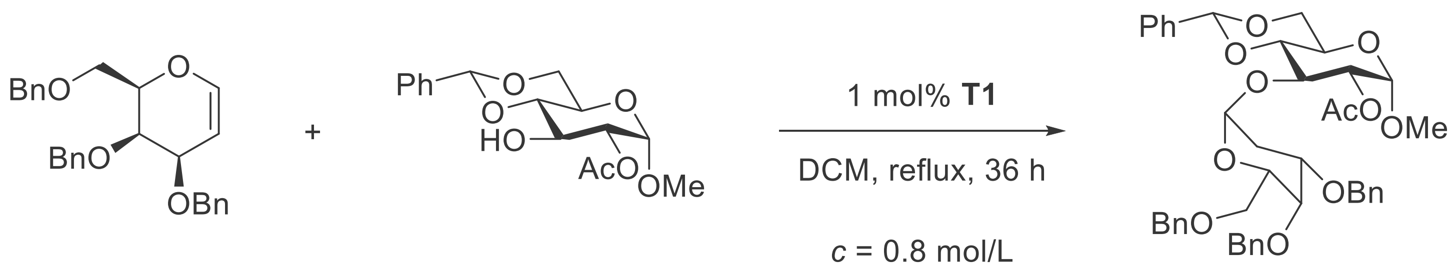
E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; M. Kotke, P. R. Schreiner, *Synthesis* **2007**, *5*, 779-790; B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510-4511; V. Bollit, C. Mioskowski, S.-G. Lee, J. R. Falck, *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

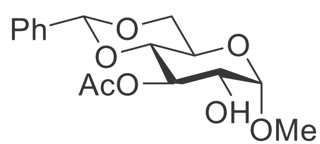


E. I. Balmond, D. M. Coe, M. C Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155;

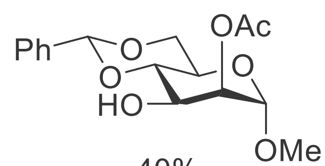
Glycosylation Reactions



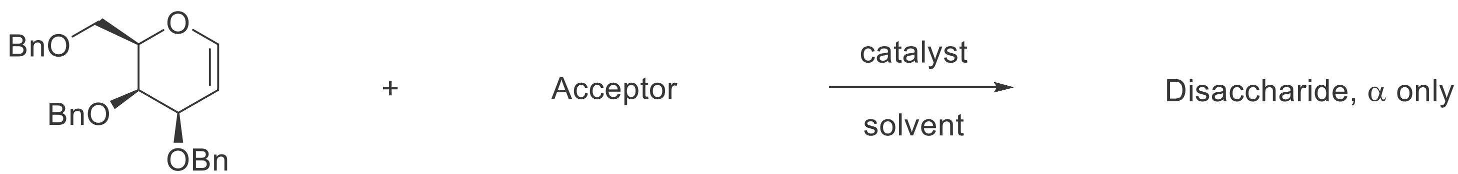
68% yield, α only

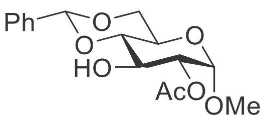
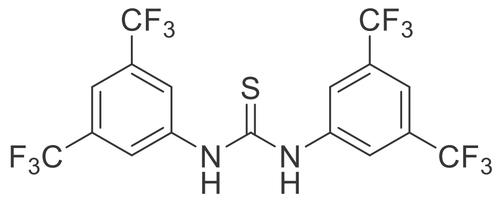
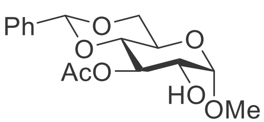
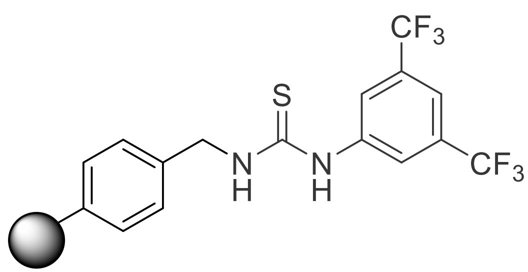
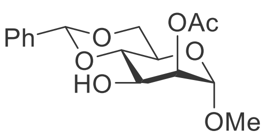


34%

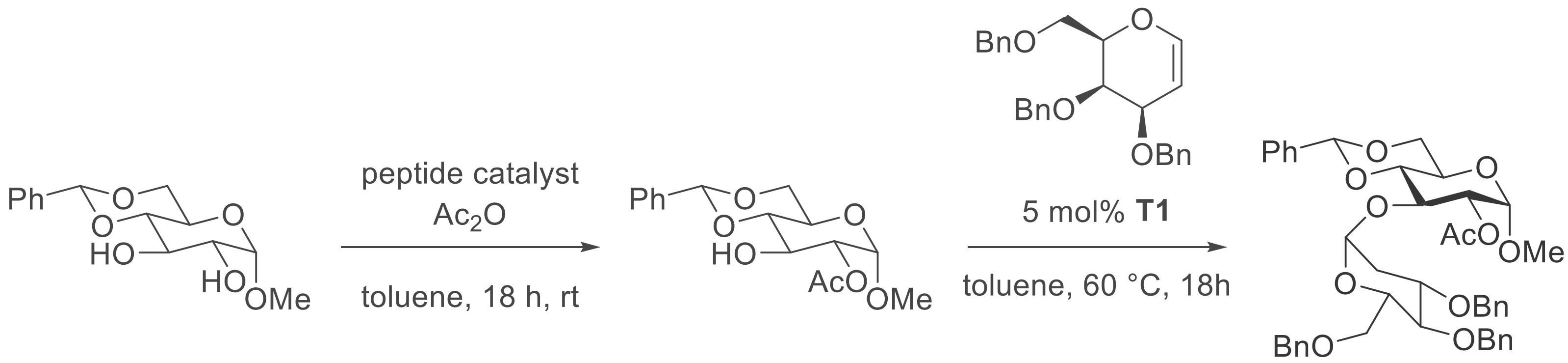


40%



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/2 mL toluene 10 mol%, 70 °C	50%
		0.1 mmol/2 mL toluene 10 mol%, 70°C	35%
		0.1 mmol/2 mL toluene 10 mol%, 70°C	65%

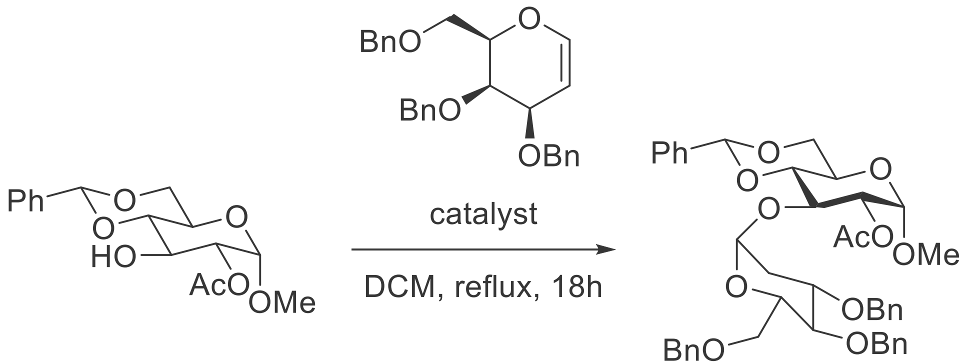
M. Kotke, P. R. Schreiner, *Synthesis* **2007**, *5*, 779-790.

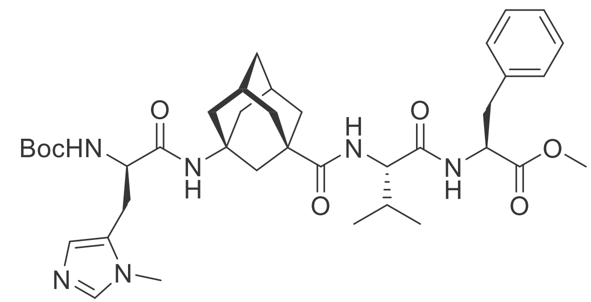


- no product formation observed

- investigation of possible interfering interactions

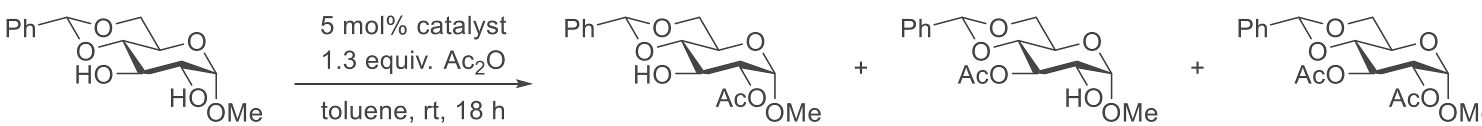
Multicatalytic Sequence





x mol% **T1:** no conversion

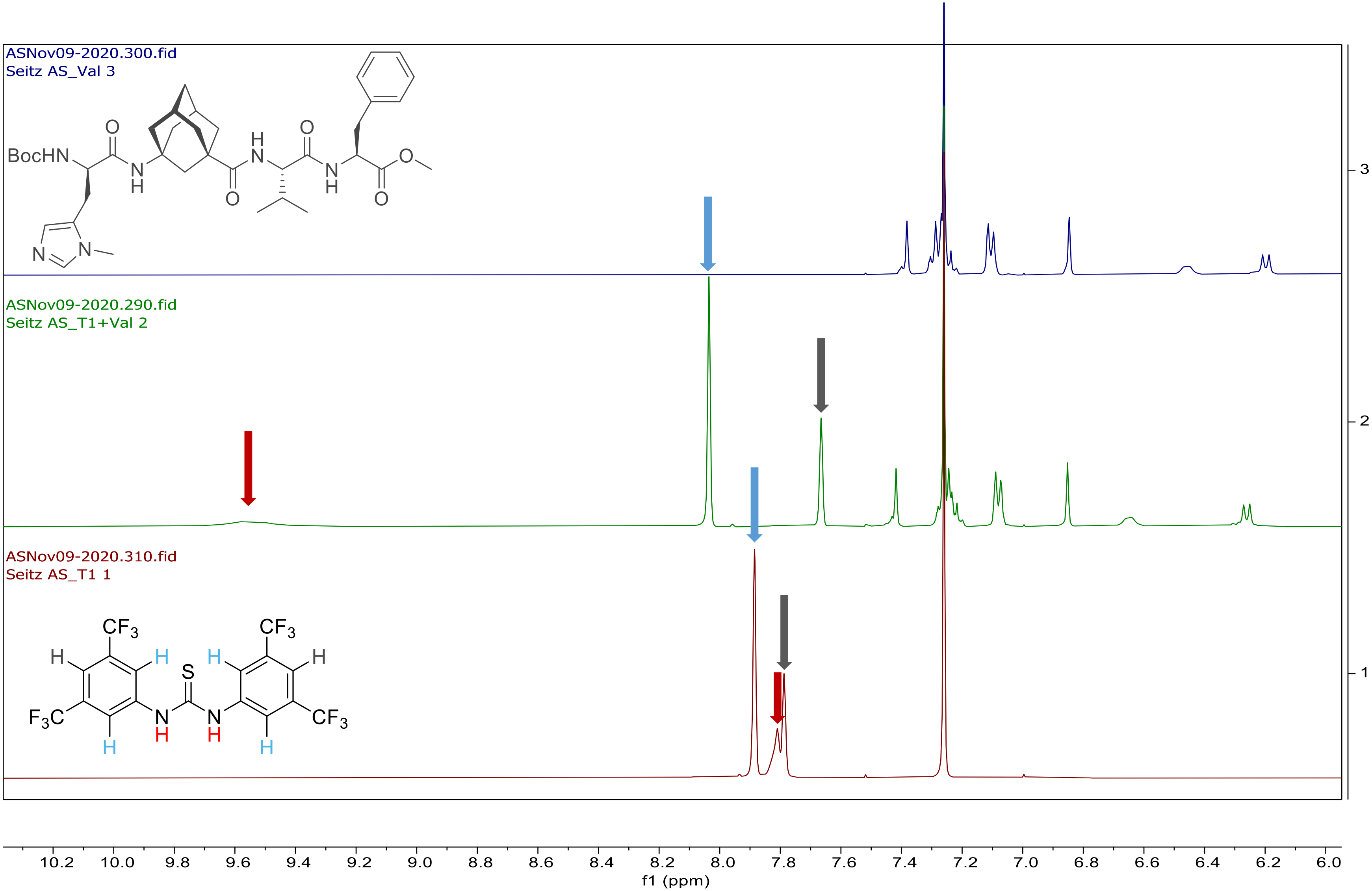
x mol% thiouracil: no conversion



2*O*Ac **3*O*Ac** **DiAc**

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 Experiments of T1 and Peptide Catalyst



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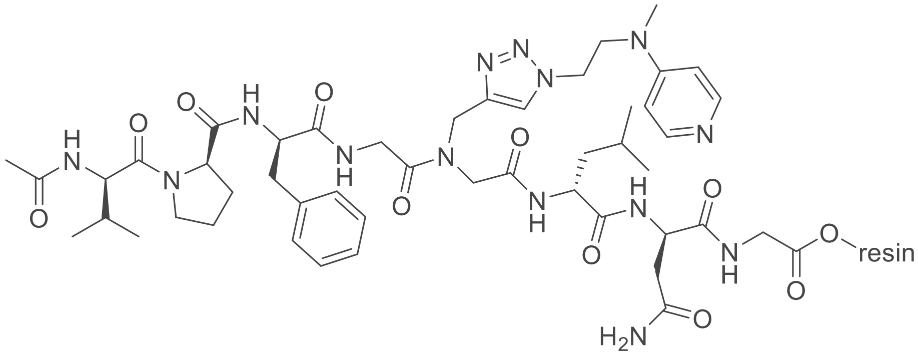
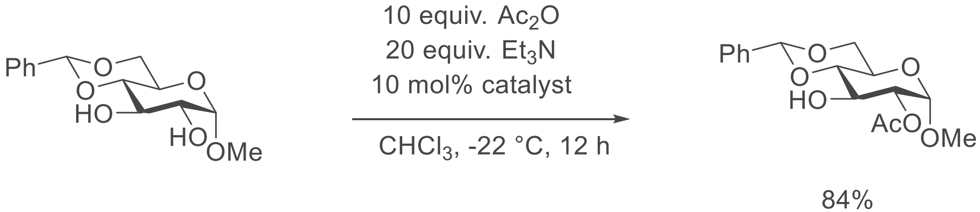
- Kirsch‘s group used DMAP based immobilized catalysts

- Preloaded Glycine Merrifield resin

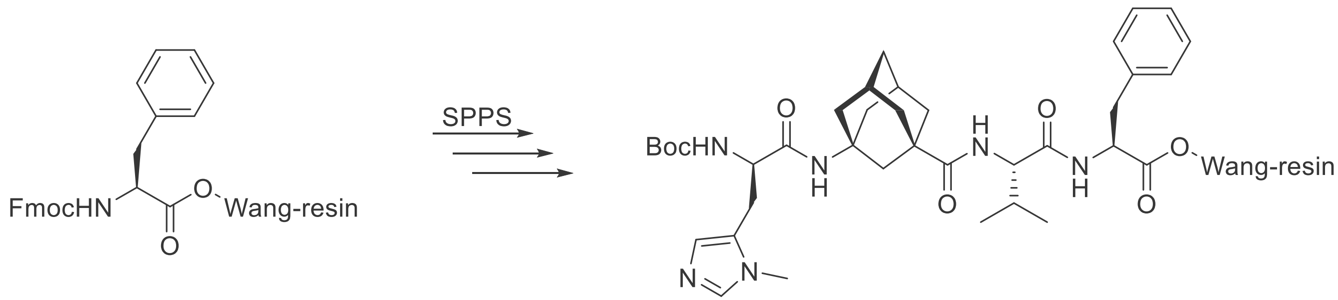




- Triethylamine (9 equiv.) can yield 80% of the desired product

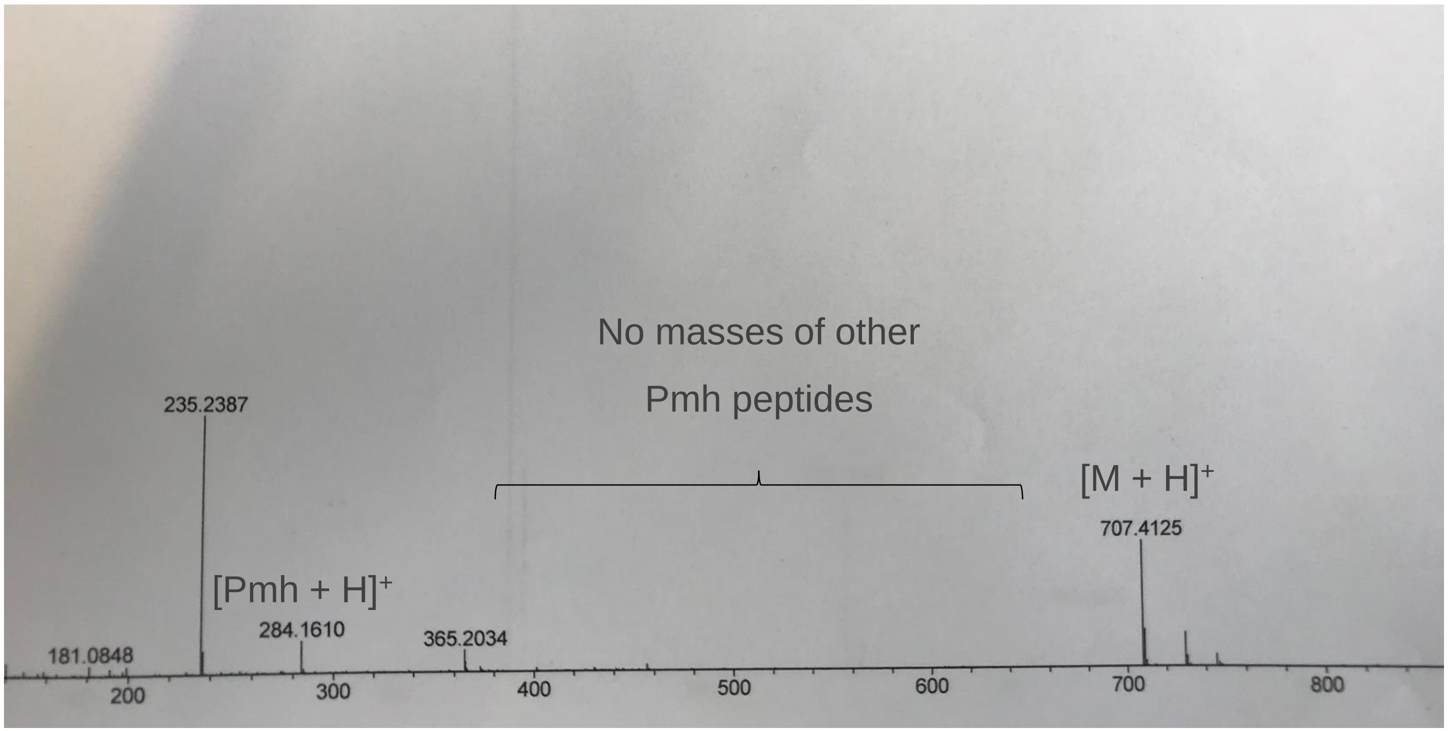
M. L. Tong, F. Huber, E. S. Taghuo Kaptouom, T. Cellnik, S. F. Kirsch, *Chem. Comm.* **2017**, *53* (21), 3068-3089; ; X.-A. Lu, C.-H. Chou, C.-C. Wang, S.-C. Hung, *Synlett* **2003**, 1364–1366.

SPPS to Immobilize Catalyst

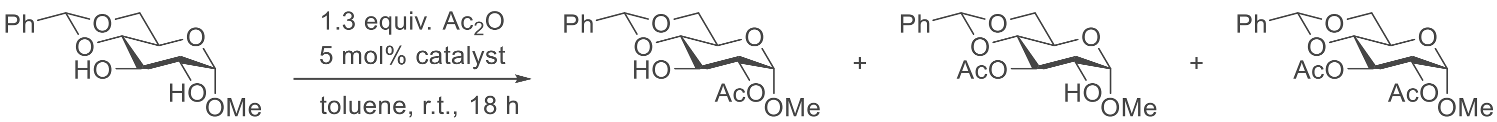


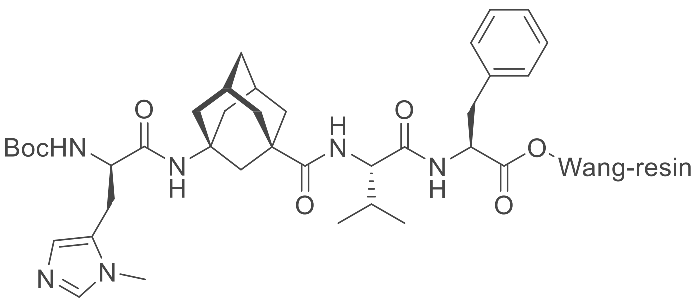
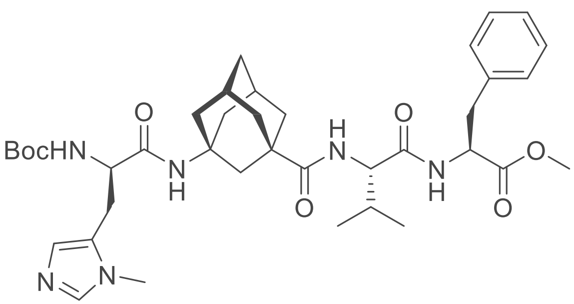
0.65 mmol/g

0.55 mmol/g



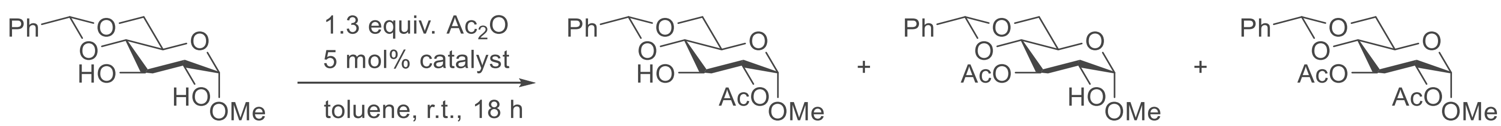
Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

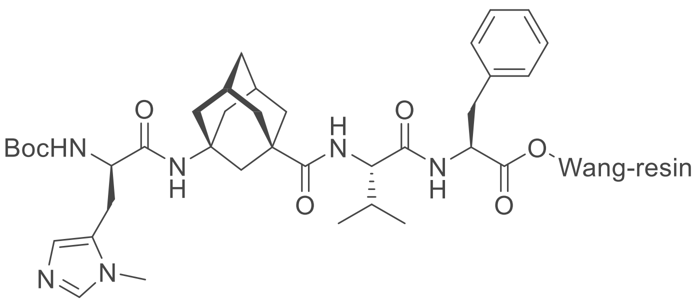
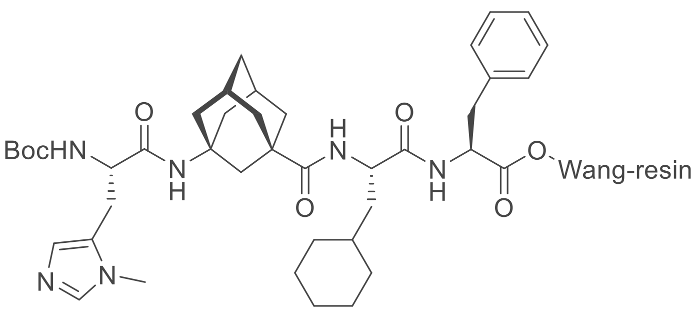


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
	58	29	7	94	62
	70	19	3	92	76
	81	17	1	>95 (DoE)[a]	82

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

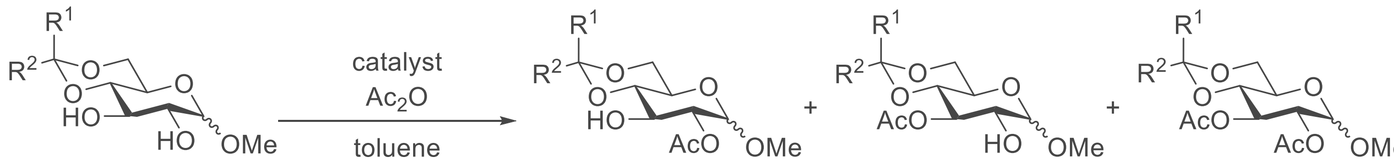
Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

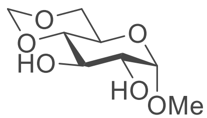


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
	58	29	7	94	62
	47	37	7	91	52

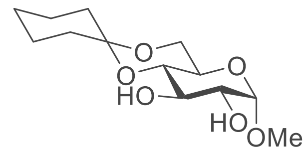
[a] conditions given by DoE: 20 mL toluene at 0 °C were used, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

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

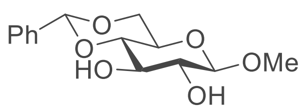




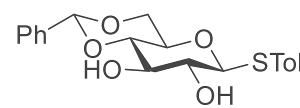
	C [%]	Selectivity[a] [%]
NMI	58	40
Peptide	>95	76
Immobilized	90	62



	C [%]	Selectivity[a] [%]
NMI	36	50
Peptide	64	86
Immobilized	77	71



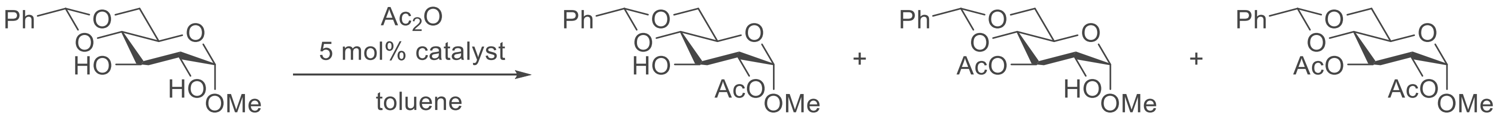
	C [%]	Selectivity[a] [%]
NMI	32	19
Peptide	75	28
Immobilized	20	40



	C [%]	Selectivity[a] [%]
NMI	62	35
Peptide	>95	53
Immobilized	89	48

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

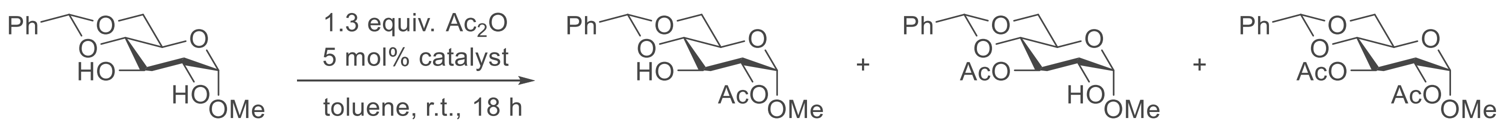
Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

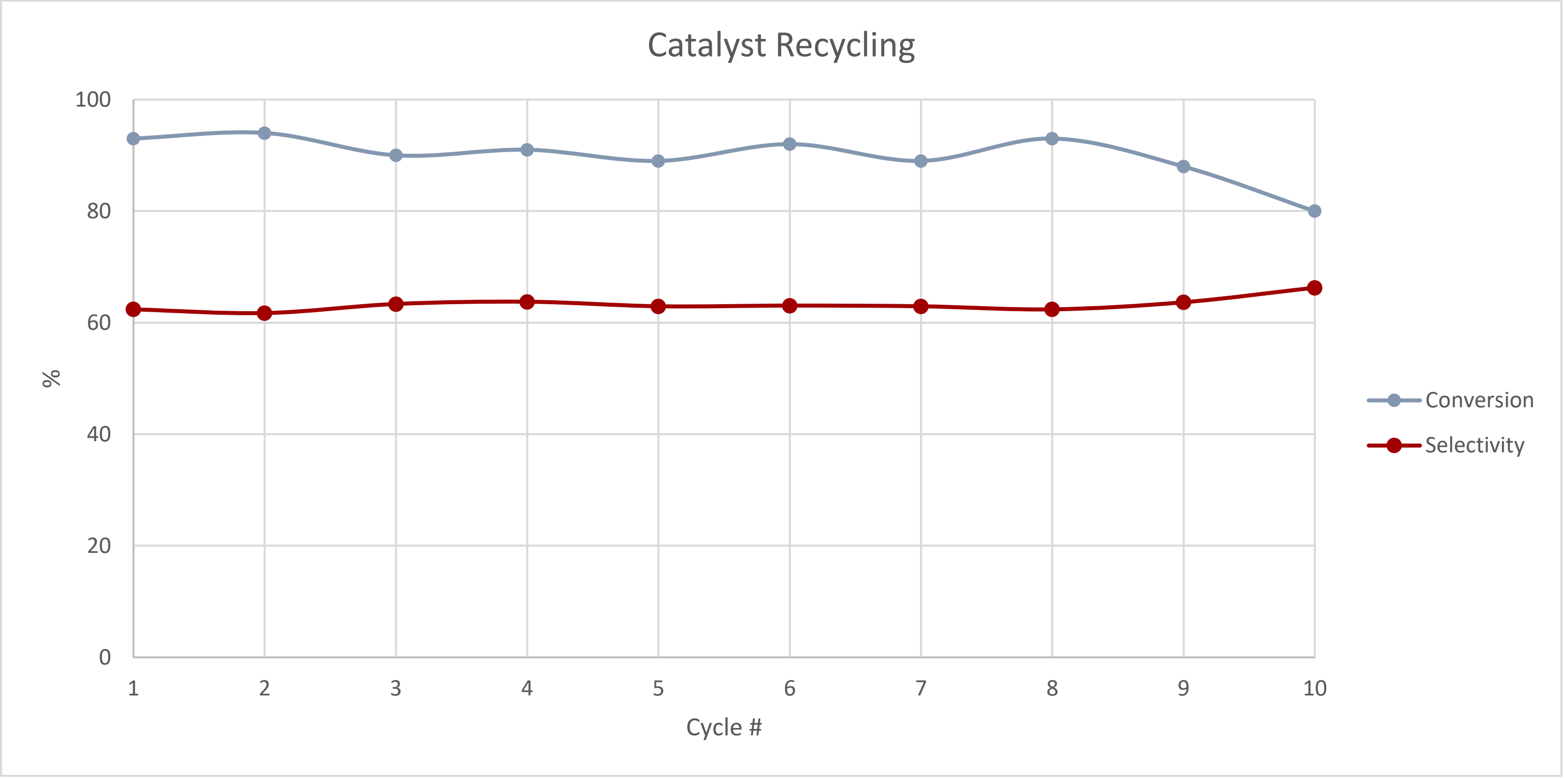


Conditions	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[a] [%]
10 mL toluene, rt, 18 h	58	29	7	94	62
10 mL toluene, 0 °C, 18 h	6	2	-	8	n.d.
20 mL toluene, rt, 18 h	49	23	3	75	65
2 mL toluene, rt 18 h	50	30	16	>95	52
2 mL toluene, 0 °C, 18 h	20	8	3	31	65
10 mL toluene, rt, 18 h, isobutyric anhydride	58	22	4	84	69

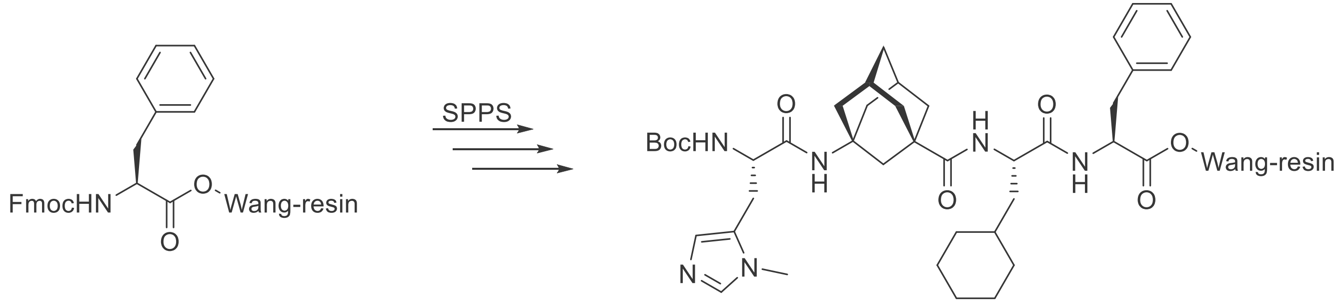
[a] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100.

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





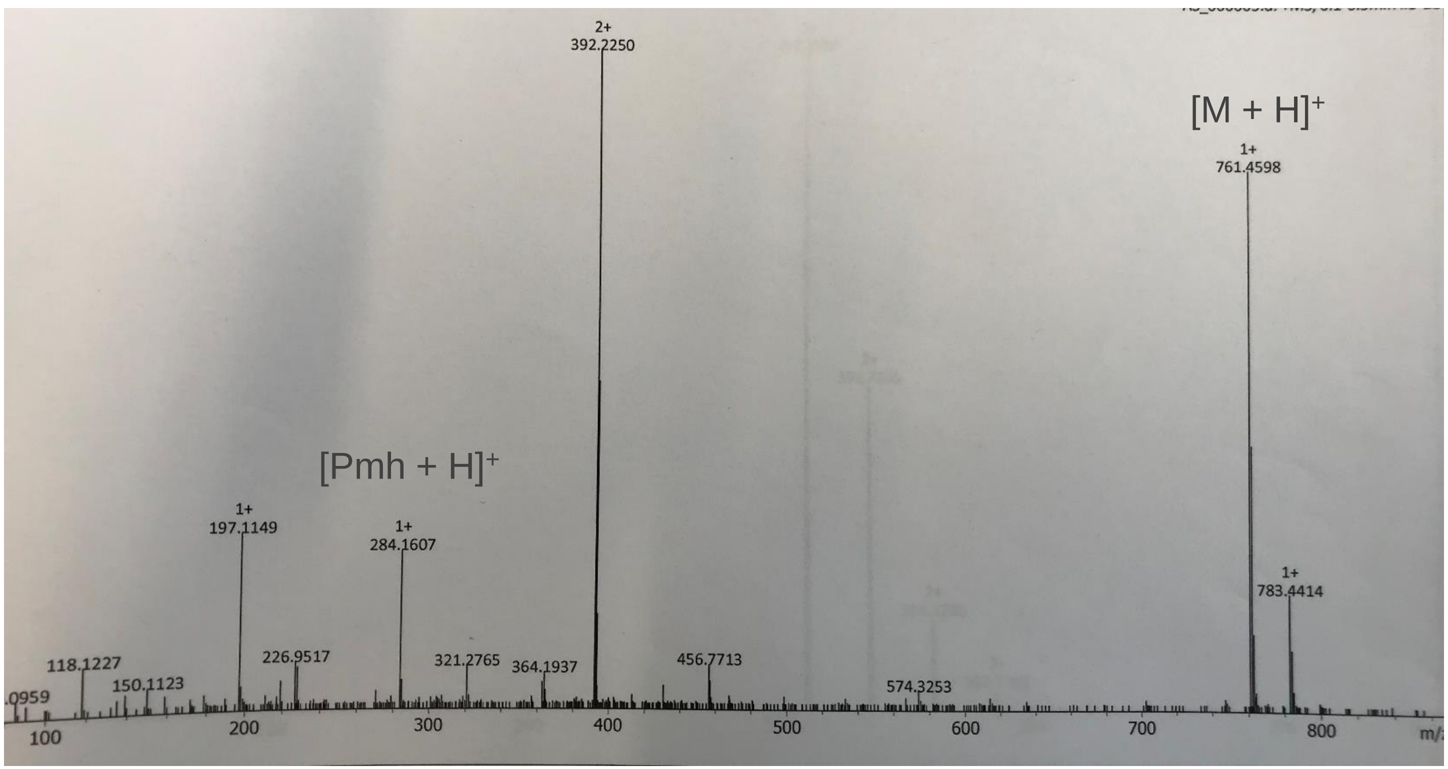
Immobilized CEM Catalyst



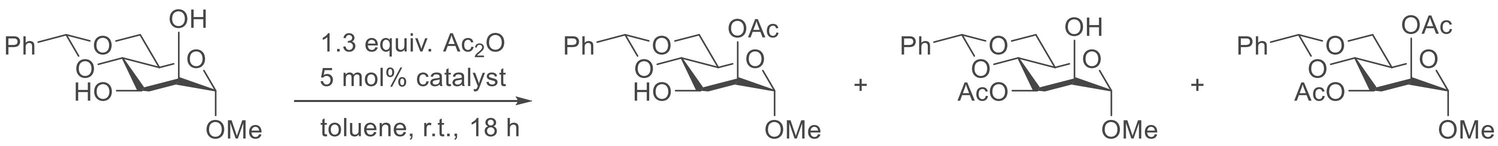
0.65 mmol/g

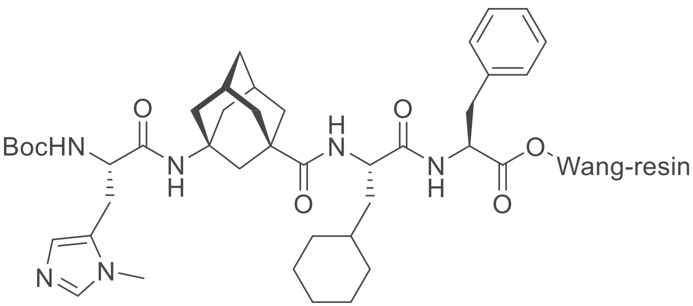
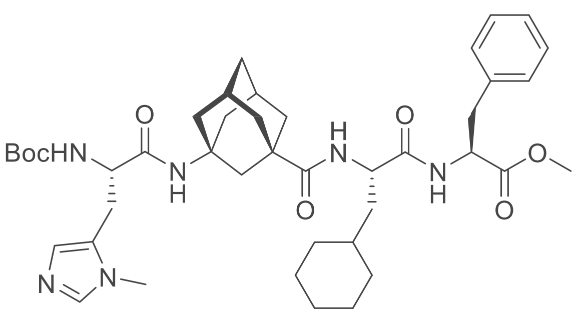
0.54 mmol/g

$[M + Na + H]^{2+}$



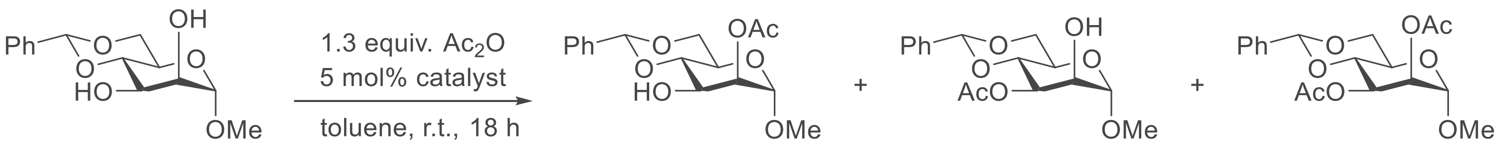
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

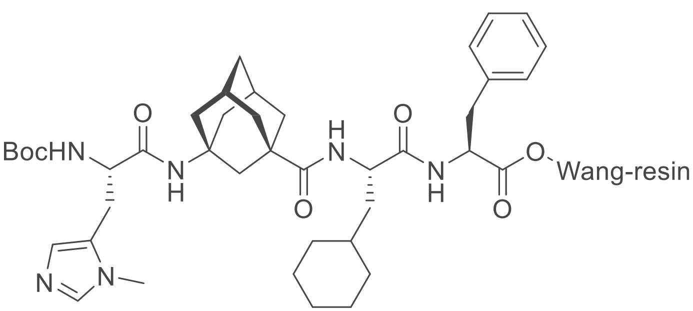
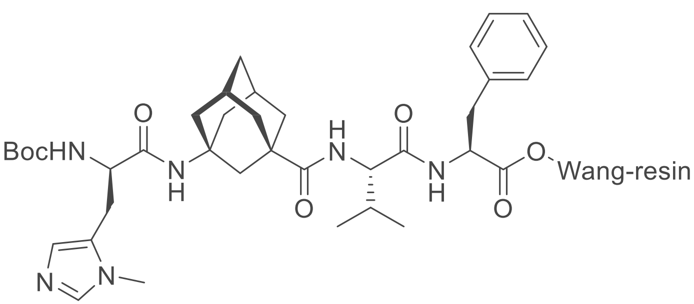


Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity[b] [%]
NMI (10mol%)	4	55	14	73	5 (75 for 3OAc)
	38	22	20	80	48
	41	21	15	77[c]	53[c]
	57	5	38	>95	57
	65	5	5	75[a]	87[a]

[a] conditions given by DoE: 10 mol% cat., 1 equiv. Ac_2O, 2 h, 20 mL toluene, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100, [c] 1.0 equiv. Ac_2O. A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

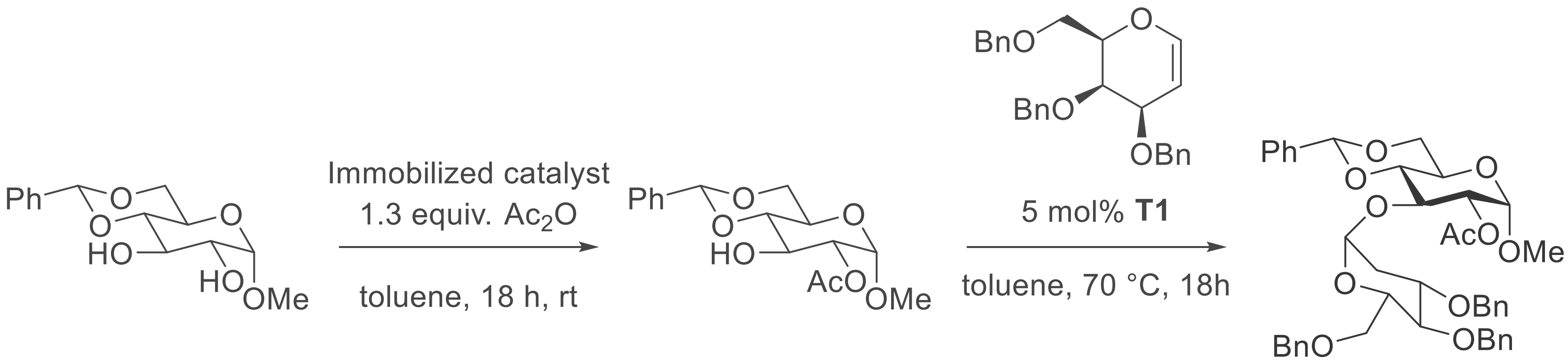
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside



Catalyst	2OAc [%]	3OAc [%]	Diac [%]	*C* [%]	Selectivity^{b} [%]
NMI (10mol%)	4	55	14	73	5 (75 for 3OAc)
	38	22	20	80	48
	41	21	15	77[c]	53[c]
	17	41	12	70	24

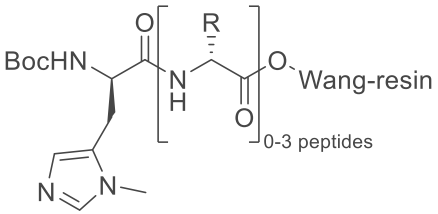
[a] conditions given by DoE: 10 mol% cat., 1 equiv. Ac_2O, 2 h, 20 mL toluene, [b] x = **2OAc**/(**2OAc**+**3OAc**+**DiAc**) × 100,
[c] 1.0 equiv. Ac_2O. A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, *86*, 3907–3922.

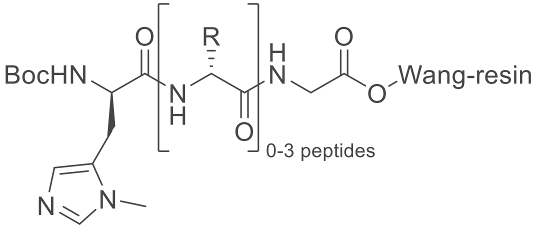
Multicatalytic Sequence – 2nd Try



- 10 mL toluene : 15% 2-OAc + 10% 3-OAc
- Polymer-T1, 10 mL toluene: 27% 2-OAc + 12 % 3-OAc
- 10 mL toluene + 2 mL DCM: 23% 2-OAc + 17% 3-OAc
- 10 mL toluene + 2 mL toluene 46% 2-OAc + 18% 3-OAc

- Synthesis and Investigation of smaller immobilized peptide catalyst





- Deeper look into the composition of immobilized cats (HPLC-MS ?)

- Find optimal and consistent conditions for glycosylation step

- Is Polymer-T1 suitable for repeating glycosylations ?

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

Thank you for your attention!