ORGANIC LETTERS

2009
Vol. 11, No. 4
879−882

Sn-Free Ni-Catalyzed Reductive Coupling of Glycosyl Bromides with Activated Alkenes

Hegui Gong, R. Stephen Andrews, Joseph L. Zuccarello, Stephen J. Lee,[†] and Michel R. Gagné*

University of North Carolina at Chapel Hill, Department of Chemistry, Chapel Hill, North Carolina 27599, and U.S. Army Research Office, P.O. Box 12211, Research Triangle Park, North Carolina 27709

mgagne@unc.edu

Received December 13, 2008

ABSTRACT

A mild, stereoselective method for the Ni-catalyzed synthesis of α-*C*-alkylglycosides is reported. This approach entails the reductive coupling of glycosyl bromides with activated alkenes at room temperature, with low alkene loading as an important feature. Diastereoselective coupling with 2-substituted acrylate derivatives was made possible through the use of 2,4-dimethyl-3-pentanol as a proton source.

The utility of *C*-glycosides as stabilized biological isosteres in pharmaceutical or biological research, as well as their appearance in natural products and their potential as useful building blocks for complex molecule synthesis, have been recognized for decades.[1,2] This has led to a variety of synthetic approaches to *C*-glycosides,[3] one of the more recognizable being the reductive trapping of glycosyl radicals with activated alkenes. First demonstrated by Giese and Baldwin for Bu_3SnH-mediated radical chain processes,[4] it has since been reported in reactions that employ transition-metal complexes[5] as stoichiometric promoters[6] or catalysts.[7] A ubiquitous feature in each variant is the stereoselective formation of an axial C−C linkage between the glycoside and the coupling partner. Unfortunately, they also suffer from needing a significant excess (6−20 equiv) of the alkene partner and the requirement for stoichiometric amounts of a toxic heavy metal and/or moderate yields.

In light of these limitations, we postulated that a Ni catalyst, if appropriately tuned and partnered with a convenient and environmentally benign stoichiometric reductant and proton source, could improve the synthesis of *C*-glycosides. Intriguing was the possibility that a glycosyl

[†] U.S. Army Research Office.

(1) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995.

(2) For recent reviews in *C*-glycoside biology, see: (a) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431. (b) Hultin, P. G. *Curr. Top. Med. Chem.* **2005**, *5*, 1299. (c) Zou, W. *Curr. Top. Med. Chem.* **2005**, *5*, 1363. (d) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (e) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55.

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

(4) (a) Cotanda, K.; Matsugi, M.; SueMura, M.; Ohira, C.; Sano, A.; Oka, M.; Kita, Y. *Tetrahedron* **1999**, *55*, 10315. (b) Giese, B.; Dupuis, J.; Nix, M. *Org. Synth.* **1987**, *65*, 236. (c) Dupuis, J.; Giese, B.; Hartung, J.; Leising, M.; Korth, H.-G.; Sustmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 4332. (d) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. (e) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944.

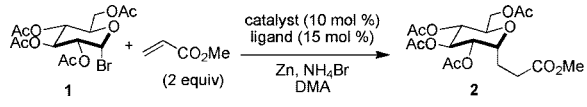
(5) For a leading review on transition-metal-mediated radical reactions, see: Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.

(6) For Mn, see: (a) DeShong, P.; Slough, G. A.; Elango, V. *Carbohydr. Res.* **1987**, *171*, 342. (b) For Ti, see: Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439. (c) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204. (d) For Cr, see: Juhasz, Z.; Micskei, K.; Gal, E.; Somsak, L. *Tetrahedron Lett.* **2007**, *48*, 7351.

(7) (a) Catalytic Co/stoichiometric Zn: Scheffold, R.; Abrecht, S.; Orlinski, R.; Ruf, H.-R. *Pure Appl. Chem.* **1987**, *59*, 363. (b) Catalytic Ni(II)/stoichiometric Mn: Readman, S. K.; Marsden, S. P.; Hodgson, A. *Synlett* **2000**, 1628.

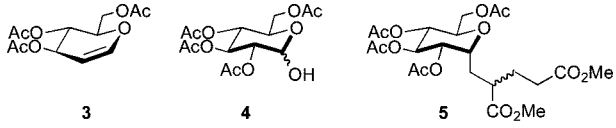
10.1021/ol8028737 CCC: $40.75
Published on Web 01/26/2009

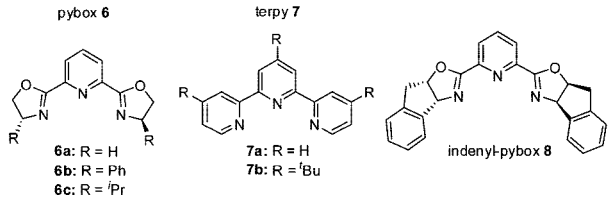
Table 1. Optimization of the Reaction Conditions for the Coupling of Glucosyl Bromide **1** with Methyl Acrylate[a]



entry	catalyst/ligand/solvent	product **2** (%)	glucal **3** (%)
1	Ni(COD)$_2$/**6a**/DMA	35	12
2	**Ni(COD)$_2$/6b/DMA**	**70**	**trace**
3	Ni(COD)$_2$/**6c**/DMA	69	5
4	Ni(COD)$_2$/(*S*)-**6b**/DMA	52	trace
5	Ni(COD)$_2$/**7a**/DMA	46	5
6	Ni(COD)$_2$/**7b**/DMA	54	8
7	Ni(COD)$_2$/**6b**/DMF	35	trace
8	Ni(COD)$_2$/**6b**/DMI	30	trace
9	Ni(COD)$_2$/**6b**/THF	trace	trace
10	Ni(COD)$_2$/**6b**/CH_3CN	40	12
11	Ni(COD)$_2$/none/DMA	37	24
12	none/none/DMA	5	major

[a] Standard reaction conditions used.[15]

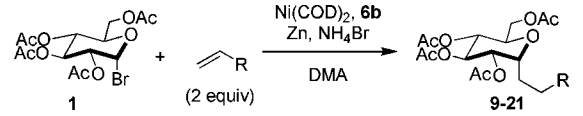




radical[8] might be accessible and interceptible from the reaction of a low-valent Ni source and a glycosyl bromide, as postulated in the mechanism of our recently disclosed Ni-catalyzed arylation of glycosyl bromides.[9,10] The intermediacy of secondary alkyl radicals in Ni-catalyzed cross-coupling has been previously proposed.[11−14]

Our investigation began with the reaction of aceto-1-bromoglucose **1** and methyl acrylate using catalytic Ni(COD)$_2$, pybox ligand **6a**, Zn as the terminal reductant, NH_4Br as a proton source, and DMA as solvent (Table 1, entry 1).[15] Encouraging was the 35% yield of the desired α-*C*-glucoside product **2**; however, this was accompanied by significant amounts of undesired byproducts from β-elimination **3**,[16] hydrolysis **4**, and overaddition **5**. Optimization studies varying ligand and solvent led to a 70% yield of **2** with (*R*)-Ph-pybox **6b** (entry 2), with only trace quantities of **3**, **4**, or **5** being observed. Though **6c** gave a similar yield, a slight increase (5%) in glucal **3** was observed (entry 3). Interestingly, the (*S*)-enantiomer of **6b** reduced the yield to 52% (entry 4), pointing to a stereochemical mismatch between ligand and sugar. Further changes with respect to ligand or solvent did not improve the yields (entries 5−10). Under no conditions was β-product detected for any reaction. Control experiments highlighted the critical role of ligand (entry 11) and Ni(0) (entry 12) for promoting the desired reactivity in favor of background elimination, which presumably occurs via a glycosyl-Zn species.[17]

Table 2. Substrate Scope for Coupling of Monosubstituted Alkenes with Glucosyl Bromide **1**[a]



entry	alkene	product	yield
1	$CO_2{}^tBu$		**9**, R = $CO_2{}^tBu$: 75%
2	CN		**10**, R = CN: 75%
3	CO_2Me		**11** 65%
4	X		**12**, X = H: trace **13**, X = 4-OMe: trace **14**, X = 4-OAc: 10% **15**, X = 4-Cl: 30% **16**, X = 4-CF_3: 45% **17**, X = 4-CO_2Me: 62% **18**, X = 4-CN: 75% **19**, X = 4-F: trace **20**, X = 3-F: 35% **21**, X = 2-F: 20%

[a] Standard reaction conditions used.[15]

(8) The glucosyl radical is known to adopt a boat conformation, while the mannosyl radical is a chair: (a) Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453. (b) Dupuis, J.; Giese, B.; Rüegge, D.; Fishcer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.

(9) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177.

(10) For a related example of Ni-catalyzed *C*-alkylation, see: Gong, H.; Sinisi, R.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 1908.

(11) (a) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (b) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594. (c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788. (d) Zhou, J. S.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

(12) For examples of cross-coupling with a putative radical cyclization prior to C−C bond formation, see: (a) Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Càrdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790. (b) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (c) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510.

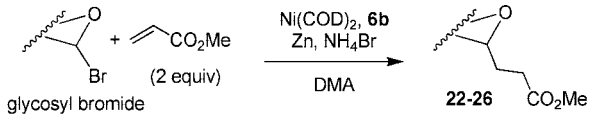
(13) For examples of SmI_2-mediated *C*-glycoside synthesis invoking radical intermediates, see: (a) Malapelle, A.; Coslovi, A.; Doisneau, G.; Beau, J.-M. *Eur. J. Org. Chem.* **2007**, 3145. (b) Yuan, X. J.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393. (c) Miquel, N.; Doisneau, G.; Beau, J.-M. *Chem. Commun.* **2000**, 2347. (d) Hung, S.-C.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2671. (e) Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 4903. (f) For an example involving Ni co-catalysis, see: Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4111.

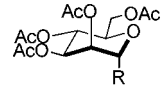
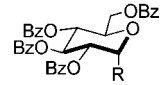
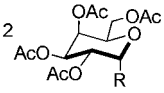
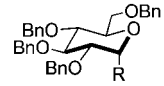
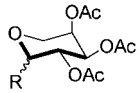
(14) For mechanistic and computational studies that implicate radical intermediates in Ni-catalyzed Negishi reactions, see: (a) Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Kanovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175.

(15) Standard reaction conditions: glycosyl bromide (100 mol %), alkene (200 mol %), Ni(COD)$_2$ (10 mol %), ligand (15 mol %), proton source (200 mol %), DMA (0.24 M), rt, 12 h. See the Supporting Informationfor further details.

(16) Subjection of glucal **3** to the standerd conditions in the presence of methyl acrylate resulted in no reaction.

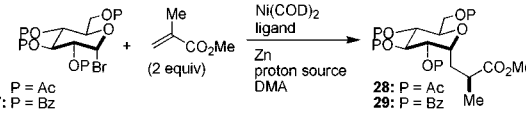
Table 3. Coupling of Glycosyl Bromides with Methyl Acrylate[a]



entry	product[b]	yield (α:β)	entry	product[b]	yield (α:β)
1	 **22**	76% (α)	4	 **25**	62% (α)
2	 **23**	60% (α)	5	 **26**	20%
3	 **24**	61%			

[a] Standard reaction conditions used.[15] [b] R = $CH_2CH_2CO_2Me$.

Table 4. Optimization of the Diastereoselectivities for the Coupling of Glucosyl Bromides and Methyl Methacrylate[a]



entry	glucosyl bromide	ligand	proton source	yield (%)	dr[b]
1	**1**	**6b**	NH_4Br	88	1.4:1
2	**27**	**6b**	NH_4Br	75	1.6:1
3	**1**	(*S*)-**6b**	NH_4Br	72	1:1
4	**1**	**6c**	NH_4Br	87	1.4:1
5	**1**	**8**	NH_4Br	63	2:1
6	**1**	**6b**	(−)-sparteine·H_2SO_4	63	2.3:1
7	**27**	**6b**	H_2O	55	4:1
8	**27**	**6b**	EtOH	76	3.2:1
9	**27**	**6b**	^{i}PrOH	81	4.2:1
10	**27**	**6b**	$^i Pr_2CHOH$	**80**	**5.0:1**
11	**27**	**6b**	^{t}BuOH	60	3.5:1
12	**27**	**6b**	(*S*)-binol	ND[c]	1:1
13	**27**	**6b**	*(R)*-2-butanol	ND[c]	3.4:1
14	**27**	**6b**	*(S)*-2-butanol	ND[c]	3.7:1
15	**1**	**6b**	$^i Pr_2CHOH$	90	2:1

[a] Standard reaction conditions used.[15] [b] The dr refers to the stereocenter α to the methyl ester;[22] in all cases, the stereocenter at the anomeric carbon was formed with exclusive α selectivity. [c] Not determined.

With optimized reaction conditions in hand, the scope of the alkene partner was examined (Table 2). Reaction with acrylate derivatives such as *tert*-butyl acrylate and acrylonitrile smoothly produced the desired products **9** and **10**, respectively, in good yields (entry 1 and 2), while (*E*)-methyl penta-2,4-dienoate gave the nonconjugated α-glucosyl ester **11** in 65% yield (entry 3). As anticipated, however, styrene-derived alkenes proved more challenging (entry 4). Reaction with styrene and 4-methoxystyrene generated only trace amounts of **12** and **13**, respectively, with pyranose **4** being the major product.[18] Given the nucleophilic character of the glycosyl radical,[19] we predicted that electron-poor styrenes would be more reactive (entry 4, products **14**−**21**), and this was indeed the case, especially for 4-carbomethoxy- and 4-cyanostyrene.

In addition to **1**, the Ni-catalyzed reductive coupling with methyl acrylate was successfully extended to other acetate-protected glycosyl bromides (Table 3, entries 1−3). The α-*C*-mannoside and α-*C*-galactoside products **22** and **23** were obtained in 76% and 60% yield, respectively, while the 5-dealkylated *C*-arabinoside was provided in 61% yield with diminished stereoselectivity.[20] Benzoate-protected sugars were similarly well-behaved (entry 4), while Bn-protected glucosyl bromide was particularly prone to hydrolysis.[21]

We next turned our attention to 1,1-disubstituted and trisubstituted alkenes, with diastereocontrol as an important goal. To this end, the coupling of glucosyl bromides **1** and **27** with methyl methacrylate was utilized as a probe system (Table 4). Using the previously optimized conditions, *C*-glycoside **28** was obtained in high yield and with excellent selectivity for the α anomer, but with poor diastereoselectivity (1.4:1) at the stereocenter α to the methyl carboxylate (entry 1). Use of Bz-protected **27** did not significantly improve the dr (entry 2), nor did variation of the chiral ligand (entries 3−5). Chiral, enantiopure methacryloyl esters such as bornyl or menthyl methacrylate (not shown) also failed to affect the diastereoselection.

Since protonation of a transition-metal enolate intermediate was presumed to be stereodetermining, we then examined the proton source itself. While the use of sterically hindered ammonium salts such as (−)-sparteine·H_2SO_4 resulted in diastereoselectivities only slightly greater than 2:1 (entry 6), alcohols elucidated clear improvement (entries 7−15).[22] Increases in steric bulk and branching improved the dr to 5:1 with $^i Pr_2CHOH$ (entry 10),[23] but chiral alcohols (entries 12−14) were inferior. Finally, reaction of Ac-protected **1** using the $^i Pr_2CHOH$ proton source (entry 15) resulted in lower diastereoselectivity than that observed for the Bz-protected **27** (entry 10).

(17) The Zn-mediated reductive elimination of aceto-1-glycosyl bromides is well known from the Fischer−Zach glycal synthesis: Fischer, E.; Zach, K. *Sitzungsber. Kl. Preuss. Akad. Wiss.* **1913**, *27*, 311.

(18) Attempts to suppress hydrolysis product **4** through the use of desiccants (molecular sieves, etc.) were unsuccessful.

(19) For example, see: (a) Liu, Y.; Gallagher, T. *Org. Lett.* **2004**, *6*, 2445. (b) SanMartin, R.; Tavassoli, B.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2000**, *2*, 4051.

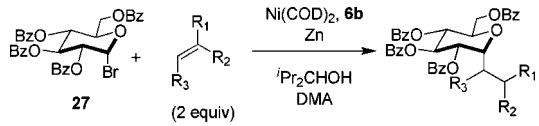
(20) For examples of the known difficulty in obtaining high selectivity in reactions of arabinosyl-type radicals, see refs 1 and 6d.

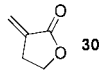
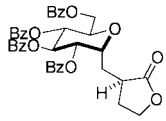
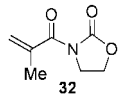
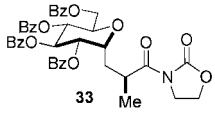
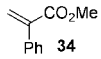
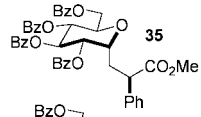
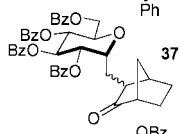
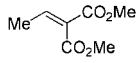
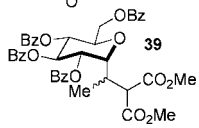
(21) Attempts to improve yields by using the Bn-protected glucosyl or mannosyl chlorides failed (no reaction).

(22) Bz-protected products simplified the assessment of dr by ^{1}H NMR; for this reason, glucosyl bromide **27** was used thereafter.

(23) The configuration of the stereocenter α to the methyl ester in the major isomer of **29** was determined by single-crystal X-ray analysis (see the Supporting Information).

Table 5. Coupling of Substituted Alkenes with Glucosyl Bromides **1** and **27**[a]



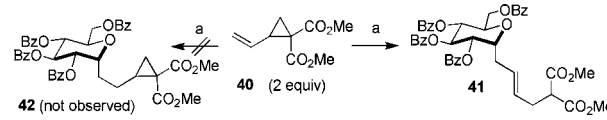
entry	alkene	product	yield (dr)[b]
1	 **30**	 **31**	50% (7:1)[c]
2	 **32**	 **33**	74% (5:1)[c]
3	 **34**	 **35**	46% (2.5:1)[c]
4	 **36**	 **37**	79% (1.8:1)[c]
5	 **38**	 **39**	56% (1.2:1)[c]

[a] Standard reaction conditions used.[15] [b] In all cases, the anomeric stereocenter was formed with exclusive α selectivity. [c] The α-stereocenter is drawn by analogy to the crystallographically characterized **29**, which was additionally corroborated by conversion of **33** to **29**.[25]

The optimal conditions for diastereoselective coupling were then applied to various geminally disubstituted alkenes (Table 5). Reaction of **27** with α-methylene-γ-butyrolactone and 3-methacryloyloxazolidin-2-one[24] proceeded smoothly and with good dr (entries 1 and 2). More sterically demanding alkenes like methyl 2-phenylacrylate and (1*S*,4*R*)-3-methylenebicyclo[2.2.1]heptan-2-one (entries 3−4) proceeded successfully, with applicability to enones being demonstrated by the latter. Although 3-substituted or trisubstituted methyl acrylates generally demonstrated poor reactivity, dimethyl 2-ethylidenemalonate gave **39** in 56% yield (1.2:1 dr) (entry 5), indicating a greater electron-withdrawing requirement for these more hindered partners.

(24) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984.

Scheme 1. Ni-Catalyzed Coupling of **27** with **40**[a]



[a] Standard reaction conditions used,[15] with glucosyl bromide **27**, ligand **6b**, and NH_4Br.

In addition to the exquisite α-selectivity for the glucosyl and mannosyl substrates and the need for activated (electrophilic) alkene acceptors,[4] the coupling of vinyl cyclopropyl malonate **40** (Scheme 1) with **27** generated the ring-opened **41** rather than cyclopropane product **42**. While the intermediacy of radicals explains each of our observations, a mechanism relying on olefin insertion into a Ni-glycosyl intermediate followed by transmetalation to zinc cannot be rigorously ruled out.[26]

In summary, we have demonstrated a mild, Sn-free Ni-catalyzed reductive coupling of glycosyl bromides with electron deficient alkenes featuring low alkene stoichiometry requirements. The diastereoselectivity of reactions with 2-substituted acrylate derivatives was significantly improved through the use of $^{i}Pr_2CHOH$ as a proton source. Efforts to expand this method are ongoing.

Acknowledgment. We thank Andrew Parsons (UNC-CH) for his generous donation of compound **40**. J.L.Z. thanks the National Research Council for a Postdoctoral Fellowship, S.J.L. thanks the ARO for Staff Research Funding, and M.R.G. thanks the Department of Energy (DE-FG02-05ER15630) for generous support.

Supporting Information Available: Experimental procedures and spectra of new compounds and CIF data for **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8028737

(25) Transesterification conditions: $Sm(OTf)_3$ (catalytic), MeOH, CH_2Cl_2, rt, 48 h. See: Evans, D. A.; Coleman, P. J.; Carlos Dias, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2738.

(26) For recent examples of Ni-catalyzed reductive coupling reactions involving transmetalation with dialkylzinc species, see: (a) Montgomery, J.; Sormunen, G. J. *Top. Curr. Chem.* **2007**, *279*, 1. (b) Cozzi, P. G.; Mignogna, A.; Zoli, L. *Pure Appl. Chem.* **2008**, *80*, 891.