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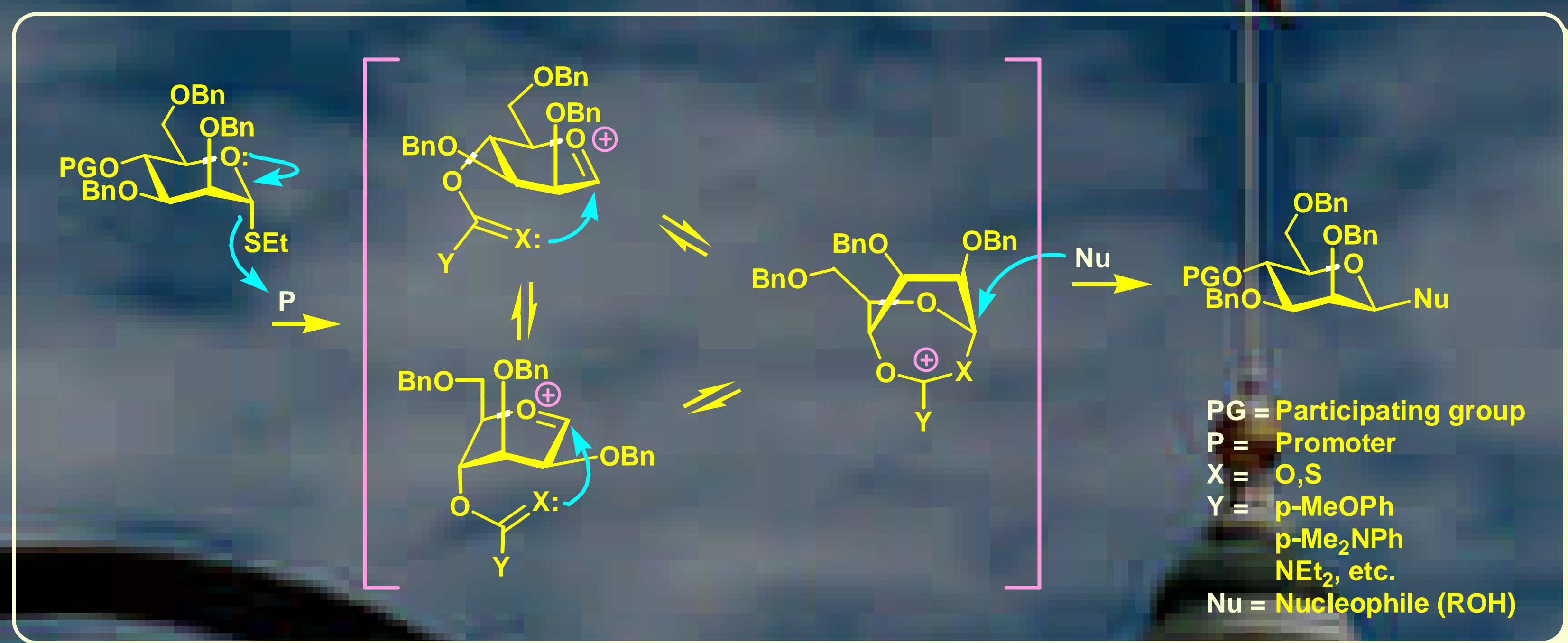
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**Introduction** The majority of carbohydrates found in nature exist as polysaccharides, glycoconjugates or glycosides in which monosaccharide units are joined together via *O*-glycosidic bonds. The necessity to form either 1,2-*cis* or 1,2-*trans* glycosidic bond with complete stereoselectivity is the main reason why chemical *O*-glycosylation is placed among the most challenging problems of modern synthetic chemistry. To address these challenges many new glycosyl donors have been developed. Highly efficient strategies for the oligosaccharide synthesis have become available. Methods for solid phase synthesis have been reported and these procedures often shorten oligosaccharide synthesis. However, all of these developments are compromised when applied to the stereoselective synthesis of  $\beta$ -mannosides, which are often present as components in a wide variety of natural compounds. Despite considerable progress made in the area [1,2], each particular case requires a careful selection of techniques, protecting groups and strategies [3].

As a part of a program to develop novel method for the synthesis of 1,2-*cis* glycosides [4] we report here our attempt to address the synthetic challenges associated with stereoselective  $\beta$ -mannosylation. We intended to demonstrate whether a participating group at C-4 of the glycosyl donor affects the stereochemical outcome of glycosidations of ethyl thiomannosides and SBox glycosides.

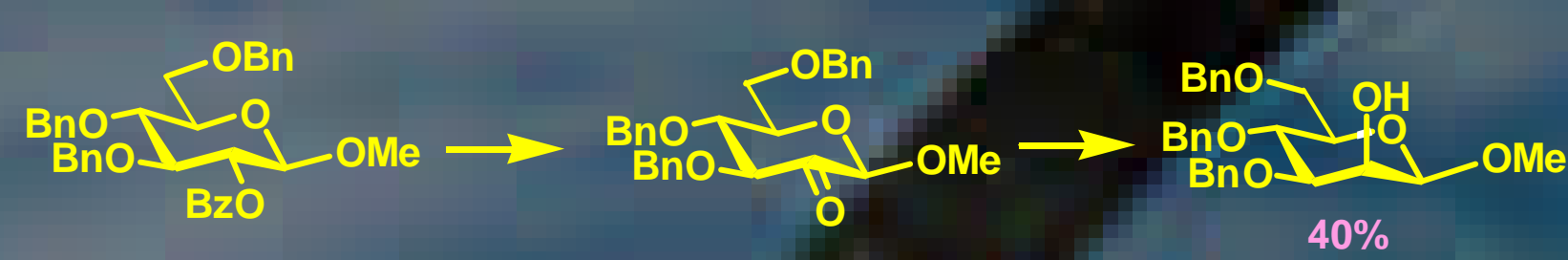
## The Idea



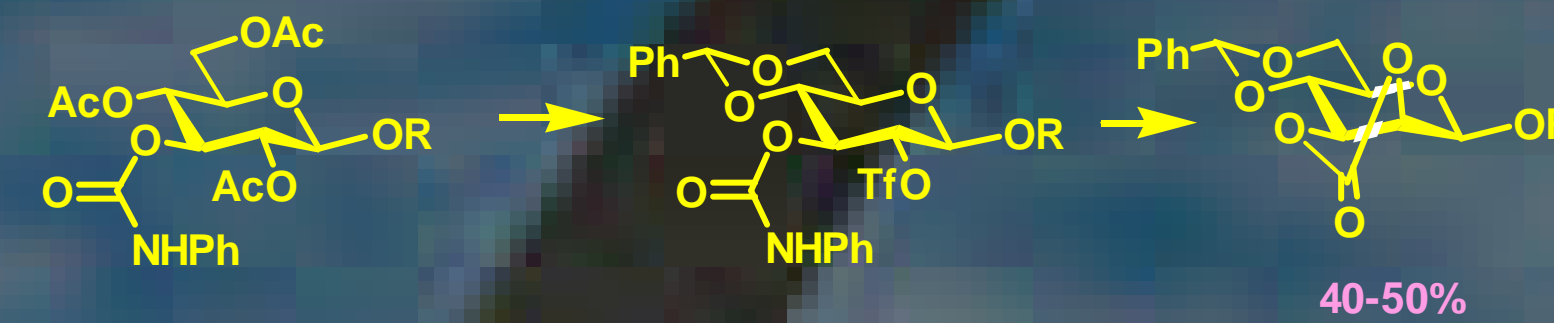
## Major Methods for the Synthesis of $\beta$ -Mannosides

### Epimerisation at C-2

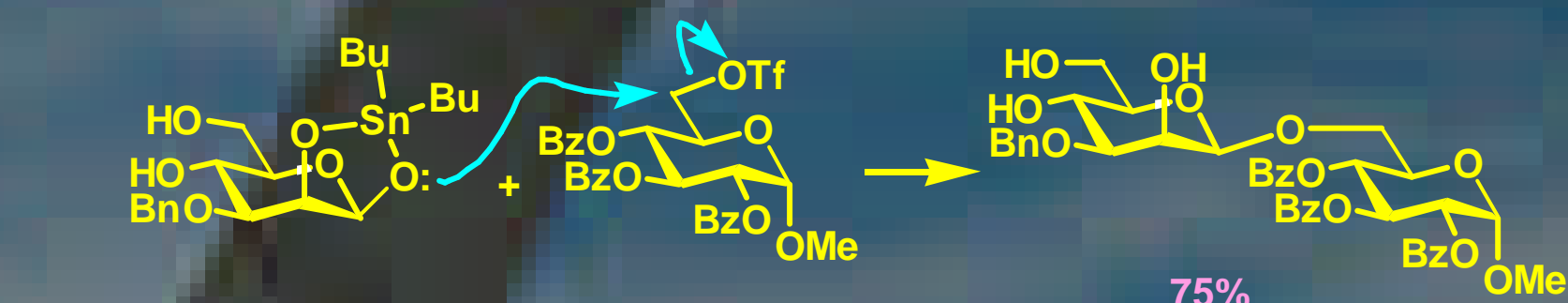
#### Oxidation-Reduction (Lindberg, 1972)



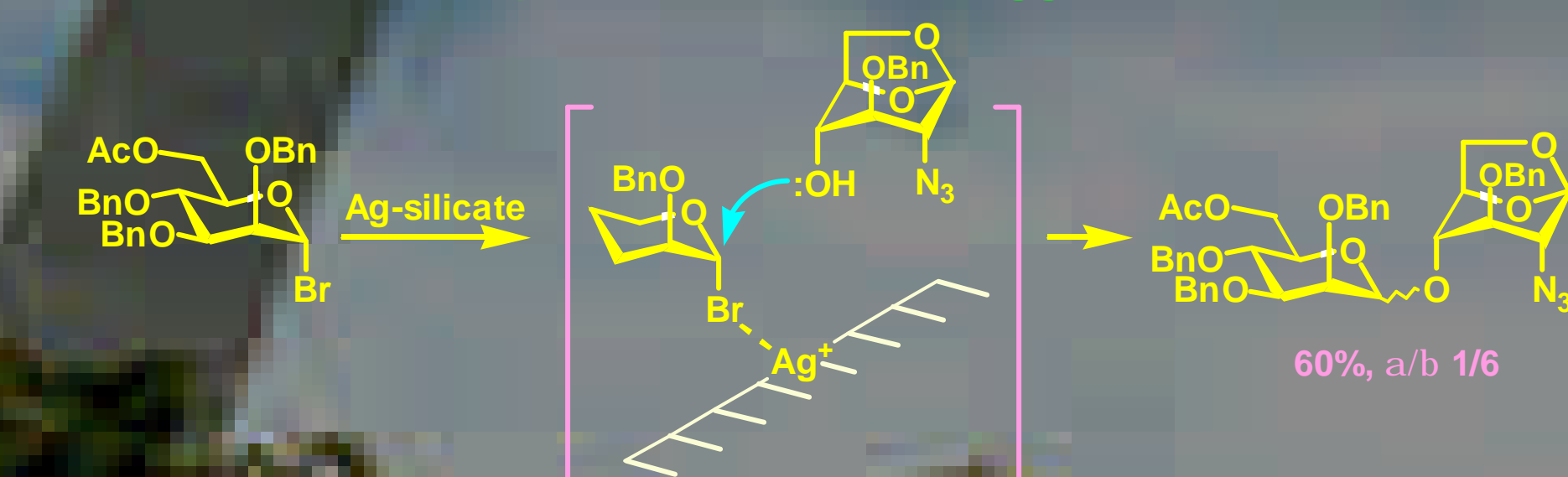
#### Nucleophilic Inversion (Miljkovic, 1974, Kunz, 1988)



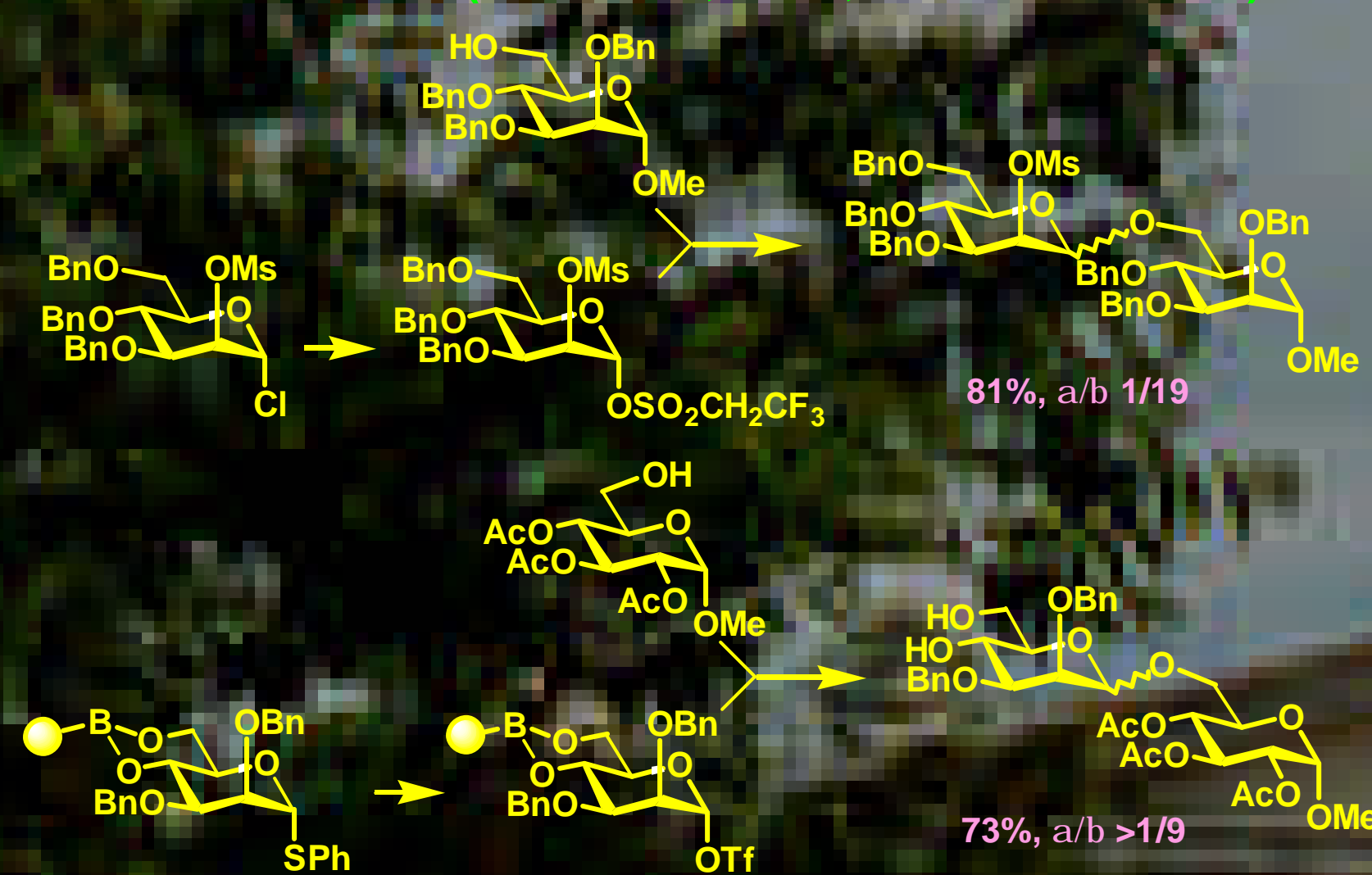
### Locked Anomeric Configuration (Schuerch, 1979; Kovac, 1997)



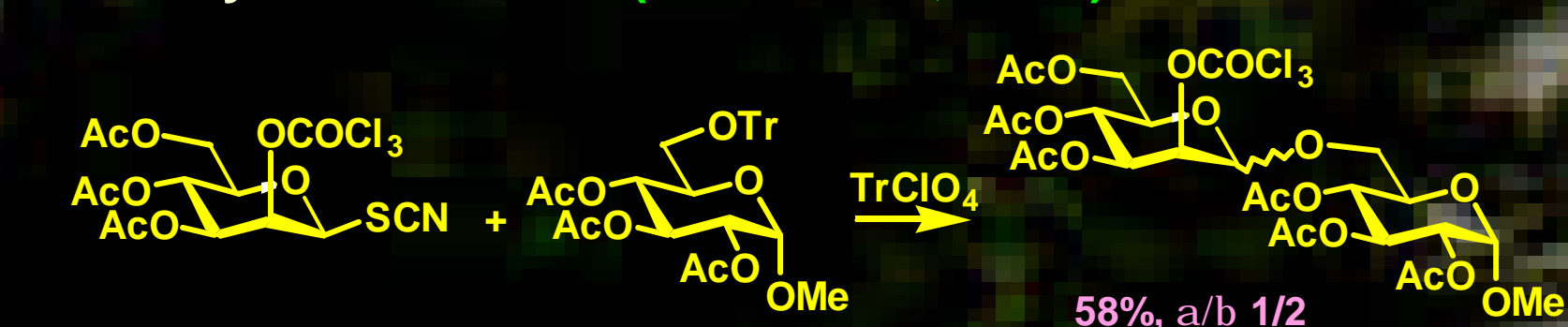
### Insoluble Promoters (Faulstich, 1981; Garegg, 1982; van Breeckel 1987)



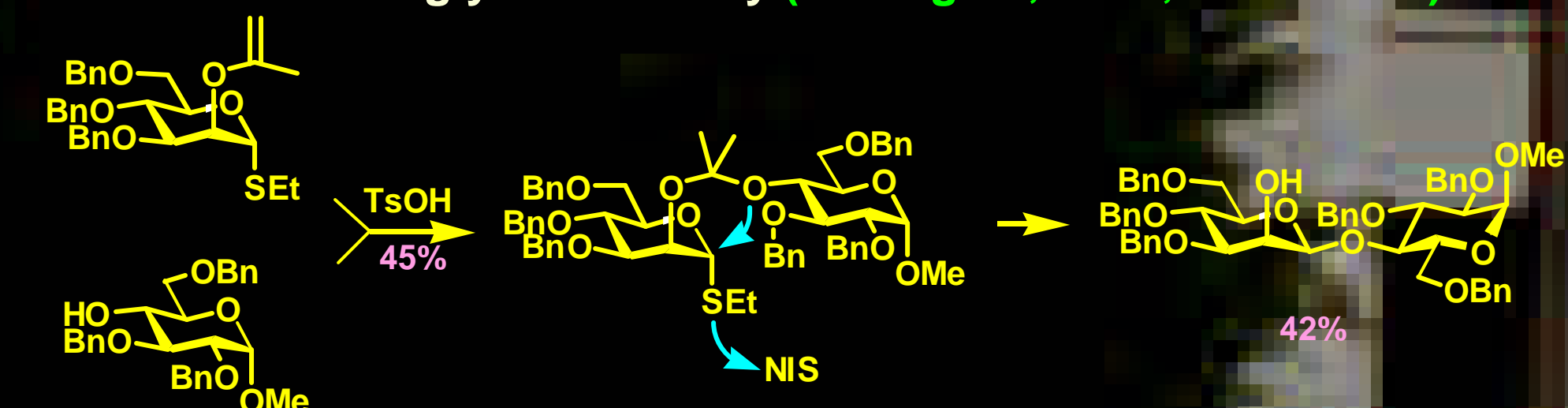
### Sulfonate Method (Schuerch, 1981; Chou, 1996-2003)



### Thiocyanate Method (Kochetkov, 1991)



### Intramolecular Aglycon Delivery (Hindsgaul, 1991; Stork, 1992)



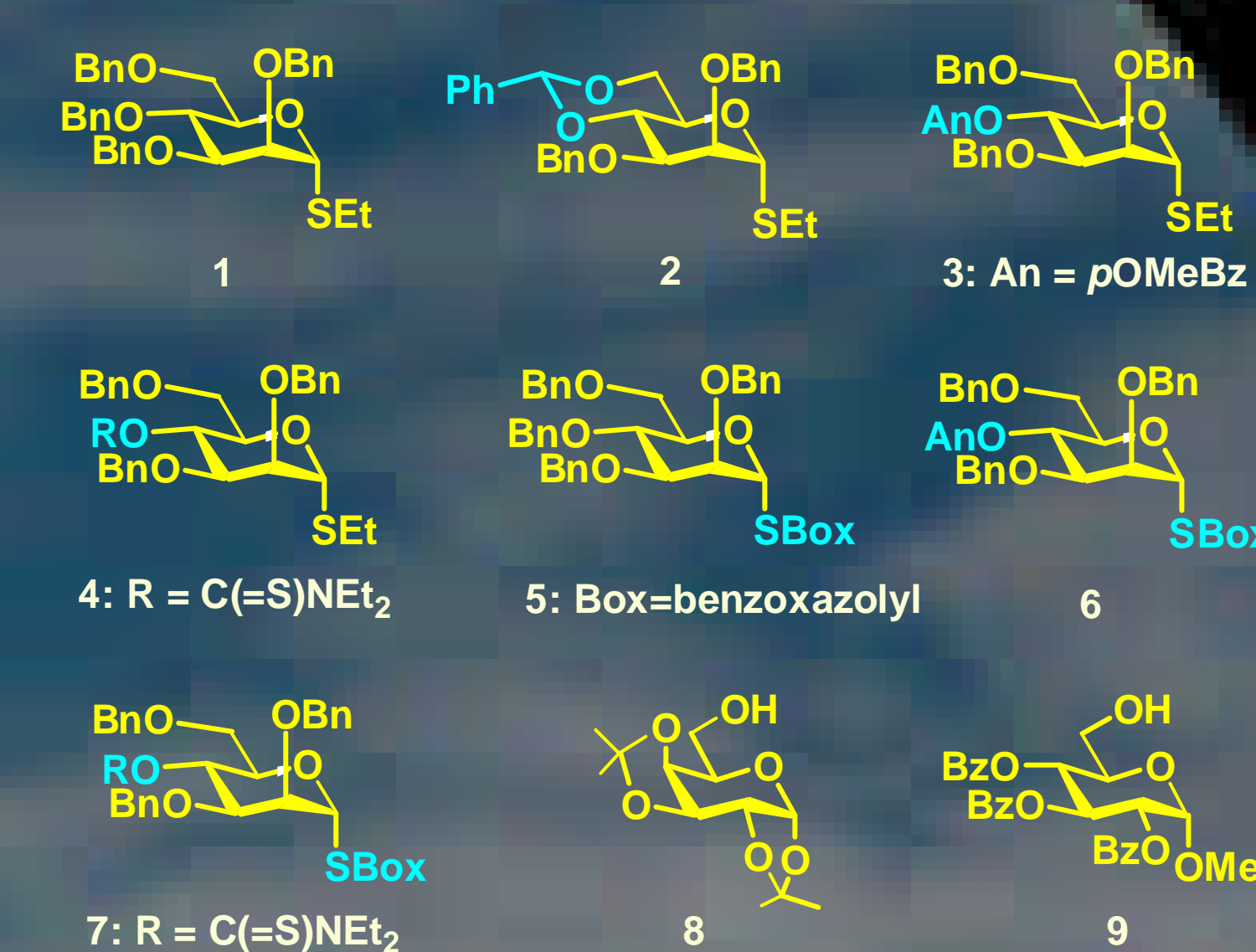
### Enzymatic Methods

#### Mannosidases (Crout, 1996)

#### Transferases (Flitsch, 1998)

## The Test

### Glycosyl Donors 1-7 and Glycosyl Acceptors 8,9



### Preliminary Glycosylations of 8 with 1-3

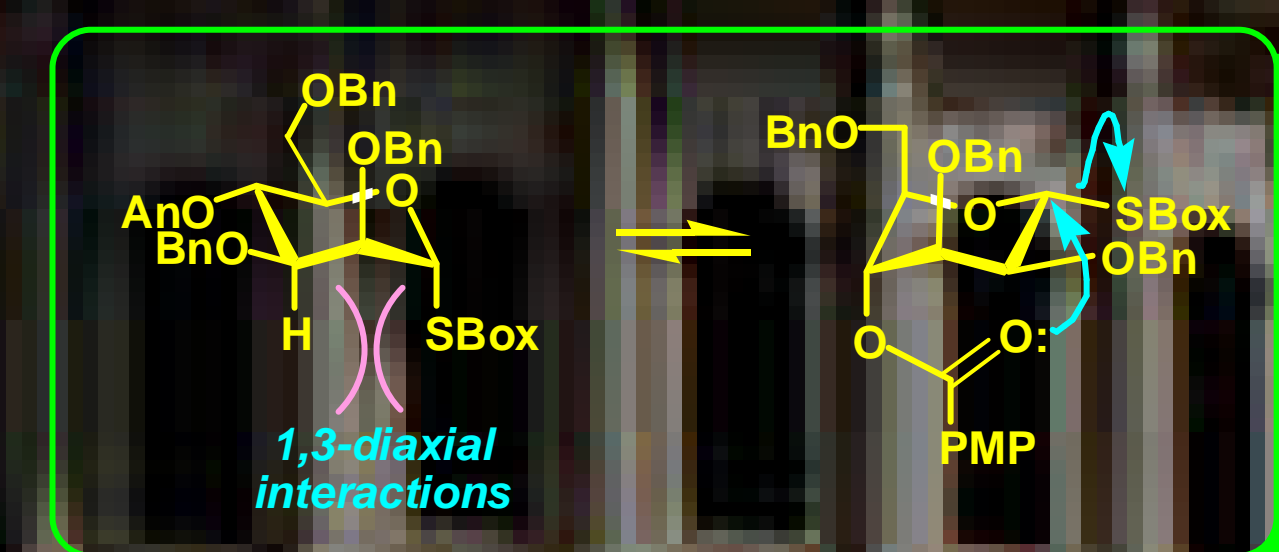
entry	donor	promoter	solvent	temper.	Yield%	a/b ratio
1	1	NIS/TMSOTf	DCM	ROOM	86	2.7/1
2	2	NIS/TMSOTf	DCM	ROOM	98	1/1.4
3	3	NIS/TMSOTf	DCM	ROOM	99	1.6/1
4	3	MeOTf	DCM	ROOM	70	1.2/1
5	3	NIS/TMSOTf	MeCN	ROOM	32	1.6/1
6	3	NIS/TMSOTf	DCM	-70	100	1/1.4
7	3	NIS/TMSOTf	DCM/Et <sub>2</sub> O	-70	88	2.7/1
8	3	NIS/TMSOTf	DCM/Tol.	-70	86	1/1.4

## The Hope

### Glycosylations of 9 with donors 1-7

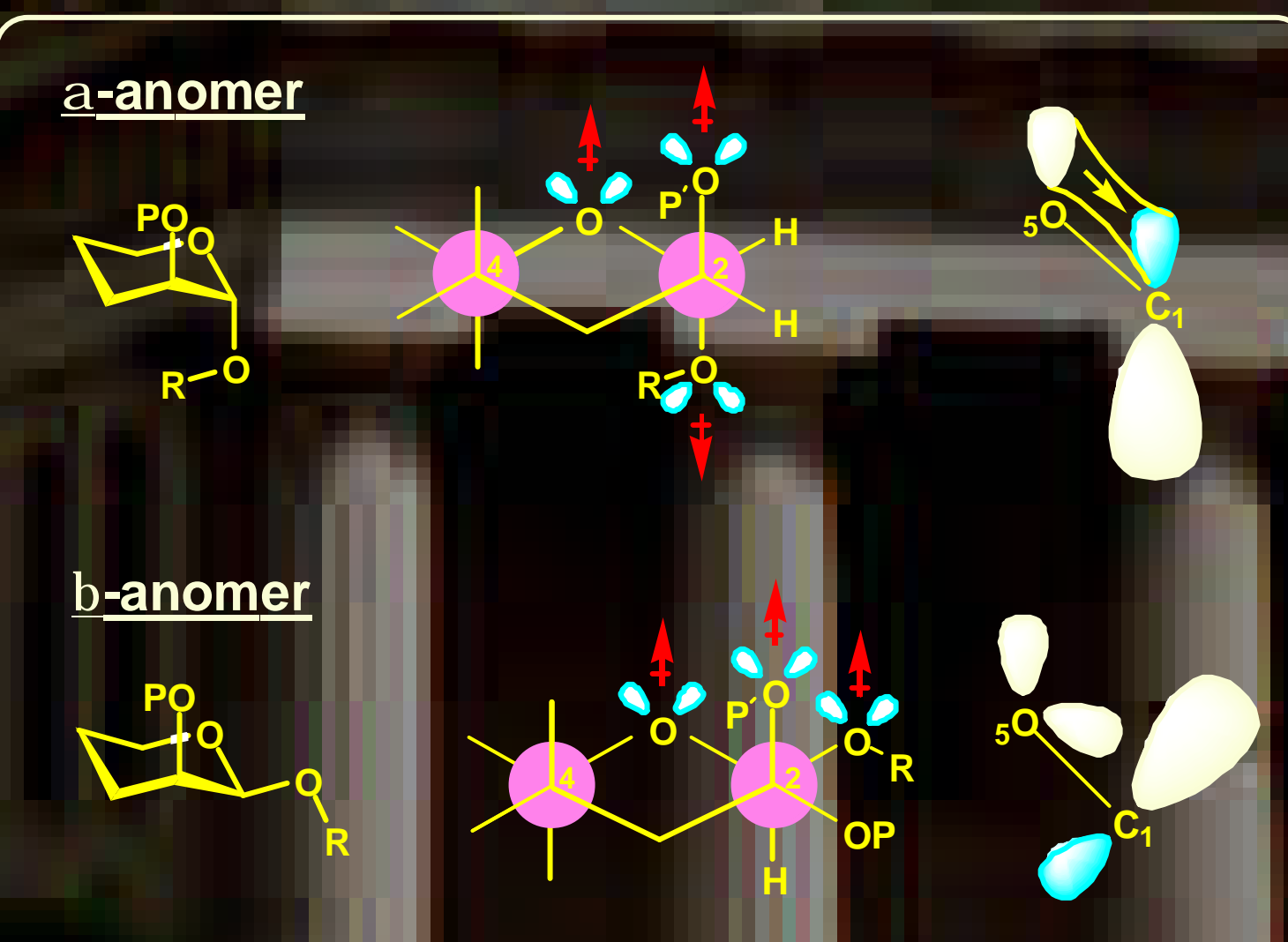
entry	donor	promoter	temper.	time	yield %	a/b ratio
1	1	NIS/TMSOTf	ROOM	5 min	98	1.6/1
2	1	IDCP	ROOM	16 hrs	75	1.5/1
3	2	IDCP	ROOM	16 hrs	35	2.1/1
4	3	NIS/TMSOTf	ROOM	1hr	99	1.2/1
5	4	NIS/TMSOTf	ROOM	1hr	63	1/1.1
6	1	NIS/TMSOTf	-70-0	2 hrs	99	1/1.2
7	4	NIS/TMSOTf	-70-ROOM	16 hrs	64	1/1.5
8	1	NIS/TMSOTf <sup>a</sup>	-70-20	3hrs	95	1/1.7
9	3	NIS/TMSOTf <sup>a</sup>	-70	3hrs	99	1/2.1
10	1	NIS/TMSOTf <sup>b</sup>	-70	5 hrs	61	1.3/1
11	2	NIS/TMSOTf <sup>b</sup>	-70	6 hrs	43	1/3
12	3	NIS/TMSOTf <sup>b</sup>	-70	3 hrs	69	1/1.5
13	5	AgOTf	-20-ROOM	5 min	65	1.5/1
14	5	MeOTf	-20-ROOM	16 hrs	72	2.2/1
15	6	AgOTf	-20-ROOM	5min	83	1/1.3
16	6	MeOTf	-70-ROOM	16 hrs	96	1/1.1
17	6	NIS/TMSOTf	-70-5	4hrs	57	1/1.2
18	7	NIS/TMSOTf	0-ROOM	16 hrs	66	1/1.3
19	7	AgOTf	-70-ROOM	16 hrs	82	1/2.3

### Expected SBox Glycoside Effect



Notes: a – promoter was added first followed by immediate addition of the acceptor; b – promoter was added first and reaction was monitored by TLC, the acceptor was added only upon complete disappearance of donor

### $\beta$ -Mannosides vs. $\alpha$ -Mannosides



## Acknowledgement



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### Ph.D. Program Applications

are invited and accepted throughout the year; Please visit <http://www.umsl.edu/chemistry> for additional information or contact Professor A.V. Demchenko directly at [demchenkoa@umsl.edu](mailto:demchenkoa@umsl.edu)