J|A|C|S
COMMUNICATIONS

Published on Web 01/30/2007

A Room Temperature Negishi Cross-Coupling Approach to C-Alkyl Glycosides

Hegui Gong, Riccardo Sinisi, and Michel R. Gagné*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

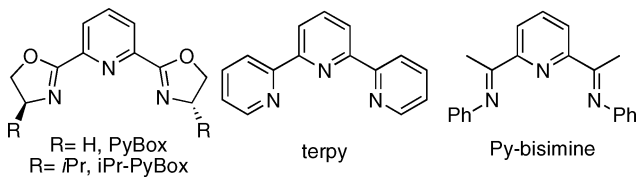
Received December 14, 2006; E-mail: mgagne@unc.edu

C-Glycosides represent an important class of bioactive compounds that are resistant to metabolic processing.[1,2] Although cross-coupling reactions are obvious approaches to these compounds, the sensitivity of C1-substituted organometallics to β-elimination processes (hydride or alkoxy) is the generally accepted reason why fully oxygenated and saturated structures are not typically accessible via these methods.[3−5] This notion is generally true of the synthetic methods that generate nucleophilic character at C1.[6] The contrastingly high number of methods for the synthesis of 2-deoxy C-glycosides[2a] reinforces the notion of an elimination problem in C1 organometallics.[7]

Recent investigations of pincer-ligated organometallic complexes have shown that these ligands can effectively inhibit β-H elimination reactions by occupying the cis coordination sites required for elimination.[8,9] Fu has recently shown that *i*Pr-PyBox/Ni ($NiCl_2$, $NiBr_2$, $Ni(COD)_2$) effectively catalyzes the cross-coupling of 2° alkyl halides with alkyl zinc reagents without competing β-H elimination.[10] These catalysts therefore seemed the ideal starting point for the search for cross-coupling methods applicable to the synthesis of C-glycosides.[11]

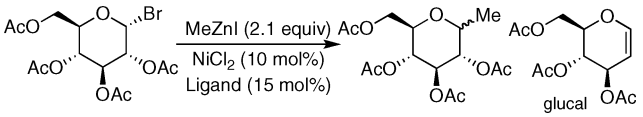
Because of the widespread use of acetate-protected carbohydrates, we initiated our studies using aceto-α-bromo-D-glucose and MeZn−I (Table 1). An initial screen of solvents indicated that DMI (*N*,*N*′-dimethylimidazolone), THF, and DMA (*N*,*N*′-dimethylacetamide) were acceptable, with the former being optimal; nonpolar solvents accelerated competing elimination processes. Additionally, $NiCl_2$•DME and $NiBr_2$•glyme could be used interchangeably. In the absence of a Ni catalyst, oligomeric baseline products were formed.

Table 1 collects results for a variety of tridentate ligands, including a variety of PyBox ligands (entries 1−5), terpyridine (terpy, entry 6),[12] a pyridyl bisimine (entry 7),[12a] and a terthiophene (entry 8). The best ligand was the unsubstituted PyBox ligand, which gave the desired product in 76% yield along with traces of the glucal elimination product.[13] The higher yields for the smaller ligand suggested that steric effects in the catalyst were important. In each of the cases, the diastereomeric ratio modestly favored the β-anomer, with the exception of terpy, where only the β-anomer was observed, though, unfortunately, at the expense of yield.[14]



Since PyBox provided the most encouraging results with MeZn−I, it was tested with a primary alkyl zinc reagent. Results for several α-bromo sugars are collected in Table 2. Particularly encouraging was aceto-α-bromo mannose, which selectively provided the α-product in good yield, perhaps a consequence of anchimeric assistance or additional stereoelectronic control by the axial OAc.

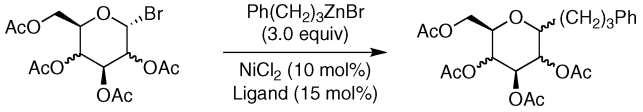
Table 1. Ligand Screening Results for the Cross-Coupling of *O*-Acetyl-α-bromo-D-glucose and MeZn−I



entry[a]	ligand	yield (α:β)	glucal
1	*S*-*i*Pr-PyBox	50% (1:1.5)	10%
2	*R*-*i*Pr-PyBox	50% (1:1.5)	9%
3	*S*-sBu-PyBox	20% (1:1.5)	trace
4	*S*-Ph-PyBox	trace	NA
5	PyBox	76% (1:2.2)	6%
6[b]	terpy	30% (β-only)	trace
7	Py-bisimine	NR	NA
8	terthiophene	trace	major

[a] Typical reaction conditions: glucosyl bromide (0.24 mmol, 0.24 M in DMI), $NiCl_2$•DME (0.024 mmol), ligand (0.036 mmol), at room temperature for 12 h. [b] $NiBr_2$•glyme in DMI was used.

Table 2. Cross-Coupling Results Using a Primary Alkyl Zinc Reagent with Various Aceto-Protected α-Bromo Sugars



entry[a]	sugar	ligand	yield (α:β)	glycal
1	glucose	PyBox	53% (1:2.5)	9%
2	mannose	PyBox	75% (8:1)	9%
3	galactose	PyBox	43% (1:2)	trace

[a] Typical reaction conditions: glycosyl bromide (0.24 mmol, 0.19 M in DMI), $NiCl_2$•DME (0.024 mmol), ligand (0.036 mmol), RZnBr in DMI at room temperature for 12 h.

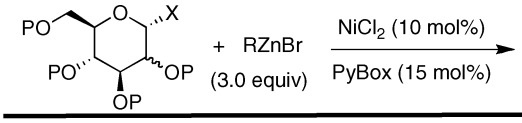
Freshly chromatographed bromide was key to obtaining reproducibly high yields.

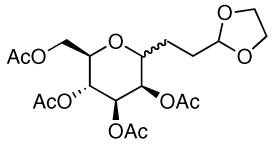
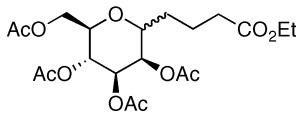
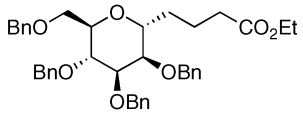
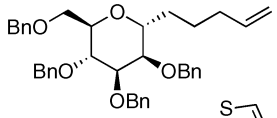
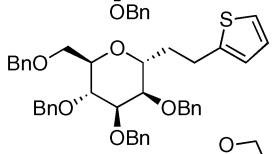
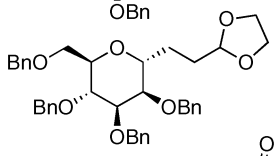
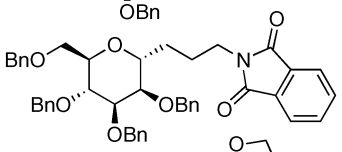
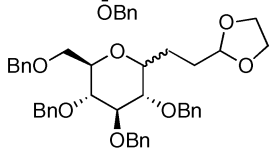
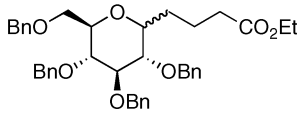
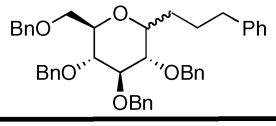
Benzyl-protected glycosyl halides were also examined; however, the α-bromides were too reactive and under the standard PyBox/$Ph(CH_2)_3Zn$−Br conditions resulted in diminished yields, the mass balance primarily consisting of hydrolysis products. The α-chlorides, however, were more stable, and excellent yields and high α-selectivities could be obtained; the α-mannosyl chloride gave no detectable β-anomer (>10:1). As shown in Table 3, glycosyl chlorides effectively partnered with a variety of functionalized primary alkyl zinc reagents, including alkene, acetal, ester, and heteroaromatic and phthalimide functional groups.

As a general rule, "fully armed" sugars were best matched to chloride leaving groups, and "disarmed" acetate-protected sugars worked best as the bromide (the chlorides were unreactive). Mannosides uniformly provided high α-selectivity, while glucosides were much less so, and while acetals, phthalimides, and esters were uniformly effective, the Zn−pentenyl and alkyl−thiophene reagents consistently gave reduced yields and higher levels of glucal, perhaps due to chelation effects in a key organo-Ni intermediate.

10.1021/ja068950t CCC: $37.00

Table 3. C-Alkylation with Functionalized Alkyl Zinc Reagents



entry[a]	X	product	yield (α : β)	glucal
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), RZnBr (in DMI), at room temperature for 12 h. [b] No β-isomer detected by TLC or NMR.

In summary, we report herein a cross-coupling method for the synthesis of fully oxygenated, fully saturated C-alkyl glycosides that utilizes glycosyl halides and functionalized alkyl zinc reagents as the reacting partners.[15] Unsubstituted PyBox ligands provide good yields of products, and mannosyl halides were particularly diastereoselective for retentive C1-alkylation.[16] In contrast, terpy (and MeZnI) provided the invertive C1-alkyl as the sole product, suggesting that cross-coupling methodologies capable of exercising catalyst control over anomer selectivity in C-glycoside synthesis may be achievable.

Acknowledgment. We warmly thank the National Science Foundation for partial support of this work (CHE-0315203), and Profs. Antony Fairbanks and George Fleet (Oxford University) for helpful discussions.

Supporting Information Available: Full synthetic and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews in C-glycoside biology and biosynthesis, see: (a) Bililign, T.; Griffith, B. R.; Thorson, J. S. *Nat. Prod. Rep.* **2005**, *22*, 742−760. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299−1331. (c) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363−1391. (d) Compain, P.; Martin, O. R. *Bioorg. Med Chem.* **2001**, *9*, 3077−3092. (e) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83.

(2) (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1995. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995.

(3) For reviews on C-glycoside synthesis, see: (a) Meo, P.; Osborn, H. M. I. *Best Synthetic Methods: Carbohydrates*; Elsevier Science Ltd.: New York, 2003; pp 337−384. (b) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959. (c) Aryl C-glycosides: ref 2 and Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem* **2005**, *5*, 1333−1350.

(4) For recent examples of C1-halo-glycal sp^2 cross-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) Jeanneret, V.; Meerpoel, L.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 543−546.

(5) For Pd-mediated Heck-type couplings, see: Daves, G. D., Jr. *Acc. Chem. Res.* **1990**, *23*, 201−206.

(6) Somsák, L. *Chem. Rev.* **2001**, *101*, 81−135.

(7) For several disparate examples of C1 organometallic compounds, see: (a) DeShong, P.; Soli, E. D.; Slough, G. A.; Sidler, R. D.; Elango, V.; Rybczynski, P. J.; Vosejpka, L. J. S.; Lessen, T. A.; Le, T. X.; Anderson, G. B.; von Philipsborn, W.; Vohler, M.; Rentsch, D.; Zerbe, O. *J. Organomet. Chem.* **2000**, *593*−*594*, 49. (b) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055−7057. (c) Ghosez, A.; Göbel, T.; Giese, B. *Chem. Ber.* **1988**, *121*, 1807−1811. (d) Trainor, G. L.; Smart, B. E. *J. Org. Chem.* **1983**, *48*, 2447−2448.

(8) For inhibition of β-H elimination in nonpincer Pd systems, see: (a) Oestereich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442. (b) Zhang, L.; Zetterberg, K. *Organometallics* **1991**, *10*, 3806−3816. (c) Arnek, R.; Zetterberg, K. *Organometallics* **1987**, *6*, 1230−1235. (d) Arai, I.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 7683.

(9) See also: (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) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013−3015. (d) Feducia, J.; Campbell, A. N.; Doherty, M. Q. *J. Am. Chem. Soc.* **2006**, *128*, 13290−13297.

(10) (a) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482−10483 and references therein. See also: (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384−387.

(11) For examples of π-allyl Pd strategies for O-glycoside synthesis, see for example: (a) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714−8715. (b) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407. (c) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336−1337.

(12) (a) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175−13183. (b) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Commun.* **2005**, 4211−4213. (c) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100−8101.

(13) In the course of the screening experiment, it was occasionally observed that β-H elimination can occur, but this product is absent in the indicated entries.

(14) Additional optimization of this reaction indicated that DMA improved the yields to 60%, while maintaining the high β-selectivity. Unfortunately, high selectivity was not maintained with larger reagents $(Ph(CH_2)_3$-Zn−Br). $^tBu_3$terpy, which significantly improves alkyl−alkyl Negishi cross-couplings (see ref 12a), did not yield the C1-methyl product in DMA, though it was observed in THF (∼40% with high β-selectivity).

(15) Preliminary experiments with aryl zinc reagents indicate that some C1-aryl product can be obtained using the standard protocol (∼40%). Experiments to optimize the reaction conditions are underway and will be reported in due course. In contrast, preliminary experiments with BnZnBr did not give the C-glycoside.

(16) In the case of aceto-α-bromo-D-mannose and $Ph(CH_2)_3Zn$−Br a lower catalyst loading (5 mol %) was also tolerated with minimal diminution in yield and diastereoselectivity.

JA068950T