New Modes of H-Bond Donor Catalysis

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Harvard University

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Napoli, Italy

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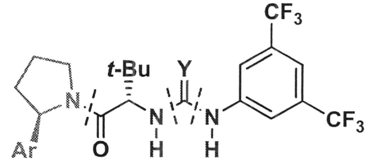
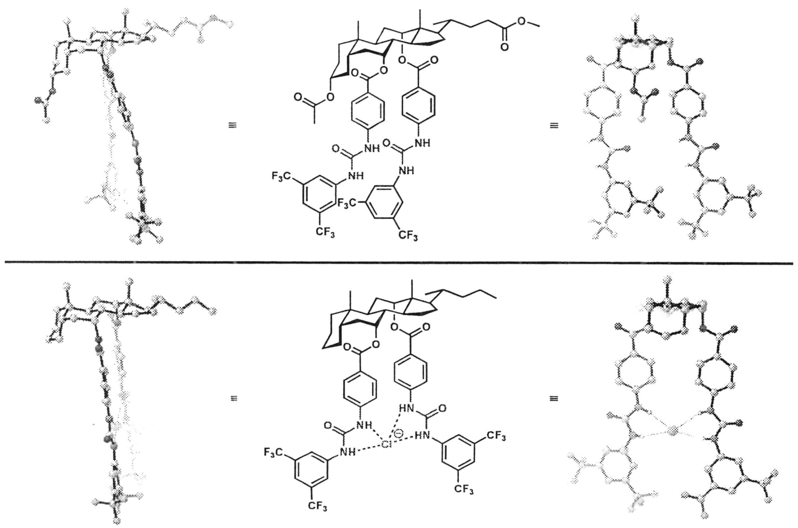
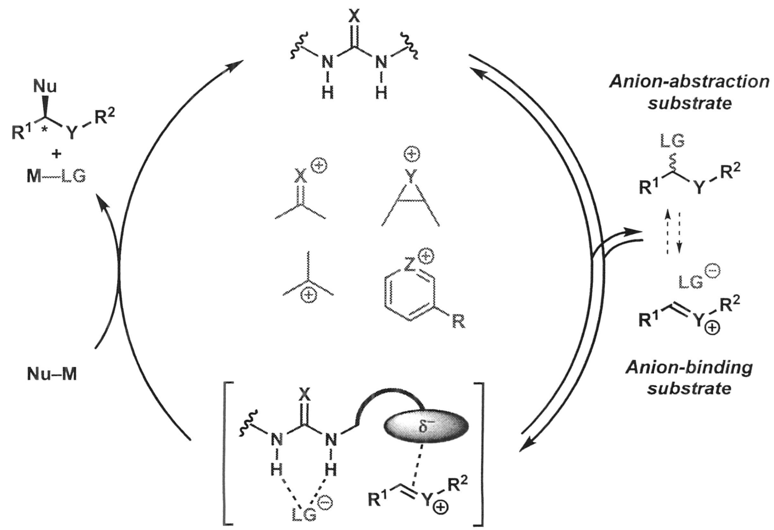
"Half-Schreiner" Arylpyrrolidine Catalysts

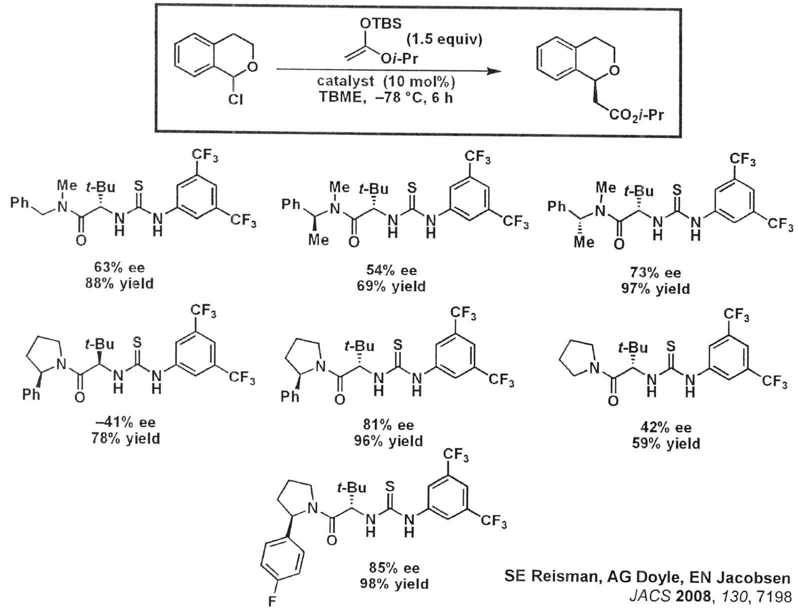


Anion-Binding Properties of Ureas and Thioureas



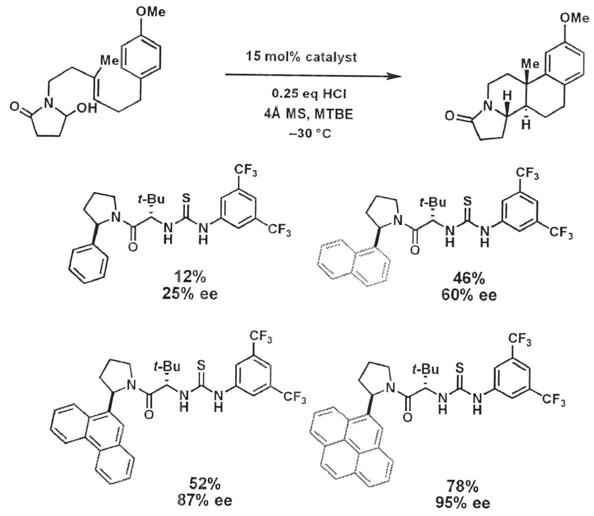
Anion-Abstraction & Anion-Binding Catalysis





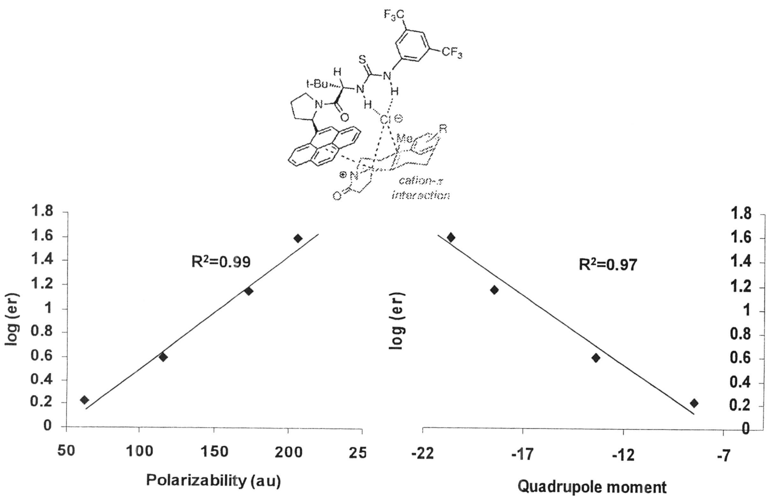
SE Reisman, AG Doyle, EN Jacobsen
JACS **2008**, *130*, 7198

A Dramatic Effect of Extended Aromatic Substituents

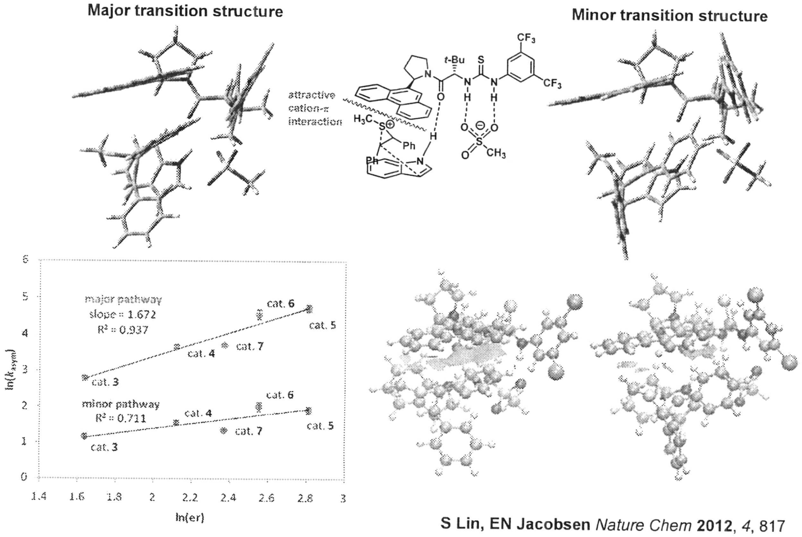


RR Knowles, S Lin, EN Jacobsen *JACS* **2010**, 132, 5030

Correlations of Enantioselectivity with Physical Properties Underlying Cation-π Interaction



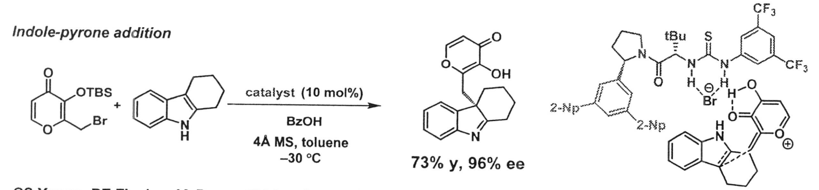
Attractive Transition Structure Interactions



S Lin, EN Jacobsen *Nature Chem* **2012**, *4*, 817

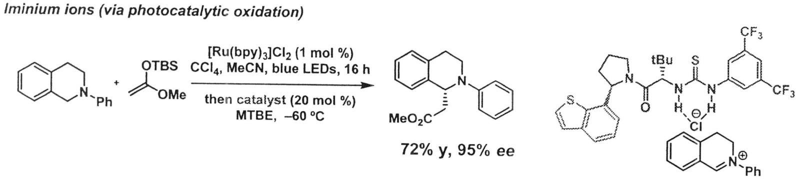
Aryl Groups as Design Elements in Chiral Catalysts

Indole-pyrone addition



CS Yeung, RE Ziegler, JA Porco, EN Jacobsen *JACS* **2014**, *136*, 13614

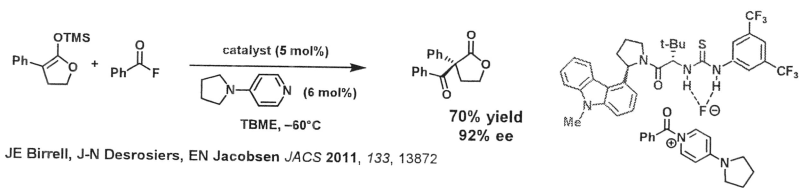
Iminium ions (via photocatalytic oxidation)



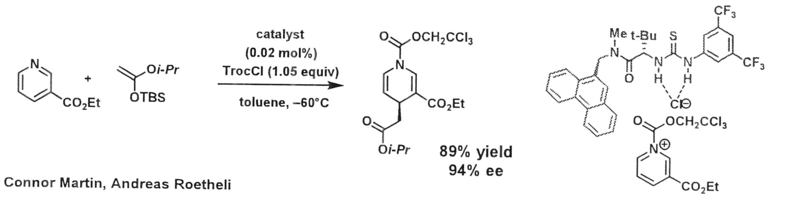
G Bergonzini, CS Schindler, C-J Wallentin, EN Jacobsen, CR Stephenson *Chem Sci* **2014**, *5*, 112

Aryl Groups as Design Elements in Chiral Catalysts

N-acylpyridinium ions

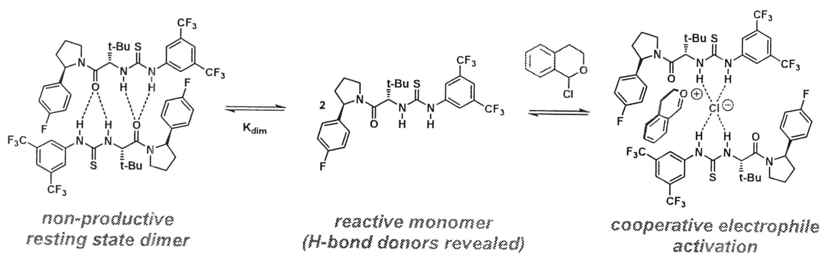


JE Birrell, J-N Desrosiers, EN Jacobsen *JACS* **2011**, *133*, 13872

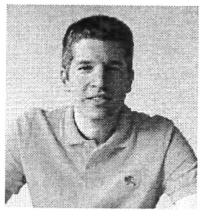


Connor Martin, Andreas Roetheli

Aggregation Phenomena in Anion-Abstraction Catalysis



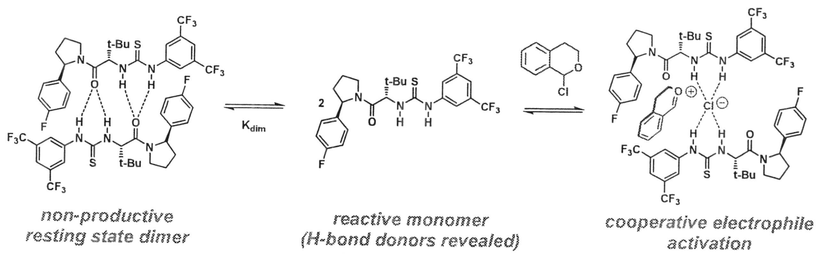
David Ford



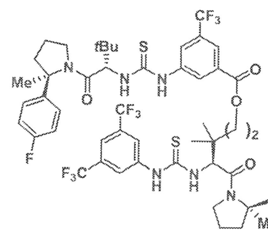
Dan Lehnherr

JACS **2016**, *138*, 7860
ACS Catal **2016**, *6*, 4616
Org Lett **2016**, *18*, 3214

"The Fully Substituted Naomi Dimer"



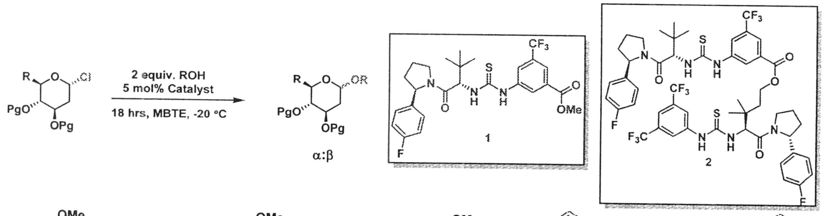
Naomi
Rajapaska

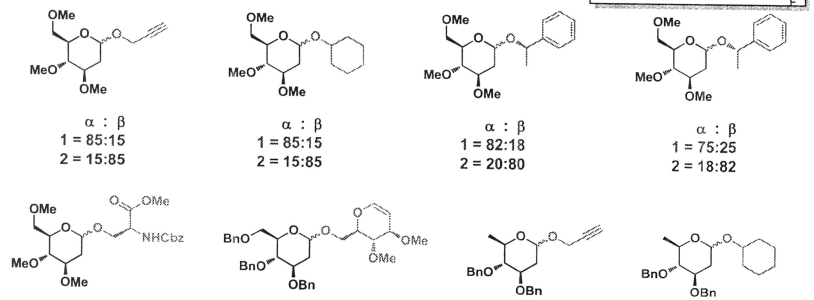


Up to 10^2 x more reactive
More enantioselective

JACS **2016**, *138*, 13525

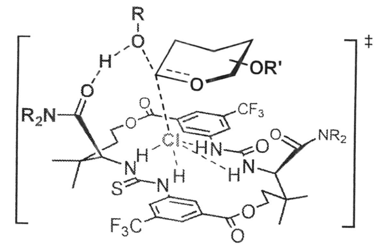
The Naomi Dimer Induces β Selectivity in Glycosylations

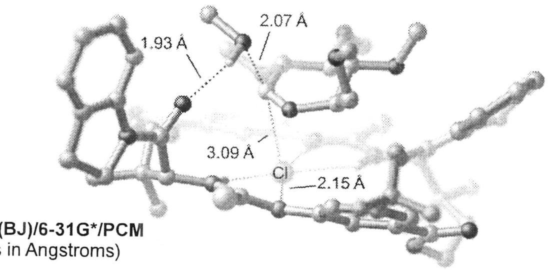




α : β 1 = 85:15 2 = 15:85	α : β 1 = 85:15 2 = 15:85	α : β 1 = 82:18 2 = 20:80	α : β 1 = 75:25 2 = 18:82
α : β 1 = 85:15 2 = 19:81	α : β 1 = 85:15 2 = 20:80	α : β 1 = 86:14 2 = 13:87	α : β 1 = 86:14 2 = 12:88

Mechanistic Model



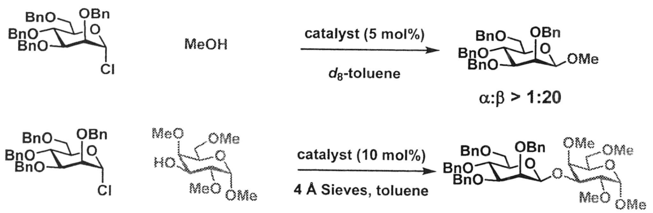


PBE0-D3(BJ)/6-31G*/PCM
(distances in Angstroms)

Y Park, KC Harper, N Kuhl, RY Liu, EE Kwan, EN Jacobsen *Science* **2017**, *355*, 162–166

Toward Useful Catalyst-Controlled Glycosylations?

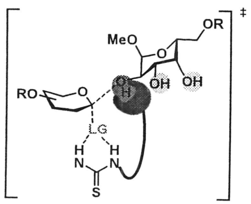
- *Complex Partners*

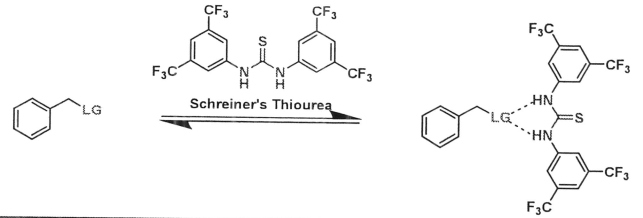


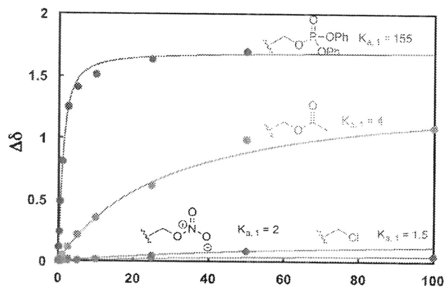
$t_{1/2}$ = 2 hr

$t_{1/2}$ > 96 hr

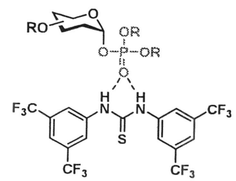
- *Site Selectivity*





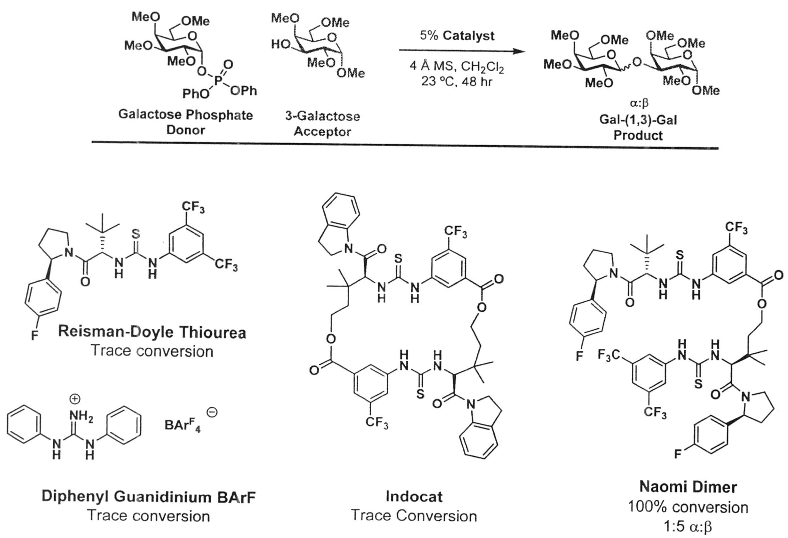


Phosphate binds >100X more strongly than -Cl

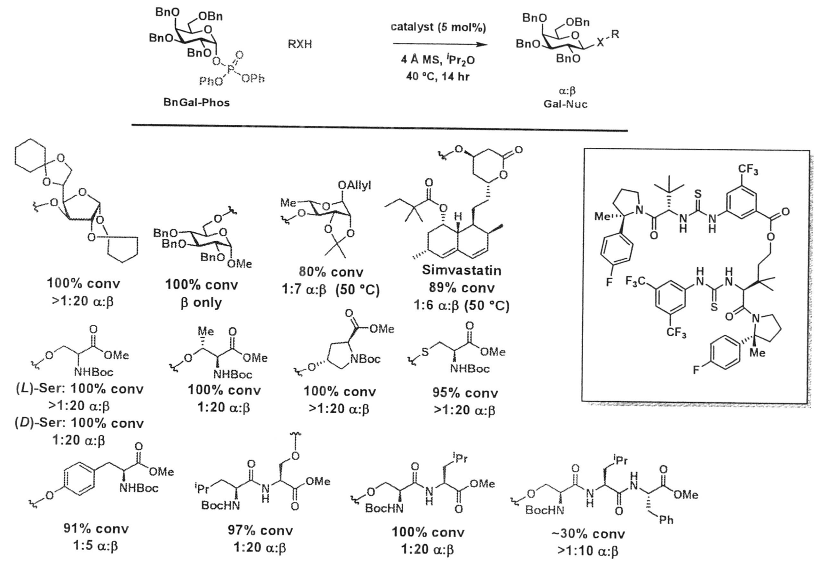


Andy Roetheli

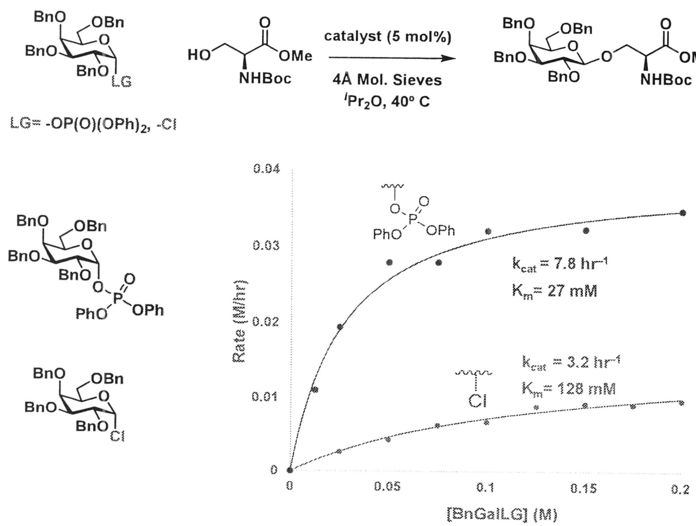
Glycosyl Phosphate Screen



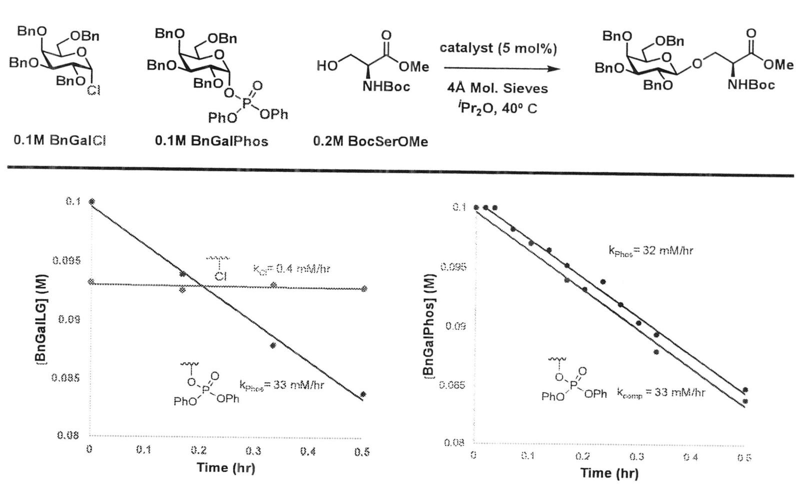
Galactosylation Scope



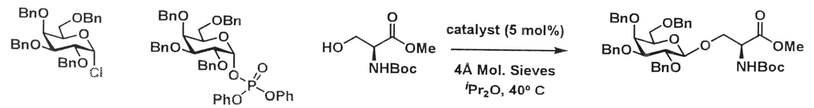
Kinetic Analysis



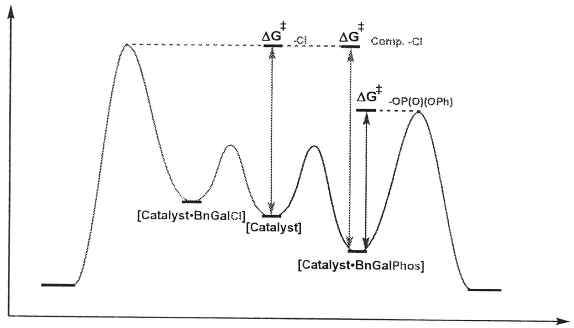
Competition Experiment



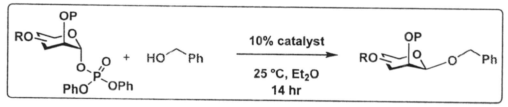
Competition Experiment

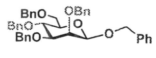


0.1M BnGalCl · 0.1M BnGalPhos · 0.2M BocSerOMe



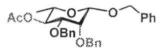
cis-1,2-Linkages



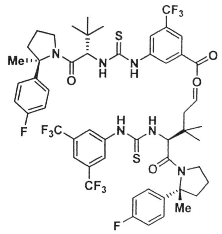


Mannose

Mannose	1:	1:2.3 α:β (7% conv)
	ent-1: (40 °C, $^iPr_2O$)	1:7.5 α:β (20% conv) 1:10 α:β (>95% conv)
	Background:	0% conv
Rhamnose	1:	1:10 α:β (80% conv)
	ent-1:	1:2 α:β (7% conv)
	Background:	0% conv

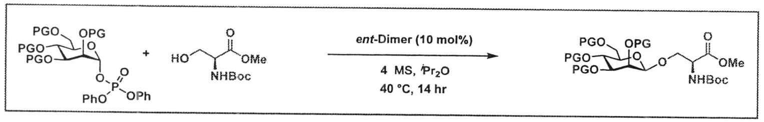


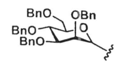
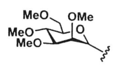
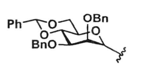
Rhamnose



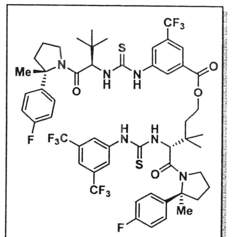
1

Mannose Protecting-Group Effects

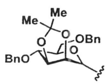
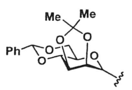
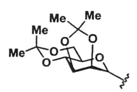


Cat	48% conversion 1:1 β:α	73% conversion 2:1 β:α	10% conversion 1:1 β:α
TMSOTf	100% conversion 1:7 β:α	100% conversion 1:1.5 β:α	73% conversion 4:1 β:α (−30 °C)

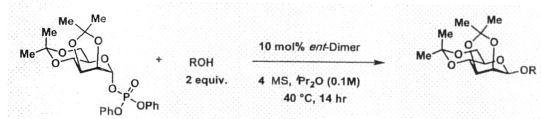


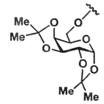
ent-Dimer

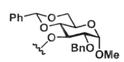
Cat	100% conversion 25:1 β:α	30% conversion 17:1 β:α	60% conversion 28:1 β:α
TMSOTf	100% conversion 1:7.8 β:α	100% conversion 1:3 β:α	100% conversion 1:8 β:α

β-Mannosylations

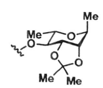




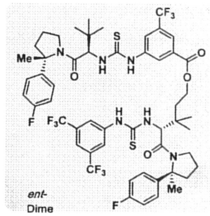
6-Gal
98% yield
19:1 β:α



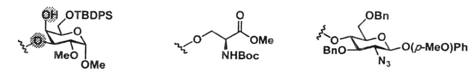
3-Glu
75% conversion
20:1 β:α



4-Rham
70% conversion
16:1 β:α



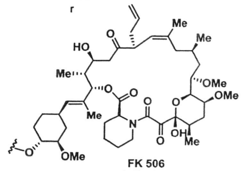
ent-Dimer



3-Gal
33% conversion
6.5:1 (1,3):(1,4)
13:1 β:α

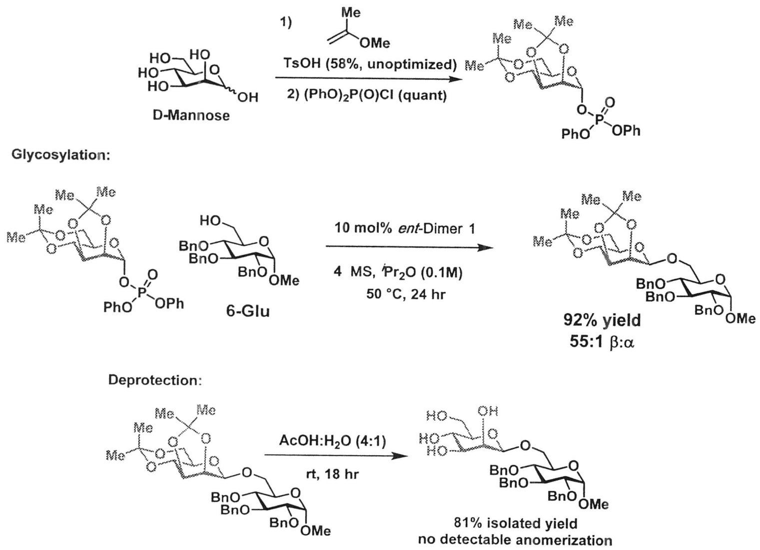
(L)-Ser
84% conversion
19:1 β:α

4-GluN$_3$ (48 hr)
74% conversion
10:1 β:α

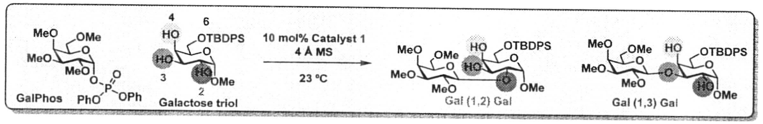


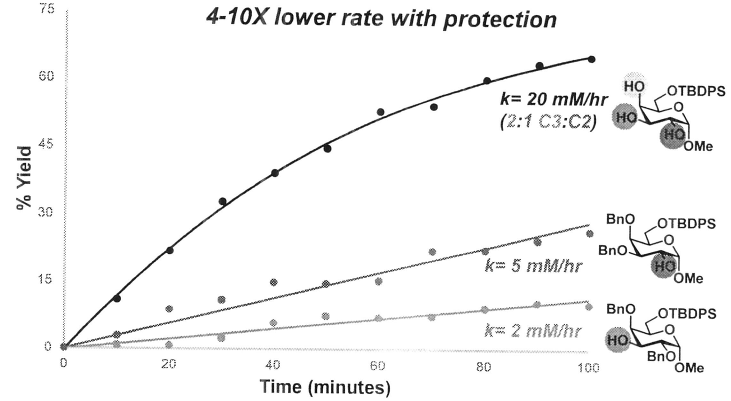
FK 506
67% yield
single regioisomer

A Practical Protocol for β-Mannosylation

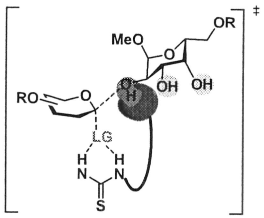


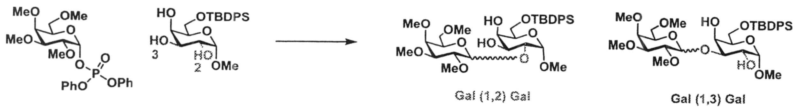
The Problem with Protection





Catalyst-Controlled Site Selectivity?

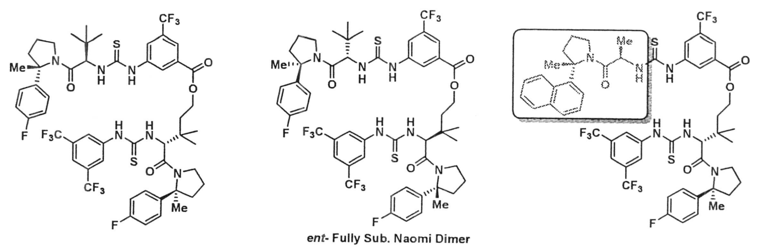




Uncatalyzed: 1.3 : 1

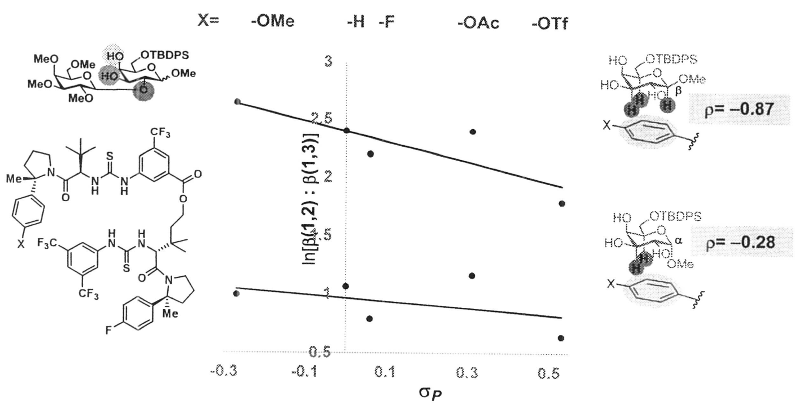
α:β (2.7:1) : **(2.1:1)**

Site-Selective Glycosylation

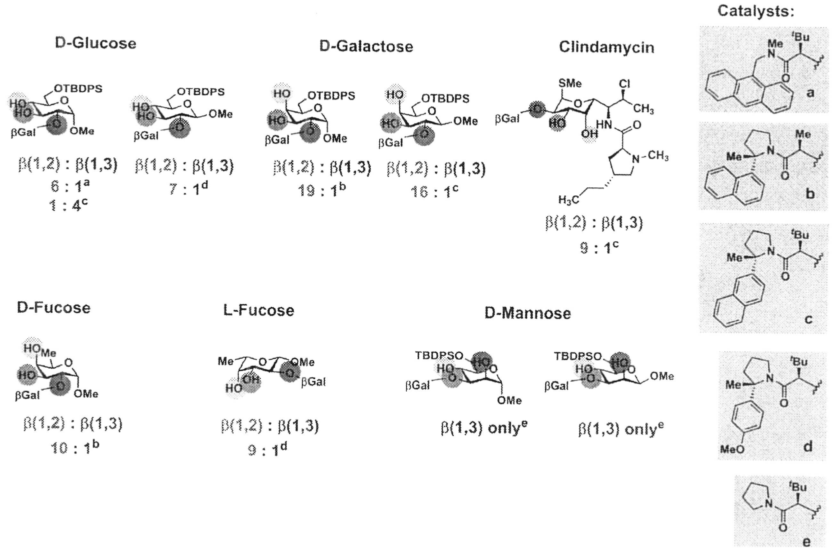


Regio 2.3 : 1	Regio 1 : 2.2	Regio 19 : 1
α:β (1:15) : (1:6)	α:β (1:8) : (1:16)	β only
67% conversion	93% conversion	95% conversion

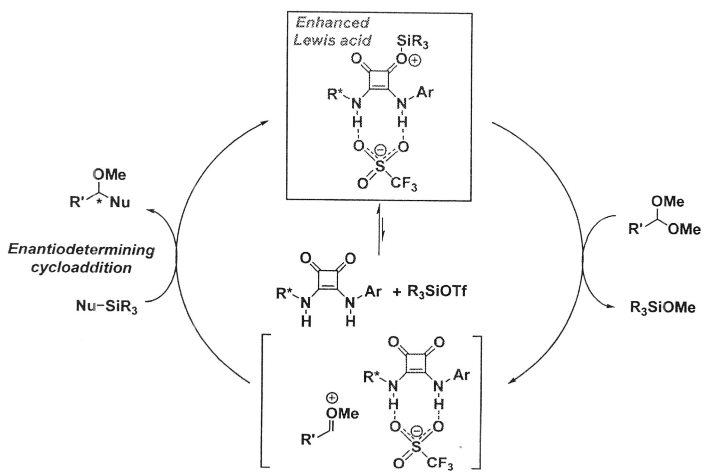
Evidence for CH–π Interaction Directing Site-Selectivity



Site-Selective Glycosylation

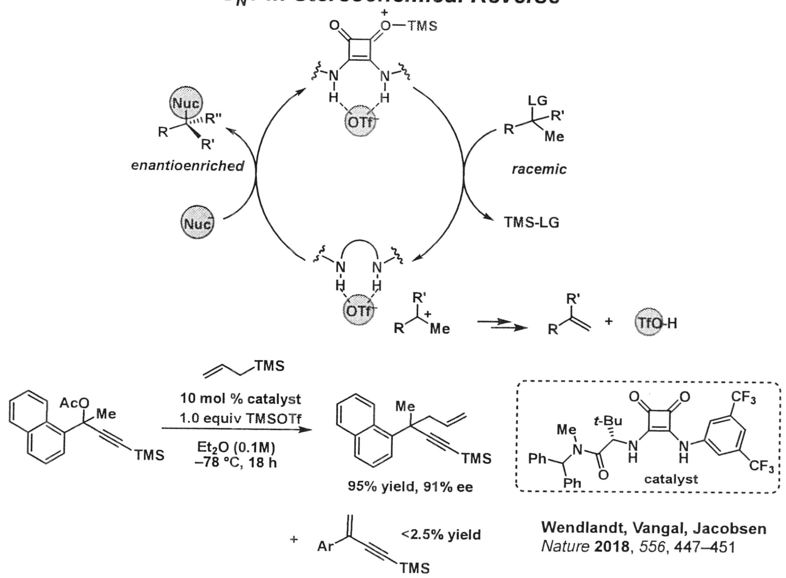


Cooperative Reactivity of H-Bond Donors and Lewis Acids



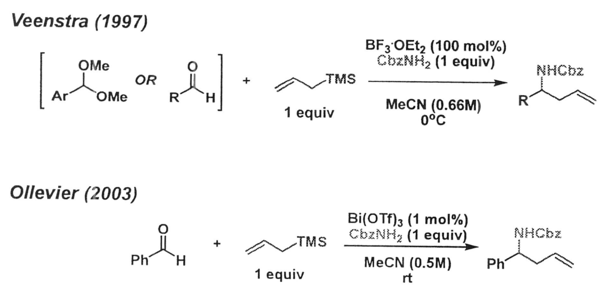
SM Banik, A Levina, AM Hyde, EN Jacobsen *Science* **2017**, *358*, 761

S_N1 in Stereochemical Reverse



Wendlandt, Vangal, Jacobsen
Nature **2018**, *556*, 447–451

Three-Component Iminium Allylation

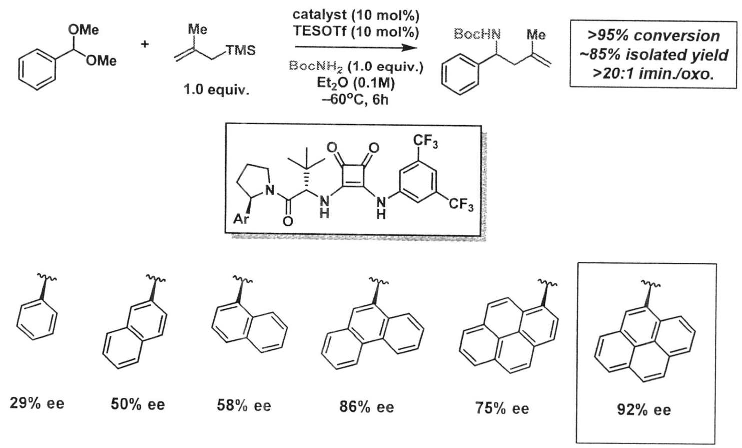


Other Lewis acids: TMSOTf, $TiCl_4$, $Cu(OTf)_2$, $Zn(ClO_4)_2$

no enantioselective examples

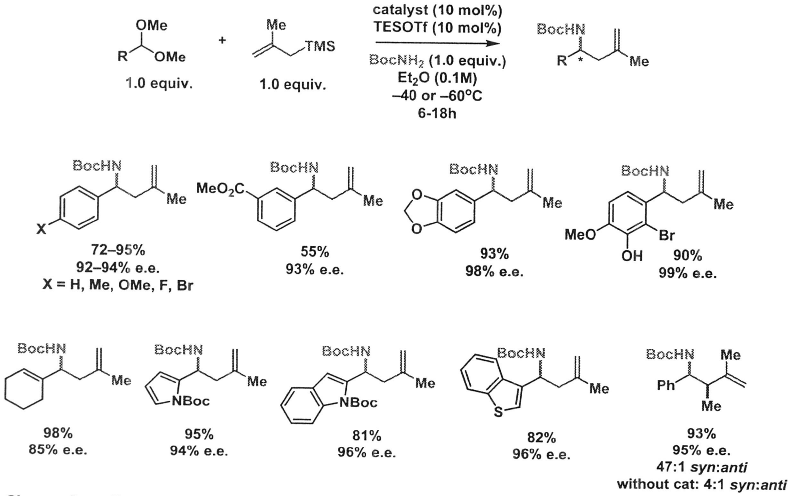
Veenstra & Schmid *TL* 1997, *38*, 997
Ollevier & Ba *TL* 2003, *44*, 9003
Billet, Klotz, Mann *TL* 2001, *42*, 631

Enantioselective Three-Component Coupling



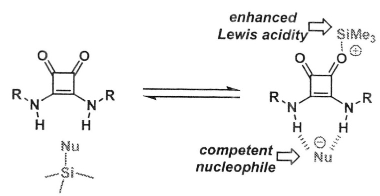
Shauna Paradine

Three-Component Iminium Allylation: Scope

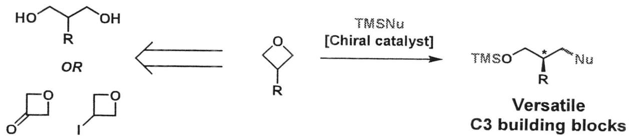


Shauna Paradine

Activation of Polarized Si–Nu Bonds



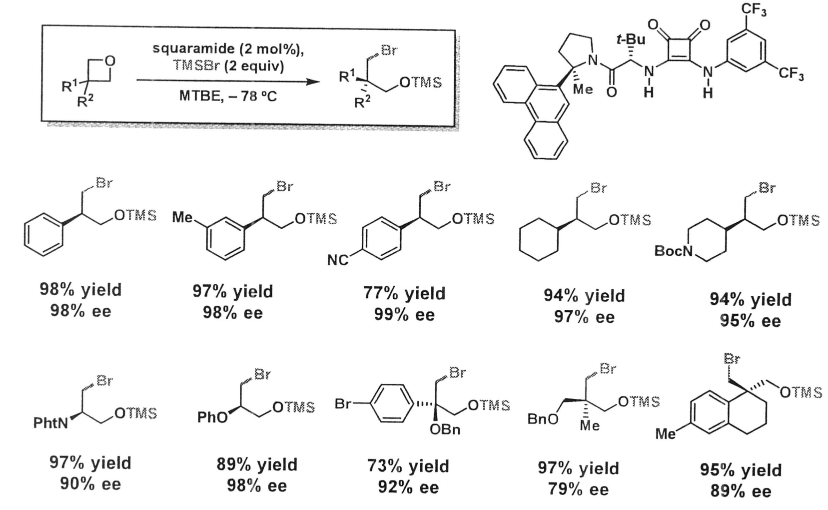
Si–Nu bond heterolysis:
- Catalyst-induced Lewis acid enhancement
- Catalyst-bound anionic nucleophile



Versatile
C3 building blocks

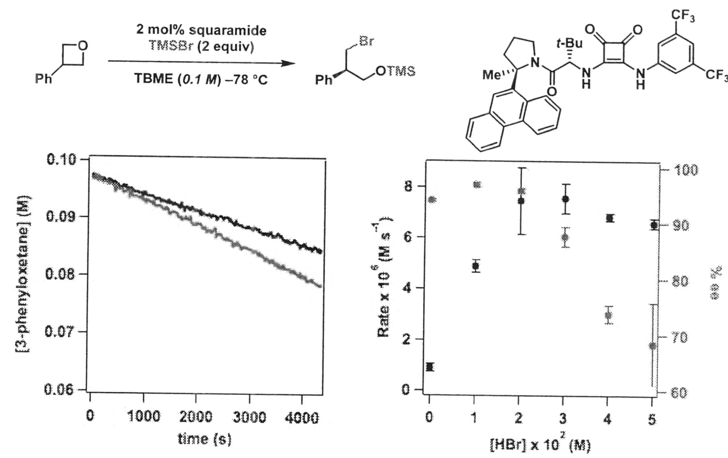
Phosphoric acid-catalyzed oxetane ring-openings: Sun *ACIE* **2016**, *55*, 6954

Enantioselective Ring-Opening of Oxetanes with TMSBr



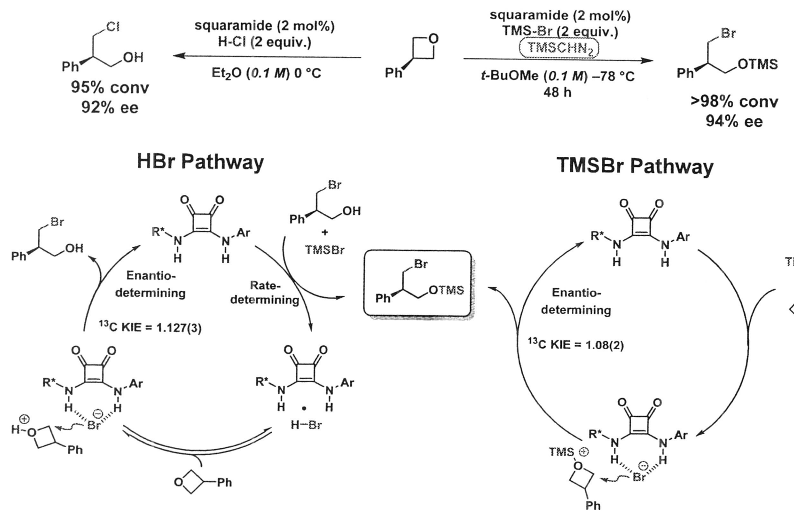
Zach Wickens, Dan Strassfeld

Kinetic Analysis



Dan Strassfeld, Russ Algera, Zach Wickens

Two Highly Enantioselective Pathways in Competition



Co-Catalysis!