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Application of Redox-Active Ester Catalysis to the Synthesis of Pyranose Alkyl *C*-Glycosides

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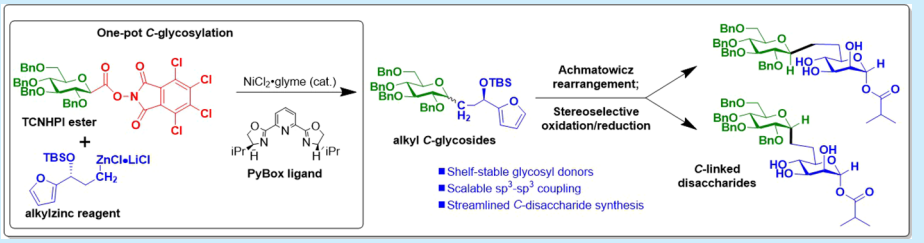

ABSTRACT: The direct coupling of shelf-stable, tetrachloro-*N*-hydroxyphthalimide ester (TCNHPI) glycosyl donors with a variety of alkylzinc reagents under redox catalysis is described. Alkyl *C*-glycosides are formed directly by a decarboxylative, Negishi-type process in 31−73% yields without the need for photocatalytic activation or additional reductants. Extension of this approach to the coupling of TCNHPI donors with stereodefined α-alkoxy furan-containing alkylzinc halides enabled *de novo* synthesis of methylene-linked *exo*-*C*-disaccharides via an Achmatowicz rearrangement.

Carbohydrates are diverse biomolecules that are implicated in multiple natural processes, such as protein folding, intracellular communication, and bacterial pathogenesis.[1,2] Much work in recent years has been devoted to the production of O-linked glycans as new therapeutics and glycobiological probes,[3−9] but the reactivity of O linkages to acid hydrolysis and enzymatic degradation can hinder the efficacy of these products *in vivo*. One way to address this issue is to replace the oxygen linkage with a methylene unit, which can increase the stability of therapeutic glycans without compromising their biological activity.[10−12] For example, alkyl *exo*-*C*-glycoside derivatives of KRN-7000, an immunostimulatory galactosyl ceramide derivative of sponge *Agelas mauritianus* glycolipid extracts (Figure 1),[13] were found to better activate natural killer T-cells against murine melanoma than *O*-glycoside derivatives at similar doses.[14,15] Alkyl *C*-glycosides have also been evaluated as competitive antagonists of DC-SIGN, a dendritic cell C-type lectin specific for L-fucose and D-mannose residues located in Le^x antigen and high-mannose-containing viral glycoproteins, respectively.[16] In a SPR competition assay against the natural ligand L-fucose, C-linked fucopyranosyl pseudodisaccharides (Figure 1) were found to have increased affinity for DC SIGN, which inspired the synthesis of multivalent C-linked L-fucose glycodendrimers for more potent inhibition.[17] These examples highlight the bioisosteric potential of synthetic alkyl *exo*-*C*-glycosides.

A broader implementation of this methylene replacement strategy remains challenging, however, given the lack of flexible and direct methods for forming anomeric sp^3-sp^3 *exo*-C linkages. While there have been significant advances in acyl and

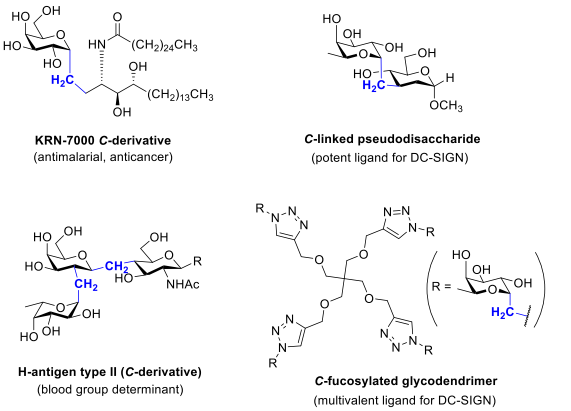

Figure 1. Bioactive *C*-glycosides with methylene linkages.

aryl C-glycosylation by several groups (Scheme 1),[18−22] catalytic sp^3-sp^3 alkyl coupling at the pyranose anomeric center is still an emerging field,[23−25] and direct coupling methods often require the use of unstable glycosyl halides (Scheme 1b,c).[26−29] In search of a more practical alkyl *exo*-C-glycosylation strategy, we were drawn to the work of the Baran

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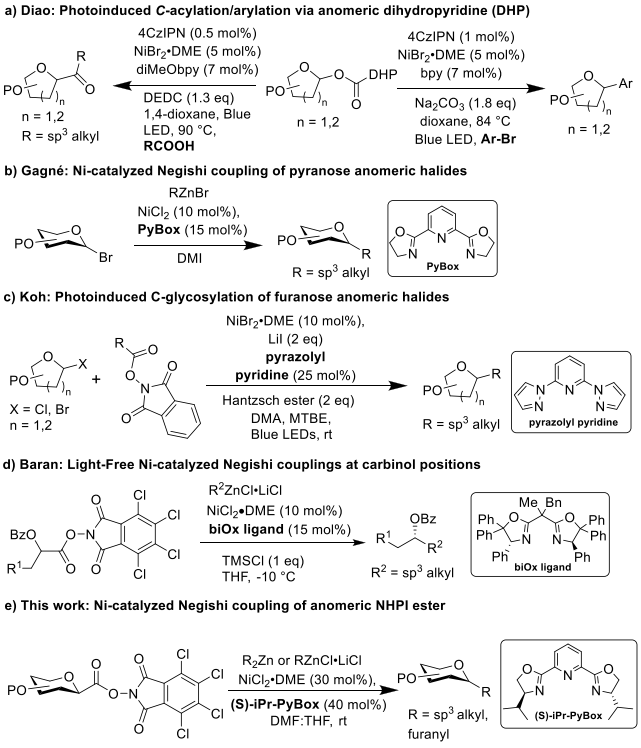
Scheme 1. Ni-Catalyzed sp^3–sp^3 Cross Coupling at α-Oxy Positions

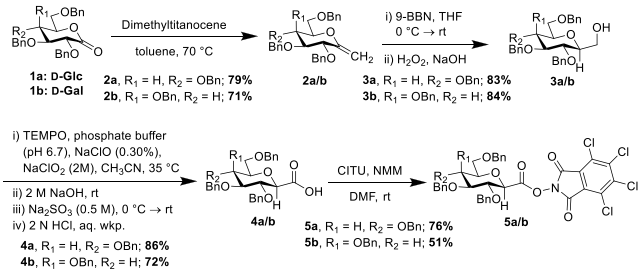


lab (Scheme 1d), which showed shelf-stable *N*-hydroxyphthalimide (NHPI) esters could be activated by Ni catalysis to forge sp^3–sp^3 linkages as a higher-yielding alternative to Barton decarboxylation.[30−33] With this precedent in mind, we proposed that a similar coupling of shelf-stable anomeric tetrachloro-*N*-hydroxyphthalimide (TCNHPI) ester donors and dialkylzinc acceptors could yield pyranose alkyl *C*-glycosides in a light-free, decarboxylative Negishi-type process (Scheme 1e). Notably, through the use of α-alkoxy furan-containing organozincs, we also envisioned it would be possible to access *exo*-C-linked disaccharides via an Achmatowicz rearrangement,[34,35] as shown in our group's prior work with homoacyl furanyl *C*-glycosides.[36]

We initially recognized that it would be necessary to gain rapid access to the anomeric TCNHPI esters to ensure the practicality of our method. To this end, we conducted the synthesis of D-glucose and D-galactose TCNHPI esters in four steps starting from readily available lactones **1a** and **1b** (Scheme 2).[37] Petasis olefination by the method of Payack et al. afforded olefins **2a** and **2b** in 79% and 71% yields, respectively.[38] β-Configured methyl alcohols **3a** and **3b** were then produced stereoselectively in 83% and 84% yields, respectively, via hydroboration–oxidation with 9-borabicyclo[3.3.1]nonane (9-BBN).[39] A one-pot Anelli–Pinnick oxidation was then applied to produce ulosonic acids **4a** and **4b** in 86% and 72% yields, respectively.[40] Finally, TCNHPI esters **5a** and **5b** were synthesized in 76% and 51% yields, respectively, by treatment with tetrachloro-*N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate (CITU).[41] From a practicality standpoint, compounds **5a** and **5b** were easily manipulated solids and shelf-stable for up to several months when stored under argon.

Having secured an efficient route to TCNHPI esters **5a** and **5b**, we conducted a ligand screen to optimize the Ni-catalyzed

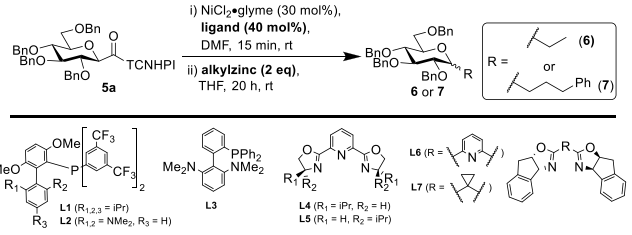
Scheme 2. Synthesis of Anomeric TCNHPI Esters[a]



[a]Abbreviations: 9-BBN, 9-borobicylo(3.3.1)nonane; TEMPO, 2,2,6,6-tetramethylpiperidinyl-1-oxyl; CITU, tetrachloro-*N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate; NMM, *N*-methylmorpholine.

coupling of D-glucose TCNHPI ester **5a** with dialkylzincs prepared from the corresponding Grignard reagents. To ensure reproducibility, the key $NiCl_2$·glyme precatalyst was prepared in house and used in place of the commercial material, which was found to contain ethanol (see the Supporting Information). During the optimization, we found that PyBox and triarylphosphine-type ligands enabled more efficient alkyl C-glycosylations than other common ligand archetypes such as bipyridines, diphosphines, and N-heterocyclic carbenes (see the Supporting Information for the full ligand scope and optimization). As detailed in Table 1, we identified that using

Table 1. Ligand Screen for Reaction Optimization



entry	ligand	alkylzinc (R_2Zn)	yield[a] (%)	anomer ratio (β:α)
1[b]	**L1**	Et_2Zn	54	1:1.1[c]
2[b,d]	**L2**	Et_2Zn	73	1:1.1
3[b]	no ligand	Et_2Zn	33	1.3:1
4[b]	**L2**	$(Ph(CH_2)_3)_2Zn$	50	1.3:1
5[b]	**L3**	$(Ph(CH_2)_3)_2Zn$	51	1:1.1
6[b]	**L4**	$(Ph(CH_2)_3)_2Zn$	56	1.4:1
7[e]	**L4**	$(Ph(CH_2)_3)_2Zn$	70	1.4:1
8[e]	**L5**	$(Ph(CH_2)_3)_2Zn$	51	1:1.1
9[e]	**L6**	$(Ph(CH_2)_3)_2Zn$	38	1.5:1
10[e]	**L7**	$(Ph(CH_2)_3)_2Zn$	18	1.3:1[c]

[a]On a 0.1 mmol scale; yields of isolated anomers unless otherwise stated. [b]Two-pot approach: $NiCl_2$·glyme and the ligand mixed 10 min prior to addition of **5a**, then mixing for an additional 5 min prior to the addition of an alkylzinc. [c]NMR yield. Products co-elute with a glycal byproduct. [d]Reaction conducted on a 0.2 mmol scale. [e]One-pot approach: $NiCl_2$·glyme with a ligand and **5a** mixed for 15 min prior to the addition of an alkylzinc.

the (*S*)-configured iPr-PyBox[42] ligand **L4** gave yields higher than those seen with phosphines **L1**–**L3** in couplings with elongated di(γ-phenylpropyl) zinc (entries 4–6, respectively). The yield and practicality of the coupling were further increased with ligand **L4** by adopting a one-pot approach in which the TCNHPI ester, Ni catalyst, and ligand were mixed

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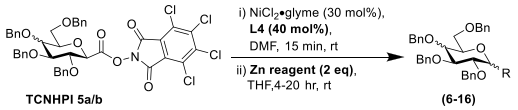
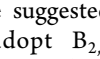
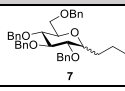
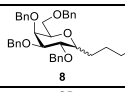
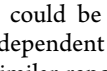
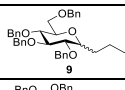
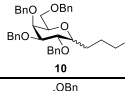
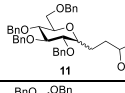
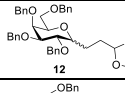
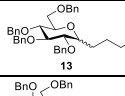
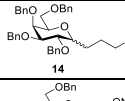
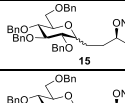
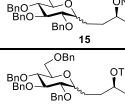
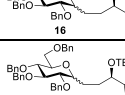
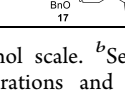
prior to addition of the alkylzinc (entry 7). With regard to stereoselectivity, we were initially surprised to find that neither enantiomer **L5**[43] nor other reported chiral Box-type ligands **L6** and **L7**[32,44] induced a significant shift in the anomeric ratio (entries 8−10). These results suggested to us that substrate stereoelectronics were the primary determinant of the anomeric ratio,[19] and not the stereochemical match/mismatch between the substrate and our catalytic system. Seminal EPR studies by Giese have suggested that D-gluco and D-manno-configured sugars adopt $B_{2,5}$ and $^4C_1$ conformations, respectively, to maximize orbital overlap among the radical, the ring oxygen lone pair, and the C2-oxy substituent bond.[45,46] Assuming an outer-sphere process, this "quasi-homo-anomeric effect" could be the major influence behind the observed substrate-dependent stereoselectivity displayed in both this work and in similar reports of catalytic pyranose *exo*-C-glycosylation.[22,26,27]

To explore the scope of our optimized method, we synthesized a collection of alkyl *exo*-*C*-glycosides (**7**−**17**) by the coupling of **5a** and **5b** with various alkylzincs (Table 2). Dialkylzinc reagents were generated from commercially available halides by reaction of the corresponding Grignard reagents with $ZnCl_2$, and the resulting organozinc solutions were used directly in the coupling without removal of Mg salt byproducts,[47] as described previously by Baran et al.[31] A number of useful functionalities (e.g., silyl and benzyl ethers and dioxolanes) were tolerated by this method to afford linear alkyl *exo*-*C*-glycosides **7**−**14** in moderate to good yields (Table 2, entries 1−8). We also explored direct C-glycosylation with *α*-alkoxy furan-containing organozincs **A1**/**A2**, **B**, and **C** (Table 2, entries 9−12), which we envisioned could function as handles for the *de novo* assembly of C-linked pyranose structures by an Achmatowicz rearrangement.[34,35] To this end, we synthesized the furan-containing bromide precursors to Zn reagents **A1**/**A2**, **B**, and **C** in eight steps from commercially available furfural in 15%, 10%, and 13% overall yields, respectively (see the Supporting Information for the full synthesis). Alkylzinc halides were then generated by reacting the corresponding Grignard reagents with equimolar $ZnCl_2$ in the presence of a LiCl additive.[32,48] Crucially, we found that alkyl zinc halide **A2** afforded a yield similar to that of dialkylzinc **A1** in the coupling (Table 2, entries 9 and 10), allowing us to reduce consumption of the valuable halide precursor in further attempts. Finally, the highest yield of furan-containing *exo*-*C*-glycoside was obtained using OTBS-protected alkylzinc halide **C** (Table 2, entry 12).

Having established a viable approach for forming an anomeric alkyl *exo*-C linkage to *α*-alkoxy furans, we turned our attention to the *de novo* synthesis of alkyl *C*-disaccharides via the Achmatowicz rearrangement (Scheme 3). To amass enough material for the two proposed pathways, we repeated the synthesis of *C*-glucosides **17*β*** and **17*α*** on a 1 mmol scale with minimal impact on the yield and complete separation of the anomers (Scheme 3A). Isolated anomers **17*β*** and **17*α*** were then treated in parallel with tetrabutylammonium fluoride (TBAF) to afford furanyl alcohols **18*β*** and **18*α*** in 72% and 81% yields, respectively (Scheme 3B).[49] Achmatowicz rearrangement of alcohols **18*β*** and **18*α*** with *N*-bromosuccinimide afforded pyranone hemiacetals **19*β*** and **19*α*** in 78% and 88% yields, respectively.[35] We then conducted a diastereoselective esterification with a (+)-benzoteramisole catalyst to afford isobutyrate pyranone acetals **20*β*** and **20*α*** in 60% (3.7:1 axial:equatorial) and 75% (7.3:1 axial:equatorial)

Table 2. Scope of TCNHPI C-Glycosylation with Different Alkylzincs



entry[a]	5a/5b	Zn reagent[b]	product	yield (β:α)[c]
1[d]	**5a**		 **7**	70% (1.4 : 1)
2[d]	**5b**		 **8**	47% (1.2 : 1)
3[d]	**5a**		 **9**	73% (1.1 : 1)
4[d]	**5b**		 **10**	58% (1 : 1)
5[d]	**5a**		 **11**	64% (1.7 : 1)
6[d]	**5b**		 **12**	72% (1 : 1.3)
7[d]	**5a**		 **13**	62% (1.2 : 1)
8[d]	**5b**		 **14**	63% (1 : 1.4)
9	**5a**	 **A1**	 **15**	35% (1.4 : 1)
10	**5a**	 **A2**	 **15**	41% (1 : 1)
11	**5a**	 **B**	 **16**	31% (1 : 1)
12	**5a**	 **C**	 **17**	49% (1.1 : 1)

[a]Reactions conducted on a 0.1 mmol scale. [b]See the Supporting Information for Zn reagent preparations and the synthesis of precursor bromides to **A1**/**A2**, **B**, and **C**. [c]Yields of isolated anomers, reactions conducted on a 0.1 mmol scale. [d]Bromide precursor to the Zn reagent obtained from commercial sources.

yields, respectively.[50] The axially configured pyranone acetals were then subjected to stereoselective Luche reduction to yield equatorial allylic alcohols **21*β*** and **21*α*** in 60% and 81% yields, respectively.[51−53] An UpJohn dihydroxylation with OsO_4 and *N*-methylmorpholine *N*-oxide was then conducted to yield fully saturated *exo*-C-linked disaccharides **22*β*** and **22*α*** in 58% and 80% yields, respectively.

To complement the ample literature precedent for the stereoselective formation of a D-mannose reducing sugar by this established reaction sequence,[35,51,52] we treated **22*β*** and **22*α*** with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid to produce the corresponding C2,3 acetonides (see the Supporting Information). This modification improved the resolution of the reducing sugar H2 and H3 signals, allowing for their assignment by COSY and HSQC experiments. Assuming an energetically favored $^4C_1$ conformation, we could then target the H2 signal by NOEDIFF to confirm the D-

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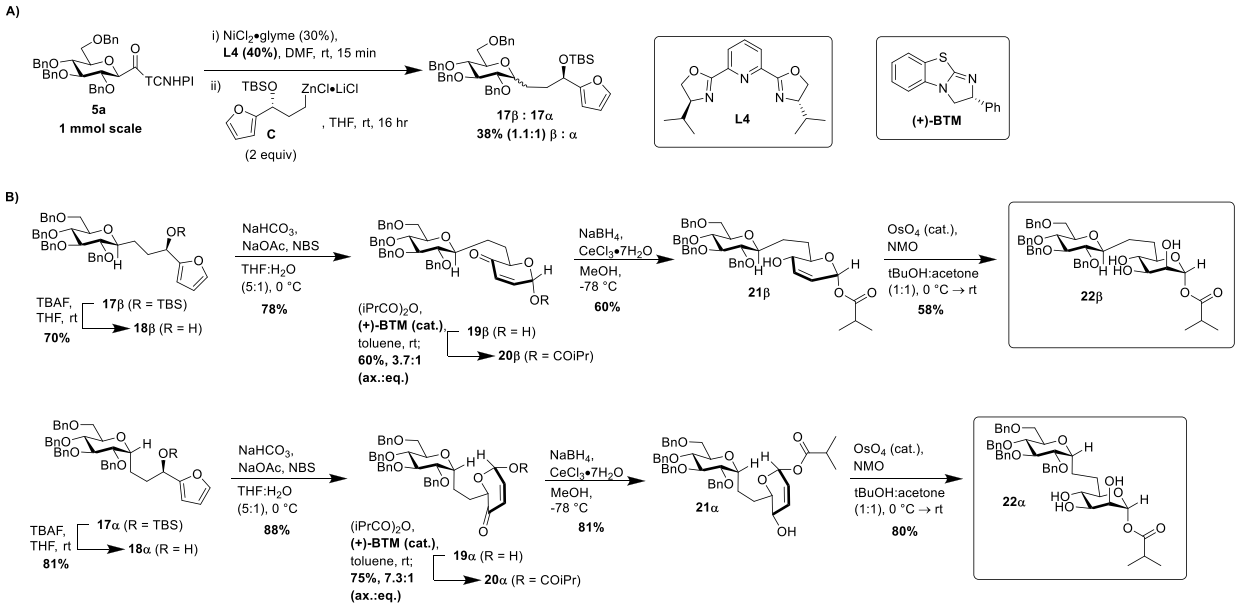
Scheme 3. Scale-up of C-Glycosylation and Route to C-Linked Disaccharides[a]



[a]Yields are of isolated products. Abbreviations: (+)-BTM, (+)-benzotetramisole; $(iPrCO)_2O$, isobutyric anhydride; NMO, *N*-methylmorpholine *N*-oxide.

mannose orientation of the C2,3 *syn* diol through the observed absence of the H2−H4 NOE effect, which would be expected for the alternate D-allose configuration (see the Supporting Information).

In summary, we have developed a practical method for the direct synthesis of sp^3−sp^3-linked pyranose *exo*-*C*-glycosides by a Negishi-type cross coupling of anomeric TCNHPI esters with alkylzinc reagents. Compounds **5a** and **5b** were easy to handle, shelf-stable, and readily accessible from commercial precursors. Extensive reaction optimization identified the substituted PyBox derivative **L4** as the ideal ligand to enable consistent couplings with **5a** and **5b**. Our coupling conditions were also scalable for the production of *C*-glycosides bearing *α*-alkoxy furans, which could in turn function as handles for accessing a variety of biologically significant structures.[54−57] Further elaboration of *C*-glycosides **17*β*** and **17*α*** to methylene-linked pseudodisaccharides was made possible by a *de novo* sequence featuring an Achmatowicz rearrangement and stereoselective oxidation/reductions. Acetonide protection of C-linked disaccharides **22*β*** and **22*α***, coupled with ^{1}H NOE and 2D NMR experiments, enabled full characterization of our final disaccharides as containing a D-mannose sugar at the reducing end, in agreement with the literature precedent (see the Supporting Information). Taken together, we believe our methodology represents a practical tool for the direct synthesis of various alkyl *exo*-*C*-glycosides, including C-linked disaccharides.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01228.

Experimental details and characterization data (PDF)

FAIR Data is available as Supporting Information and includes the primary NMR FID files for compounds **1**−**22**, **S2**, and **S5**−**S23** (ZIP)

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Notes

The authors declare no competing financial interest.

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