XU LAB
Innovation through Catalysis

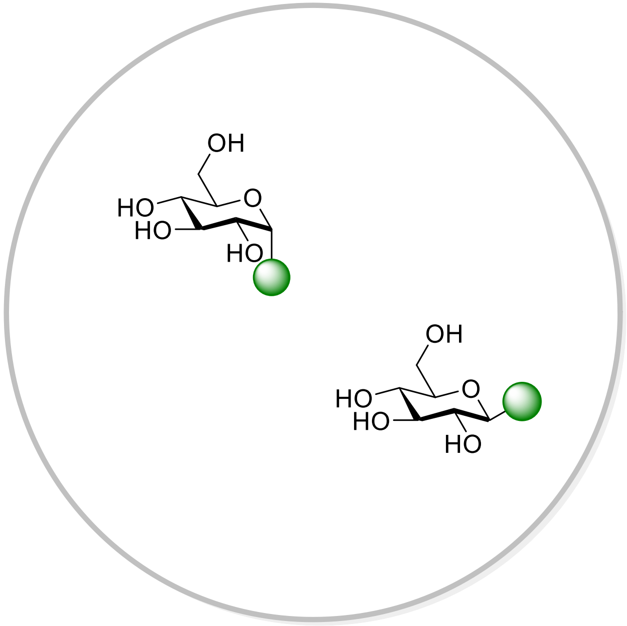
北京大学
PEKING UNIVERSITY

XU GROUP
Department of Chemistry, Peking University

Selected Weekly Literature Presentations

Disclaimer:
These slides contain personal interpretations and may include errors or subjective views.

Stereoselective Chemical Glycosylation Reactions



Yinyan Su

Group meeting

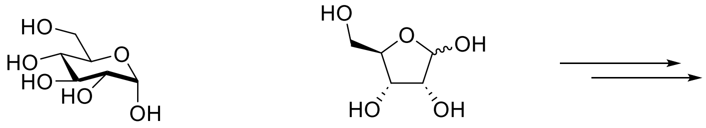
2025.3.15

Catalog

- Background
- Reactions
    - Glycosyl Electrophiles as Donors
    - Glycosyl Nucleophiles as Donors
    - Glycosyl Radical Precursors as Donors
- Conclusion and Perspective

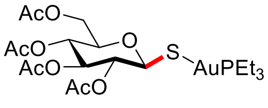
Glycosides

monosaccharide

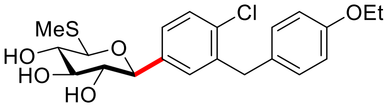


$CO_2 + H_2O$

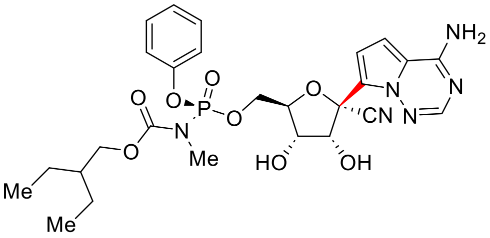
glycoside



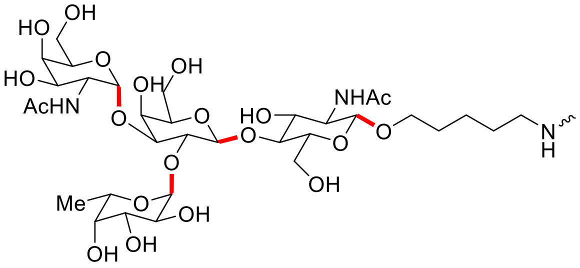
Auranofin

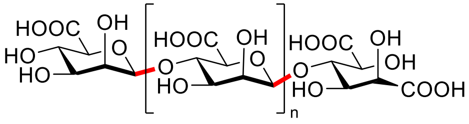


Sotagliflozin



Remdesivir

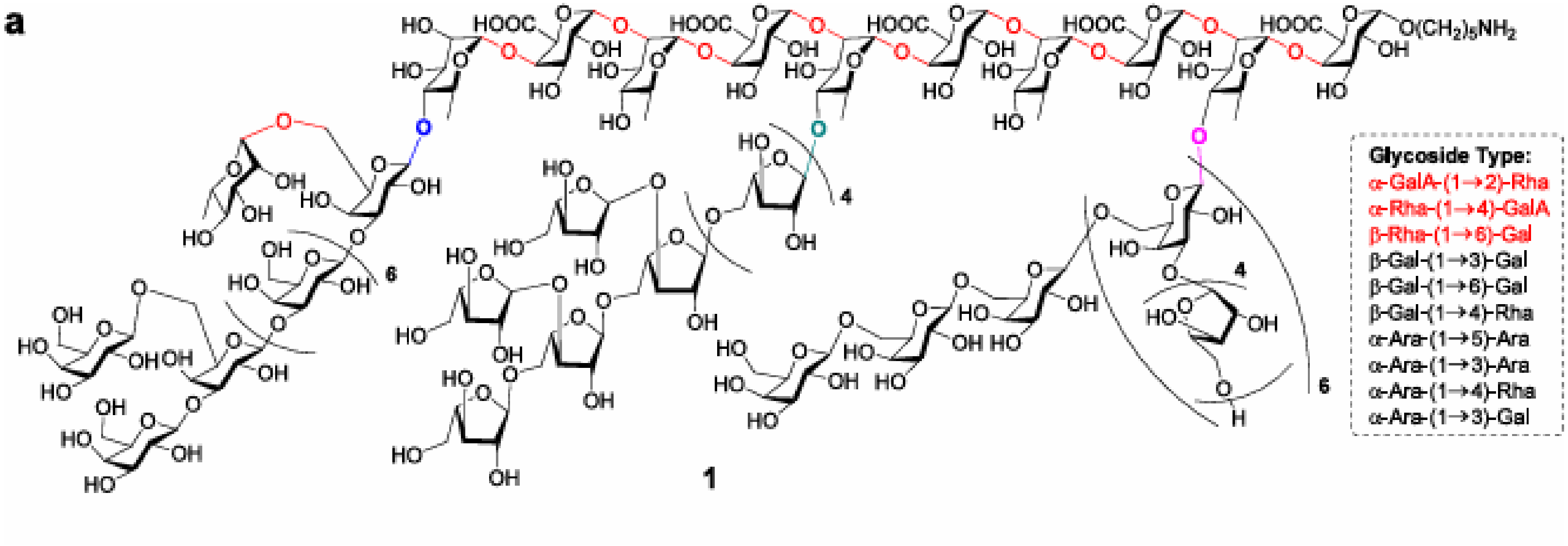




GV-971

Glycoside: Diverse physiological functions

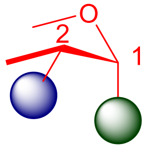
Why Stereoselective



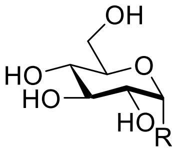
- 2^{40} isomers?

Tiehai Li, et al. *J. Am. Chem. Soc.* **2025**, 147, 8422−8432.

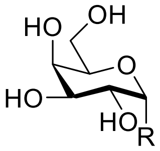
Major Types of O-glycosides



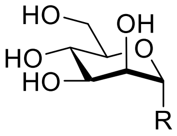
1,2-cis



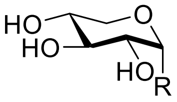
α-D-Gluco-pyranoside



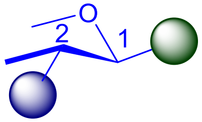
α-D-Galacto-pyranoside



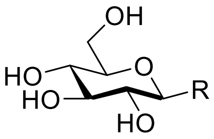
α-D-Manno-pyranoside



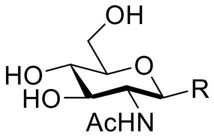
α-D-Xylo pyranoside



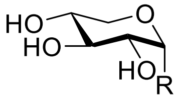
1,2-trans



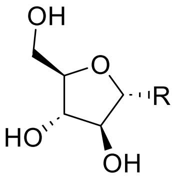
β-D-Gluco-pyranoside



2-Acetamido-2-deoxy β-D-glucopyranose

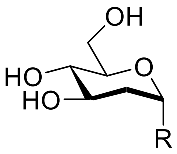


β-D-Xylo-pyranoside

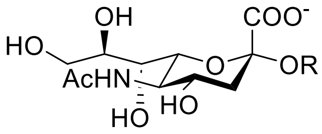


α-D-Arabino-furanoside

classified as α or β only



2-Deoxy-α-D-glucopyranoside

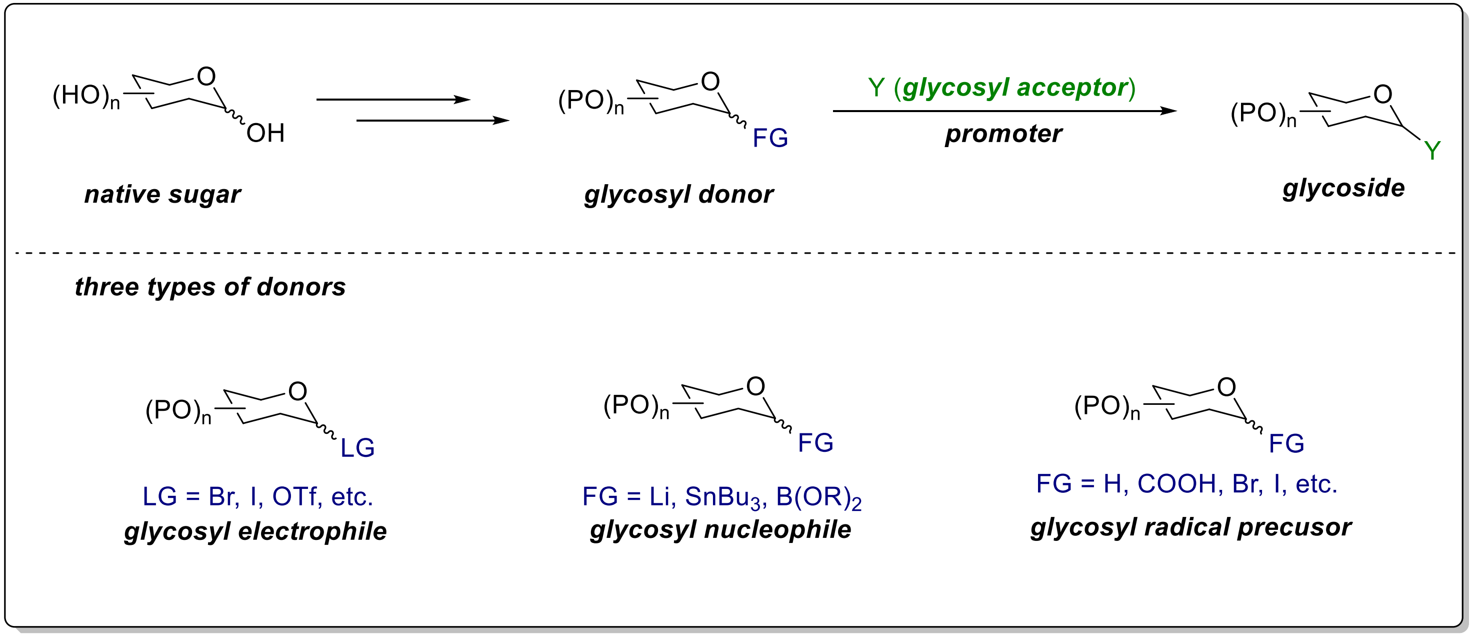


α-Sialoside

- Synthetic difficulty: *1,2-cis > 1,2-trans*

Alexei V. Demchenko, et al. *Chem. Sci.* **2015**, 6, 2687–2704.

Outline of Chemical Glycosylation



native sugar ***glycosyl donor*** ***glycoside***

three types of donors

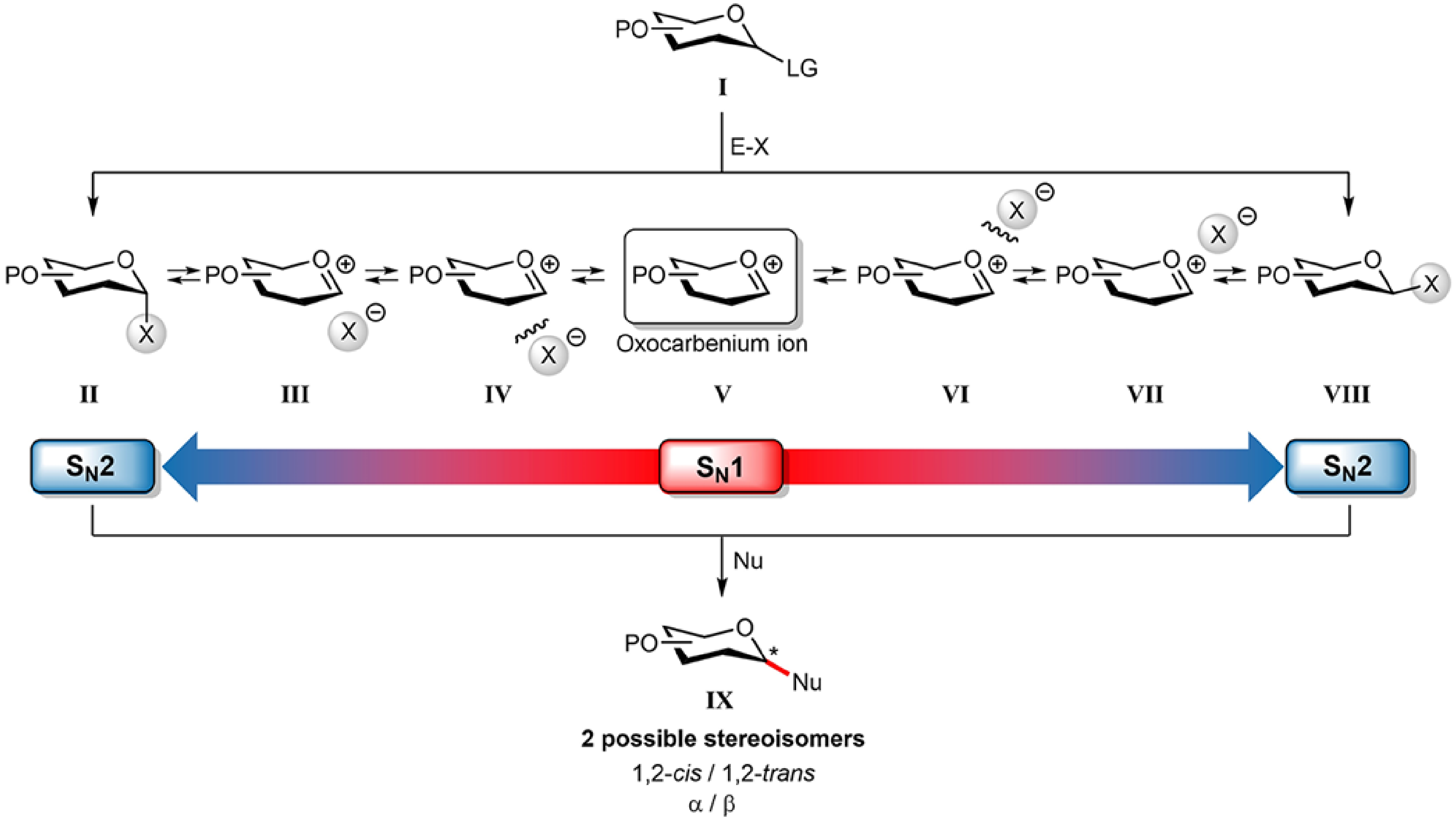
LG = Br, I, OTf, etc.
glycosyl electrophile

FG = Li, $SnBu_3$, $B(OR)_2$
glycosyl nucleophile

FG = H, COOH, Br, I, etc.
glycosyl radical precusor

- Differ in strategies to selectivity and application

Glycosyl Electrophiles as Donors



2 possible stereoisomers

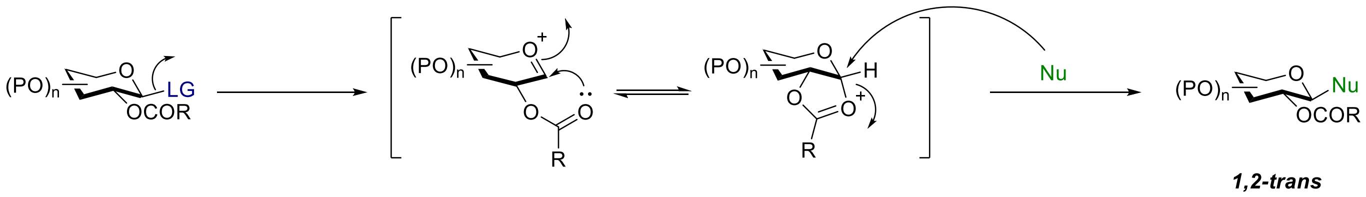
1,2-*cis* / 1,2-*trans*

α / β

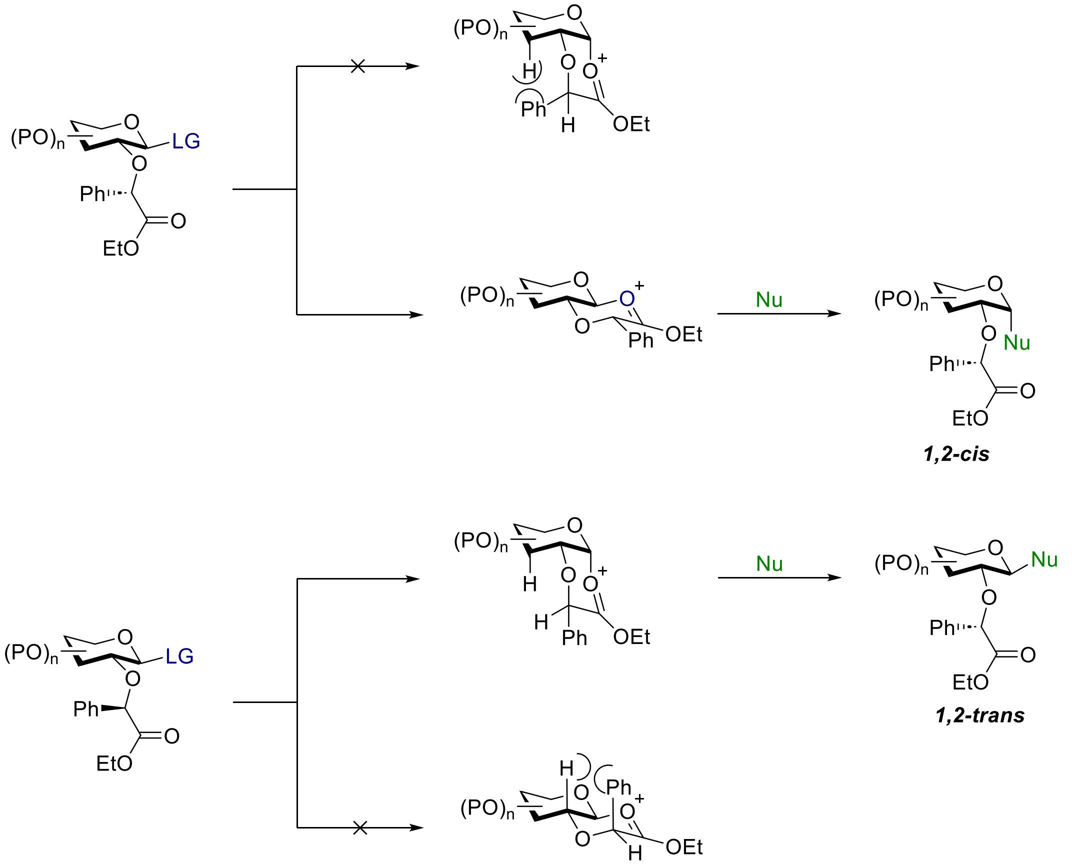
Jeroen D. C. Codee, et al. *ACS Cent. Sci.* **2019**, 5, 781−788.

Participating Protecting Group at C-2

particapating group at C-2

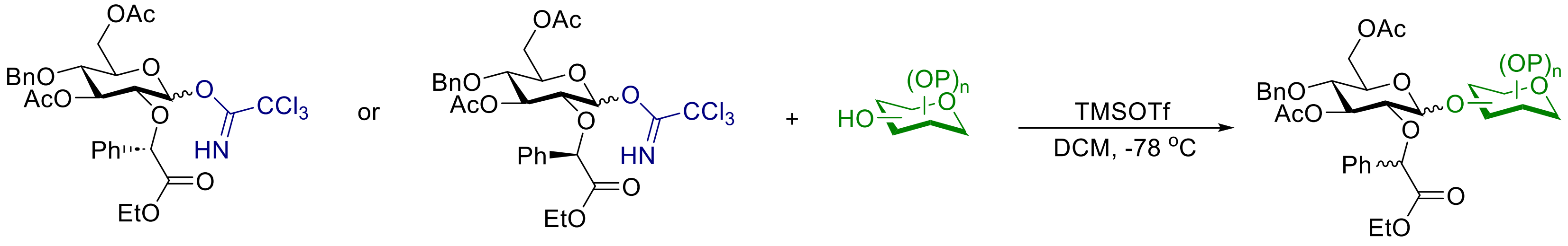


1,2-cis ? ***controlled by particapating group***



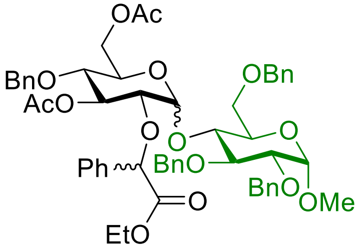
Geert-Jan Boons, et al. *Angew. Chem. Int. Ed.* **2005**, 44, 947-949.

Participating Protecting Group at C-2

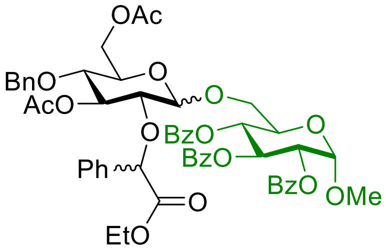


α or β

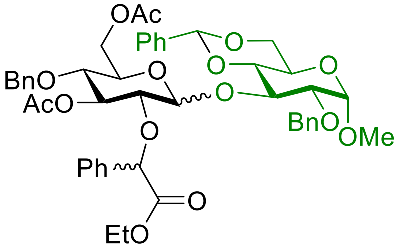
Selected Examples



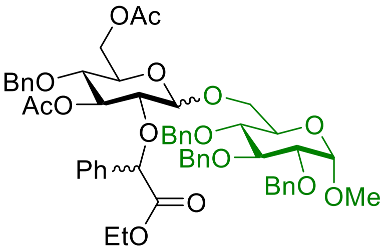
S: 95%, *α*:*β* = 20:1
R: 93%, *α*:*β* = 1:5



S: 94%, *α*:*β* = 18:1
R: 89%, *α*:*β* = 1:1



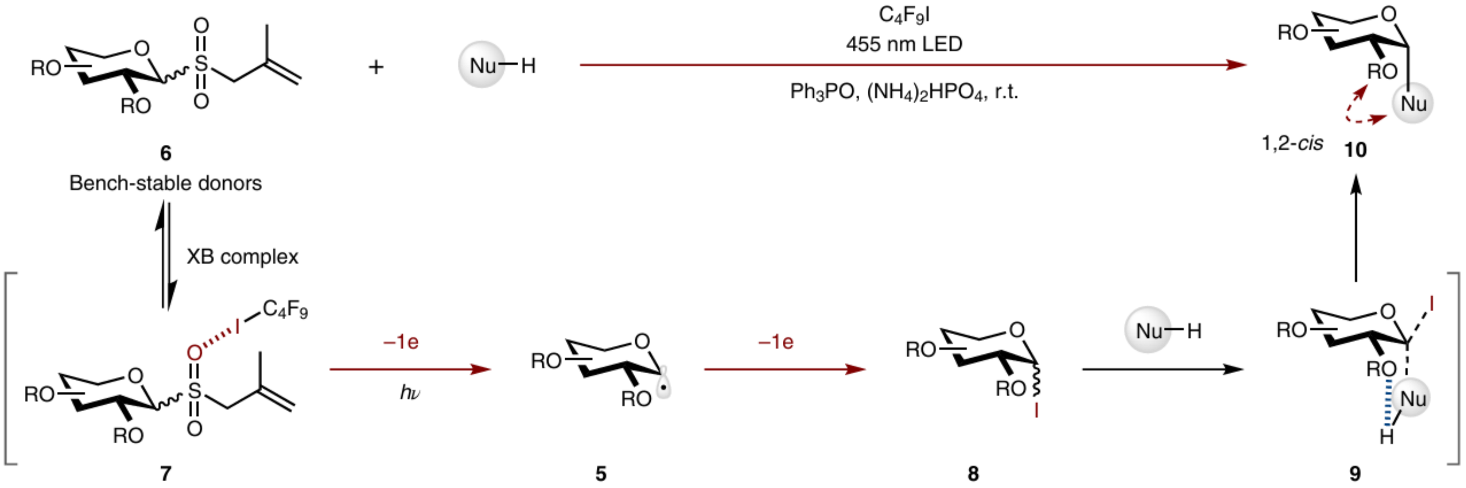
S: 92%, *α*:*β* = 12:1
R: 88%, *α*:*β* = 1:3

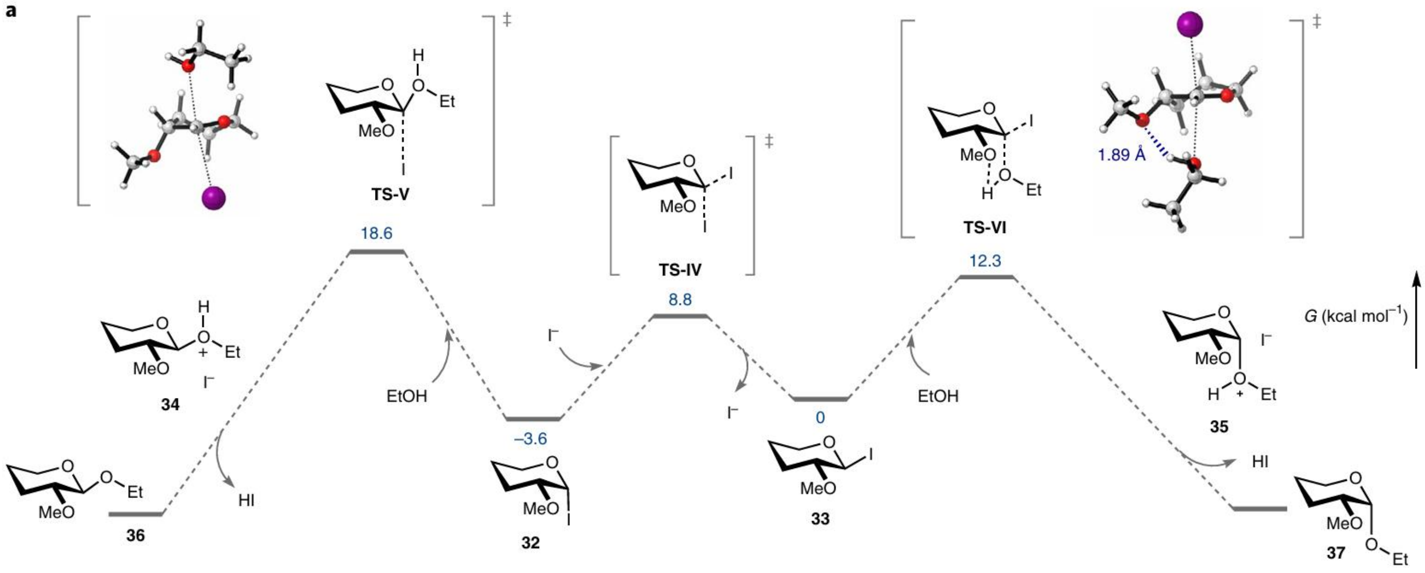


S: 94%, *α*:*β* = 4:1
R: 89%, *α*:*β* = 1:8

Geert-Jan Boons, et al. *Angew. Chem. Int. Ed.* **2005**, 44, 947-949.

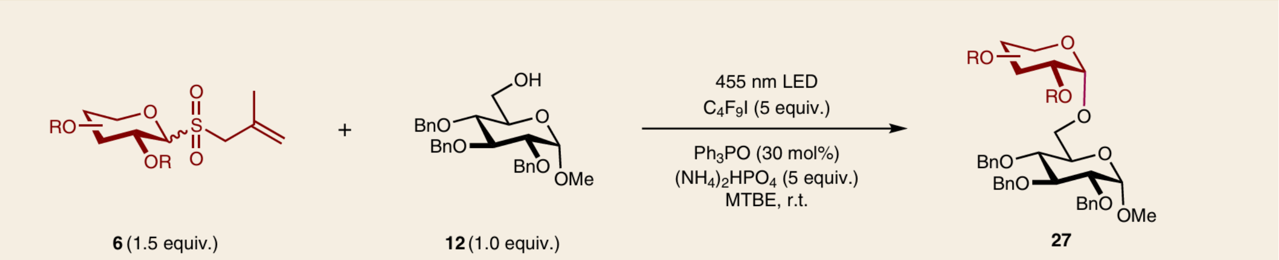
Directing Group at C-2





Dawen Niu, et al. *Nat. Chem.* **2022**, 14, 686-694.

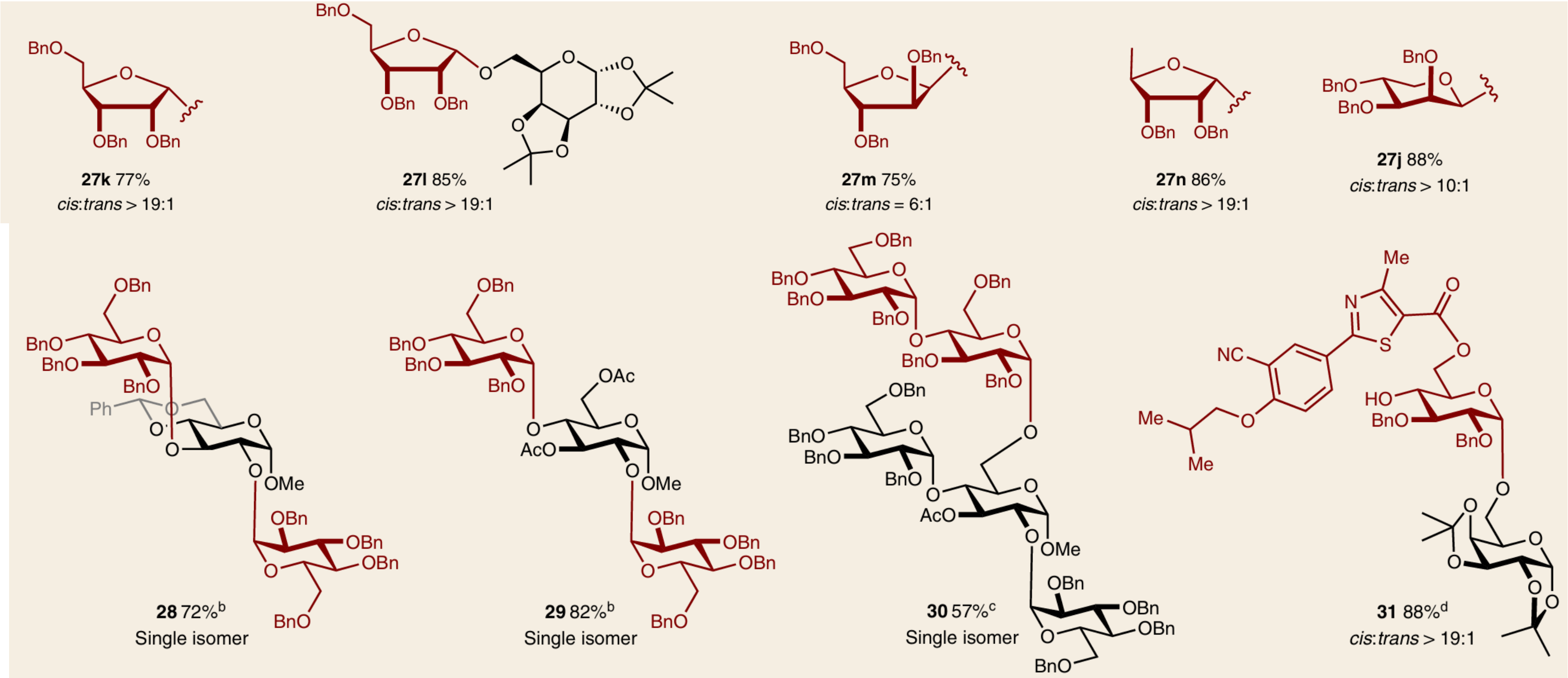
Directing Group at C-2



455 nm LED
C_4F_9I (5 equiv.)

Ph_3PO (30 mol%)
$(NH_4)_2HPO_4$ (5 equiv.)
MTBE, r.t.

6 (1.5 equiv.) **12** (1.0 equiv.) **27**



27k 77%
cis:*trans* > 19:1

27l 85%
cis:*trans* > 19:1

27m 75%
cis:*trans* = 6:1

27n 86%
cis:*trans* > 19:1

27j 88%
cis:*trans* > 10:1

28 72%[b]
Single isomer

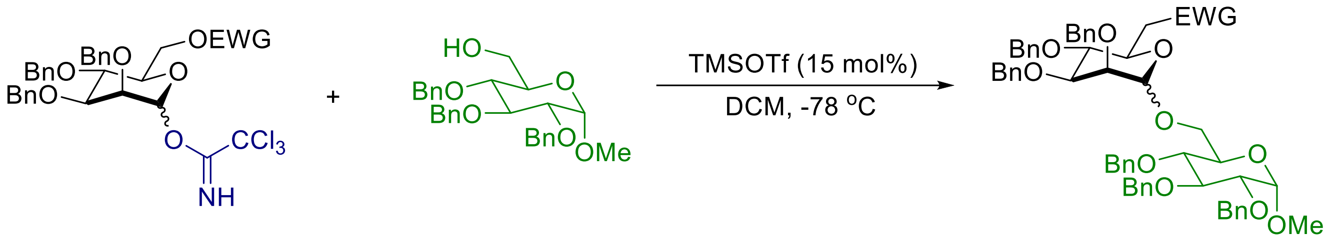
29 82%[b]
Single isomer

30 57%[c]
Single isomer

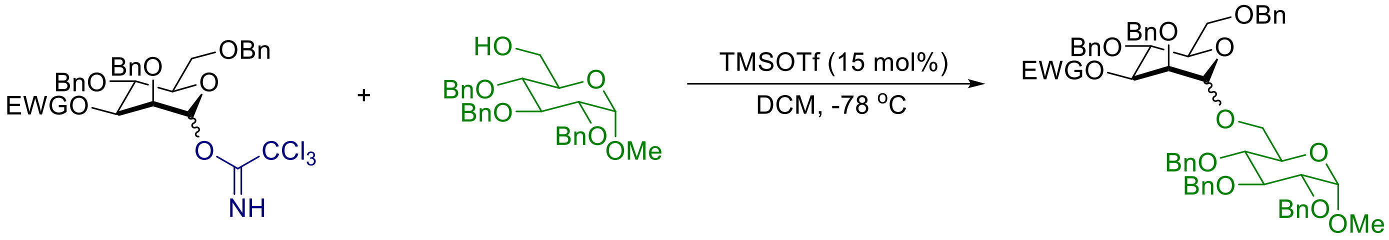
31 88%[d]
cis:*trans* > 19:1

Dawen Niu, et al. *Nat. Chem.* **2022**, 14, 686-694.

Participating Protecting Group at Remote Sites



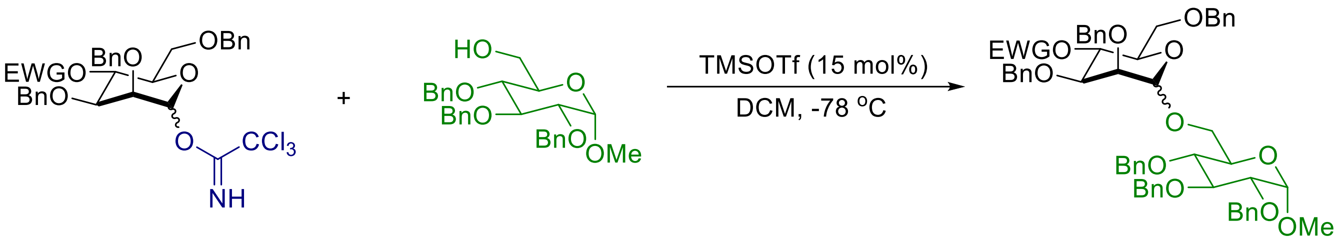
entry	EWG	*α*:*β*	Yield/%
1	Bzp-NO_2	5.2:1	83
2	Bz	6.8:1	83
3	Ac	*α* only	84



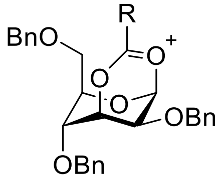
entry	EWG	*α*:*β*	Yield/%
1	Bzp-NO_2	1.7:1	83
2	Bz	9.8:1	83
3	Ac	25.9:1	84

Kwan Soo Kim, et al. *J. Am. Chem. Soc.* **2009**, 131, 17705–17713.

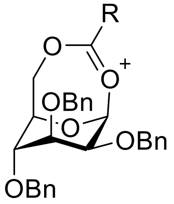
Participating Protecting Group at Remote Sites



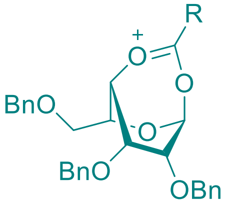
entry	EWG	*α*:*β*	Yield/%
1	Bzp-NO_2	1:7.2	83
2	Bz	1:7.1	83
3	Ac	1:4	84
4	Bn	1:2.7	91



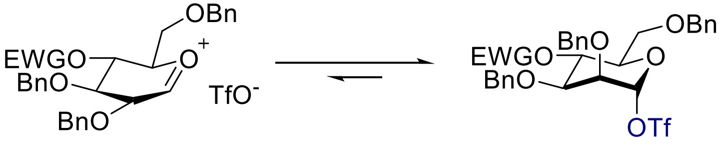
3-O-Acyl-participation



6-O-Acyl-participation

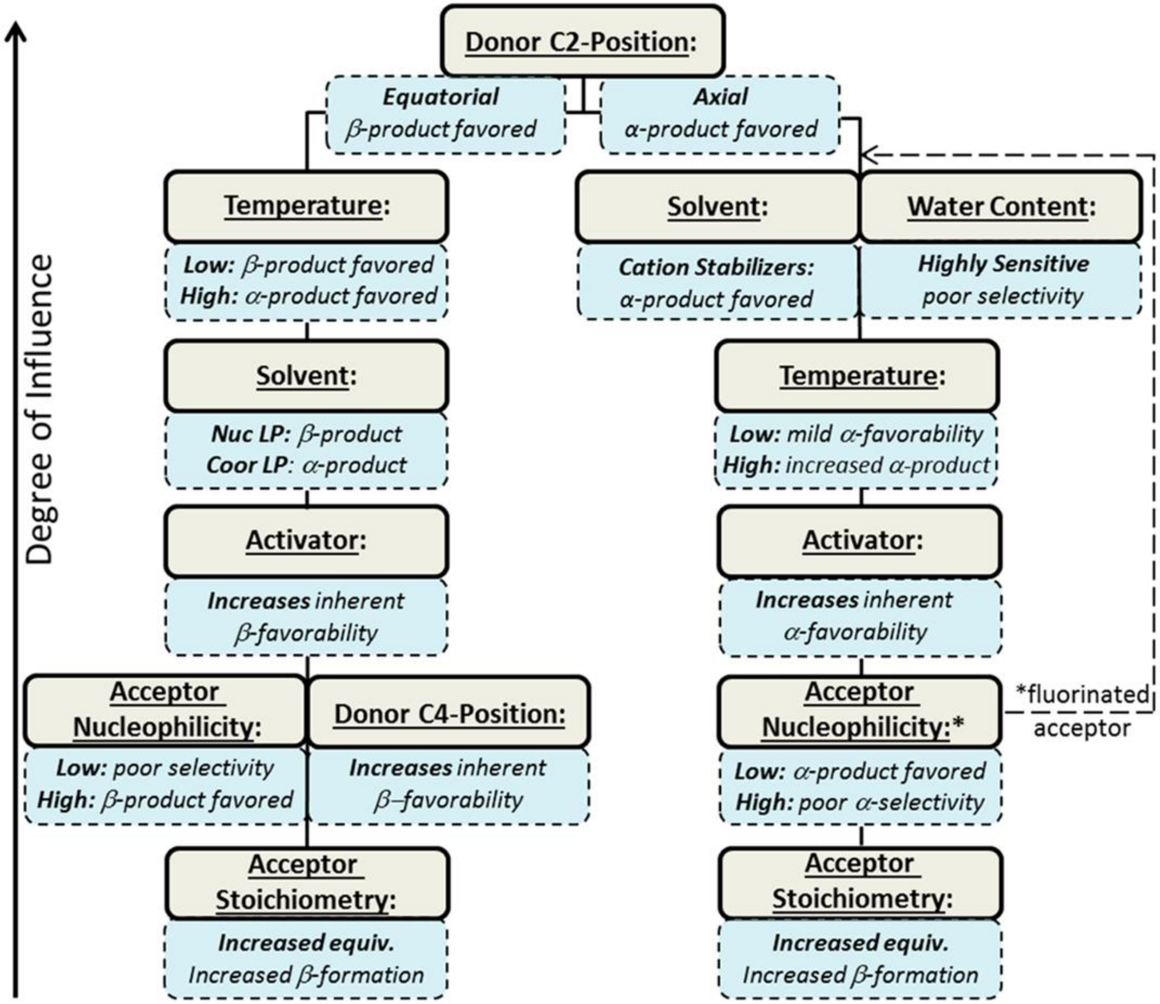


4-O-Acyl-participation



Kwan Soo Kim, et al. *J. Am. Chem. Soc.* **2009**, 131, 17705–17713.

Empirical Understanding of the Glycosylation Reaction



Degree of Influence

Donor C2-Position:

Equatorial
β-product favored

Axial
α-product favored

Temperature:
Low: *β-product favored*
High: *α-product favored*

Solvent:
Nuc LP: *β-product*
Coor LP: *α-product*

Activator:
Increases *inherent β-favorability*

Acceptor Nucleophilicity:
Low: *poor selectivity*
High: *β-product favored*

Donor C4-Position:
Increases *inherent β–favorability*

Acceptor Stoichiometry:
Increased equiv.
Increased β-formation

Solvent:
Cation Stabilizers:
α-product favored

Water Content:
Highly Sensitive
poor selectivity

Temperature:
Low: *mild α-favorability*
High: *increased α-product*

Activator:
Increases *inherent α-favorability*

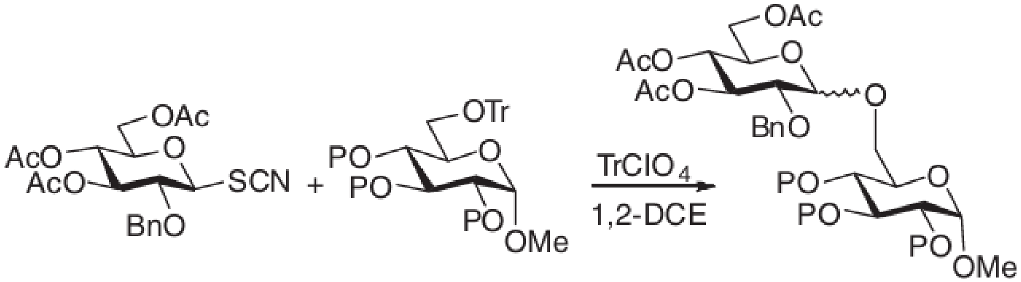
Acceptor Nucleophilicity:*
Low: *α-product favored*
High: *poor α-selectivity*

*fluorinated acceptor

Acceptor Stoichiometry:
Increased equiv.
Increased β-formation

Peter H. Seeberger, et al. *J. Am. Chem. Soc.* **2018**, 140, 11492–11953.

Glycosyl Acceptor and Reaction Conditions

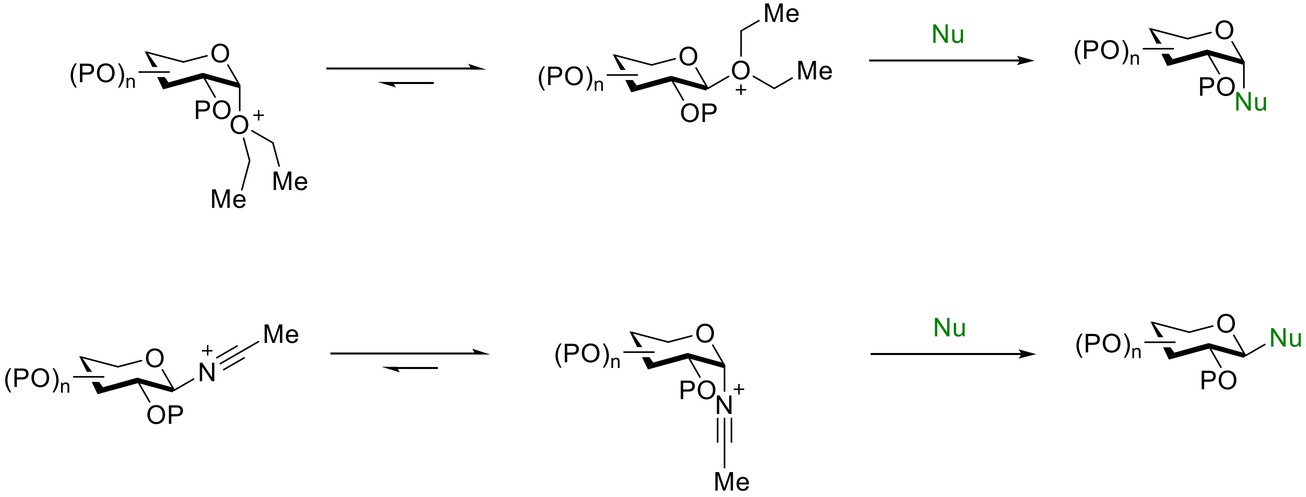


1

2: P = Ac
3: P = Bz
4: P = Bn

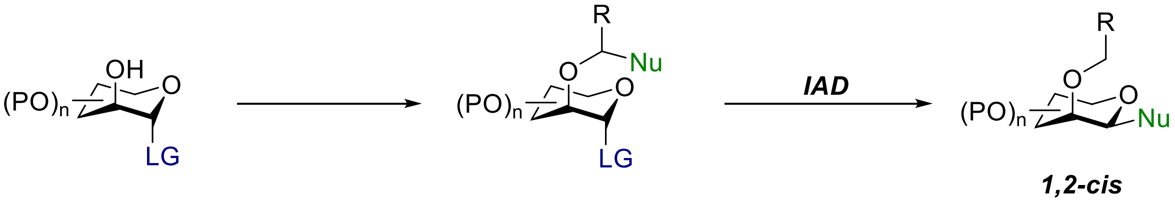
5: P = Ac, 65%, α/β > 25/1
6: P = Bz, 78%, α/β > 25/1
7: P = Bn, 72%, α/β = 8.3/1

solvent

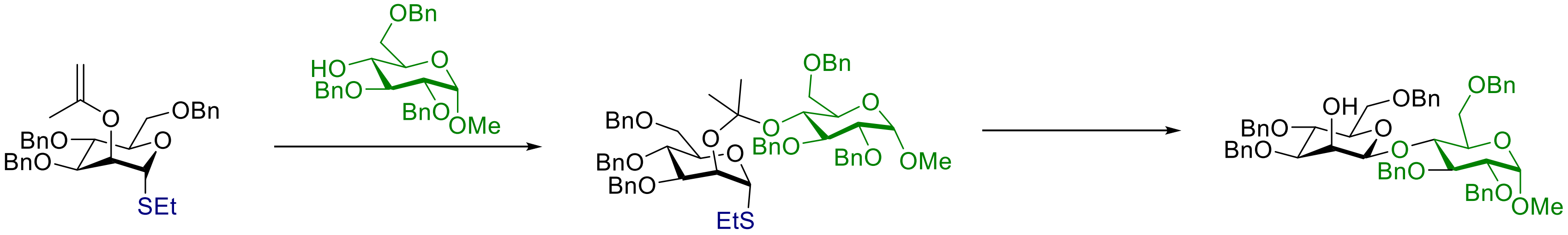


A. V. Demchenko, et al. *Carbohydr.Res.,* **2010**, 345, 2146–2150.
B. K. Mong, et al. *Chem.–Eur. J.* **2011**, 17, 12193–12202.

Intramolecular Aglycone Delivery



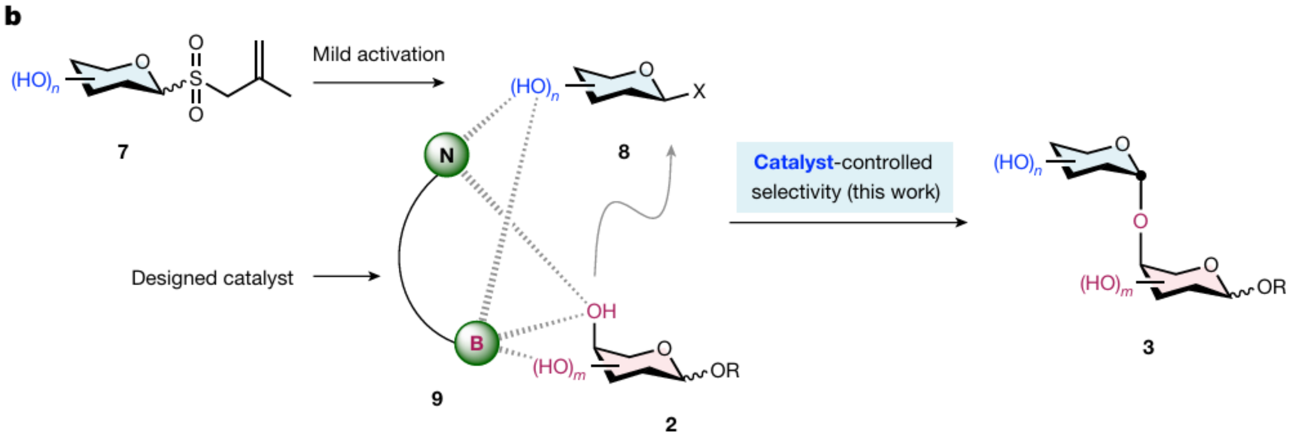
1991, Hindsgaul

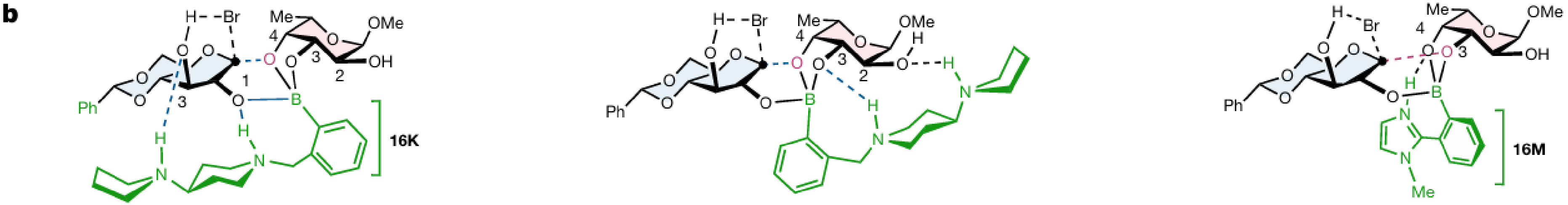


42%, *β* only

Ole Hindsgaul, et al. *J. Am. Chem. Soc.* **1991**, 113, 9376-9377.

Aminoboronic Acid Catalyst





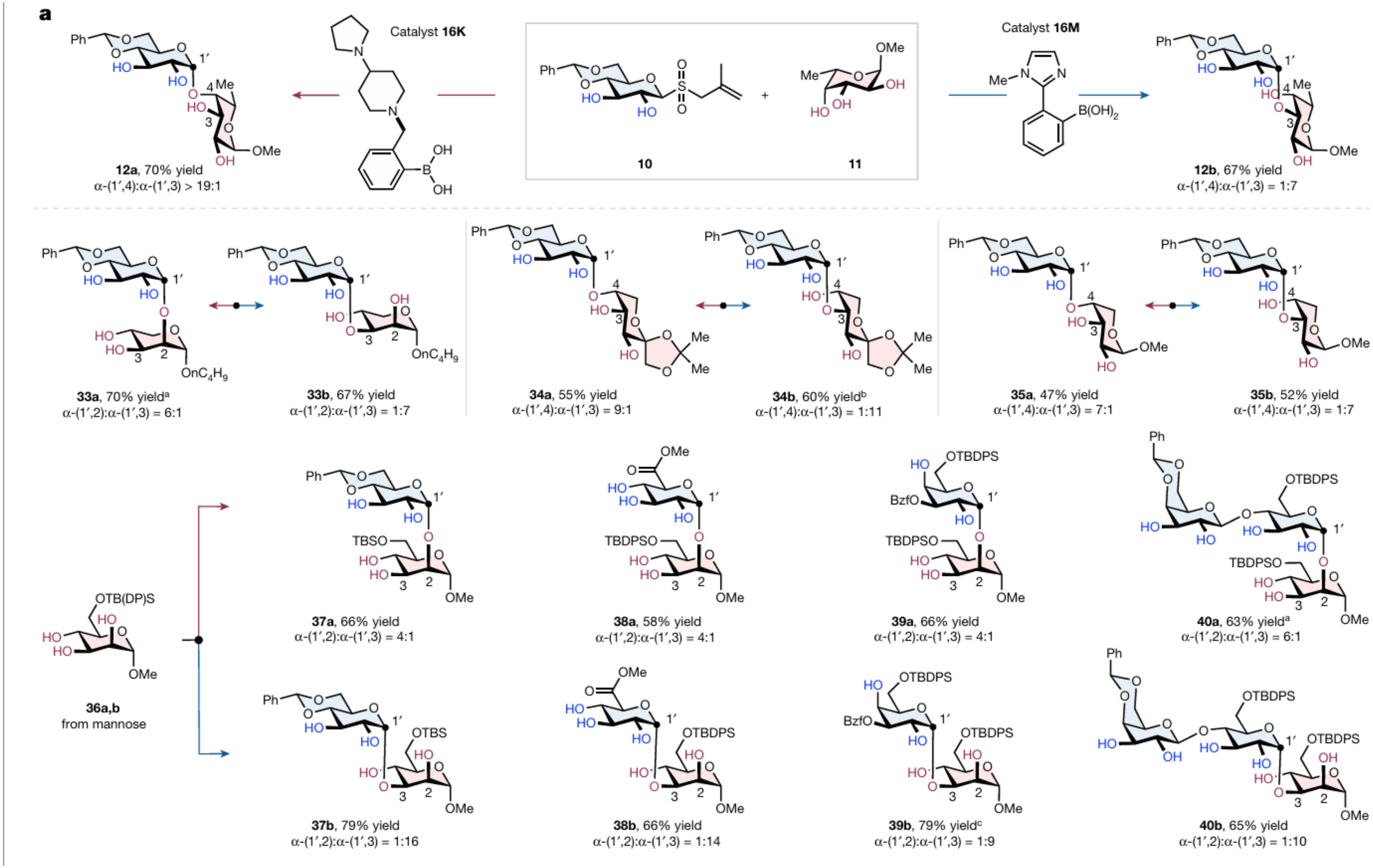
TS-I (to **12a**)
C4-OH attack (0 kcal mol^{-1})
C3-OH attack (2.2 kcal mol^{-1})

TS-II (to **12a**)
C4-OH attack (3.7 kcal mol^{-1})
C3-OH attack (8.5 kcal mol^{-1})

TS-III (to **12b**)
C4-OH attack (1.0 kcal mol^{-1})
C3-OH attack (0 kcal mol–1)

Dawen Niu, et al. *Nature.* **2024**, 632, 313-319.

Aminoboronic Acid Catalyst



12a, 70% yield
α-(1′,4):α-(1′,3) > 19:1

10

11

12b, 67% yield
α-(1′,4):α-(1′,3) = 1:7

33a, 70% yield[a]
α-(1′,2):α-(1′,3) = 6:1

33b, 67% yield
α-(1′,2):α-(1′,3) = 1:7

34a, 55% yield
α-(1′,4):α-(1′,3) = 9:1

34b, 60% yield[b]
α-(1′,4):α-(1′,3) = 1:11

35a, 47% yield
α-(1′,4):α-(1′,3) = 7:1

35b, 52% yield
α-(1′,4):α-(1′,3) = 1:7

36a,b
from mannose

37a, 66% yield
α-(1′,2):α-(1′,3) = 4:1

38a, 58% yield
α-(1′,2):α-(1′,3) = 4:1

39a, 66% yield
α-(1′,2):α-(1′,3) = 4:1

40a, 63% yield[a]
α-(1′,2):α-(1′,3) = 6:1

37b, 79% yield
α-(1′,2):α-(1′,3) = 1:16

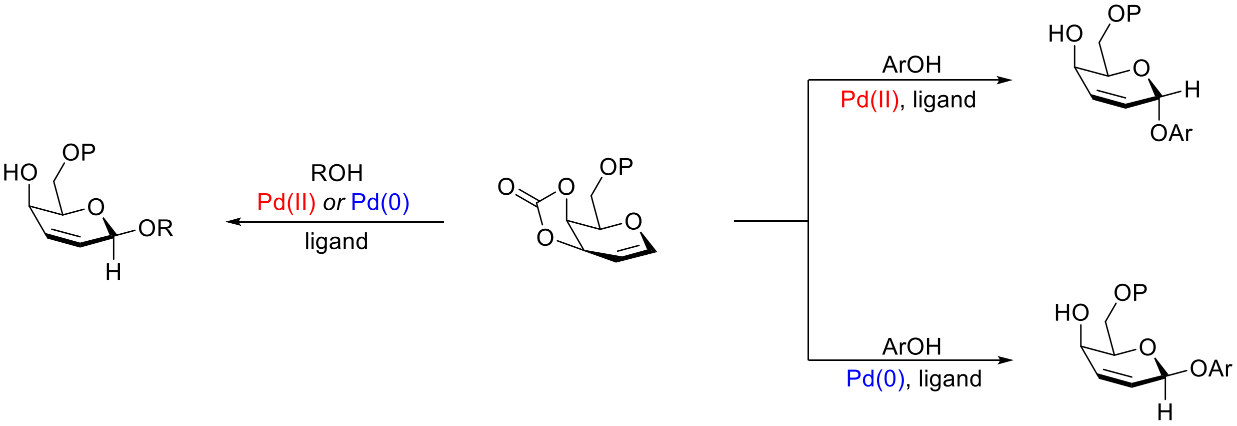
38b, 66% yield
α-(1′,2):α-(1′,3) = 1:14

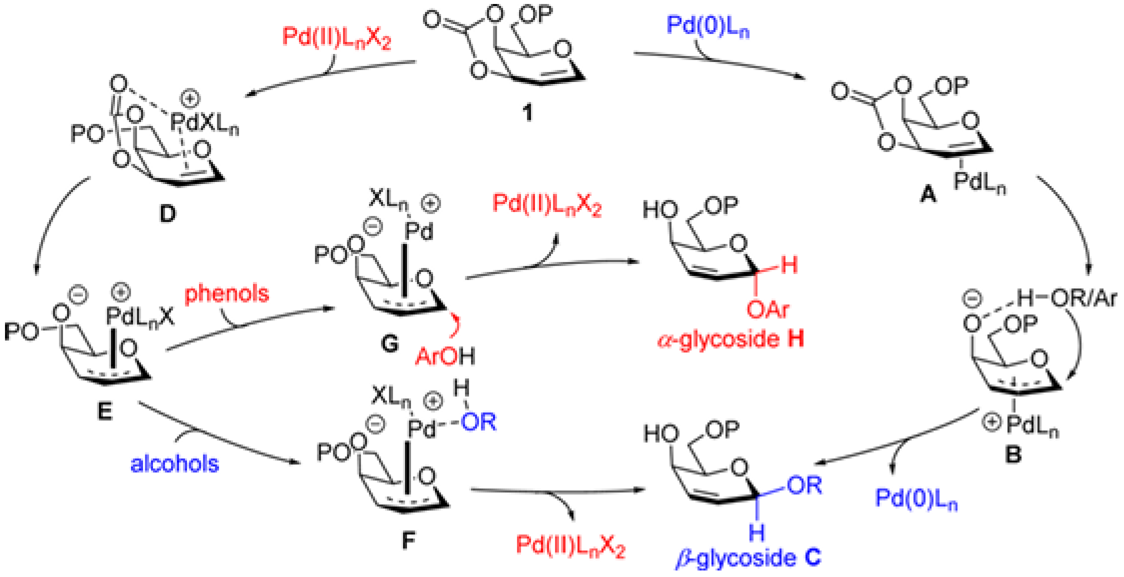
39b, 79% yield[c]
α-(1′,2):α-(1′,3) = 1:9

40b, 65% yield
α-(1′,2):α-(1′,3) = 1:10

Dawen Niu, et al. *Nature.* **2024**, 632, 313-319.

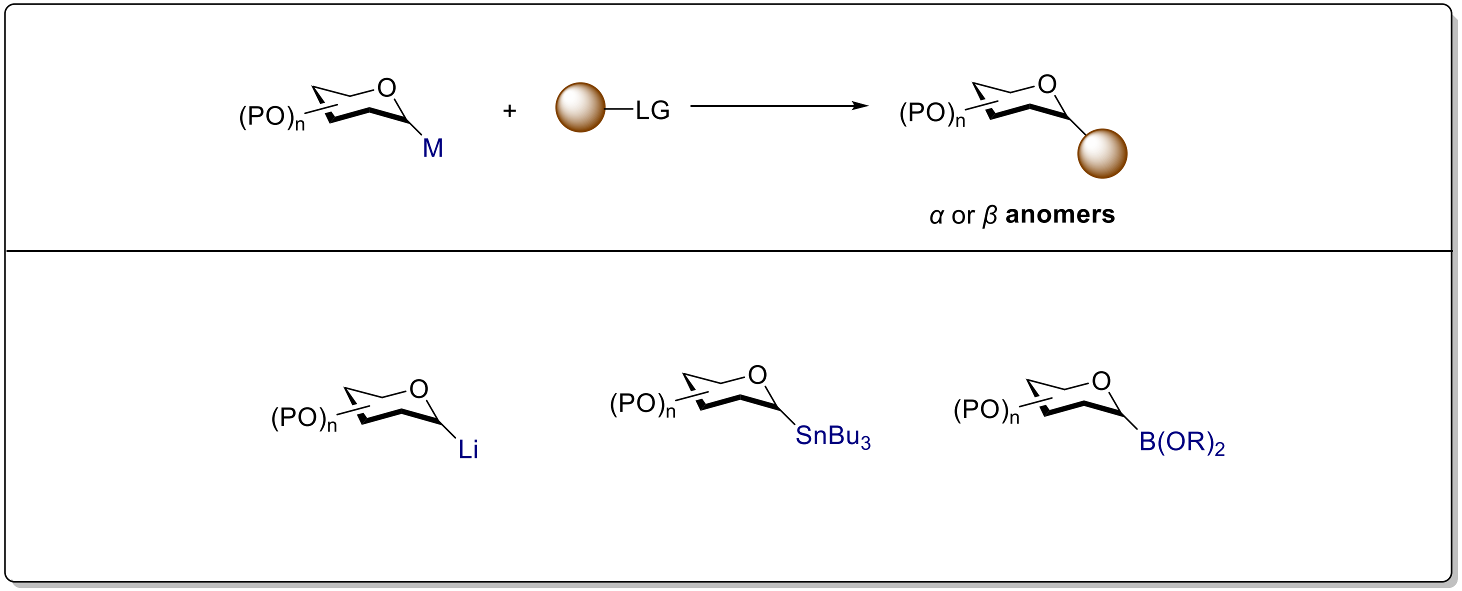
Tsuji-Trost Reaction





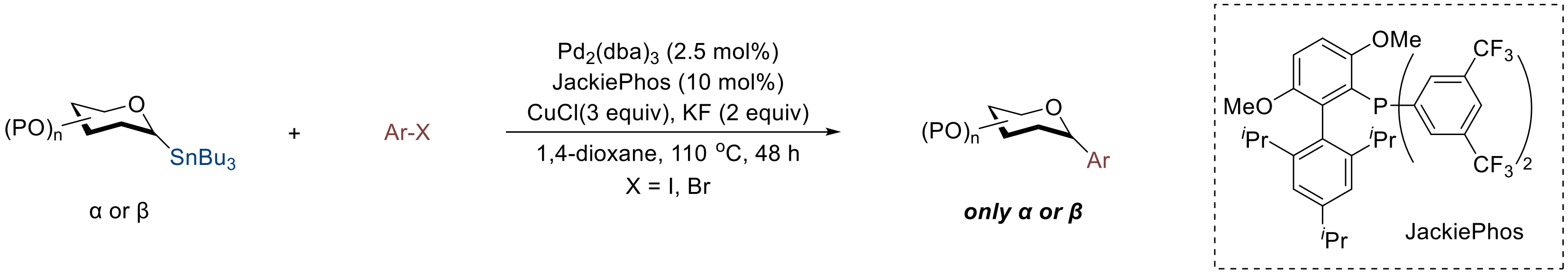
Xue-Wei Liu, et al. *ACS Catal.* **2017**, 7, 5456-5460.

Glycosyl Nucleophiles as Donors



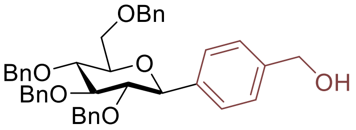
- *Functional group compatibility?*

Stereoretentive Stille Coupling

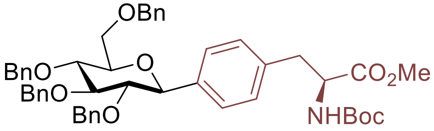


$Pd_2(dba)_3$ (2.5 mol%)
JackiePhos (10 mol%)
CuCl(3 equiv), KF (2 equiv)
1,4-dioxane, 110 °C, 48 h
X = I, Br

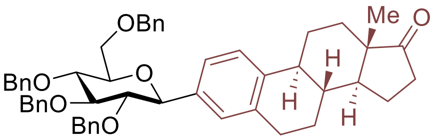
Selected Examples



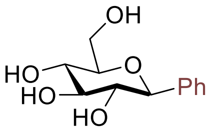
84%
X = I



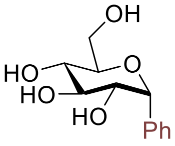
72%
X = Br



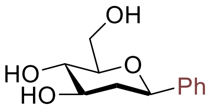
83%
X = Br



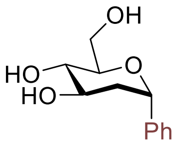
84%
only β



88%
only α



92%
only β



92%
only β

Maciej A. Walczak, et al. *J. Am. Chem. Soc.* **2016**, 138, 12049−12052.

Stereoretentive Stille Coupling

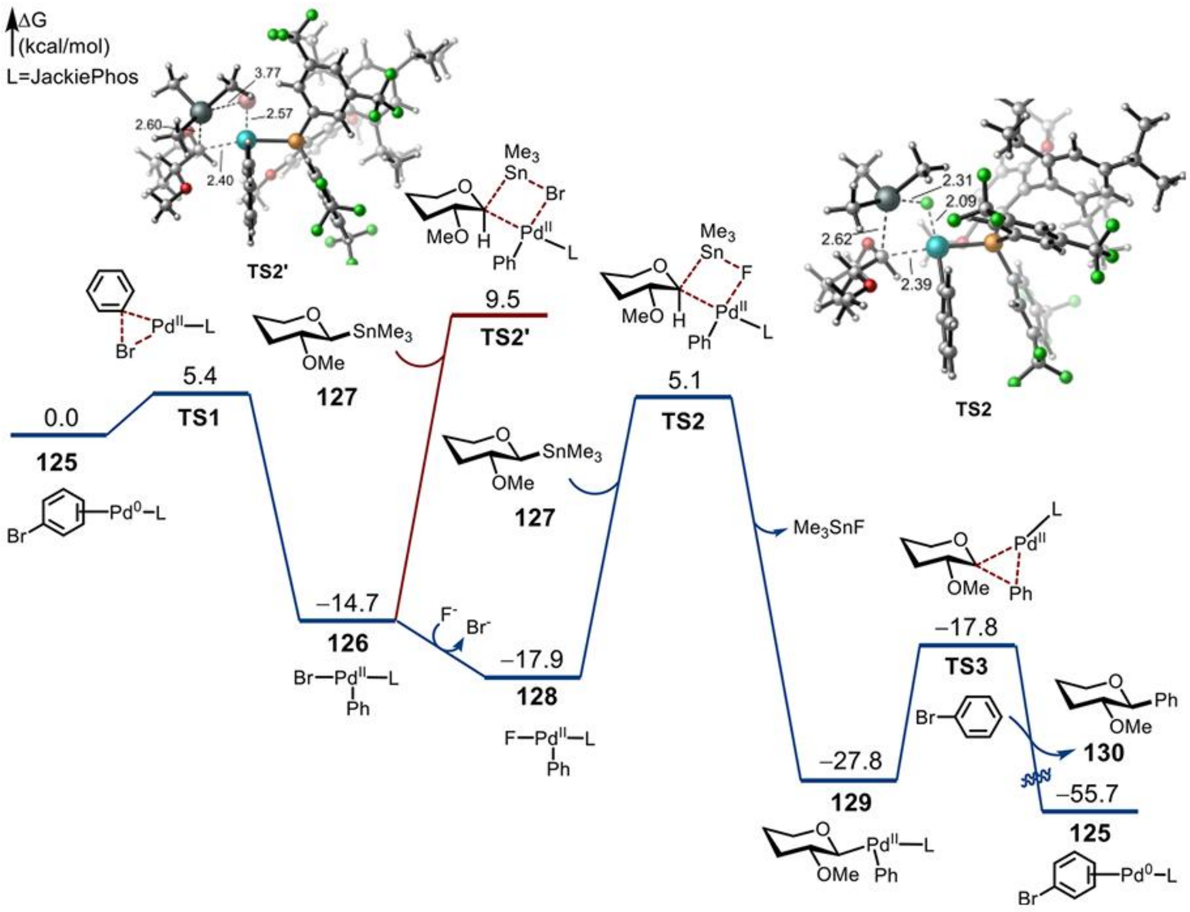
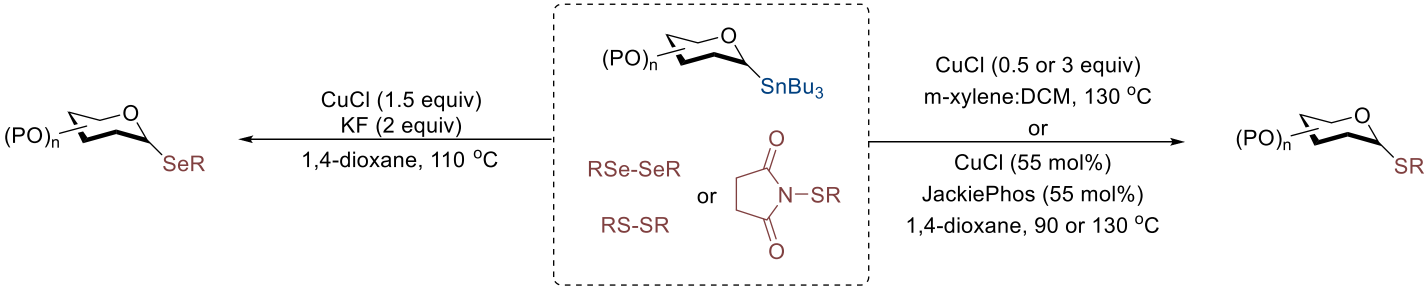


Figure 4. Reaction energy profile of the Pd-catalyzed Stille coupling of bromobenzene and tetrahydropyranyl stannane **127** using JackiePhos ligand. All energies are with respect to the reactant complex **125**. Calculations were performed at the M06/SDD-6-311+G(d,p)/SMD(dioxane)//B3LYP/SDD-6-31G(d) level of theory.

Maciej A. Walczak, et al. *J. Am. Chem. Soc.* **2017**, 139, 17908−17922.

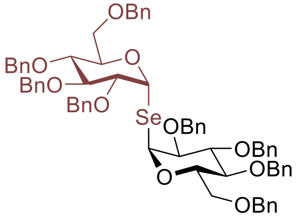
Stereoretentive Copper(I)-Mediated Cross-coupling



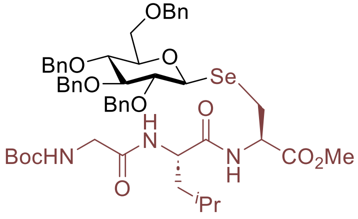
CuCl (1.5 equiv)
KF (2 equiv)
1,4-dioxane, 110 °C

CuCl (0.5 or 3 equiv)
m-xylene:DCM, 130 °C
or
CuCl (55 mol%)
JackiePhos (55 mol%)
1,4-dioxane, 90 or 130 °C

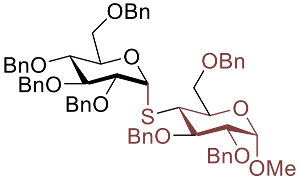
Selected Examples



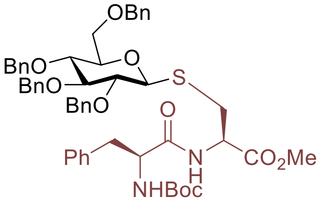
54%



44%



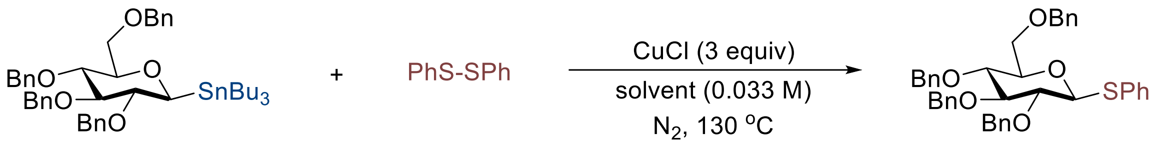
48%



60%

(a)Maciej A. Walczak, et al. *Angew. Chem. Int. Ed.* **2018**, 57, 7091 -7095.
(b) Maciej A. Walczak, et al. *J. Am. Chem. Soc.* **2018**, 140, 18140-18150.

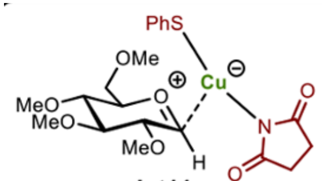
Stereoretentive Copper(I)-Mediated Cross-coupling



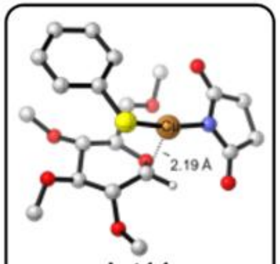
entry	solvent	time (h)	*α*:*β*	Yield/%
1	*m*-xylene	24	*β* only	20
2	DCE	24	*β* only	42
3	1,4-dioxane	24	1:2.1	28
4[a]	1,4-dioxane	72	*β* only	15

[a] CuCl (50 mol%), JackiePhos (55 mol%)

- *Contact ion pair*
- *Short-lived anomeric Cu(III) intermediate*



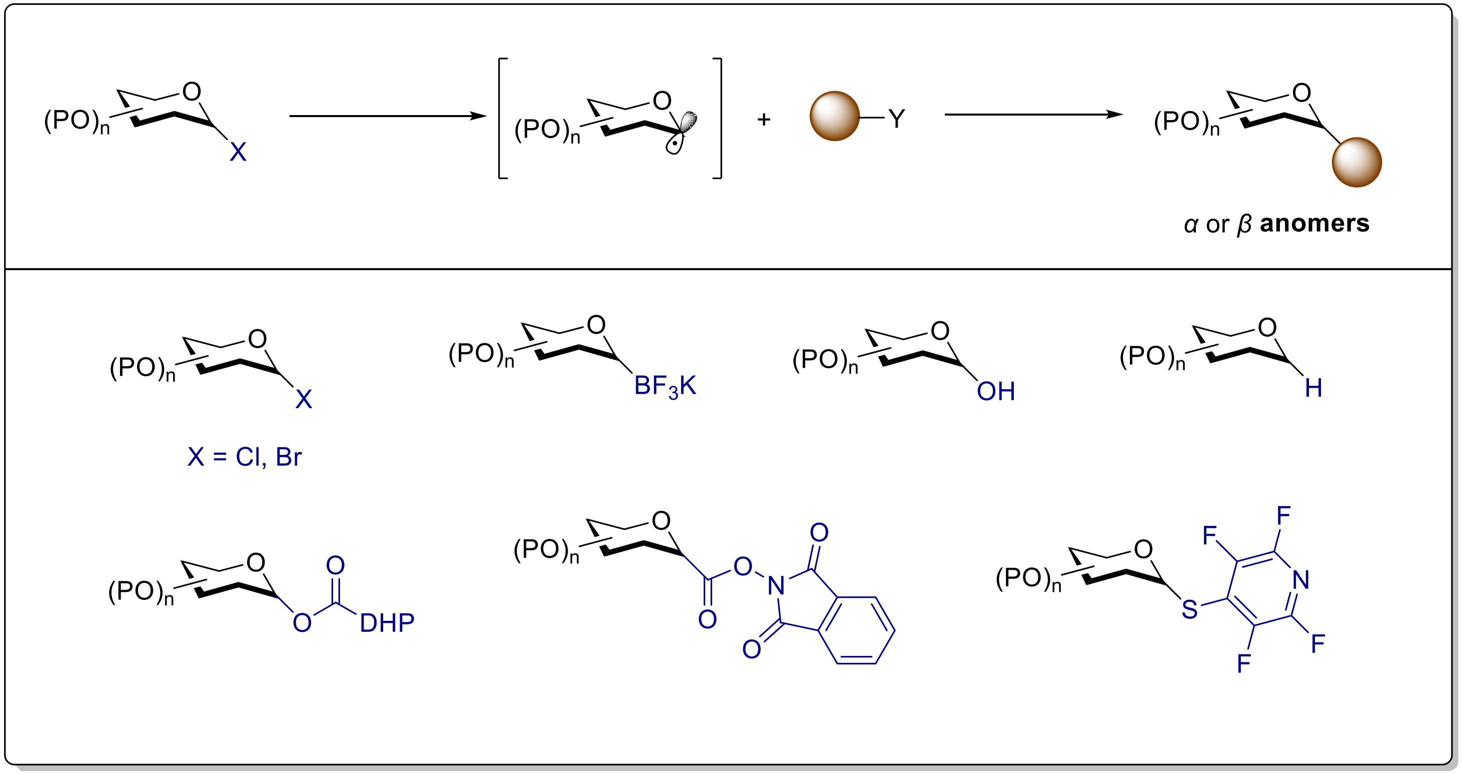
int11



int11

(a)Maciej A. Walczak, et al. *Angew. Chem. Int. Ed.* **2018**, 57, 7091 -7095.
(b) Maciej A. Walczak, et al. *J. Am. Chem. Soc.* **2018**, 140, 18140-18150.

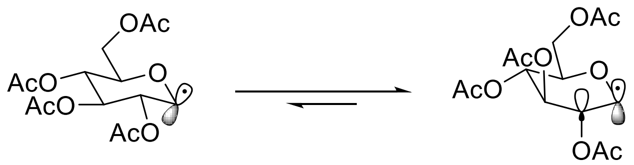
Glycosyl Radical Precursors as Donors



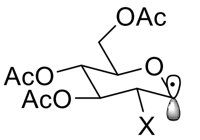
α or *β* **anomers**

X = Cl, Br

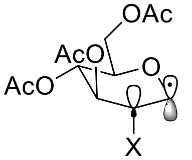
Conformation of Glycosyl Radical



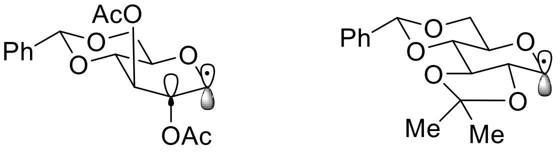
chair-boat interconversation



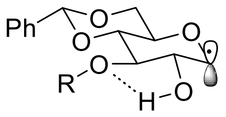
favored when
X = NHTs, D, ^{n}Pr



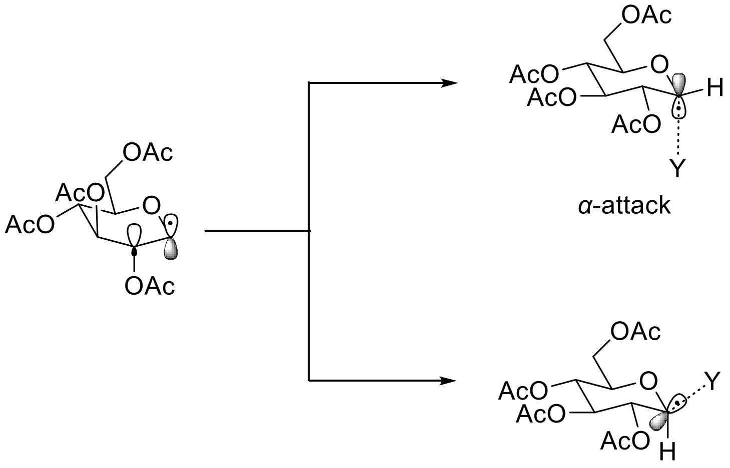
favored when
X = OAc, OMe, F



ring annelation



hydrogen bonding

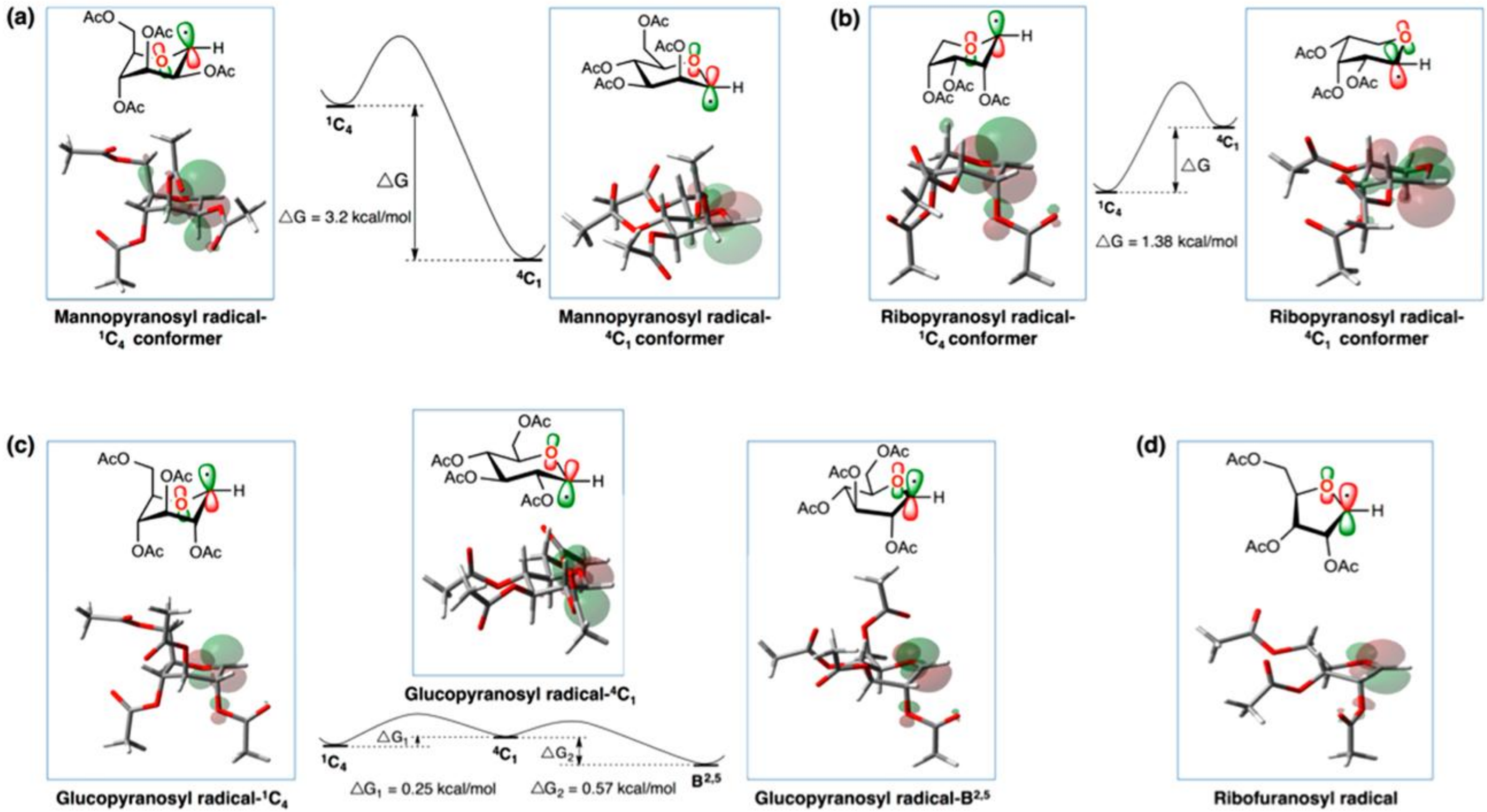


α-attack

β-attack

Bernd Giese, et al. *Angew. Chem. Int. Ed.* **1989**, 28, 969-1146.

Conformation of Glycosyl Radical



Mannopyranosyl radical-$^1C_4$ conformer

Mannopyranosyl radical-$^4C_1$ conformer

Ribopyranosyl radical-$^1C_4$ conformer

Ribopyranosyl radical-$^4C_1$ conformer

Glucopyranosyl radical-$^4C_1$

Glucopyranosyl radical-$^1C_4$

Glucopyranosyl radical-$B^{2,5}$

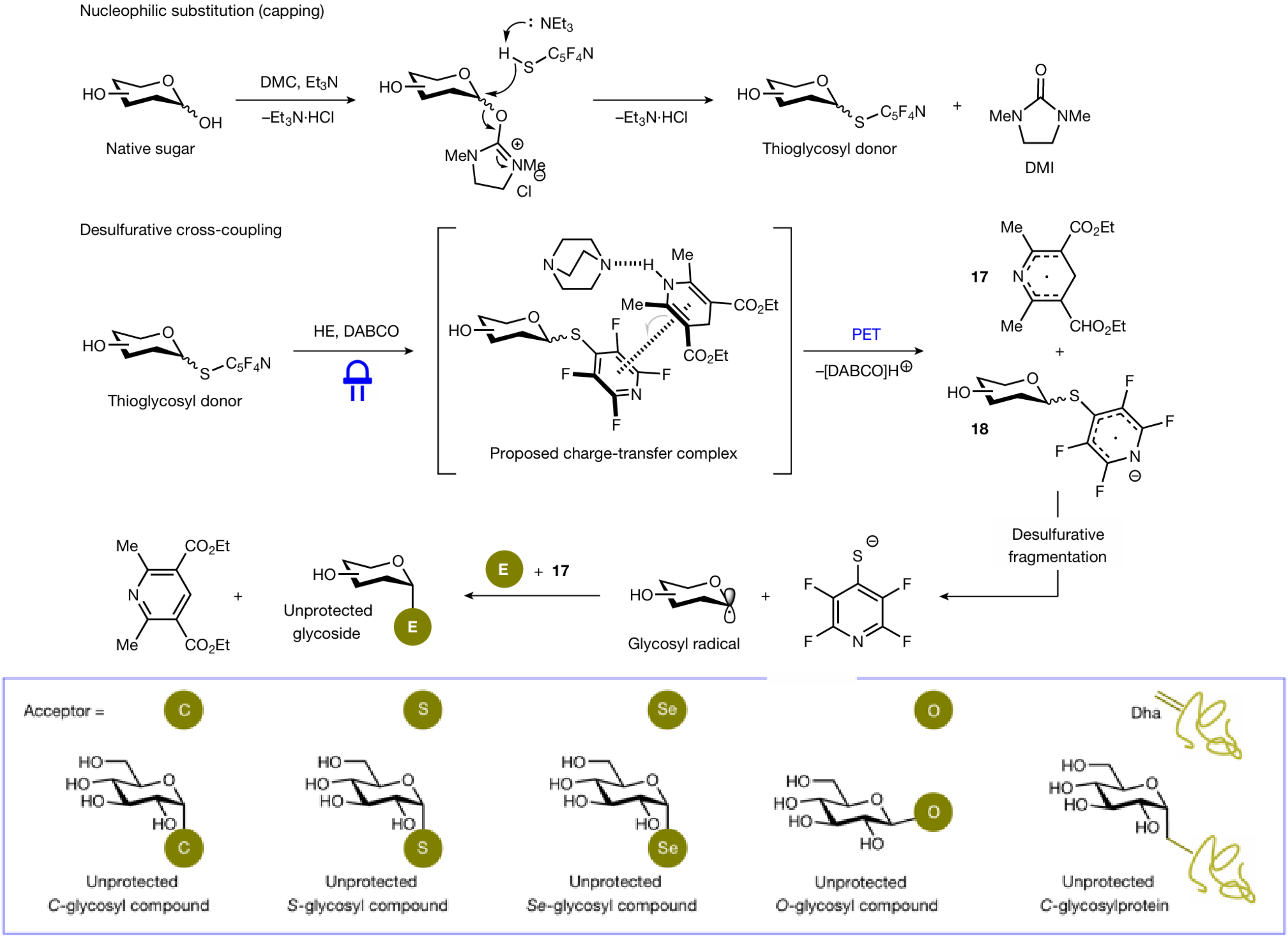
Ribofuranosyl radical

Figure 2. Relative DFT stabilities of conformers of glycosyl radical intermediates.

- *Stereoelectronic effects*

Masaharu Nakamura, et al. *J. Am. Chem. Soc.* **2017**, 139, 10693−10701.

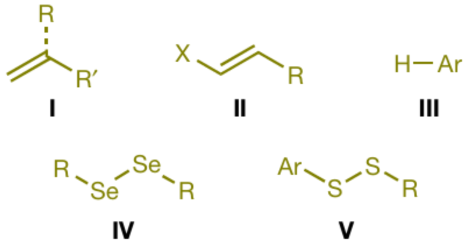
Direct Radical Functionalization of Native Sugars

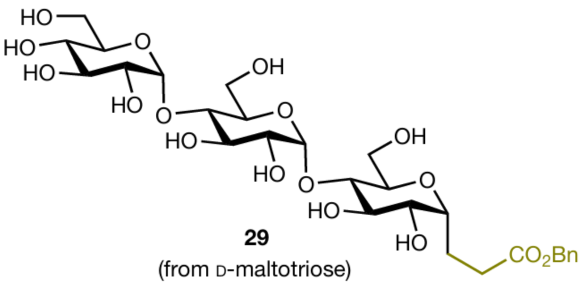


Ming Joo Koh, *et al. Nature* **2024**, 631, 319–327.

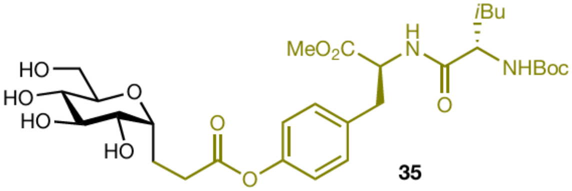
Direct Radical Functionalization of Native Sugars

Coupling partners:

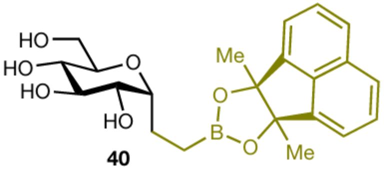




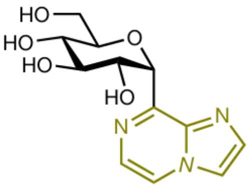
29
(from D-maltotriose)
74% (65%), >95:5 α:β
58%, >95:5 α:β (in situ)



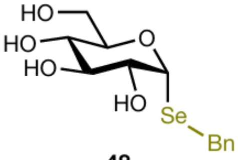
35
66% (61%),
>95:5 α:β



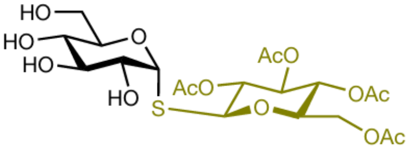
40
78% (51%),
>95:5 α:β



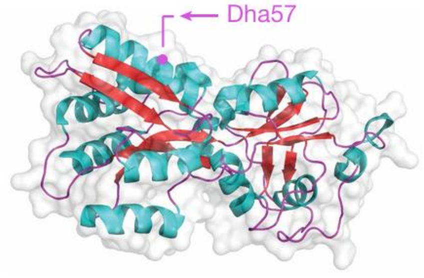
45
31% (22%),
>95:5 α:β



48
40% (36%),
>95:5 α:β



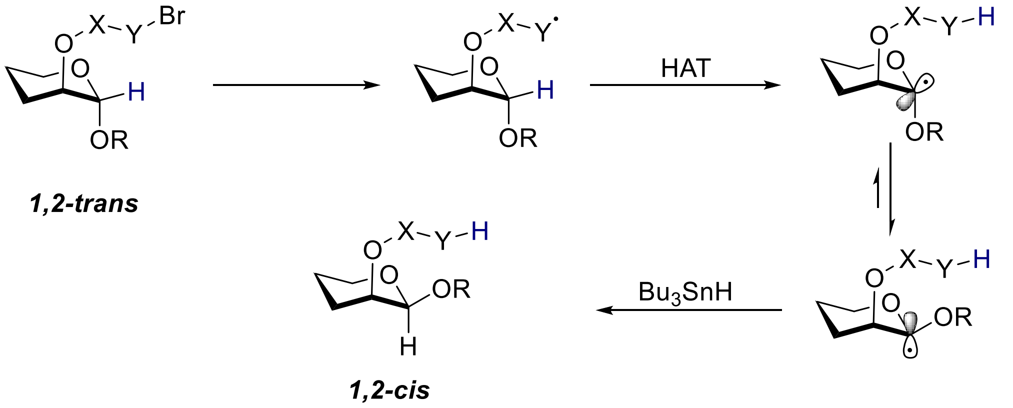
54
34% (17%),
>95:5 α:β

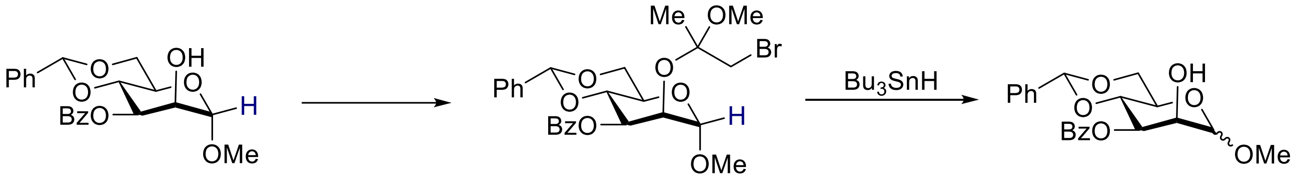


PstS–Man–Ala57 66% (77%)
PstS–Gal–Ala57 80% (75%)
PstS–GlcNAc–Ala57 78%

Ming Joo Koh, *et al. Nature* **2024**, 631, 319–327.

Inversion of α- to β-Pyranosides via Intramolecular HAT

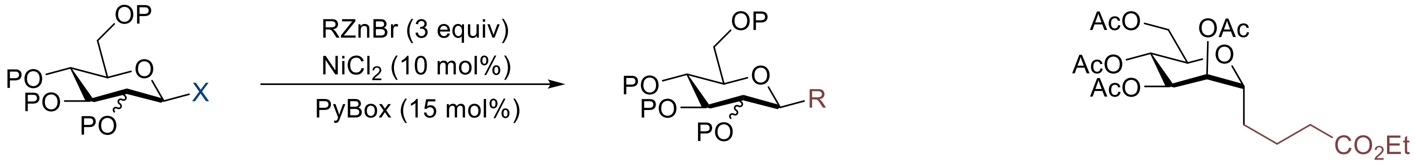




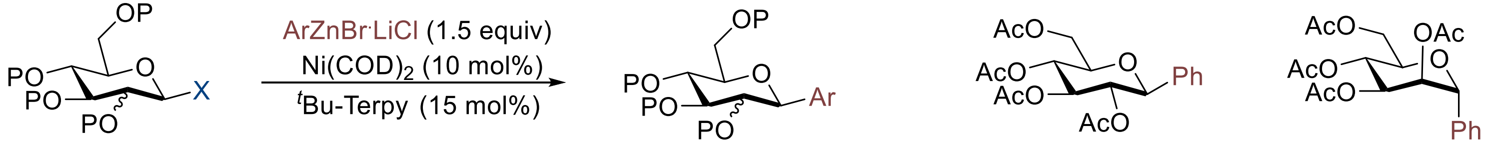
up to *α*:*β* = 1:1

David Crich, *et al. J. Org. Chem.* **1996**, 60, 605-615.

Cross Coupling of Halosugars

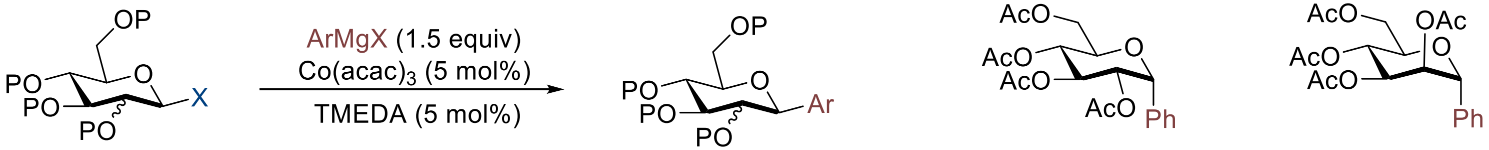


70%, α:β = 8:1



71%, α:β = 1:12

80%, α:β > 20:1

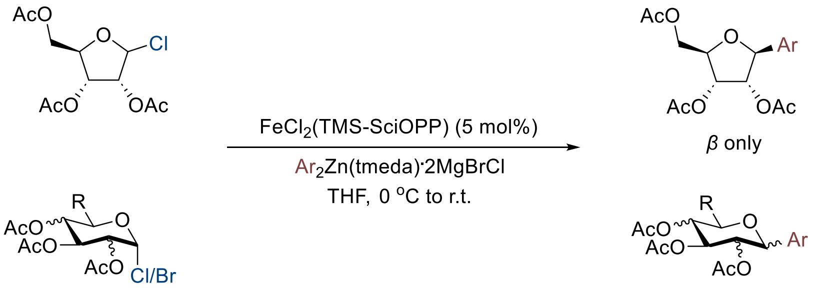


96%, α:β = 3:1

76%, α:β > 9:1

(a) Michel R. Gagne, et al. *J. Am. Chem. Soc.* **2007**, 129, 1908-1909.
(b) Michel R. Gagne, et al. *J. Am. Chem. Soc.* **2008**, 130, 12177-12183.
(c) Janine Cossy, et al. *Angew. Chem. Int. Ed.* **2012**, 51, 11101-11104.

Fe-Catalyzed Cross Coupling of Halosugars



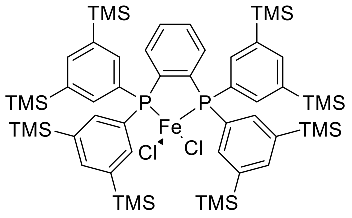
$FeCl_2$(TMS-SciOPP) (5 mol%)

$Ar_2Zn(tmeda)\cdot 2MgBrCl$

THF, 0 °C to r.t.

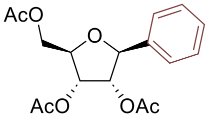
β only

α:*β* = 1>99 to 99>1

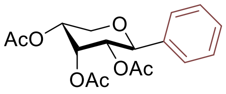


$FeCl_2$(TMS-SciOPP)

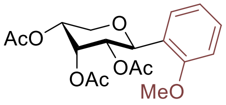
Selected Examples



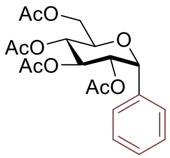
81%, *α*:*β* > 1:99



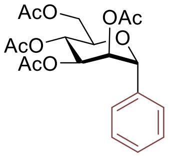
86%, *α*:*β* > 1:99



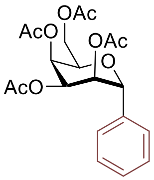
65%



96%, *α*:*β* = 73:27



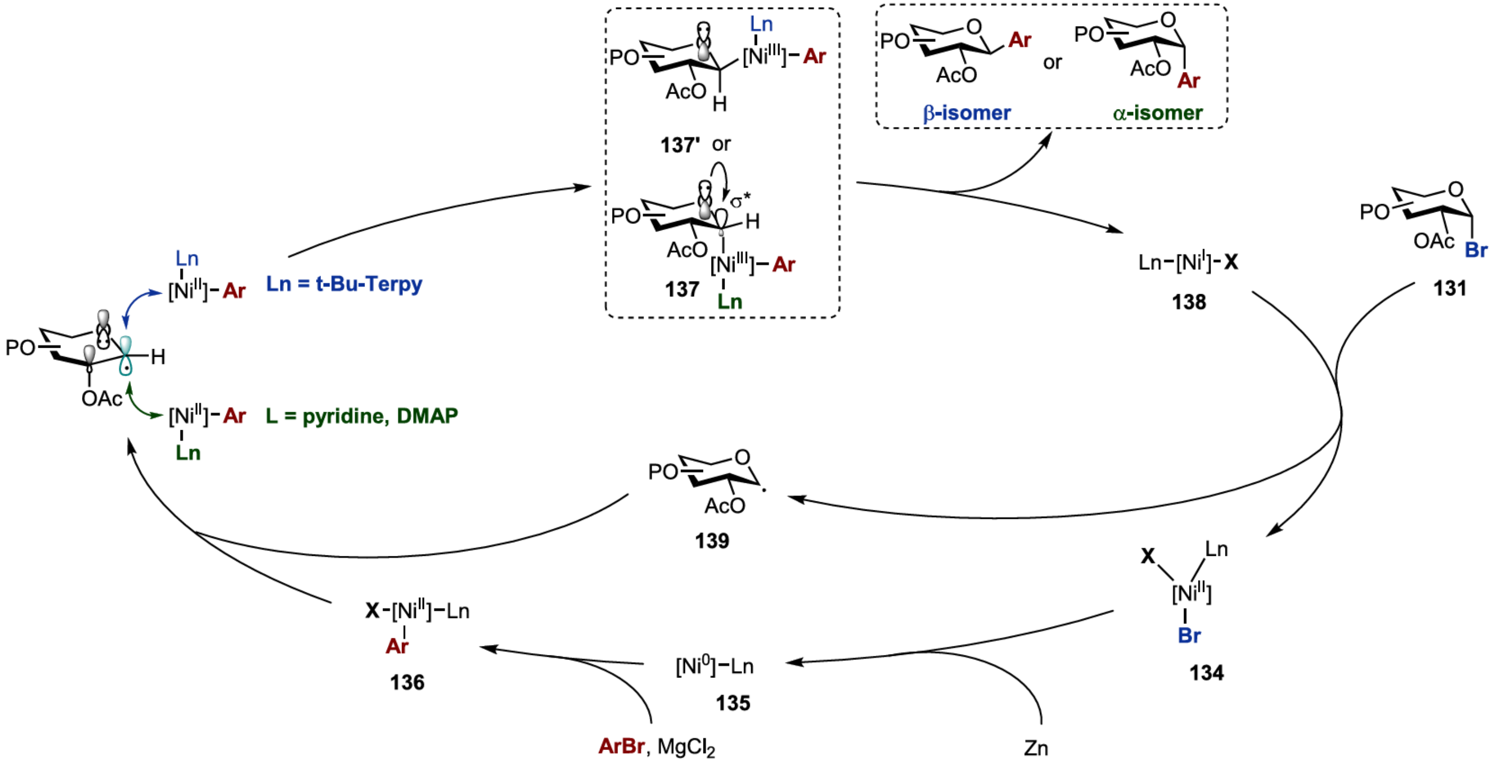
98%, *α*:*β* > 99:1



89%, *α*:*β* > 99:1

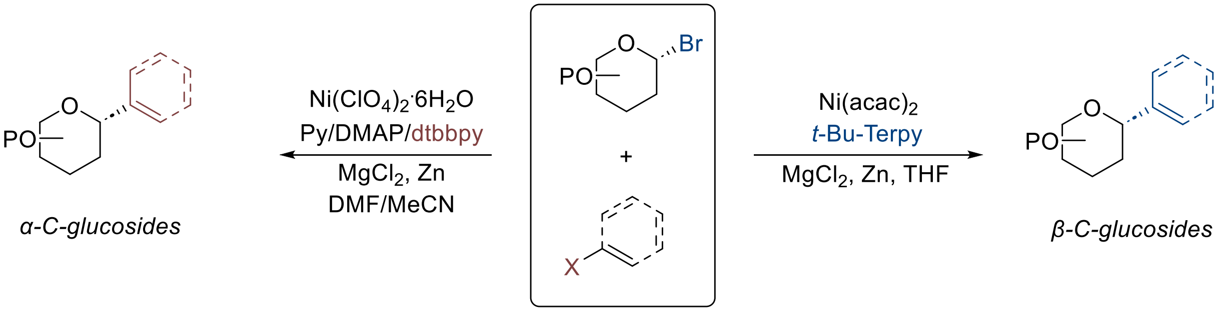
Masaharu Nakamura, et al. *J. Am. Chem. Soc.* **2017**, 139, 10693−10701.

Ni-Catalyzed XEC of Halosugars

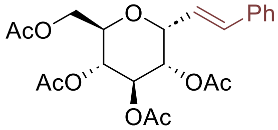


(a)Gong, H., et al. *Org. Lett.* **2018**, 20, 7991–7995.
(b)Gong, H., et al. *Sci. China Chem.* **2019**, 62, 1492–1496

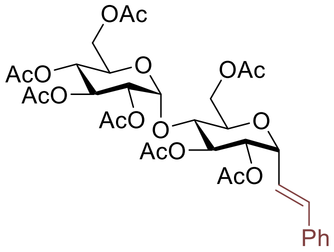
Ni-Catalyzed XEC of Halosugars



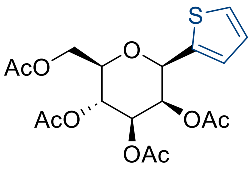
Selected Examples



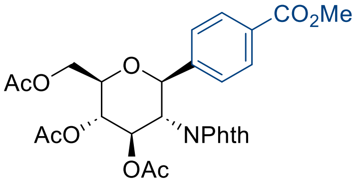
81%, *α*:*β* = 8.3:1



71%, *α*:*β* = 32:1



53%, *α*:*β* > 1:20

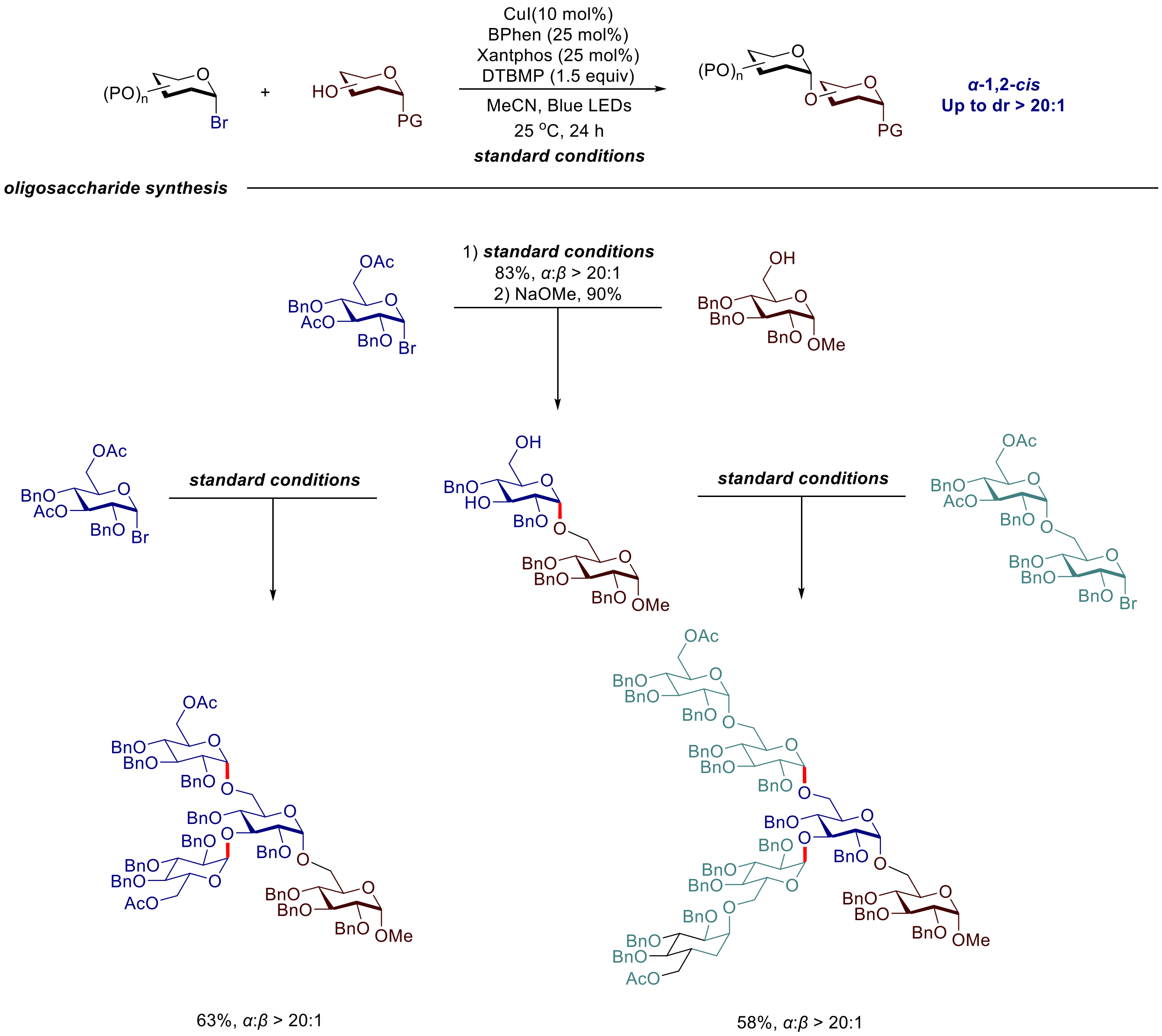


67%, *α*:*β* =1:19

- *ligand-controlled*

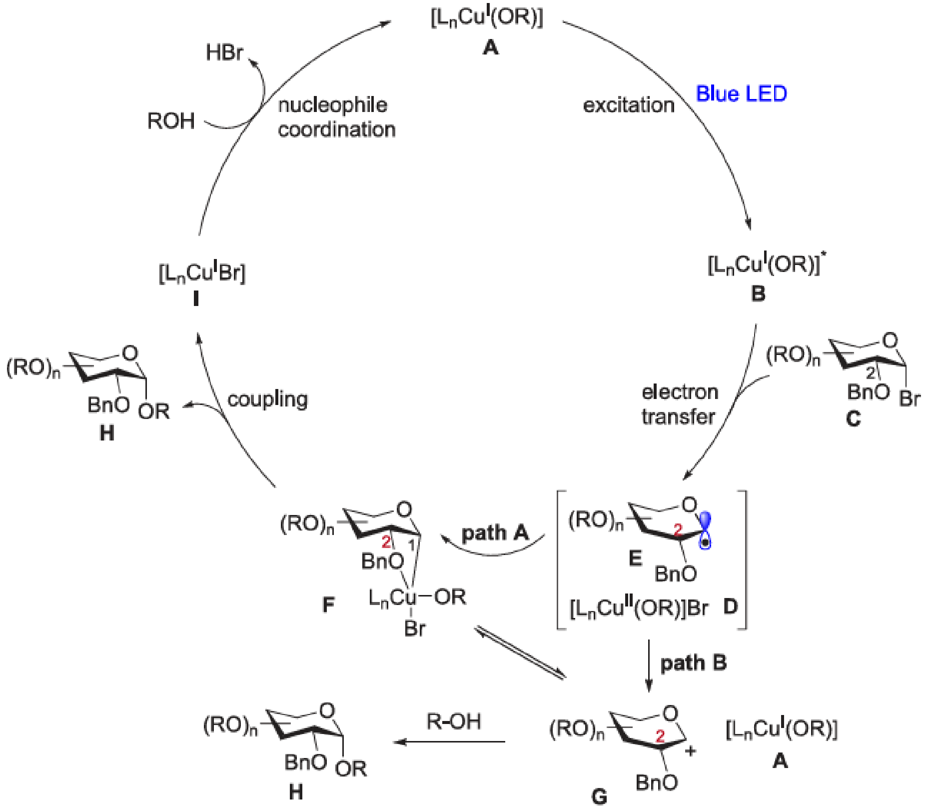
(a)Gong, H., et al. *Org. Lett.* **2018**, 20, 7991–7995.
(b)Gong, H., et al. *Sci. China Chem.* **2019**, 62, 1492–1496

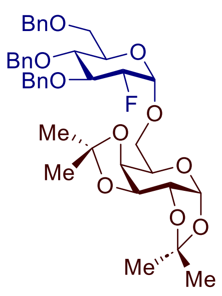
Dual Photoredox/Cu-catalyzed C(sp3)-O Cross-coupling



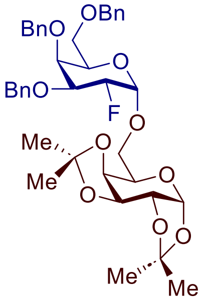
Hien M. Nguyen., et al. *ACS Catal.* **2020**, 10, 5990−6001.

Dual Photoredox/Cu-catalyzed C(sp3)-O Cross-coupling





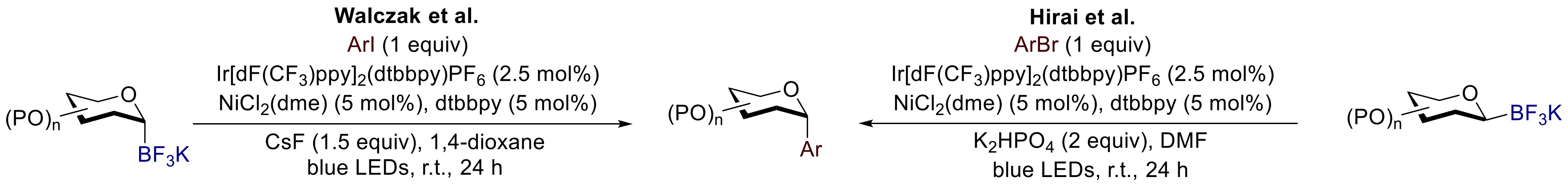
70%, α:β = 13:1



78%, α:β = 19:1

Hien M. Nguyen., et al. *ACS Catal.* **2020**, 10, 5990−6001.

Photoredox/Ni-dual-catalyzed C-glycosylation



Walczak et al.

ArI (1 equiv)

Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.5 mol%)

$NiCl_2$(dme) (5 mol%), dtbbpy (5 mol%)

CsF (1.5 equiv), 1,4-dioxane

blue LEDs, r.t., 24 h

Hirai et al.

ArBr (1 equiv)

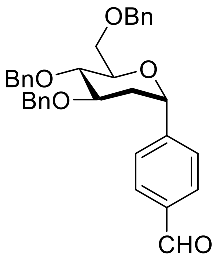
Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.5 mol%)

$NiCl_2$(dme) (5 mol%), dtbbpy (5 mol%)

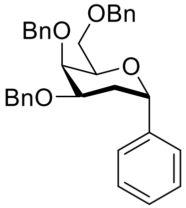
K_2HPO_4 (2 equiv), DMF

blue LEDs, r.t., 24 h

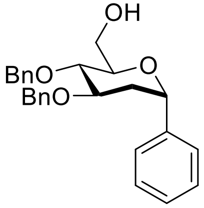
selected examples



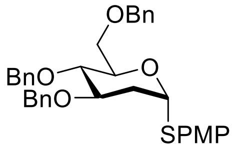
82%, α only



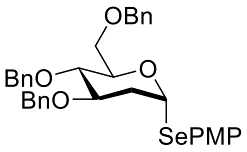
95%, α only



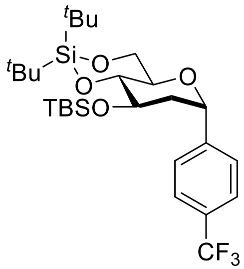
67%, α only



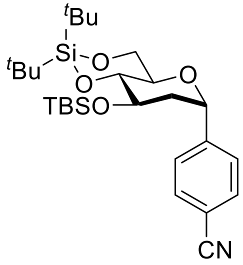
63%, α only



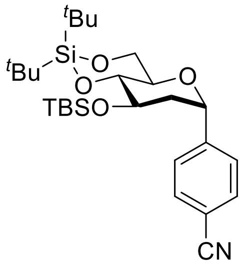
48%, α only



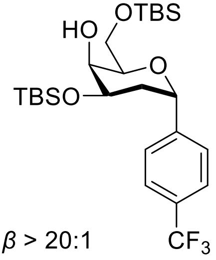
71%, α:β = 11:1



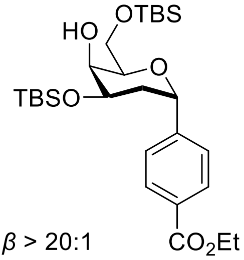
59%, α:β = 14:1



76%, α:β = 14:1



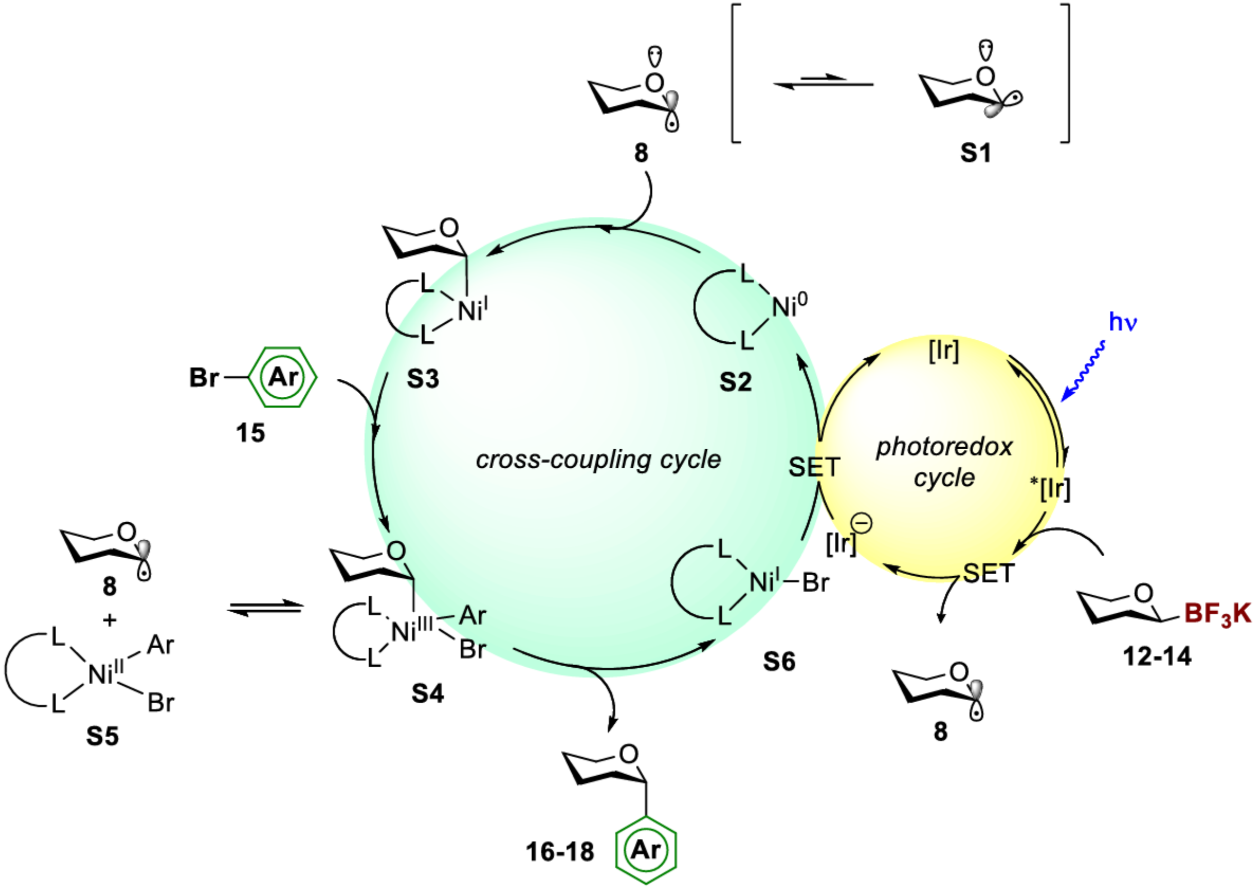
53%, α:β > 20:1



53%, α:β > 20:1

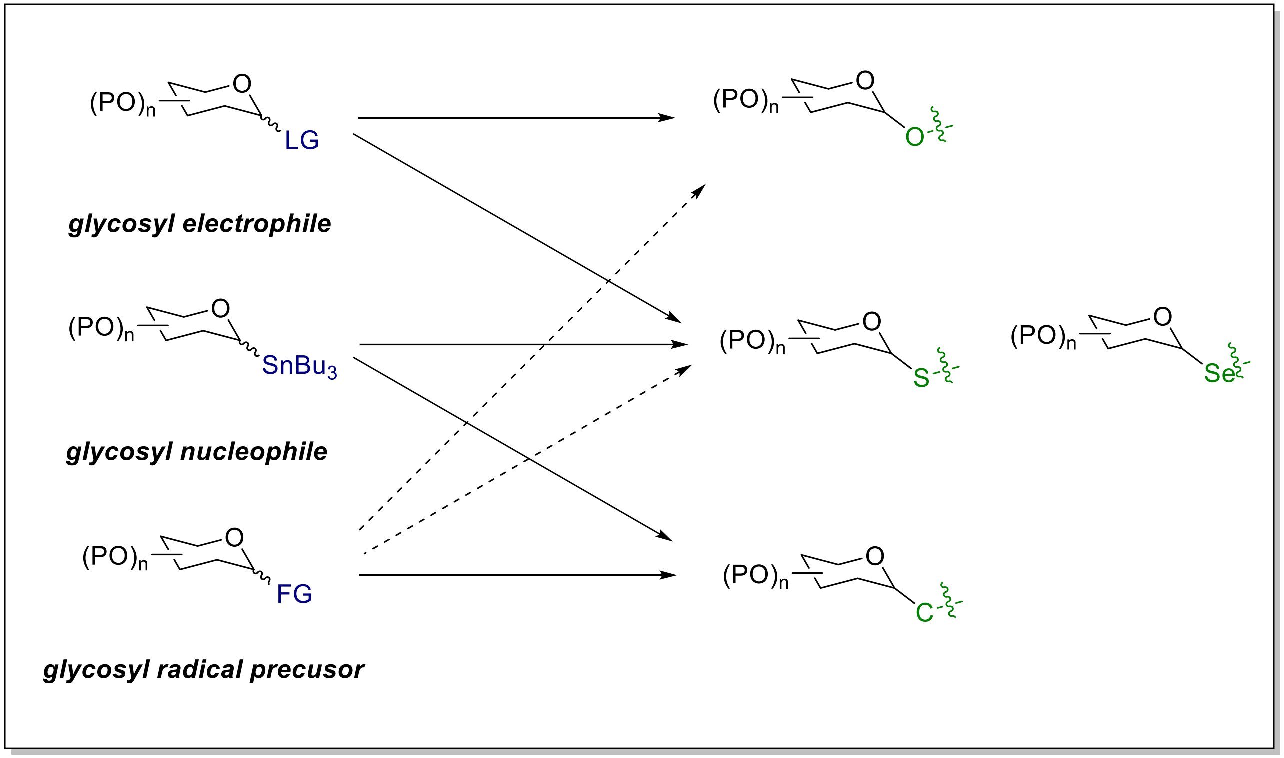
(a) Maciej A. Walczak, et al. *Org. Lett.* **2021**, 23, 4289-4293.
(b) Go Hirai, et al. *Org. Lett.* **2021**, 23, 1940-1944.

Photoredox/Ni-dual-catalyzed C-glycosylation



(a) Maciej A. Walczak, et al. *Org. Lett.* **2021**, 23, 4289-4293.
(b) Go Hirai, et al. *Org. Lett.* **2021**, 23, 1940-1944.

Conclusion and Perspective



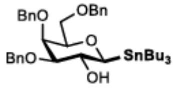
- Protecting groups
- Doner
- Condition

There is no universal glycosylation method to synthesize all possible glycosides.

Acknowledgement

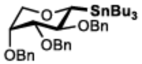
- ***Prof. Yan Xu***
- ***Prof. Jianbo Wang***
- ***All members in Xu group***
- ***Everyone here***

4. Detailed experimental procedures for compounds 10 - 124



10

(3,4,5-Tri-*O*-benzyl-*β*-D-galactosyl)tri-*n*-butylstannane (10).[2] To a solution of tri-*O*-benzyl-D-galactal[3] (1.04 g, 2.50 mmol) in a cooled (0 °C), vigorously stirring biphasic solution of CH_2Cl_2 (20 mL), saturated aq. $NaHCO_3$ (33 mL), and acetone (2.0 mL), a solution of Oxone® (6.16 g, 10.0 mmol) in H_2O (25 mL) was added dropwise over 15 min. The reaction mixture was stirred at 0 °C for 0.5 h then at rt for 2 h, the organic phase was separated, and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried (Na_2SO_3) and concentrated to afford the epoxide as a white solid. The crude epoxide was dissolved in anh. and degassed THF (30 mL), cooled to -20 °C, and a solution of $MeMgSnBu_3$ (1.24 g, 3.75 mmol) in THF was added. The reaction was stirred at -20 °C for 2 h, quenched with H_2O (30 mL), filtered twice through Celite®, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography on SiO_2 (Hexanes:EtOAc, 1:0 then 20:1) to afford **10** (1.10 g, 61%) as a pale yellow oil: $[a]_D^{25}$ = +4.9 (c = 1.00, $CHCl_3$); IR (ATR) ν = 3029, 2918, 2857, 2359, 1453, 1358, 1207, 1064, 574, 731, 694, 595 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 15H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.54-4.49 (m, 2H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.24-4.17 (m, 1H), 4.05-4.04 (m, 1H), 3.62-3.52 (m, 2H), 3.48-3.40 (m, 2H), 3.34-3.30 (m, 1H), 2.22 (dd, *J* = 2.6, 1.9 Hz, 1H), 1.65-1.40 (m, 6H), 1.36-1.24 (m, 6H), 1.06-0.91 (m, 6H), 0.87 (td, *J* = 7.2, 1.1 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 138.3, 138.2, 128.7, 128.5, 128.3, 128.0 (3), 127.8, 127.7, 127.4, 86.6, 81.3, 76.2, 74.5, 73.7, 73.6, 71.7, 70.3, 69.4, 29.2, 27.5, 13.9, 9.1; HRMS (ESI) *m/z* calcd for $C_{39}H_{56}O_5SnNa$ $[M + Na]^+$ 747.3042, found 747.3043.



11

(2,3,4-Tri-*O*-benzyl-*β*-D-arabinosyl)tri-*n*-butylstannane (11). To a solution of 3,4-di-*O*-benzyl-D-arabinal[3] (500 mg, 1.69 mmol) in a cooled (0 °C), vigorously stirring biphasic solution of CH_2Cl_2 (10 mL), satd. aq. $NaHCO_3$ (18 mL), and acetone (1.0 mL), a solution of Oxone® (4.16 g, 6.76 mmol) in H_2O (18 mL) was added dropwise over 15 min. After the addition was complete, the mixture was stirred for 0.5 h at 0 °C then for 2 h at rt. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL). The combined organic phases were dried over Na_2SO_3 and concentrated to afford the epoxide as a white solid. The crude epoxide was dissolved in anh. and degassed THF (15 mL) under N_2 and cooled to -20 °C for the addition of $MeMgSnBu_3$ (837 mg, 2.53 mmol). The solutions were stirred at -20 °C for 2 h and then quenched with H_2O (18 mL). The mixture was filtered twice through Celite® and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3x 15

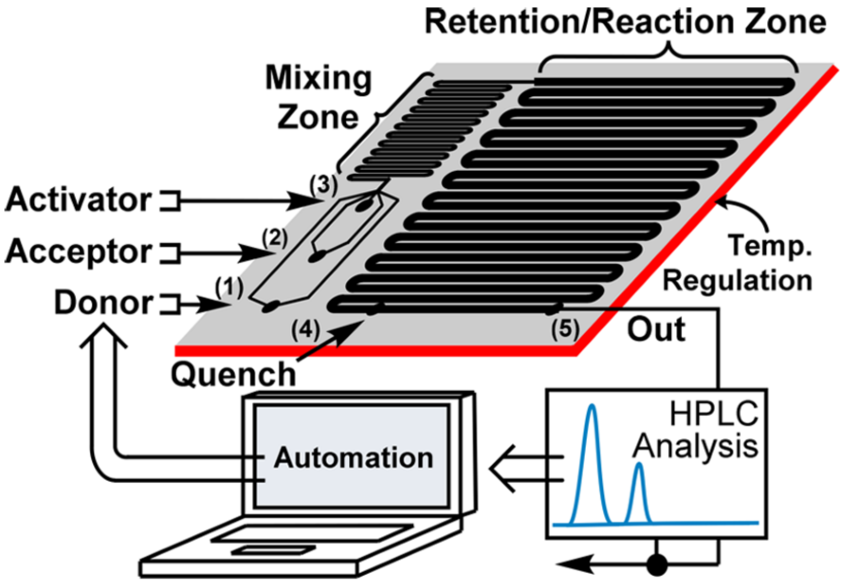
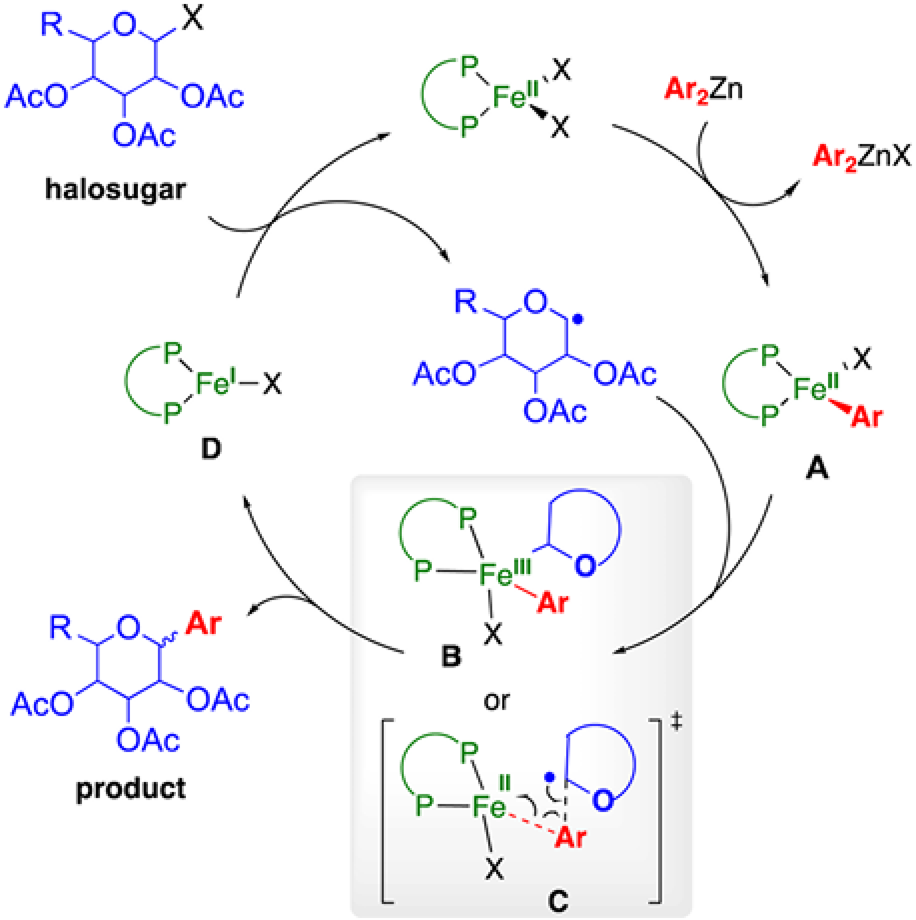


Figure 4. Automated glycosylation instrument consisting of three sections: multipart reaction section, HPLC analysis, and automation. For complete system details, see Supporting Information.


halosugar
R
O
X
AcO
OAc
OAc
P
Fe^II
X
X
P
Ar₂Zn
Ar₂ZnX
Fe^II
Ar
A
Fe^I—X
D
B
Fe^III
or
C
Fe^II
‡
Ar
product