Phenanthroline-Catalyzed Stereoselective Formation of α-1,2-*cis* 2-Deoxy-2-Fluoro Glycosides

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ABSTRACT

Phenanthroline is a heterocyclic aromatic organic compound and commonly used in coordination chemistry acting as a bidentate ligand. The C4 and C7 positions of phenanthroline can often be substituted to change the binding capabilities of the ligand. Recently, there has been a push in the field of chemistry to create "green" chemical methodologies by utilizing catalysts and minimizing solvent. Herein, we have demonstrated how, at high concentrations with minimal use of solvent, the C4 and C7 positions of phenanthroline can be tuned to develop an efficient and stereoselective catalyst for the formation of 2-deoxy-2-fluoroglycosides. By activating 2-deoxy-2-fluoroglycosyl halides with the phenanthroline based catalysts, we have been able to achieve glycosylations with high levels of α-selectivity and moderate to high yields. The catalytic system has been applied to several glycosyl halide electrophiles with a range of glycosyl nucleophilic acceptors. The proposed mechanism for this phenanthroline type catalyst has been investigated by density-functional theory calculations which indicates that the double S_N2 displacement pathways with phenanthroline catalysts have lower barriers and ensure stereoselective formation of α-1,2-*cis*-2-fluoro glycosides.

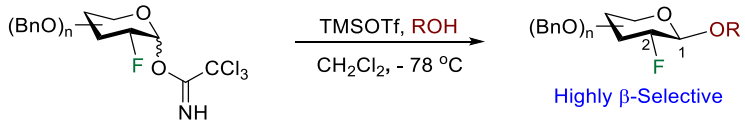
KEYWORDS: *Catalytic glycosylation, stereoselective, phenanthroline catalyst, 1,2-cis-2- fluoro glycosides, oligosaccharides*

INTRODUCTION

Carbohydrates are widespread in nature and have been considered as the frontier of medicinal chemistry.[1] In general, the sugar based biomolecules are constructed from rudimentary glycosylation reactions, which take place between a glycosyl donor (electrophile) and glycosyl acceptor (nucleophile).[2] These reactions allow for the establishment of two different α- and β-stereoisomers that differ in the configuration of the anomeric carbon. In many cases, α-glycosides have a *cis* relationship between the substituents on the anomeric carbon and the second carbon of the electrophilic coupling partner; with the exclusion of a few rare sugars. Conversely, β-glycosides would have a 1,2 *trans* relationship with the same exceptions.[3] By taking advantage of neighboring group participation of acyl protecting groups at the second carbon of glycosyl donor, 1, 2-*trans* glycosides can be made with high levels of selectivity.[4] For this reason, many methods focuses on the development of the stereoselective formation of 1,2-*cis* linked glycosides, which is the principal challenge of complex oligosaccharide synthesis.[5]

Although fluorine is the least abundant halogen present in natural products, it has been an essential element as a bioisotere of hydrogen and hydroxyl functionality in medicinal chemistry for the creation of new drugs and the improvement of existing ones.[6-10] Exchange of a hydrogen atom for a fluorine can impact the pharmacokinetics on the molecules, including pKa, lipophilicity, binding affinity, and metabolic stability, without significantly altering the sterics of the molecule.[11] Currently, about 20% of the market pharmaceuticals contain at least one fluorine atom.[12] Even though both carbohydrates and fluorine play a significant role to the field of medicinal chemistry, there is a lack of methods for the stereoselective formation of fluorinated glycosides.[13,14] Recently, Gilmour and coworkers have established effective methodology for selectively forming β-linked fluorinated glycosides (Figure 1a).[15-18] The Gilmour approach is highly stereoselective towards β-1,2-*trans* glycosides. On the other hand, methodologies to selectively produce α-linked fluorinated glycosides remain largely underdeveloped.

(a) **Previous work**: β-selective 1,2-*trans*-2-fluoro glycosides



(b) **This work**: α-selective 1,2-*cis*-2-fluoro glycosides

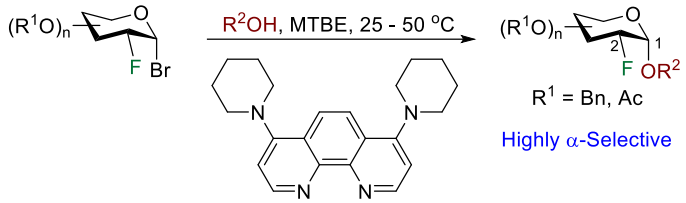


Figure 1. Stereoselective formation of α- and β-fluorinated glycosides

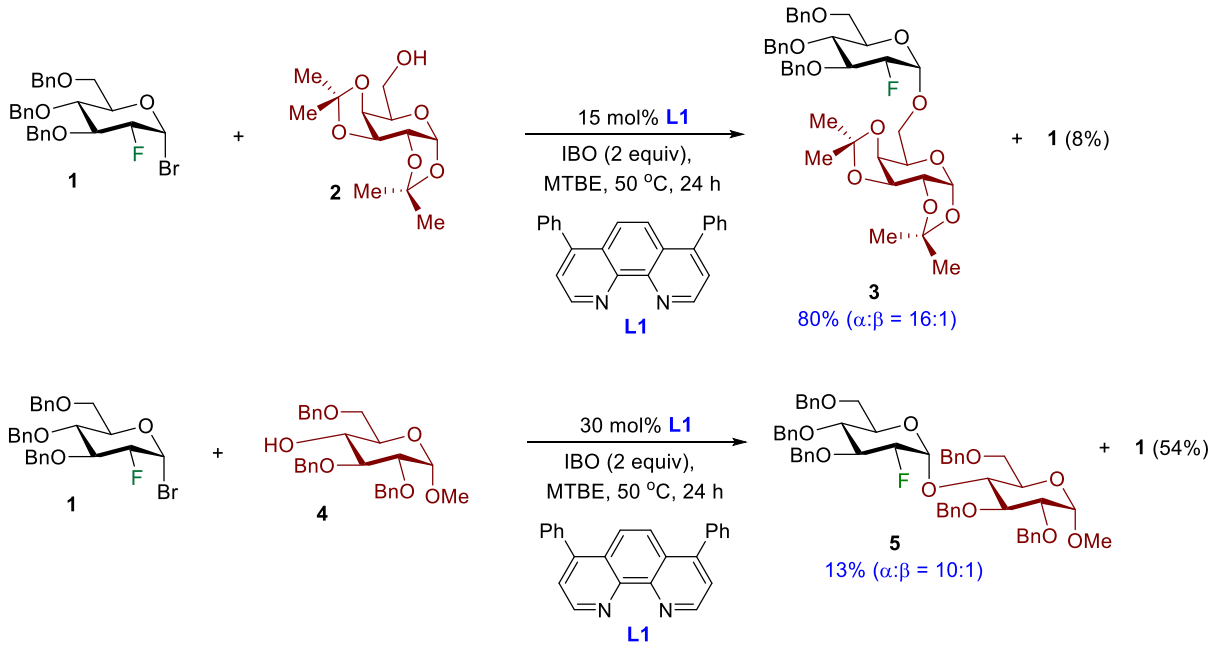
The ability of phenanthroline to effectively catalyze α-linked glycosidic bond formation when reacted with glycosyl bromides was recently discovered by our group.[19] This catalyst-controlled approach is highly predictable and provides efficient access to a myriad of α-1,2-*cis* glycosides. The phenanthroline-catalyzed glycosylation methodology mimics glycosyltransferase-catalyzed retentive mechanisms, wherein the stereochemistry of the products is influenced by the anomeric α-configuration of glycosyl bromides. As a result, we question if this catalyst-controlled system gives an alternative stereochemical outcome of the inherently electronic bias of 2-fluoro substrates, providing efficient access to α-1,2-*cis*-2-fluoro glycosides (Figure 1b). If successful, it will be complementary to the Gilmour's β-1,2-*trans*-2-fluoro glycoside approach. Herein, we demonstrate that α-1,2 *cis* 2-fluoro glycosides can be stereoselectively accessed for the first time using commercially available and easily synthesized phenanthroline based catalysts.

RESULTS AND DISCUSSION

We initially investigated the reactivity of tribenzyl 2-fluoro glucosyl bromide **1** as an electrophilic coupling partner in the reaction with galactoside nucleophile **2** (Scheme 1) using our previously optimized conditions.[19] Accordingly, the coupling was performed with 15 mol%

bathophenanthroline, **L1**, as a catalyst in MTBE and isobutylene oxide (IBO) as acid scavenger of the HBr by-product at 50 °C for 24 h, effectively producing fluorinated disaccharide **3** in good yield (80%) and α-1,2 *cis* selectivity (α:β = 16:1). Encouraged by this result, we next explored the glycosylation with the more challenging C(4)-hydroxyl acceptor **4**. Although compound **4** displayed high levels of α-selectivity (α:β = 10:1), we observed low reactivity of this secondary alcohol. The desired disaccharide **5** was isolated in only 13% yield, along with recovery of glucosyl bromide donor **1** (54%). This result became clear that the existing conditions were not effective for the coupling of challenging nucleophilic acceptor with 2-fluoro glycosyl bromide donor.

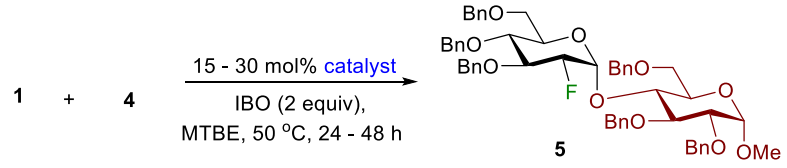
Scheme 1. Preliminary studies with bathophenanthroline **L1** catalyst



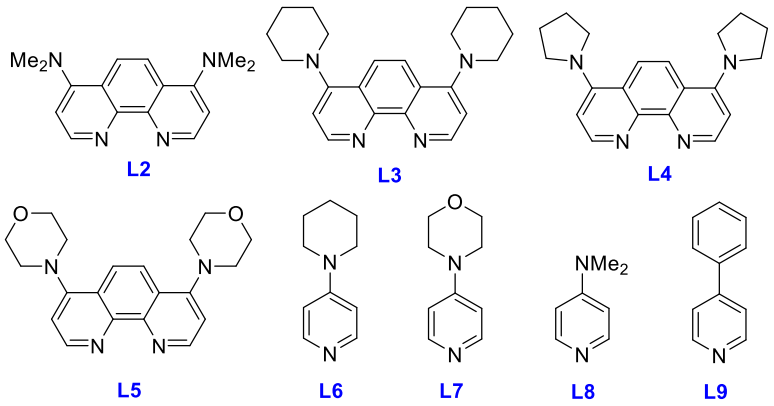
The starting point of optimization was the identification of reaction parameters that could further improve the yield of the coupling product **5** (Table 1). Increasing the catalyst loading of **L1** and reaction temperature (entry 2) further improved the coupling efficiency, furnishing 27% of **5**. Further exploration revealed that switching the ratio of donor and acceptor slightly increased the yield of the coupling product (entry 3). Low conversion under **L1**-catalyzed glycosylation conditions with sterically hindered acceptor **4** appears to be likely due to the nucleophilic nature of the catalyst. With these observations in mind, several catalysts were investigated to determine the significance of the two nitrogen system seen in bathophenanthroline, **L1**, and how changing the phenyl substituent at the C4 and C7 position can affect the reactivity of the system. First, it was decided to investigate a *N*,*N*-dimethylamino substituent (**L2**) in replacement of the C4- and C7-phenyl group. We hypothesized that switching to **L2** (entry 4) could further improve the yield because it is more nucleophilic than **L1** catalyst due to the electron donating nature of the *para*-substituted dimethylamino group. However, the reaction gave only trace reactivity (entry 4). In addition, significant by-products were observed and glycosyl bromide donor **1** was recovered in only 12% yield. We hypothesized that the *N*,*N*-dimethylamino substituent could be acting as a competing nucleophile leading to the formation of many side products. To resolve this issue, we proposed that using a sterically hindered nitrogen at the C4 and C7 positions of phenanthroline

could suppress these side reactions. To validate our hypothesis, the steric and electronic nature of the *para*-substituent, piperidine (**L3**), pyrrolidine (**L4**), and morpholine (**L5**) derivatives of phenanthroline were investigated (entries 5–9). Using **L3** catalyst (entry 5) under analogous conditions showed the highest improvement in yield (68%) along with the preservation of glycosyl bromide starting material **1** (39%). Lowering the catalyst loading of **L3** (30 →15 mol%, entry 6) resulted in no diminishment in selectively while decreasing the yield of the coupling product **5** (68→45%). Shortening reaction times (48→24 h) also diminished in yield (68→40%, entry 7).

Table 1. Optimization of C4-hydroxyl Tribenzyl Glycosides



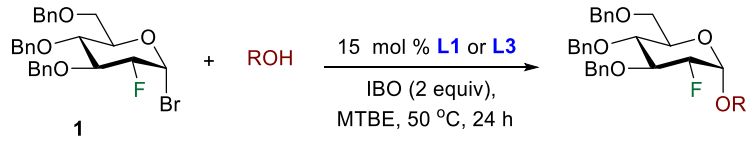
entry	catalyst	loading (mol%)	**1** (equiv.)	**4** (equiv.)	time (h)	**5** yield (%)[b]	**5** (α:β)[c]	recovered **1** (%)[b]
1	**L1**	15	1	3	24	13	10:1	54
2	**L1**	30	1	3	48	27	10:1	38
3	**L1**	30	2	1	48	33	10:1	34
4	**L2**	30	2	1	48	Trace	-	12
5	**L3**	30	2	1	48	68	10:1	39
6	**L3**	15	2	1	48	45	10:1	44
7	**L3**	30	2	1	24	40	10:1	21
8	**L4**	30	2	1	48	56	10:1	25
9	**L5**	30	2	1	48	43	10:1	29
10	**L6**	30	2	1	48	66	10:1	9
11	**L7**	30	2	1	48	37	10:1	4
12	**L8**	30	2	1	48	38	10:1	3
13	**L9**	30	2	1	48	20	10:1	4

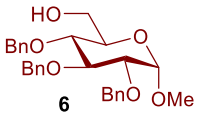
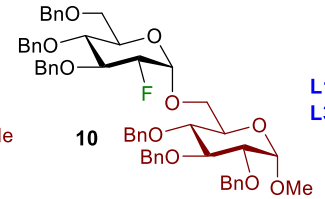
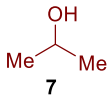
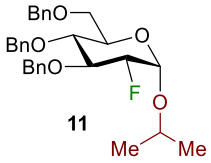
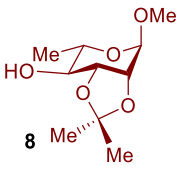
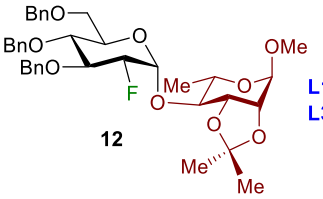
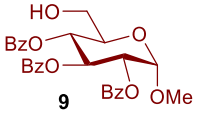
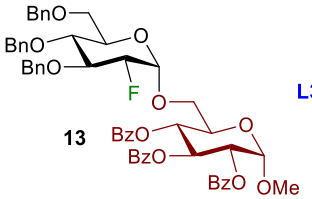


[a] The reaction was conducted using 15-30 mol% catalyst **L1**-**L9**.
[b] Isolated yield. [c] Diastereoselective (α:β) ratio of the coupling product **5** determined by ^{19}F NMR.

To determine the importance of the dual nitrogen system displayed in the phenanthroline class, we next evaluated the corresponding pyridine type catalysts in promoting the glycosylations. The effects of the mono-nitrogen catalysts compared to the dual nitrogen catalysts are illustrated in Table 1. Although both phenanthroline- and pyridine-derived catalysts provided disaccharide **5** with similar levels of selectivity (α:β = 10:1), it is noted by the consistently low amount of glycosyl bromide **1** recovered at the end of the reaction with the pyridine type catalysts (entries 10 – 13). For instance, while the 4-piperidine substituted pyridine catalyst, **L6**, provided **5** in similar yield (66%, entry 10) to that the 4,7-piperidine substituted phenanthroline catalyst **L3** (68%, entry 5), only 9% of starting material **1** was recovered for **L6** in comparison to 39% for **L3**. In all cases, the starting material **1** was recovered exclusively as α-bromide.

Table 2. Reactions of Tribenzyl 2-Fluoro Glucosyl Bromide Using **L1** and **L3** Catalysts[a]



entry	acceptors	products	results yield[b] (α/β ratio)[c]
1	 **6**	 **10**	**L1**: 62% (α:β = 7:1) **L3**: 89% (α:β = 8:1)
2	 **7**	 **11**	**L1**: 52% (α:β = 7:1) **L3**: 85% (α:β = 7:1)
3	 **8**	 **12**	**L1**: 42% (α:β > 20:1) **L3**: 61% (α:β > 20:1)
4	 **9**	 **13**	**L3**: 85% (α:β = 7:1)

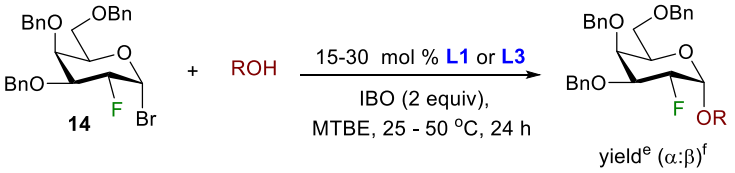
[a] The reaction was conducted using 1 equiv. of donor **1** and 3 equiv. of acceptor. [b] Isolated yield. [c] Diastereoselective (α:β) ratio of the coupling products determined by ^{19}F NMR.

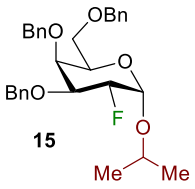
With optimized conditions fully developed, the scope of the phenanthroline-catalyzed stereoselective coupling reaction was examined with a number of primary and secondary alcohols. We chose to focus only on benzyl protected 2-fluoro electrophilic donors as they are known to be highly β-selective under Gilmour's conditions.[15-18] Accordingly, the standard tribenzyl 2-fluoro glucosyl bromide **1** was evaluated first with nucleophilic acceptors **6** – **8** to compare the efficiency of catalyst **L3** relative to catalyst **L1** (Table 2). The system employing **L3** uniformly furnished the coupling products **10** – **12** with higher yields compared to those using **L1**. In addition, our system relies on the phenanthroline catalyst to enforce stereocontrol of the newly-formed glycosidic linkage. On the other hand, the Gilmour's methodology relies on the electronic bias of the 2-fluoro substrates to effect the stereoselective glycosidic bond formation.[15-18] For instance, the coupling of primary alcohol **6** with 2-fluoro glucosyl bromide **1** under **L3**-catalyzed conditions provided the desired disaccharide **10** with high α-selectivity (α:β = 8:1, entry 1). In contrast, the Gilmour's method provided **10** with excellent levels of β-selectivity (α:β = 1:74).[15] Similarly, high α-selectivity was also observed for secondary alcohols **7** and **8** (entries 2 and 3) with use of **L3** as a catalyst while the Gilmour's method favors the β-selectivity for these acceptors.[15] Next, we examined the efficacy of this method to promote the coupling with electron-withdrawing alcohol nucleophile **9** (entry 4). Under these conditions, electron-poor acceptor **9** is well tolerated to furnish disaccharide **13** in comparable yield and selectivity (entry 4, **13**: 85%, α:β = 7:1) to the reaction with electron-donating alcohol **6** (entry 1, **10:** 89%, α:β = 8:1).

Reactivity of galactosyl bromide **12** with different glycosyl acceptors was next investigated utilizing catalysts **L1** and **L3** (Table 3) at a high (0.5 M) concentration. In many cases, replacement of catalyst **L1** with catalyst **L3** results in improvement in both α-selectivity and yield of the coupling products. It was significant to note that galactose donor **14** is more reactive than its glucose counterpart **1** as reactions can take place at ambient temperature with use of catalyst **L3**. For instance, the glycosylation of isopropanol **7** with tribenzyl 2-fluro galactosyl bromide **12** using **L1** did not take place at 25 °C. In contrast, use of **L3** proceeded smoothly at 25 °C under optimized conditions to afford the glycoside product **15** in 60% yield. The yield of the coupling product **15** was further improved (60%→79%) when the reaction was allowed to stir for 48 h. Significantly, α-selectivity improved three-fold (**15**: α:β = 3:1 → 10:1) when the catalyst was switch from **L1** to **L3**. This signficant improvement in α-selectivity is also observed with other hydroxyl acceptors (**2** and **6**) to afford fluorinated disaccharides **16** (α:β = 4:1→12:1) and **17** (α:β = 3:1→11:1). To determine the effect of concentration on the reaction rate and the selectivity, the coupling of isopropanol **7** with galactosyl bromide **14** was conducted at a lower concentration (0.2 M); fluorinated glycoside **15** was obtained in comparable selectivity (α:β = 9:1) to that obtained from the reaction conducted at a higher concentration (0.5 M), albeit in lower conversion (79%→55%). Under **L3**-catalyzed glycosylation conditions, use of electron-withdrawing alcohol acceptor **18** proceeded sluggishly at room temperature and only 30% conversion was observed for the desired disaccharide **18**. We were pleased to find that **18** was obtained with much higher yield (80%) and excellent α-selectivity (α:β >20:1) when the reaction was conducted at 50 °C. When sterically hindered alcohols **4** and **8** were employed, the yield of the desired disaccharides **19** (35 →81%) and **20** (38 →75%) was significantly improved switching from **L1** to **L3**. Furthermore, we were encouraged by the observation that, under these optimized conditions, a significant increase in selectivity (α:β = 3:1 →7:1) was observed with use of serine amino acid to afford glycoconjugate **21**. In addition, the coupling proceeded smoothly at room temperature with use of **L3** to afford **21**

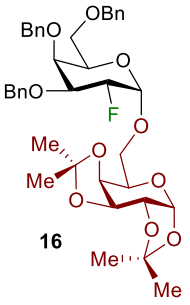
in 73% yield. To compare, the Gilmour's method is also highly β-selective for tribenzyl 2-fluoro galactose.[16]

Table 3. Reactions of Tribenzyl 2-Fluoro Galactosyl Bromide Using **L1** and **L3** Catalysts

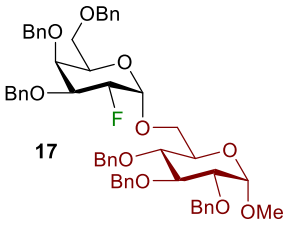




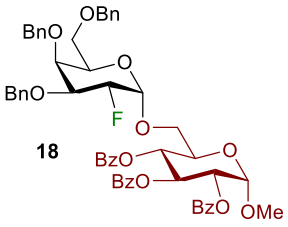
L1[a]: 50 °C, 80% (α:β = 3:1)
L1[a]: 25 °C, No reaction
L3[a]: 25 °C, 60% (α:β = 10:1)
L3[b]: 25 °C, 79% (α:β = 9:1)
L3[d]: 25 °C, 55% (α:β = 9:1)



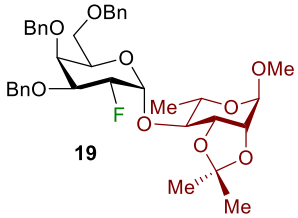
L1[a]: 50 °C, 76% (α:β = 4:1)
L3[c]: 25 °C, 75% (α:β = 12:1)



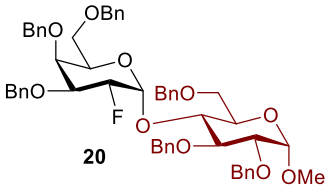
L1[a]: 50 °C, 63% (α:β = 3:1)
L3[a]: 25 °C, 85% (α:β = 11:1)



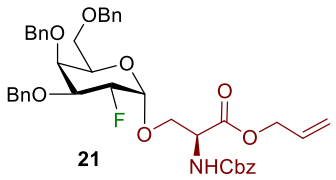
L3[a]: 50 °C, 80% (α:β > 20:1)



L1[a]: 50 °C, 35% (α:β = 8:1)
L3[a]: 50 °C, 81% (α:β = 8:1)



L1[b]: 50 °C, 38% (α:β = 9:1)
L3[c]: 50 °C, 75% (α:β = 10:1)



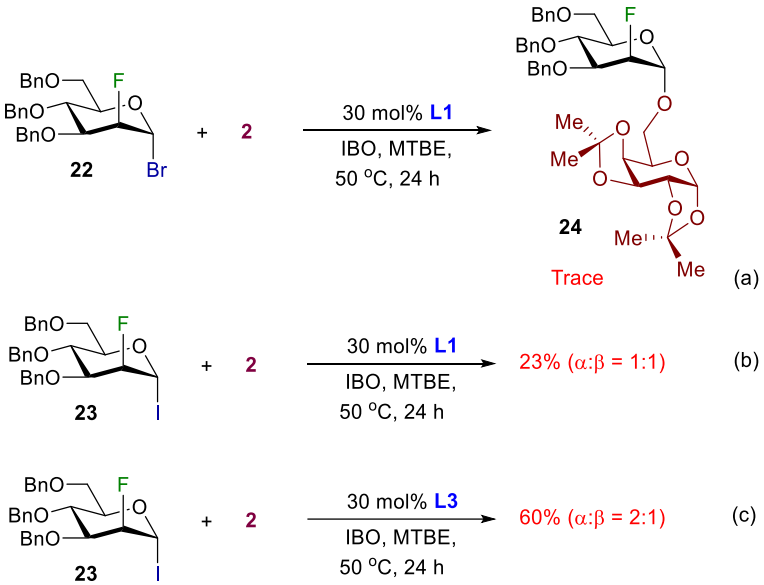
L1[a]: 50 °C, 80% (α:β = 3:1)
L3[b]: 25 °C, 73% (α:β = 7:1)

[a] The reaction was conducted using 15 mol% **L1** or **L3** at 0.5 M concentration for 24 h. [b] The reaction was conducted using 15 mol% **L1** or **L3** at 0.5 M concentration for 48 h. [c] The reaction was conducted using 30 mol% **L1** or **L3** at 0.5 M concentration for 24 h. [d] The reaction was conducted using 15 mol% **L3** at 0.2 M concentration for 48 h. [e] Isolated yield. [f] Diastereoselective (α:β) ratio of the coupling products determined by ^{19}F NMR.

Unlike glucose **1** and galactose **14** bromide donors, 2-deoxy-2-fluoro mannosyl bromide **22** (Scheme 2a) is extremely stable and rather unreactive. For instance, the reaction gave trace reactivity with use of **22** as a glycosyl donor in the coupling to galactoside acceptor **2** (Scheme 2a) Traditionally, glycosyl iodides have been utilized to increase the reaction rates of unreactive substrates.[20-25] As a result, the reactivity of the 2-fluoro mannosyl iodide **23** was evaluated (Scheme 2b). This change in leaving group improved the yield of disaccharide **24** (trace→23%), albeit with no selectivity (α:β = 1:1). When changing from **L1** to **L3** not only showed significant improvements in yield (23→60%), but diasteroselectivity still favors the α-product **24**. (Scheme 2c). This result underscores the distinct feature of the **L3** catalyst to increase the reaction reactivity

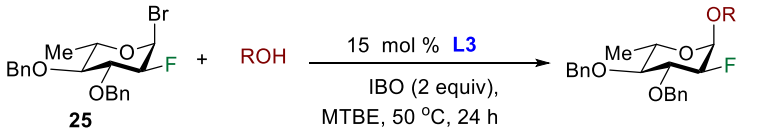
and control diastereomeric outcome. In our proposed catalytic cycle (Figure 2, *vide infra*), a double S_N2 pathway involving phenanthroline-catalyzed reaction with α-glycosyl bromide. However, the S_N1-S_N2 reaction paradigm was shifted to favor the S_N1 pathway for the 2-fluoro mannose substrates.[5] As a result, poor diastereoselectively (α:β = 2:1) was observed for disaccharide **24**. To compare, the Gilmour's methodology also shows poor selectivity and slight favors β-diastereomer (α:β = 1:3.2) for the product **24**.[15]

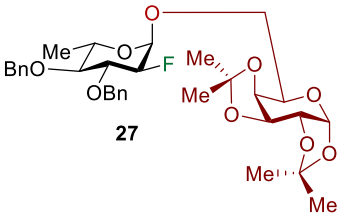
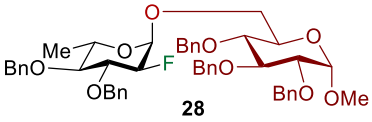
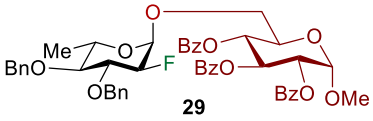
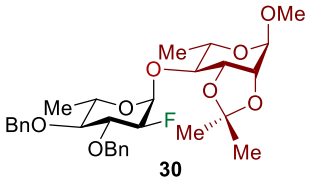
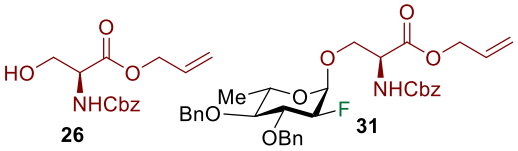
Scheme 2. Glycosylation with 2-Fluoro Mannosyl Halides



2,6-Dideoxy sugars are important motifs of a variety of potent anti-bacterial and anti-tumor natural products.[26] Replacing a hydrogen atom at C(2) with a fluorine atom in 2,6-dideoxy sugars could facilitate the discovery of new potential antibiotics. In addition, a recent report illustrates that the coupling with 2,6-dideoxy-2-fluoro-L-glucose donors is highly β-selective under Gilmour conditions.[18] We question whether **L3** catalyst could be highly α-stereoselective towards the 2,6-dideoxy-2-fluoro substrate. Due to the highly reactive nature of dideoxy substrates, we explored the coupling of C6-hydroxyl galactoside acceptor **2** with 2,6-dideoxy-2-fluoro-L-glucosyl bromide **25** in the presence of 15 mol% **L3** at ambient temperature for 24 h (Table 4). The reaction proceeded smoothly to provide the desired disaccharide **27** (entry 1) in 88% yield with excellent levels of α-selectivity (α:β > 20:1). Interestingly, switching to the C6-hydroxyl glucoside acceptor **6** reduced the selectivity of the coupling product **28** (α:β=7:1, entry 2). Next, we investigated the reaction with electron-withdrawing alcohol acceptor **9** (entry 3) to determine how this nucleophile compared to its electron-rich counterpart **6**. Gratifyingly, we observed that this electron deficient alcohol **9** was equally competent to provide disaccharide **29** (entry 3) in 59% yield with high levels of α-selectivity (α:β = 11:1). Encouraged by these results, we examined a more challenging secondary alcohol **8.** To our excitement, disaccharide **30** (entry 4) was isolated in excellent yield (96%) and diastereoselectivity (α:β > 20:1). Protected serine residue **26** (entry 5) was also well tolerated under **L3**-catalyzed glycosylation conditions to provide glycoconjugate **31** in good yield (78%) and excellent α-selectivity (α:β = 13:1).

Table 4. Glycosylation with 2,6-Dideoxy 2-Fluoro L-Glucosyl Bromides[a]



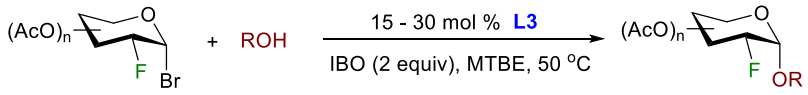
entry	acceptors	products	yield[b]	α/β[c]
1	**2**	 **27**	88%	>20:1
2	**6**	 **28**	85%	7:1
3	**9**	 **29**	59%	11:1
4	**8**	 **30**	96%	>20:1
5	**26**	 **31**	78%	13:1

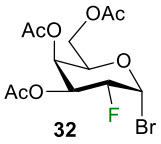
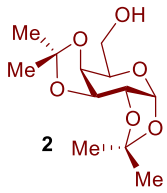
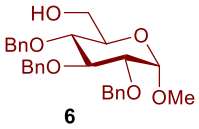
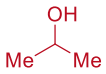
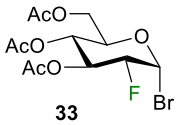
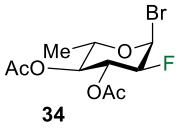
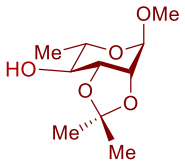
[a] The reaction was conducted using **L3** catalyst. [b] Isolated yield. [c] Diastereoselective (α:β) ratio of the coupling products determined by ^{19}F NMR.

Having probed the effect of tribenzyl protected 2-fluoro bromide donors **1**, **14**, and **25** in the reaction with a broad range of alcohol coupling partners with use **L1** and **L3** catalysts, we next investigate whether the diastereoselectivity of the coupling products could be impacted by the influence of the protecting groups on glycosyl bromide donors. The Gilmour's method showed that substitution of the benzyl protecting group by the acetyl moiety on 2-fluoro glucose donor provided the product with only marginal β-selectivity (α:β = 1: 21 → 1:2).[15] To determine the ability of **L3** catalyst to overturn the substrate's inherent selectivity preference, acetyl protected 2-fluoro bromide donors **32** – **34** were coupled with a number of alcohols (Table 5) and compared

to similar couplings with benzyl protected donors **1**, **14**, and **25** as well as the Gilmour's method.[15] The results obtained with acetyl protected donors **32** – **34** in Table 5 deserved comments. First, all glycosylations were conducted at 50 °C for 24 – 48 h. Second, the acetyl bromides **32 - 34** furnished the desired disaccharides **35** – **42** in good to excellent α-selectivity under **L3**-catalyzed conditions. Third, the benzyl bromide donors are more α-selective than their acetyl counterparts in some cases. For instance, while the coupling of primary alcohol **2** with triacetyl galactose bromide **32** provided disaccharide **35** with α:β = 9:1 (Table 5, entry 1), the coupling of **2** with tribenzyl counterpart **14** provided disaccharide **16** with α:β = 12: 1 (Table 3). Fourth, in contrast to the Gilmour's method whose acetyl 2-fluoro donors provided the coupling products as a mixture of α- and β-isomers,[15] the **L3**-catalyzed method selectively favors α-products. For instance, **L3**-catalyzed coupling with triacetyl 2-fluoro glucose bromide **33** afforded disaccharides **38** and **39** (entries 5 and 6) with high diastereoselectivity (α:β = 7:1 – 10:1) while the Gilmour's method afforded the products with marginal β-selectivity (α:β = 1:2).[15] Finally, both acetyl (**34**) and benzyl (**25**) protected 2,6-dideoxy bromide donors uniformly furnished the coupling products with high levels of α-selectivity. Overall, the results demonstrate the ability of **L3** catalyst to control the α-selectivity of the glycosidic bonds regardless of whether the electron-rich (Bn) or electron-deficient (Ac) protected 2-fluoro donors are employed in the reaction.

Table 5. Glycosylation with Triacetyl Glycosyl Bromides

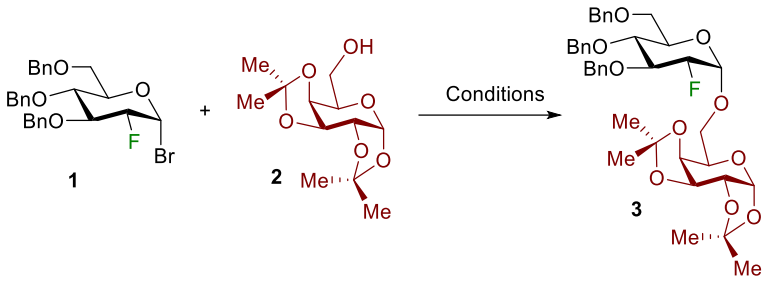


entry	donors	acceptors	products	yield[c] (α/β ratio)[d]
1	 **32**	 **2**	**35**	80% (α:β = 7:1)[a,]
2	**32**	 **6**	**36**	80% (α:β = 9:1)[a]
3	**32**	 **7**	**37**	51% (α:β = 5:1)[b]
4	 **33**	**6**	**38**	72% (α:β = 7:1)[a]
5	**33**	**2**	**39**	67% (α:β = 10:1)[a]
6	 **34**	**2**	**40**	76% (α:β = 11:1)[a]
7	**34**	**6**	**41**	88% (α:β = 8:1)[a]
8	**34**	 **8**	**42**	52% (α:β = 20:1)[b]

[a] The reaction was conducted using 15 mol% **L3** for 48 h. [b] The reaction was conducted using 30 mol% **L3** for 24 h. [c] Isolated yield. [d] The α/β ratio of the coupling products determined by ^{19}F NMR.

To illustrate that phenanthroline **L3** is not only a bond-forming catalyst, but also enforces the stereoselective formation of α-glycosidic bond, we conducted the reaction of glycosyl bromide **1** with nucleophilic acceptor **2** in the absence of **L3** catalyst (Scheme 3a). As expect, only trace amount of the desired disaccharide **3** was observed. For comparison, we also performed the coupling utilizing silver triflate, AgOTf, as a Lewis acid (Scheme 3b), wherein the reaction often proceeds through an S_N1-like pathway, to provide a mixture of α-1,2-*cis*- and β-1,2-*trans* products. As we anticipated, the use of a stoichiometric amount of AgOTf afforded disaccharide **3** as a 1:1 mixture of α- and β-diastereomers. Furthermore, using isobutylene oxide (IBO) as a hydrogen bromide scavenger was beneficial to the yield. In the absence of IBO, the desired disaccharide **3** was isolated in only 45% yield (Scheme 3c).

Scheme 3. Control Experiments



Conditions	Results	
No Catalyst, IBO, MTBE, 50 °C, 24 h	Trace	(a)
AgOTf (1 equiv), DTBMP, CH_2Cl_2, 25 °C	83%, α:β = 1:1	(b)
15 mol% **L3**, No IBO, MTBE, 50 °C, 24 h	45%, α:β = 10:1	(c)

On the basis of the aforementioned data, a proposed catalytic cycle for the phenanthroline-catalyzed formation of α-1,2-*cis*-2-fluoro glycosides is illustrated in Figure 2. In the first step, the **L3** catalyst can engage in electrophilic activation of the bromide leaving group of glycosyl electrophile **42** to form the covalent β-glycosyl phenanthrolium intermediate **43** via an invertive S_N2 pathway. The glycosyl phenanthrolium ion formed in the reaction prefers the equatorial position to avoid the steric and electrostatic interactions associated with positioning that group in the axial orientation.[27-29] Subsequent S_N2 displacement of the phenanthrolium species **43** by an alcohol acceptor takes place in such a way that the stereochemistry of the protonated 2-fluoro glycoside product **44** would be dictated by the anomeric configuration of the phenanthrolium intermediates **43**. In the presence of isobutylene oxide (IBO) **45** as a hydrogen bromide scavenger, the α-1,2-*cis*-2-fluoro glycoside **46** is ultimately generated with regeneration of **L3** catalyst. For certain alcohol nucleophiles, the S_N1-S_N2 reaction paradigm was slightly shifted, wherein the covalent β-glycosyl phenanthrolium intermeidate **43** dissociate to form a transient oxocarbenium ion in the reaction. An alcohol nucleophile is then approached on either α- or β-face of the oxocarbenium intermediate to provide the coupling product with moderate α/β ratio.

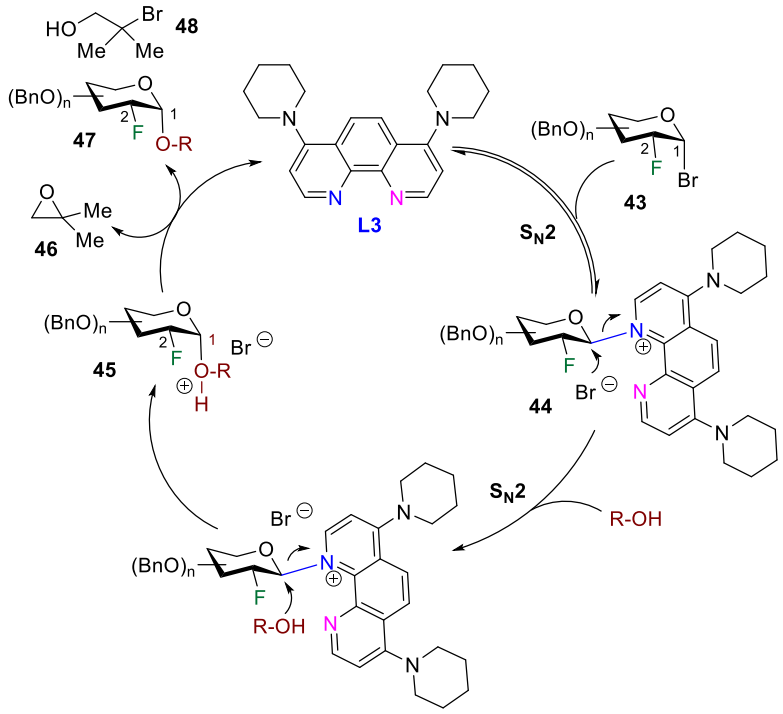
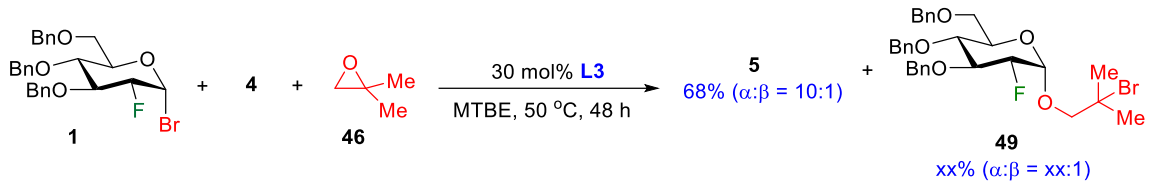


Figure 2. Proposed catalytic cycle of **L3**-catalyzed formation of α-1,2-*cis*-2-fluoro glycosides.

To further gain insight into the mechanism, we attempted to detect a transient β-covalent phenanthrolinium ion (Figure 2) using NMR spectroscopy. Although we were not successful to detect by NMR spectroscopy, a transient β-covalent phenanthrolinium intermediate having C2-*O*-benzyl functionality was detected by electrospray ionization (ESI) mass spectrometry.[19] This result suggests that formation of the β-covalent phenanthrolinium intermediate is reversible. In addition, we previously observed that β-bromide only slowly anomerized to the corresponding α-bromide without the phenanthroline **L1** catalyst.[19] However, β-bromide rapidly converted into α-bromide in the presence of 15 mol% of **L1** catalyst within 1 h at ambient temperature.[19] We also previously conducted the coupling of β-anomer of glycosyl bromide with alcohol **2** in the presence of **L1**, and we observed that isomerization of β-bromide to α-bromide is faster than formation of the coupling product.[19]

To determine that alcohol **48** derived from isobutylene oxide (IBO) **46** is generated in the reaction and potentially react with the β-glycosyl phenanthrolium intermediate **44**, the coupling of sterically hindered C4-hydroxyl **4** with glucosyl bromide **1** (Scheme 4) was examined in the presence of IBO (**46**, 2 equiv.). We chose **1** and **4** as coupling partners because we observed that alcohol **48** derived IBO **46** did compete with sterically hindered nucleophiles in the reaction (Table 1). Accordingly, **L3**-mediated coupling of acceptor **4** with donor **1** proceeded at 50 °C to provide the desired disaccharide **5** and glycoside product **49**. Formation of **49** supports that alcohol **48** is indeed formed in the reaction and compete with nucleophilic acceptor to react with a transient β-glycosyl phenanthrolium ion (Figure 2).

Scheme 4. Detection of Alcohol **48** Derived from Isobutylene Oxide and Glycosyl Bromide.



To provide further insight into the reaction mechanism that phenanthroline catalyst plays a key role in controlling the 1,2-*cis* selectivity and to understand the differences between the catalysts, density functional theory (DFT) calculations were used to examine the transition states and intermediates along the reaction pathway. The geometries of structures were optimized and vibrational frequencies were calculated with the B3LYP functional[29-33] and the Def2SVPP basis set[34] with the GD3BJ empirical dispersion correction[35,36] and the SMD implicit solvation model[37] for diethyl ether. Free energies were obtained by combining single point calculations using the Def2TZPP basis set[38] at the Def2SVPP optimized geometries and zero point energies. Thermal corrections and entropies calculated with the Def2SVPP basis. Calculations were carried out with the Gaussian series of programs.[39]

The energy profile for the best catalysts, **L3** and **L6**, is shown in Figure 3. The results for the other substituted phenanthroline and pyridine catalysts (**L1**, **L2**, **L4**–**L9**) can be found in the Supporting Information, along with unsubstituted phenanthroline (**L0**) and pyridine (**L10**). The first step is an S_N2 displacement of the bromide by the catalyst. For the phenanthroline catalysts (**L0**–**L5**), **L3** has the lowest barrier transition state 1, **TS1**, (26.8 kcal/mol relative to separated reactants). It is observed that one phenanthroline nitrogen displaces the bromide leaving group while the other nitrogen is in close contact with the hydrogen on C1 of the sugar. Formation of the intermediate **Int1**, follows with the displaced bromide interacting with the hydrogens on C1, C3 and C5 of the sugar and one of the phenanthroline hydrogens. This intermediate is 8.1 kcal/mol less stable than separated reactants. For the pyridine catalysts (**L6**–**L10**), the bromide of **Int1** interacts with the hydrogens on C1 of the sugar and C2 of the catalyst, and these intermediates are about 10 kcal/mol more stable than the corresponding ones for phenanthroline catalysts (see **L6** in Figure 3). We hypothesized that the differences in the energies of **Int1** between the phenanthroline catalysts and the pyridine catalysts are likely due to steric interactions. The bulky phenanthrolines are higher in energy and have longer C-N bonds (see SI) than the pyridine catalysts. The increased steric bulk of the phenanthroline catalysts seem to outweigh any C-H- - -N hydrogen bonding, which is enough to explain the phenanthroline/pyridine bind energy differences. We hypothesized that this also makes the reverse barriers for **TS1** lower and may result in more of **Int1** returning to reactants and more of the reactants recovered for the phenanthroline catalysts (Table 1, entries 1–9). In contrast, **Int1** of pyridine-based catalysts (**L6**–**L10**) is less likely to reverse to reactants because the reverse barriers for **TS1** is significantly larger than those of phenanthroline catalysts (**L1**–**L5**). This is consistent with our observed experimental data (Table 1, entries 10–13) that low amount of glycosyl bromide **1** recovered at the end of the reaction. It is observed in **TS2** that the C2-fluoride of the sugar and the bromide interact with the hydrogen of methanol. Substituents on the phenanthrolines and the pyridines lower both **TS1** and **TS2** (see SI), suggesting that the substituted catalysts should be better than the unsubstituted catalysts.

For the formation of the α-glycoside linkage in the second step, the alcohol group (in this case modeled by methanol) displaces the catalyst in an S_N2 manner, with the bromide accepting

the proton from the alcohol (Figure 3). In second intermediate, **Int2**, hydrogen bromide (HBr) is hydrogen-bonded to the C1-oxygen and the C2-fluorine. In the final step, IBO reacts with HBr. The overall reaction is exergonic by 16.4 kcal/mol. For all of the catalysts considered, the barriers relative to separated reactants are 25–35 kcal/mol, in accord with the thermal conditions needed for the reaction. Formation of the β-glycoside through an oxocarbenium intermediate has a similar but more energetically demanding barrier compared to the double S_N2 displacement barrier for the species tested (See SI). In addition, pathways involving dissociation into oxocarbenium ion and bromide are disfavored in non-polar solvents. Collectively, the double S_N2 displacement pathways with phenanthroline or pyridine catalysts have lower barriers and ensure stereoselective formation of α-1,2-*cis*-2-fluoro glycosides.

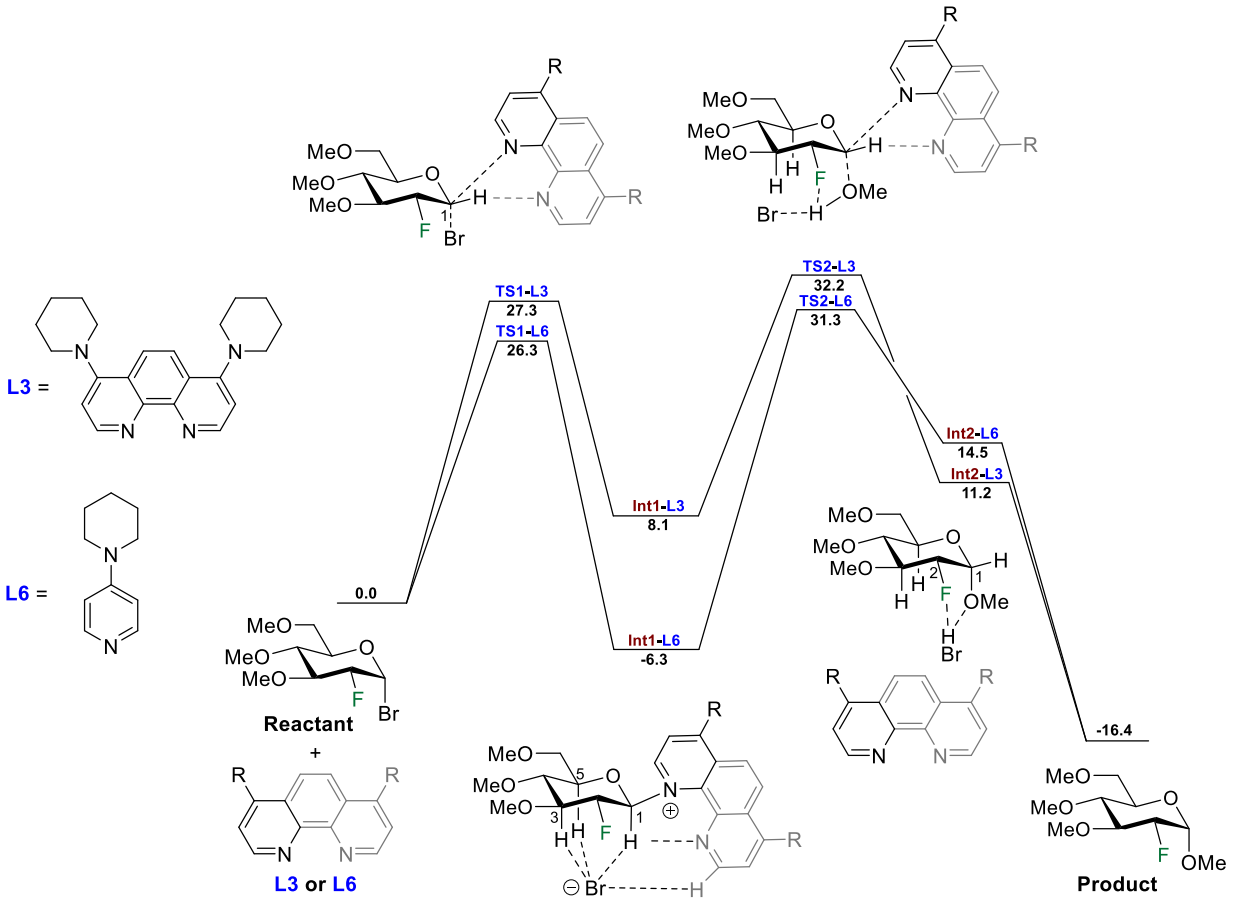


Figure 3. Energetic profile for the coupling of methanol with glycosyl bromide (**reactant**) to form α-1,2-*cis* glycoside (**product**) using **L3** and **L6** catalysts and IBO as an HBr scavenger (Units = kcal/mol).

Although phenanthroline catalysts selectively favor the α-1,2-*cis* glycosylation products, some coupling partners result in low to moderate α-selectivities. As a result, computational studies into a mechanism for the formation of the β-selective glycosylation determined a likely divergence point of the α- and β- pathways at the first intermediate, **Int1**, after S_N2 attack by the catalyst (Figure 4). Complete dissociation of Br- ion from the intermediate is not energetically feasible due

to the use of the non-polar solvent MTBE (75.1 kcal/mol) and dissociation of catalyst from **Int1** will lead to the rapid collapse back to reactants due to the proximity of Br- ion to the generated phenothrolinium cation. However, migration of Br- ion away from the anomeric carbon of **Int1** is quite feasible, ultimately forming the species designated **Int1'** (Figure 4). Subsequent dissociation of catalyst from **Int1'** yields a metastable oxocarbenium species (**Oxo**) with a free energy greater than but comparable to that of the second S_N2 reaction of the main pathway. Nucleophilic attack on the C1-anomeric carbon of the oxocarbenium can then lead to the formation of either the α- or β-glycosylation product. Thus, we can expect that the formation of the β-product to be possible under reaction conditions but production of the α-anomer should dominate.

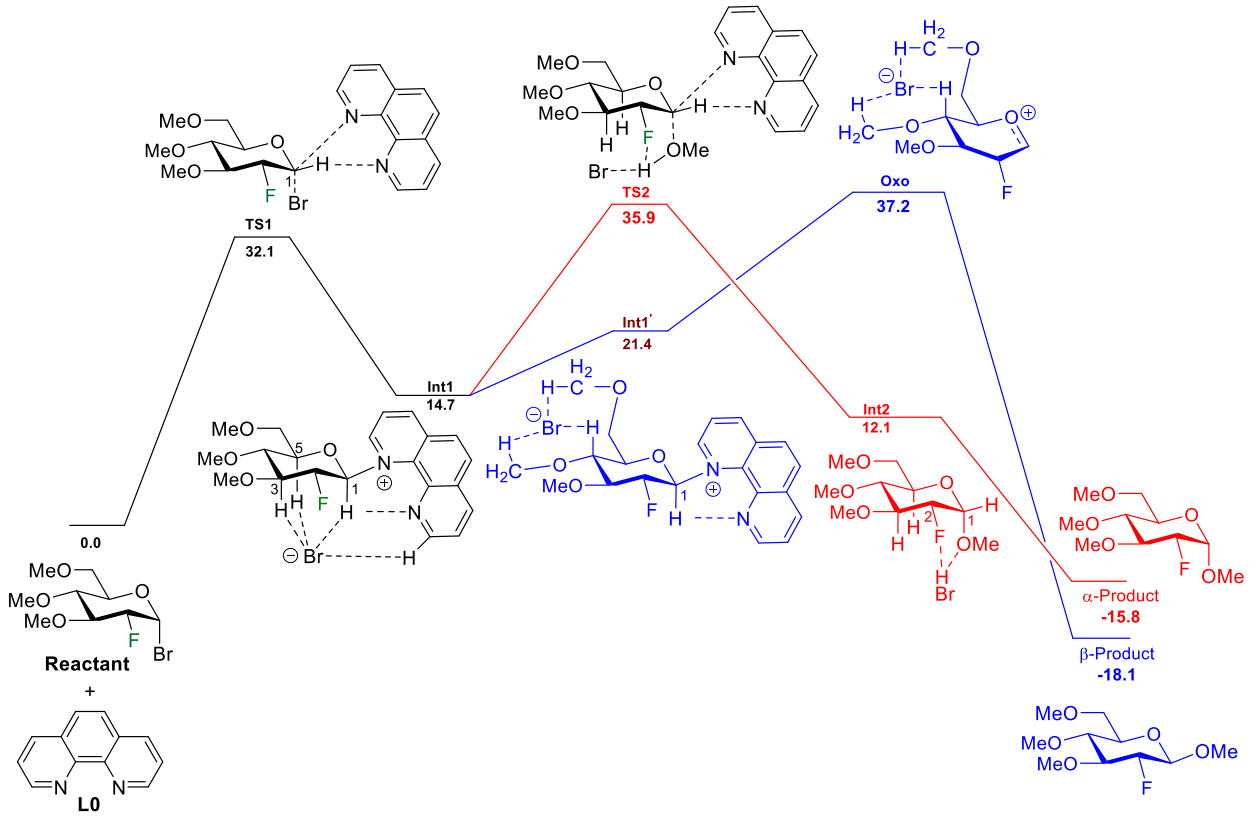


Figure 4. Reaction coordinate diagrams showing the diverging pathways for formation of α- (red) and β-(blue) glycosylation product using phenathroline **L0** as a catalyst as it results in lower glycosylation selectivity than **L1** and **L3**. Also see Figure S1 in the supporting information for calculations of pyridine **L10** as a catalyst.

CONCLUSION

An efficient method for stereoselective formation of α-1,2-*cis*-2-fluoro glycosides utilizing phenanthroline based catalysts **L1** and **L3** has been established. **L3** is more effective than **L1** at promoting the coupling to provide the desired α-1,2-*cis* fluorinated glycoside products in higher yield and selectivity. The Gilmour group demonstrated a preference for the formation of β-1,2-

trans-2-fluoro glycosides using trihaloacetimidate donors.[15-18] By the use of glycosyl halides and phenanthroline as a catalyst, we have been able to invert the selectivity of the glycosidic bond formation. We hypothesize that the α-selectivity is partly due to a double S_N2 inversion mechanism promoted by phenanthroline catalyst. With the intention to better understand the mechanism of this catalytic glycosylation system, dinitrogen (phenanthroline type) and mononitrogen (pyridine type) catalysts were evaluated. The reaction yields and the stereoselectivity of the pyridine vs. phenanthroline catalysts were rather consistent. The major differences found in the catalytic system was the amount of starting glycosyl halides recovered. In the case of the pyridine catalysts the amount of recovered donor was significantly less in comparison to that of the phenanthroline catalysts. The substantial amount of starting glycosyl bromide recovered, in combination with less formation of byproducts, suggests that the phenanthroline catalysts allow a more mild form of activation, resulting in a more efficient glycosylation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Full experimental procedures and characterization data for all new compounds (PDF).

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Notes: The authors declare no competing financial interest.

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Table of Contents