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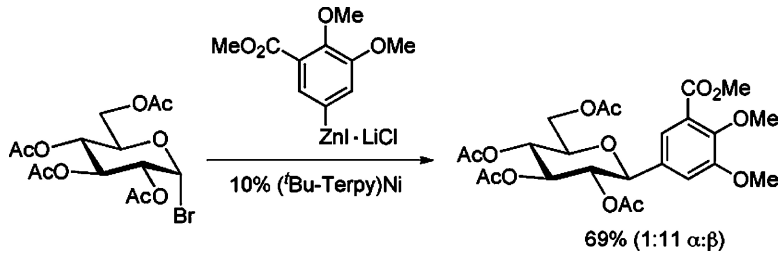

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Diastereoselective Ni-Catalyzed Negishi Cross-Coupling Approach to Saturated, Fully Oxygenated *C*-Alkyl and *C*-Aryl Glycosides

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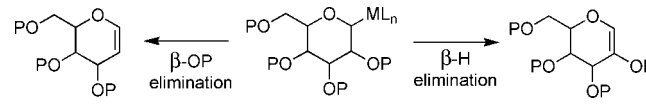
Abstract: A Ni-catalyzed Negishi cross-coupling approach to *C*-glycosides is described with an emphasis on *C*-aryl glycosides. The combination of $NiCl_2$/PyBox in *N,N*′-dimethylimidazolidinone (DMI) enabled the synthesis of *C*-alkyl glycosides under mild reaction conditions. Moderate yields and β-selectivities were obtained for *C*-glucosides, and good yields and high α-selectivities were the norm for *C*-mannosides. For *C*-aryl glycosides, reactions employing $Ni(COD)_2$/^{t}Bu-Terpy in *N,N*-dimethylformamide (DMF) were typically high yielding and provided *C*-glucosides with high β-selectivities (1:>10 α:β) and *C*-mannosides in moderate α-selectivities (3:1 α:β); α-*C*-aryl glycosides could be obtained by the combination of $Ni(COD)_2$/PyBox in DMF (>20:1 α:β). The collective studies suggest that stereochemical control of the *C*-glycosides is dependent on the substrate and catalysts combination. The Negishi protocol displays excellent functional group tolerance, as demonstrated by its use in the first total synthesis of the natural product salmochelin SX.

1. Introduction

C-Glycosides are an important class of naturally occurring and synthetic bioactive products.[1−4] In contrast to their *O*-analogues, *C*-glycosides are less vulnerable to metabolic processing, which has led to significant interest in their viability as drug candidates and inhibitors of carbohydrate processing enzymes.[1,2] These interests have advanced the synthesis of *C*-glycosides, with the construction of the key anomeric C−C bond centering on approaches that generate nucleophilic, electrophilic, or radical character at the C1 center; concerted reactions have also been examined.[3−5] In general, these methods rely on substrate control to achieve a stereoselective construction of the anomeric center. Unfortunately, many reaction protocols are prone to β-elimination of C2 substituents, leading to an emphasis on C2-deoxy *C*-glycoside syntheses.[5]

Catalytic approaches to *C*-glycosides, on the other hand, are relatively rare, though they promise to provide catalyst control over the anomeric center. Most transition metal-catalyzed protocols to *C*-glycosides utilize sp^2-hybridized anomeric carbons (e.g., 1-halo glycals in Heck-type cross-couplings) or π-allyl types, with both providing unsaturated products.[6,7] These constraints are the result of the sensitivity of putative, fully saturated C1-organometallic intermediates to β-elimination reactions (Scheme 1).

Scheme 1



As part of an effort to develop cross-coupling approaches to fully oxygenated *C*-glycosides, we became interested in catalysts for the construction of C−C bonds at the C1 of sp^3-hybridized glycosyl halides. This strategy would provide a convergent route to *C*-glycosides with the potential for catalyst control over the stereochemistry of the anomeric center. As discussed above, this approach is challenged by the susceptibility of C1-organometallic intermediates to β-elimination of the C2 substituent (H or OR, Scheme 1).

Fu, Knochel, and others have demonstrated that transition metal-catalyzed cross-coupling of alkyl halides with β-hydrogens

(1) For recent reviews in *C*-glycoside biology, see: (a) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299–1331. (b) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363–1391. (c) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077–3092. (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55–83.

(2) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995. (b) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431–1457.

(3) For reviews in C-glycoside synthesis, see: (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1995. (b) Somsak, L. *Chem. Rev.* **2001**, *101*, 81–135. (c) Meo, P.; Osborn, H. M. I. *Best Synthetic Methods: Carbohydrates*; Elsevier Science Ltd.: New York, 2003; pp 337−384. (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.

(4) For reviews in *C*-aryl glycoside biology and synthesis, see: (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742–760. (b) Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333–1350. (c) Wellington, K. W.; Benner, S. A. *Nucleosides Nucleotides Nucleic Acids* **2006**, *25*, 1309–1333.

(5) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54.

(6) For recent examples of C1-sp^2 Heck, Suzuki, Hiyama, and Stille couplings, see: (a) Chen, C.-L.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 4810–4817. (b) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797–1801. (c) Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776. (d) Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 543–546.

(7) For allyl type, see: (a) Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201–206. (b) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890–1896.

can be achieved under the guidance of suitable ligands.[8] In particular, Ni-catalyzed Negishi cross-coupling conditions have been developed wherein pincer ligands effectively inhibit detrimental β-elimination reactions that would serve to bypass productive cross-coupling cycles.[9] One presumes that the pincer ligands operate by blocking the vacant site of the transition metal *cis* to the putative metal−alkyl.[10] If this reactivity pattern could be transferred to elimination-prone glycosyl-type electrophiles, Fu's procedure might also enable stereoselective C−C bond formation at the carbohydrate anomeric carbon.

Recently, we demonstrated our first successful implementation of this strategy to synthesize *C*-alkyl glycosides.[11] Herein, we present additional discussion of this development and extend the methodology to include the stereoselective synthesis of *C*-aryl glycosides. To the best of our knowledge, this latter work represents the first Ni-catalyzed cross-coupling of an arylzinc and a secondary sp^3 carbon.[12] The application of our *C*-aryl glycoside methodology to an expedient synthesis of the enteric bacterium natural product salmochelin SX is also described.[13]

2. Results and Discussion

After extensive experimentation, we discovered that a variant of Fu's Ni-catalyzed Negishi coupling conditions was compatible with the dense functionality of a carbohydrate, thus enabling an efficient synthesis of a variety of *C*-alkyl glycosides.[11] The conditions found by Fu to be optimum for unhindered cross-couplings (^{i}Pr-PyBox) were not suitable to glycosyl electrophiles, where elimination to glycal was particularly problematic. As a general observation, slow catalysts led to products that were the result of RZnX-mediated decomposition of the glycosyl halide (glycal formation and hydrolysis/oligomerization).

Optimal was the combination of $NiCl_2$·glyme (5 mol %) and an unsubstituted PyBox in *N*,*N*′-dimethylimidazolidinone (DMI). This catalyst afforded the desired *C*-glycosides in moderate to good yields, along with glucal (up to 15%) and baseline oligomeric byproducts.[14] The diastereoselectivity of the reactions depended on the carbohydrate, with mannosyl halides providing good to excellent yields and uniformly high α-selectivities, whereas glucosyl halides gave moderate yields and a slight preference for β-selectivities (Scheme 2).

Scheme 2

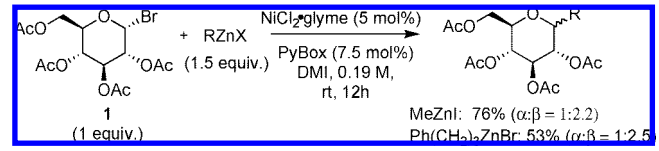
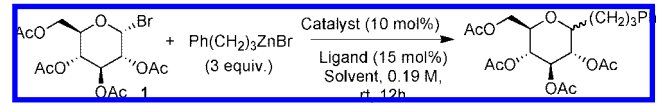


Table 1. Ligand Effects on the Coupling of $Ph(CH_2)_3ZnBr$ and Aceto-α-1-bromo-glucose



Entry[a]	Catalyst/Ligand	Solvent[b]	Product (α:β)	Glucal
1	$NiCl_2$·glyme/Terpy	DMI	15% (β only)	major
2	$NiCl_2$·glyme/Terpy	DMA	ND[c]	major
3	$NiCl_2$·glyme/Terpy	DMF	trace	major
4	$NiCl_2$·glyme/EtO-Terpy	DMA	15% (β only)	major
5	$NiCl_2$·glyme/Pyr-Terpy	DMI	10% (β only)	32%
6	$NiCl_2$·glyme/Pyr-Terpy	DMA	trace	trace
7	$NiCl_2$·glyme/^{t}Bu-Terpy	DMF	trace	NA
8	$Ni(COD)_2$/^{t}Bu-Terpy	DMF	trace	major
9	$NiCl_2$·glyme/BBP	DMI	trace	trace
10	$NiBr_2$·diglyme/*R*-^{i}Pr-PyBox	DMI	30% (1:1)	19%
11	$NiBr_2$·diglyme/*S*-^{i}Pr-PyBox	DMI	10% (1:1)	10%
12	$NiCl_2$·glyme/*R*-Ph-PyBox	DMI	trace	trace
13	$NiBr_2$·diglyme/terthiophene	DMI	trace	major
14	$NiCl_2$·glyme/PMDETA	DMI	ND	15%

[a] Reaction conditions: **1** (0.24 mmol, 0.19 M in solvent), Ni catalyst (0.024 mmol), ligand (0.036 mmol), and RZnX (~0.9 M, 0.72 mmol) at room temperature for 12 h. [b] DMI, *N*,*N*′-dimethylimidazolidinone; DMA, *N*,*N*-dimethylacetamide; DMF, *N*,*N*-dimethylformamide. [c] ND, not detected by NMR.

In the course of optimizing this reaction, it was noted that the Terpy/$NiCl_2$·glyme catalyst formed the β-product only with MeZnI in *N*,*N*-dimethylacetamide (DMA) (60% yield),[15] in contrast to the PyBox result in Scheme 2 (1:2.2 α:β). Unfortunately, this selectivity did not extend to primary alkylzinc reagents, where poor yields were the norm (entries 1−8, Table 1). To improve this situation, the ligands in Chart 1 were screened with MeZnI, and those that were promising were additionally examined with a primary alkylzinc reagent (Table 1).

As mentioned above, increasing the size of the ligands and/or the organozinc reagent generally decreased the yields, with the mass balance being glycal or oligomeric products. This general trend was rationalized as reflecting competitive background decomposition by the alkylzinc reagent, bulkier catalysts being slower to consume the starting material before decomposition ensued.

With regard to anomer selectivity, the catalysts obtained from the enantiomeric ^{i}Pr-PyBox ligands were similarly selective, though the *R*-antipode was higher yielding (entries 10 and 11,

(8) For leading reviews, see: (a) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663–672. (b) Knochel, P.; Calaza, M. I.; Hupe, E. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vol. 2, pp 619−670. (c) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (d) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (e) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387.

(9) For pincer ligands used in the Ni-catalyzed Negishi approach to (sp^3−sp^3) C−C bonds, see: (a) Arp, F. O.; Fu, G. C *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Kanovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183. (c) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795.

(10) For other examples using pincer ligands, see: (a) Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038–9039. (b) Cucciolito, M. E.; D'Amora, A.; Vitagliano, A. *Organometallics* **2005**, *24*, 3359–3361. (c) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290–13297.

(11) Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908–1909.

(12) (a) For Ni-catalyzed Negishi coupling of arylzincs with primary halides, see: Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (b) For Ni-catalyzed Kumada coupling of PhMgBr with primary alkyl halides, see: Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223.

(13) (a) Hantke, K.; Nicholson, G.; Rabsch, W.; Winkelmann, G. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3677–3682. (b) Bister, B.; Bischoff, D.; Nicholson, G. J.; Valdebenito, M.; Schneider, K.; Winkelmann, G.; Hantke, K.; Suessmuth, R. D. *BioMetals* **2004**, *17*, 471–481.

(14) The baseline mixture was subject to ESI-MS studies. The peaks at *m*/*z* 889.1 and 540.0 suggest the formation of probable *O*-linked trisaccharide and disaccharide, respectively.

(15) Although the ^{t}Bu-Terpy/$NiCl_2$·glyme catalyst gave only traces of product in DMA (and none in DMI), it gave the β-methyl product in 40% yield in THF.

Chart 1

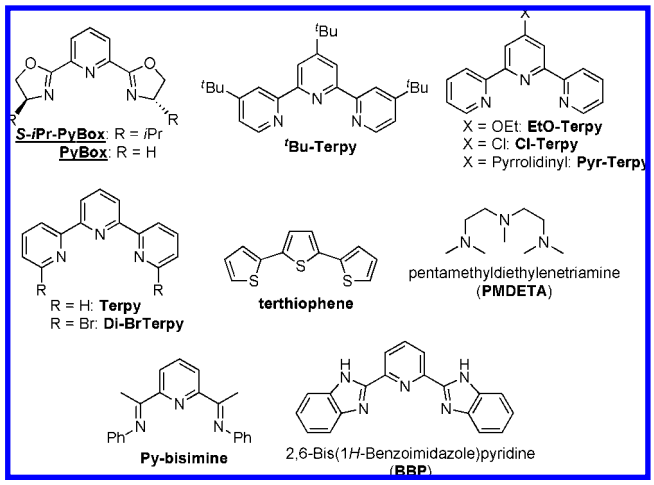


Table 1).[16] Other ligands such as terthiophene, PMDETA, and ^{t}Bu-Terpy collectively failed to provide more than trace amounts of the coupling product. A number of Ni sources were investigated, and $NiBr_2$ provided results comparable to those obtained with $NiCl_2$, whereas $Ni(COD)_2$, NiF_2, NiI_2, $Ni(PPh_3)_2Cl_2$, and Ni(dppp)Cl_2 were all inferior (data not shown).

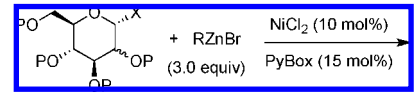
Although the optimum catalyst (PyBox/$NiCl_2$ in DMI) was only slightly β-selective with glucosyl halides, it was very α-selective with mannosyl halides. Examples of these transformations are collected in Table 2. It should be noted that benzyl-protected carbohydrates required the use of chloride leaving groups, as these more electron rich (armed) compounds were too sensitive to hydrolysis and elimination as the bromide.

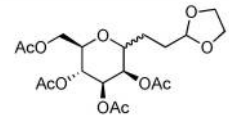
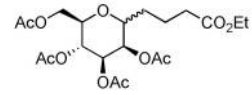
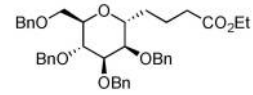
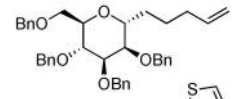
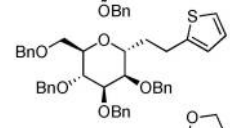
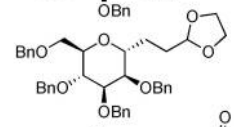
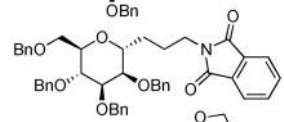
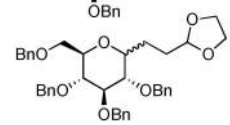
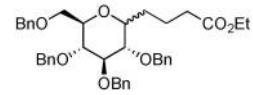
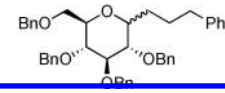
2.1. *C*-Aryl Glycoside. Extension of the Ni-catalyzed Negishi strategy to *C*-aryl glycosides was compelling since many natural products and drug candidates contain the *C*-aryl glycoside core.[4] More importantly, the current synthesis of *C*-aryl glycosides is often limited to the addition of electron-rich aromatic systems to glycosyl electrophiles,[4,17] reduction of 1-*C*-aryl-glucosides,[18] or chemistry involving anomeric sp^2 carbons.[4,19] A direct conversion of glycosyl halides to *C*-aryl glycosides employing a transition metal-catalyzed cross-coupling protocol would overcome many of these limitations.

Our first experiments to this end utilized the optimized *C*-alkyl glycoside synthesis conditions ($NiCl_2$/PyBox in DMI) to investigate the cross-coupling of PhZnI·LiCl[20] and aceto-α-D-bromoglucose (**1**); however, only the glucal elimination product was observed (entry 1, Table 3). A trace amount of the desired product was obtained using $Ni(COD)_2$/PyBox, and changing the solvent from DMI to DMA further increased the yield to 20% with moderate α-selectivity (entry 3, Table 3). Screening various ligands (entries 4−11, Table 3, Chart 2) in DMA demonstrated that terpyridine (entry 10, Table 3) was superior to PyBox, providing the Ph-*C*-glucoside in 45% yield with moderate β-selectivity. The β-selectivity was enhanced markedly when ^{t}Bu-Terpy was used (1:18 α:β, entry 11, Table 3). Finally, it was found that, in DMF, the $Ni(COD)_2$/^{t}Bu-Terpy combination furnished the phenyl product in 71% yield, with a slightly lowered diastereomer ratio (dr) of 1:12 α:β (entry 12, Table 3).[21] Further screening of ligands (Chart 2) and solvents did not offer additional improvement (entries 13−15, Table 3).

The scope of arylzinc reagents was next investigated using the $Ni(COD)_2$/^{t}Bu-Terpy/DMF conditions. Gratifyingly, the

Table 2. Optimum Conditions for the *C*-Alkylation of Glycosyl Halides



Entry[a]	X	product	Yield (α : β)	Glycal
1	Br		69% (8:1)	9%
2	Br		70 (8:1)	6%
3	Cl		76% (α)[b]	3%
4	Cl		40% (α)[b]	25%
5	Cl		43% (α)[b]	20%
6	Cl		65% (α)[b]	9%
7	Cl		61% (α)[b]	7%
8	Cl		65% (1:1.1)	9%
9	Cl		65% (1:1.2)	3%
10	Cl		70% (1:1.2)	7%

[a] Typical reaction conditions: glycosyl bromide (0.24 mmol, 0.19 M in DMI), $NiCl_2$·DME (0.024 mmol), ligand (0.036 mmol), and RZnBr (in DMI) at room temperature for 12 h. [b] No β-isomer detected by TLC or NMR.

(16) Similar results were observed with MeZnI, see ref 11

(17) For recent examples, see: (a) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721. (b) Rousseau, C.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3763–3766.

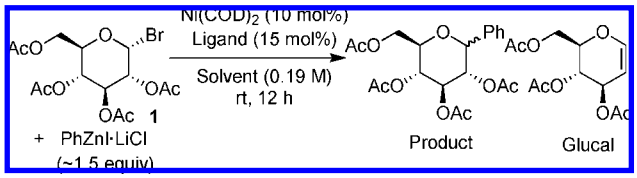
(18) Deshpande, P. P.; Ellsworth, B. A.; Buono, F. G.; Pullockaran, A.; Singh, J.; Kissick, T. P.; Huang, M.-H.; Lobinger, H.; Denzel, T.; Mueller, R. H *J. Org. Chem.* **2007**, *72*, 9746–9749.

(19) For lactone substrates, see: (a) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696–13697. (b) Martin, S. F. *Pure. Appl. Chem* **2003**, *75*, 63–70. For examples using cross-coupling approaches, see ref 6. For nucleophilic sp^2 anomeric center, see ref 5 and references cited therein.

(20) Krasovskiy, A; Malakhov, V; Gavryushin, A; Knochel, P *Angew. Chem., Int. Ed.* **2006**, *45*, 6040–6044.

(21) The Ph-*C*-glucoside was obtained in 68% yield (1:10 α:β) when 5 mol % $Ni(COD)_2$ and 7.5 mol % ^{t}Bu-Terpy were employed.

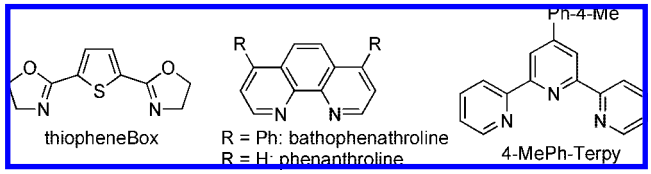
Table 3. Reaction Optimization for the Coupling of PhZnI·LiCl with Acetobromo-α-D-glucose



Entry[a]	Precatalyst/Ligand	Solvent[b]	Product (α:β)	Glucal
1	$NiCl_2$·glyme/PyBox	DMI	ND[c]	70%
2	$Ni(COD)_2$/PyBox	DMI	trace	substantial
3	$Ni(COD)_2$/PyBox	DMA	20% (2:1)	substantial
4	$Ni(COD)_2$/ThiopheneBox	DMA	trace	substantial
5	$Ni(COD)_2$/bathophenanthroline	DMA	13% (1:1.5)	37%
6	$Ni(COD)_2$/phenanthroline	DMA	21% (2:1)	35%
7	$Ni(COD)_2$/2,2′-dibromoTerpy	DMA	trace	substantial
8	$Ni(COD)_2$/EtO-Terpy	DMA	22% (1:4)	6%
9	$Ni(COD)_2$/Cl-Terpy	DMA	20% (1:2.5)	substantial
10	$Ni(COD)_2$/Terpy	DMA	45% (1: 3.5)	10%
11	$Ni(COD)_2$/^{t}Bu-Terpy	DMA	45% (1:18)	15%
12	**$Ni(COD)_2$/^{t}Bu-Terpy**	**DMF**	**71% (1:12)**	**7%**
13	$Ni(COD)_2$/4-MePh-Terpy	DMF	46% (1:4.7)	13%
14	$Ni(COD)_2$/Terpy	DMF	69% (1:2.8)	trace
15	$Ni(COD)_2$/^{t}Bu-Terpy	NMP	10%	10%
16	$Ni(COD)_2$/^{t}Bu-Terpy	THF	10%	10%

[a] Reaction conditions: **1** (0.24 mmol, 0.19 M in DMF), $Ni(COD)_2$ (0.024 mmol), ligand (0.036 mmol), PhZnI·LiCl (~0.5 M in DMF) at rt for 12 h. [b] DMI, *N*,*N*′-dimethylimidazolidinone; DMA, *N*,*N*-dimethylacetamide; DMF, *N*,*N*-dimethylformamide; NMP, *N*-methylpyrrolidone; THF, tetrahydrofuran. [c] ND = not detected by NMR.

Chart 2

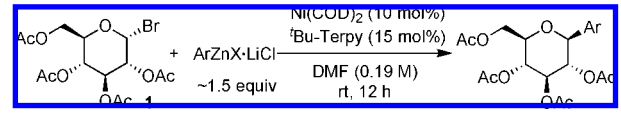


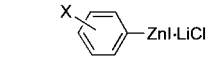
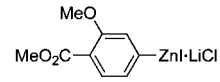
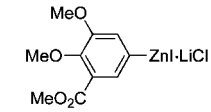
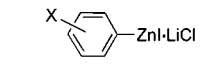
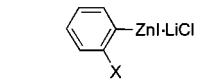
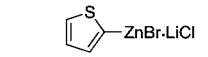
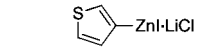
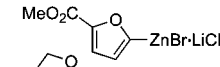
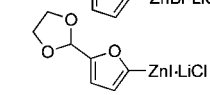
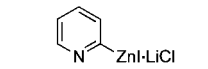
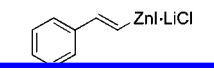
reaction was tolerant of a diverse array of functionalities such as halides, nitriles, acetals, ethers, and esters. Both electron-rich and electron-deficient arylzinc reagents provided good to excellent yields of the desired products (entries 1−3, Table 4), and excellent β-selectivities (1:>10 α:β) were observed throughout. While *meta* and *para* substituents were tolerated (entries 1−4, Table 4), *ortho* substituents generally produced poor results (entry 5, Table 4).

Extending the arylation method to heteroaromatic systems was also pursued. Furan and both 2- and 3-thiophene derivatives were good partners (entries 6−9, Table 4), the latter two derivatives being electronically quite different.[22] Unfortunately, pyridine-based zinc reagents failed to give the desired products. Finally, formation of the *trans*-phenyl vinyl derivate (entry 11, Table 4) was obtained in good yield, but with a low dr (1:1 α:β). A literature search did not uncover other Ni-catalyzed Negishi coupling of vinylzinc reagents with sp^3 alkyl halides.[23]

The versatility of the Ni-catalyzed Negishi protocol for other glycosyl halides was studied using PhZnI·LiCl as the coupling

Table 4. Scope of Organozinc Reagents in the Coupling with **1**



Entry[a]	ArZnX·LiCl	Prodcut (α: β)	Glucal
1		X = 4-OMe: 64% (1:13) X = 4-CN: 79% (1: >12) X = 4-CO_2Me: 66% (1:10) X = 3-CO_2Me: 72% (1:14)	11% trace trace 8%
2		82% (1:13)	ND[b]
3		69% (1:11)	ND[b]
4		X = 3-Cl: 75% (1:13) X = 3-Br: 77% (1:14) X = 4-I: 30% (1:10)	5% trace trace
5		X = CO_2Me: ND[b] X = OMe: Trace X = Cl: ND[b]	
6		78% (1:16)	14%
7		83% (1:16)	5%
8		65% (1:14)	ND[b]
9		80% (1:>10)	ND[b]
10		ND[b]	ND[b]
11		60% (1:1)	ND[b]

[a] Reaction conditions: **1** (0.24 mmol, 0.19 M in DMF), $Ni(COD)_2$ (0.024 mmol), ^{t}Bu-Terpy (0.036 mmol), and ArZnI·LiCl (~0.5 M in DMF, 0.75 mL) at room temperature for 12 h. [b] ND = not detected by NMR.

partner. Whereas the aceto-α-D-bromo mannose provided phenyl *C*-mannoside as a 2.9:1 mixture of α:β anomers, the aceto-α-D-bromo galactose was considerably more β-selective, giving the phenyl *C*-galactoside as a 1:10 mixture of α:β anomers (entries 1 and 2, Table 5). The 5-dealkylated glucose analogue, tri-*O*-acetyl-β-D-arabinosyl bromide, gave the desired product with a 1:2.5 α:β ratio (entry 3, Table 5). Perhaps mechanistically revealing was the observation that both the isomerically pure α-Br and the 1:1 mixture of α- and β-2-phthalimido glucosyl bromides converge to the same yield of β-Ph product (entry 4, Table 5). Ironically, the 2-deoxyglucose failed to give product due to decomposition of the glycosyl bromide and chloride.

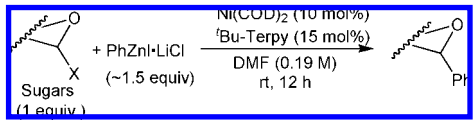
Several furanose derivatives were also investigated. Whereas the benzoyl-protected 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide produced largely the hydrolysis product, 2,3,5-tri-*O*-aceto-D-ribofuranosyl chloride gave the desired product in low yield with high β-selectivity (entries 6 and 7, Table 5). We continue to seek improvements in furanoside reactivities.

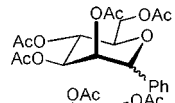
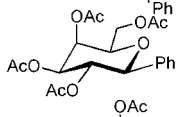
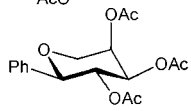
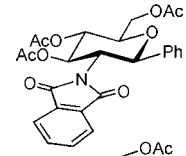
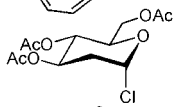
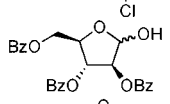
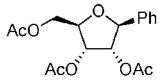
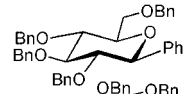
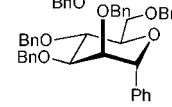
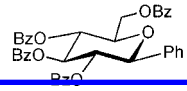
The impact of protecting groups on the reactivity of the sugar derivatives was also studied. For the benzyl-protected sugars,

(22) While 2-thiophene−zinc reagent can be prepared from the bromo precursor, 3-thiophene−zinc reagent can only be prepared from 3-iodothiophene (see Supporting Information for organozinc preparation).

(23) Only trace amount of Kumada coupling products was detected in the Ni-catalyzed coupling of vinyl Grignard reagents with primary alkyl halides, see: Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc.* **2005**, *127*, 3656–3657.

Table 5. Investigation of the Scope of Sugars under the Ni-Catalyzed Negishi Cross-Coupling Conditions



Entry[a]	Halides (α)	Products	Results Yield (α: β)
1	Br		76% (2.9:1) Glycal: 19%
2	Br		75% (1:10) Glycal: trace
3	β–Br		40% (1: 2.5) Glycal: trace
4	Br 1:1 α: β or pure α		45% (1:20)
5	Cl		decomposition
6	Br		65%
7	Cl		20% (1:20)
8	Cl		23% (1:4.4) Glycal: trace Hydrolysis: ~40%
9	Cl		28% (>20:1) Glycal: trace Hydrolysis: ~40%
10	Br		80% (1:15) Glycal: trace

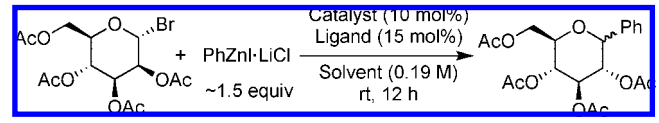
[a] Reaction conditions: glycosyl bromide (0.24 mmol, 0.19 M in DMF), $Ni(COD)_2$ (0.024 mmol), ^{t}Bu-Terpy (0.036 mmol), and ArZnI·LiCl (~0.5 M in DMF) at room temperature for 12 h.

the arming effect[24] required the use of α-glucosyl and mannosyl chlorides (for *C*-alkylation), since the bromo analogues undergo rapid hydrolysis in air. Nevertheless, the use of benzyl-protected α-chloro substrates gave low yields of the *C*-aryl glycoside (entries 8 and 9, Table 5), accompanied by substantial amounts of hydrolysis. As anticipated, the benzoyl-protected glucose gave results comparable to those obtained with the acetyl-protected glucose (entry 10, Table 5).

The optimal reaction conditions for *C*-Ph-mannoside were examined more carefully, as the standard conditions with ^{t}BuTerpy provided the product as a 1.6:1 ratio of α:*β* isomers (entry 4, Table 6), in contrast to the *β*-selective *gluco* series. The effect of ligand was considerable, as good to excellent α-selectivities were achieved using Terpy (10:1, entry 6, Table 6) and PyBox (>20:1, entry 5, Table 6), the latter in 80% yield.

(24) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.

Table 6. Reaction Optimization for PhZnI·LiCl and Aceto-α-Br-D-mannose



Entry[a]	Conditions	Product (α:*β*)	Glucal
1	$NiCl_2$·glyme, PyBox, DMI	40% (α)	30%
2	$Ni(COD)_2$, PyBox, DMA	~30% (α)	15%
3	$Ni(COD)_2$, Terpy, DMA	56% (6.6:1)	trace
4	$Ni(COD)_2$, ^{t}Bu-Terpy, DMA	65% (1.6:1)	15%
5	**$Ni(COD)_2$, PyBox, DMF**	**80% (20:1)**	**7%**
6	$Ni(COD)_2$, Terpy, DMF	79% (10:1)	10%
7	$Ni(COD)_2$, ^{t}Bu-Terpy, DMF	76% (2.9:1)	10%

[a] Reaction conditions: mannosyl bromide (0.24 mmol, 0.19 M in DMF), $Ni(COD)_2$ (0.024 mmol), ligand (0.036 mmol), and PhZnI·LiCl (~0.5 M in DMF) at room temperature for 12 h.

The ability to at least partially overcome the strong bias of a mannoside for α-products suggested that a proper ligand might eventually provide the desired catalyst control.

2.2. Catalyst or Substrate Control? Our experiments, aimed at developing efficient and selective catalysts for the *C*-alkylation of glycosyl halides, showed that the combination of PyBox/$NiCl_2$ in DMI was effective for the stereoselective generation of *C*-glycosides of biased sugars. For example, the C2 axial substituent of mannosides sterically (and perhaps electronically) favored axial alkylation and high α-selectivities. In contrast, when the carbohydrate had a less defined anomer preference (glucose, galactose), the α:*β* ratios were significantly eroded.

Like the high α-selectivities observed in mannosyl bromide alkylation reactions with PyBox/$NiCl_2$ in DMI, the PyBox/$Ni(COD)_2$ catalyst in DMF was similarly α-aryl selective and high yielding. Despite the different optimum solvent and nickel sources, the PyBox-based catalysts appear to be inherently unselective and prone to strong substrate control (mannosides).

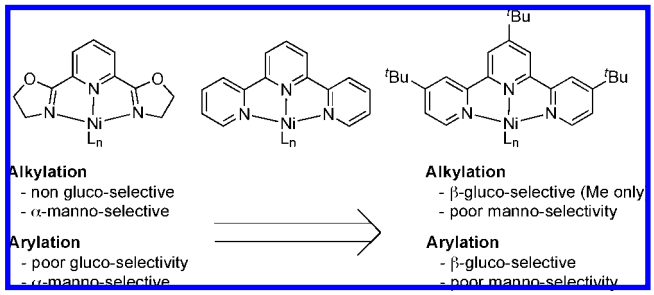
Experiments using Terpy/$NiCl_2$ catalysts in DMA showed that this catalyst had a significant preference for the *β*-methylation of **1** (*vide supra*), and although primary alkyl zinc reagents were poor yielding, they also were *β*-selective (entries 1, 4, and 5, Table 1). In a seemingly parallel fashion, the ^{t}Bu-terpy/$Ni(COD)_2$ arylation catalysts provided excellent *β*-selectivities for glucosides and galactosides in DMF.

Taken together, these data suggest that the PyBox-nickel and Terpy- or ^{t}Bu-terpy-Ni catalysts functioned by *different* mechanisms, with oxidative addition to the former occurring with little inherent stereochemical bias, while the latter preferred an invertive pathway (assuming retentive transmetalation and reductive elimination elementary steps).

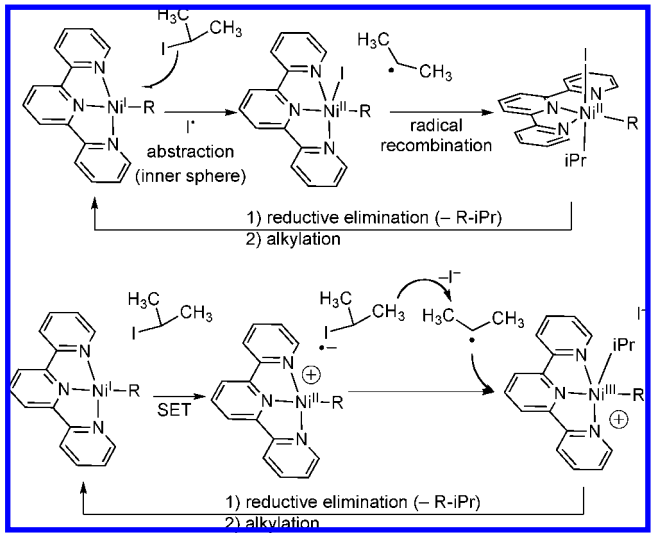
Potentially conflicting evidence for this simple notion are the notable differences in the alkylation and arylation protocol's optimum nickel source and solvent. For both *C*-alkylation-based methods, Ni(II) was optimum, while the arylation procedure required a Ni(0) source. Similarly, all alkylation reactions worked best in DMI, while the arylations worked best in DMF, regardless of the specific catalyst in question. Unanswerable as of yet is why ligand-dependent mechanisms, as implied above, would have optimum metal and solvent coupled to whether the reaction was alkylative or arylative rather than the overall mechanism. Of course, without knowing the mechanisms, it is difficult to reconcile these observations.

The propensity for equatorial arylation by ^{t}BuTerpy/$Ni(COD)_2$ catalysts in DMF was consistent with the convergence of α-

Scheme 3



Scheme 4. Mechanistic Proposals for Ni-Catalyzed Cross-Coupling

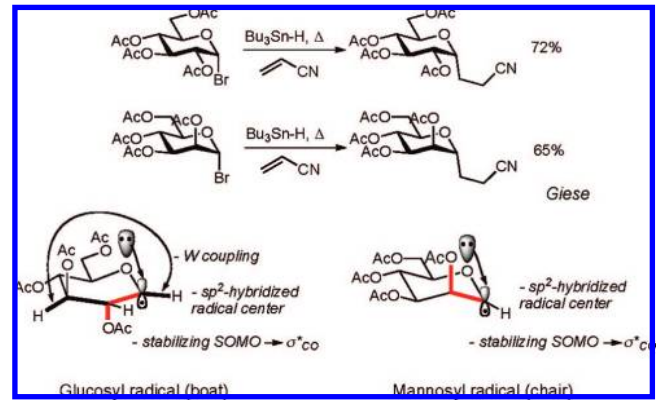


and 1:1 α:*β*-glucosaminyl bromide substrates to the *β*-Ph product (entry 4, Table 5), and also with arylation trends in the mannosyl bromide substrate. In this *manno* series, the catalyst most prone to *β*-arylation of glucosides (^{t}BuTerpy) performed most poorly, with the α-product only being favored by 2.9:1 (entry 7, Table 6). However, as the catalysts became progressively less *β-gluco*-selective, the reaction became progressively more α-*manno*-selective (10:1 for Terpy/Ni(COD)$_2$ and 20:1 for PyBox/Ni(COD)$_2$). This trend was indicative of a stereochemical mismatch between the catalyst and substrate, the ^{t}BuTerpy/Ni(COD)$_2$ catalyst preferring to *β*-arylate while the mannosyl framework favored α-products. Catalysts without a predilection (PyBox/Ni(COD)$_2$) provided good α-arylation selectivities by substrate control, while *β*-selective catalysts led to compromised results (Scheme 3).

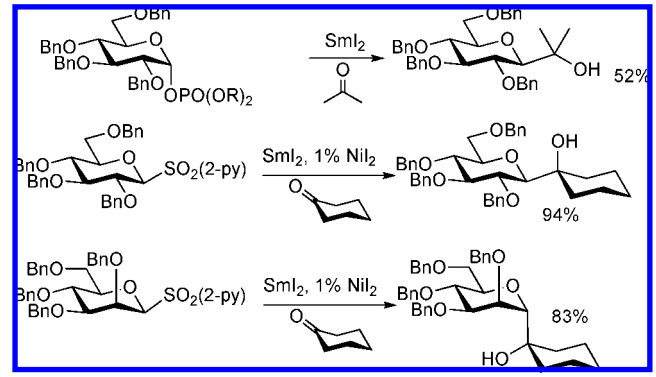
Recent mechanistic studies of Ni-catalyzed Negishi cross-coupling reactions have provided evidence for stepwise oxidative addition mechanisms involving alkyl halide-derived free radicals prior to Ni−C bond formation.[9b,c] Two variants on this mechanism, a halogen abstraction (inner sphere) and a single electron transfer (outer sphere), are outlined in Scheme 4. They differ in the details of how the C-radical is generated (single electron transfer versus halogen abstraction) but are similar in that the oxidative addition to a Ni(I) alkyl is stepwise, proceeding via a sequence of one-electron elementary steps and not via two-electron processes.[25]

(25) Phillips has recently reported a detailed DFT study on the cross-coupling process and has shown inner-sphere I$^\bullet$ abstraction from I-^{i}Pr by (Terpy)Ni^I-CH$_3$ to be energetically feasible, see: Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680–3688.

Scheme 5. Free Radical Reactivity of Glucosyl and Mannosyl Radicals and Their Respective EPR-Derived Structures



Scheme 6. Stereochemical Outcome of the Reaction of Glycosyl Radicals with Reducing Metals



If such radicals were generated in the present case, they would be subject to anomeric effects. Giese has shown that both glucosyl and mannosyl radicals selectively react with alkenes to form α-addition products (Scheme 5).[26] In conjunction with these synthetic studies, the structure of these radicals was obtained by EPR.[27] If a stereochemistry-determining Ni−C bond formation were to occur in analogy to the addition of acrylates or acrylonitrile to these radicals, then one would expect that all catalysts would generate the α-organometallic intermediate and α-products, again assuming retentive transmetalation and reductive elimination elementary steps (Scheme 3). The change in selectivity for alkylation and arylation reactions, coupled with the ligand effects, argues against a simple scenario.

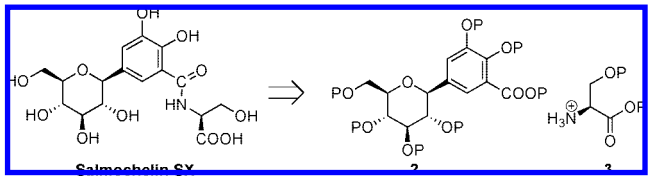
Perhaps reflective of the complexity of radical−metal addition reactions are the three reactions in Scheme 6.[28] Each of these results reasonably invokes the reaction of a glycosyl radical and a reducing metal (SmI_2 or NiI_2). In these cases, the stereochemical data follow exactly the general trends observed herein: glucosyls can be made *β*-selective, and mannosyls can be made α-selective. The divergence from the Giese free radical cases

(26) (a) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622–623. (b) Dupuis, J.; Giese, B.; Hartung, J.; Leising, M.; Korth, H.-G.; Sustmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 4332–4333. (c) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944–945.

(27) (a) Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453–1459. (b) Dupuis, J.; Giese, B.; Rüegge, D.; Fishcer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896–897.

(28) (a) Hung, S.-C.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2671–2674. (b) Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4111–4114.

Scheme 7. Retrosynthesis of Salmochelin SX

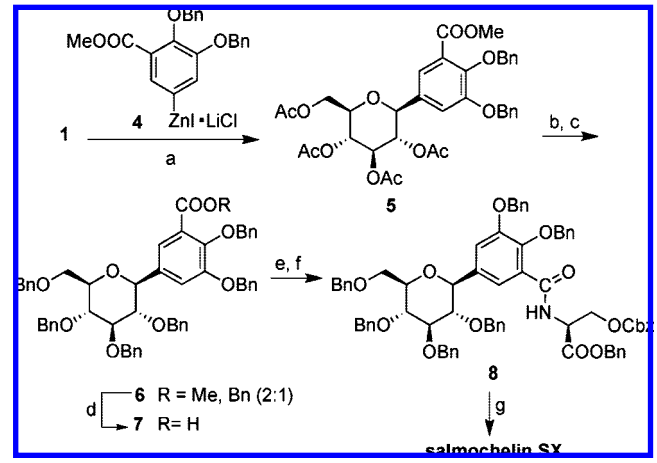


(pure α-selectivity) may reflect the more sterically encumbered reducing metals choosing the β-face of a free boat-like glucosyl radical (Scheme 6), or the unique stereoselectivity of putative radical anion intermediates. The ligand effects observed herein also suggest the possibility of a gradient of mechanisms that respond to changes in the catalyst structure, once again raising the intriguing possibility of eventual catalyst control over this important C−C bond-forming reaction.

2.3. Total Synthesis of Salmochelin SX. The applicability of this methodology to natural product synthesis was examined by synthesizing the β-*C*-aryl-glucoside, salmochelin SX,[13] a metabolite of the ferric-binding siderophores produced by *Escherichia coli* and *Salmonella enterica*.[29] A retrosynthesis provides the aryl-*C*-glucoside **2** and the doubly protected serine **3** (Scheme 7). The key step in the synthesis of **2** was the cross-coupling of arylzinc **4**[30] and acetobromo-α-D-glucose (**1**) using the standard conditions to afford **5** in moderate yield (55%) and with high β-selectivity (1:20 α:β, Scheme 8). The methyl-protected catechol zinc reagent was slightly more well behaved, and better yields and selectivities were obtained.

Unfortunately, the Bn-protected glucosyl chloride was prone to hydrolysis and decomposition by the zinc reagent, requiring a change of protecting groups. Deacetylation of **5**, followed by perbenzylation, yielded the aryl-*C*-glucoside **6** in 75% yield over two steps. Saponification, conversion to the acid chloride, and immediate addition to the trifluoroacetate salt of **3**, obtained by TFA deprotection of Boc-Ser(Cbz)-OBn,[31] in the presence of NEt_3 provided the perbenzylated salmochelin precursor **8** after 30 min at room temperature (88%); debenzylation gave salmochelin SX in 94% yield.

Scheme 8. Total Synthesis of Salmochelin SX[a]



[a] Reaction conditions: (a) $Ni(COD)_2$ (10 mol %), ^{t}Bu-Terpy (15 mol %), ArZnI•LiCl (150 mol %), DMF, room temperature, 12 h, α:β = 1:20, 55%. (b) Na_2CO_3 (500 mol %), MeOH. (c) BnBr (600 mol %), Bu_4NI (10 mol %), NaH (480 mol %), DMF, 75% over two steps. (d) NaOH (1000 mol %), THF:MeOH (3:1), 82%. (e) $SOCl_2$ (400 mol %), DMF (catalytic), DCM. (f) *S*-(BnOOC)CH(CH_2OCbz)$CHNH_2$−CF_3COOH salt (150 mol %), Et_3N (150 mol %), DCM, 0 °C then room temperature, 30 min, 88% over two steps. (g) H_2, $Pd(OH)_2$ (20 wt % on carbon), MeOH:EtOAc 1:1, 18 h, 94%.

3. Conclusions

In summary, we have demonstrated that existing Ni-catalyzed Negishi coupling methodologies can be adapted to the stereoselective synthesis of *C*-alkyl and *C*-aryl glycosides. The approach furnishes *C*-aryl glycosides in high yields and with a tolerance for a variety of *para* and *meta* substituents, heteroaromatics, and vinylzinc nucleophiles. High β-selectivities for aceto-α-D-glucose and excellent α-selectivities for aceto-α-D-mannose could be achieved by suitable choice of the N_3 ligand. The former selectivity enabled the efficient synthesis of salmochelin SX. We continue to search for catalysts capable of broad control over product stereoselectivity.

Acknowledgment. Andrew Blanchard and Riccardo Sinisi are thanked for help. We additionally thank the Department of Energy, Office of the Basic Energy Sources, for generous support (DE-FG02-05ER15630).

Supporting Information Available: Full experimental details and characterization data for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

JA8041564

(29) Fischbach, M. A.; Lin, H.; Liu, D. R.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 571–576.

(30) The zinc reagent was prepared according to a standard procedure from the iodo precursor that was synthesized from commercially available 2-hydroxy-3-methoxybenzoic acid methyl ester in three steps. See Supporting Information.

(31) Ramesh, R.; De, K.; Chandrasekaran, S. *Tetrahedron* **2007**, *63*, 10534–10542.