JOC Article

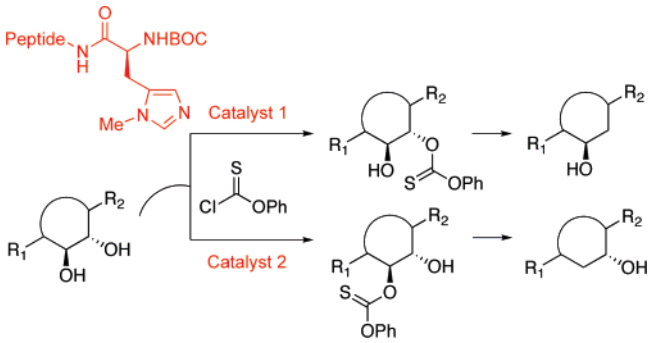
Site-Selective Catalysis of Phenyl Thionoformate Transfer as a Tool for Regioselective Deoxygenation of Polyols

María Sánchez-Roselló,† Angela L. A. Puchlopek,† Adam J. Morgan,‡ and Scott J. Miller*,†,‡

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107, and Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

scott.miller@yale.edu

Received October 29, 2007



We report the application of peptide-embedded imidazoles as catalysts for the site-selective delivery of the phenyl thionoformate unit as a prelude to deoxygenation reactions of polyols. Methodology was developed that allows for the synthesis of thiocarbonyl derivatives based on a combination of additives that include *N*-alkylimidazoles and $FeCl_3$ as co-catalysts. The use of this reagent combination leads to increased reaction rates and efficient yields relative to those of simple base-mediated reactions. In terms of controlling regioselectivity during the course of polyol modification, we found that histidine-containing peptides, in combination with $FeCl_3$, could lead to modulation of the product distribution. Through screening of peptides and control of reaction conditions, products could be observed that reflected both the inherent preference of substrates and also reversal of inherent selectivity.

Introduction

The deoxygenation of alcohols is a fundamental transformation in organic synthesis.[1] The development of catalysts that could selectively remove a hydroxyl group from a polyol structure would be a particularly advantageous method in medicinal chemistry settings because one might use the technique to obtain deoxyanalogs of polyol agents without elaborate syntheses or complicated protecting group schemes (Scheme 1).[2] To develop such methodology, we began an investigation of site-selective transfer of the thiocarbonyl group as a prelude to substrate deoxygenation, utilizing the venerable Barton−McCombie reaction.[3] Any successful approach to this problem requires catalysts that are particularly effective for mediating regioselective reactions, a current challenge in stereoselective synthesis.[4]

Our overall strategy was to employ the emerging paradigm of asymmetric nucleophilic catalysis[5] for the projected group transfer reactions. While this field has exploded with a myriad of exciting catalyst types, including DMAP analogs,[6] phosphines,[7] amidines,[8] and other nucleophilic functional groups,[9]

† Yale University.
‡ Boston College.

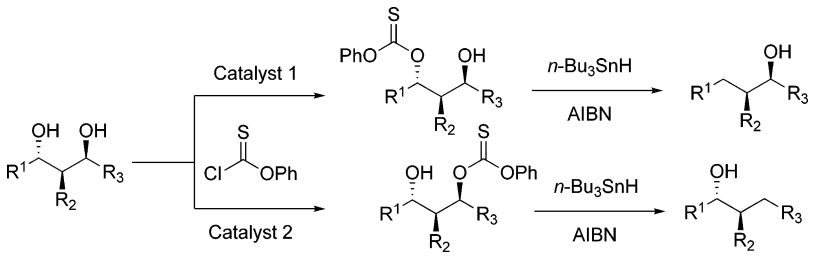
(1) (a) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609−2645. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413−1432. (c) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949−6950. (d) Yasuda, M.; Onisi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741−7744. (e) Schlaf, M.; Ghosh, P.; Fagan, P. J.; Hauptman, E.; Bullock, R. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3887−3890.

(2) (a) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem.* **2000**, *65*, 2583−2585. (b) Morgan, A. J.; Wang, Y. K.; Roberts, M. F.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 15370−15371. (c) Gómez, A. M.; Moreno, E.; Valverde, S.; López, J. C. *Eur. J. Org. Chem.* **2004**, 1830−1840. (d) Wang, Y. K.; Morgan, A. J.; Stieglitz, K.; Stec, B.; Thompson, B.; Miller, S. J.; Roberts, M. F. *Biochemistry* **2006**, *45*, 3307−3314.

(3) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (b) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron* **1991**, *47*, 8969−8984. (c) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs. *Tetrahedron* **1992**, *48*, 7435−7446.

10.1021/jo702334z CCC: $40.75
Published on Web 01/30/2008

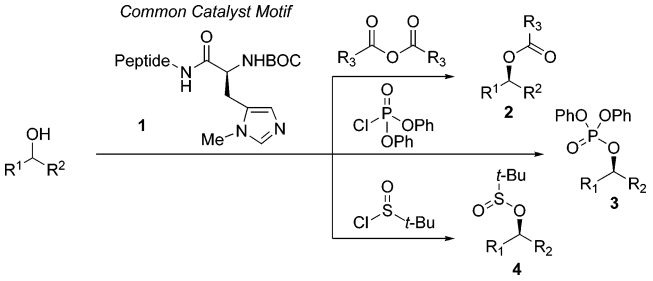
SCHEME 1



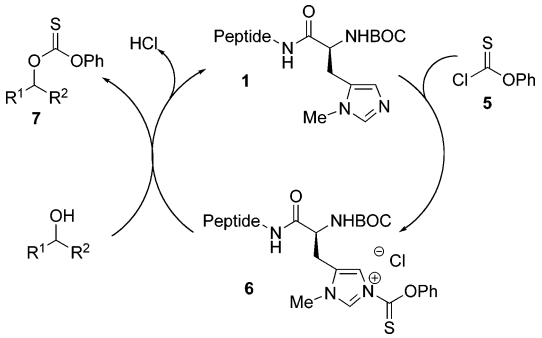
we sought to capitalize on developments in our own laboratory around peptide-embedded nucleophiles (e.g., **1**).[10] In this spirit, we have demonstrated that short peptide derivatives of histidine allow for highly enantioselective and site-selective alcohol derivatizations,[11] among them acylations (i.e., to deliver **2**),[12] phosphorylations (**3**),[13] and transfer of sulfur-based electrophiles (**4**) (Scheme 2).[14,15]

The portability of the catalysis strategy to thiocarbonyl transfer is not straightforward. Although the literature contains numerous examples of thiocarbonylation as a prelude to deoxygenation,[16] the details of catalytic protocols are often

SCHEME 2



SCHEME 3



variable. There are cases in which nucleophilic catalysts such as DMAP are employed,[17] but often pyridine is used simultaneously;[18] there are also reports where thiocarbonylation is carried out at high temperature in the absence of a catalyst.[19] Nonetheless, we began our studies with the goal of exploring whether the catalytic cycle described in Scheme 3 might be viable. Our plan was to examine the potential of catalysts like **1** to capture phenyl chlorothionoformate (**5**) with the expectation that intermediates related to **6** would be formed. Transfer of thiocarbonyl to substrate would then deliver product **7**, while regenerating catalyst **1**. Described below are our findings in connection to our exploration of this potential catalytic cycle.

(4) (a) Kurahashi, T.; Mizutani, T.; Yoshida, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 465−473. (b) Gani, D. *Nature* **2001**, *414*, 703−705. (c) Kurahashi, T.; Mizutani, T.; Yoshida, J. *Tetrahedron* **2002**, *58*, 8669−8677. (d) Hu, G.; Vasella, A. *Helv. Chim. Acta* **2002**, *85*, 4369−4391. (e) Kattnig, E.; Albert, M. *Org. Lett.* **2004**, *6*, 945−948. (f) Moitessier, N.; Englebienne, P.; Chapleur, Y. *Tetrahedron* **2005**, *61*, 6839−6853. (g) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896−899.

(5) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (b) Vedejs, E.; Daugulis, O., MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499−1505. (c) France, S.; Guerin, D. J.: Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012. (d) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167−170. (e) Spivey, A. C.; Arseniyadis, S.; Fekner, T.; Maddaford, A.; Leese, D. P. *Tetrahedron* **2006**, *62*, 295−301.

(6) (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810. (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170. (c) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236. (d) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368−13369. (e) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, L. R. *J. Org. Chem.* **2003**, *68*, 7379−7385. (f) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547. (g) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436−5441.

(7) (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488−9489. (b) Vedejs, E.; Daugulis, O.; Harper, L. A.; MacKay, J. A.; Powell, D. R. *J. Org. Chem.* **2003**, *68*, 5020−5027. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035−1050 and references therein.

(8) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226−12227. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445−3447. (c) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285−294. (d) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37−40.

(9) Chiral diamines: (a) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397−400. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529−3532. Nucleophilic carbenes: Enders, D.; Balensiefer, B. *Acc. Chem. Res.* **2004**, *37*, 534−541.

(10) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610.

(11) (a) Griswold, K. S.; Miller, S. J. *Tetrahedron* **2003**, *59*, 8869−8875. (b) Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616−5619.

(12) (a) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643. (b) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496−6502. (c) Fierman, M. B.; O' Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967−6971. (d) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454−16455.

(13) (a) Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126. (b) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653−11656. (c) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781−1785. (d) Sculimbrene, B. R.; Xu, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 13182−13183.

(14) Evans, J. W.; Fierman, M. B.; Miller, S. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8134−8135.

(15) For a related approach involving alcohol silylation, see: (a) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243−244. (b) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67−70.

(16) Barton, D. H. R.; Ferreira, J. A.; Jaszberenyi, J. C. *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 151−172.

(17) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181−5183.

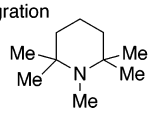
(18) For three examples of syntheses where both DMAP and pyridine are used in combination to effect thiocarbonylation, see: (a) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672−5680. (b) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569−10582. (c) Shimokawa, J.; Shirai, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1559−1562.

(19) Gaudino, J. J.; Wilcox, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 4374−4380.

TABLE 1. Thiocarbonylation Reaction of 2,4,6-Tribenzyl *myo*-Inositol

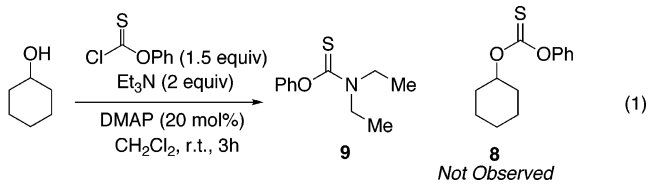
Entry	Thionoformate (equiv)	Base (equiv)	Catalyst (20 mol%)	Conversion (%)[a]
1		(1.1) Pyridine (1.2)	-	20
2		(1.1) Pyridine (1.2)	DMAP	25
3		(1.1) 2,6-Lutidine (1.2)	DMAP	<5
4		(1.5) PEMP (2)	-	N.R.
5		**(1.5) PEMP (2)**	**NMI**	**90**
6		(1.5) PEMP (2)	DMAP	76
7		(1.5) K_2CO_3 (2)	NMI	N.R.
8		(1.5) Proton Sponge (2)	NMI	13
9		(1.5) DABCO (2)	NMI	N.R.
10		(1.5) DIPEA (2)	NMI	45
11	ClC(S)O-*p*-tolyl (1.5)	PEMP (2)	NMI	91
12	ClC(S)O-*p*-C_6H_4Cl (1.5)	PEMP (2)	NMI	78
13	ClC(S)O-*p*-C_6H_4F (1.5)	PEMP (2)	NMI	76

[a] Conversions determined by ^{1}H-NMR integration

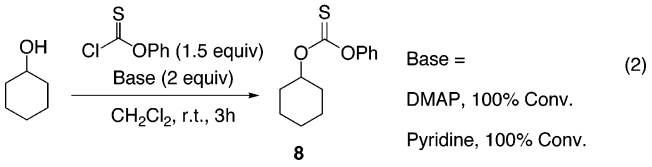
PEMP = 1,2,2,6,6-pentamethyl piperidine: 

Results and Discussion

Preliminary Experiments. To clarify the basics of catalytic thiocarbonyl transfer, we carried out several simple experiments that show that neither DMAP nor NMI is generally effective as a substoichiometric catalyst for the thiocarbonylation of simple substrates to give **8** from cyclohexanol. Notably, as shown in eq 1, when reactions are conducted with DMAP in the presence of Et_3N, thiocarbonate **8** is not formed. Rather, the addition product **9**, derived from triethylamine addition to phenyl chlorothionoformate followed by dealkylation, is formed preferably as the major product (eq 1).[20] On the other hand, thiocarbonate **8** is readily obtained when the reaction is performed with a variety of pyridines, suggesting that a general base mechanism may result in efficient reactions at room temperature (eq 2).

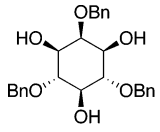


(1)

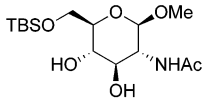


(2)

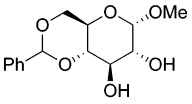
To explore a possible catalytic reaction in which an *N*-alkylimidazole might function by a nucleophilic mechanism,[21] we sought to identify conditions that would employ a base (to scavenge the full equivalent of HCl generated in these reactions) that was not itself a promoter of the reaction. During the course of these studies, we found an intriguing difference in reactivity between simple substrates such as cyclohexanol and oxygenated substrates such as carbohydrate derivatives like inositide **10**,[22] glucosamine derivative **11**,[23] and glucose derivative **12a**.[24]



10



11



12a

As shown in Table 1, with *myo*-inositol derivative **10** as a substrate, we observed generally slower *base-promoted* thiocarbonylation reactions. Thus, as shown in entry 1, use of pyridine as a promoter allowed observation of (±)-**13** in only 20% conversion, as measured by ^{1}H NMR. Inclusion of DMAP (20 mol %) in the reaction mixture led to essentially identical results (entry 2), whereas the combination of 2,6-lutidine with DMAP actually led to no reaction (entry 3). On the other hand,

(20) (a) Hsu, F. L.; Zhang, X.; Hong, S. S.; Berg, F. J.; Miller, D. D. *Heterocycles* **1994**, *39*, 801−809. (b) Millan, D. S.; Prager, R. H. *Aust. J. Chem.* **1999**, 841−849.

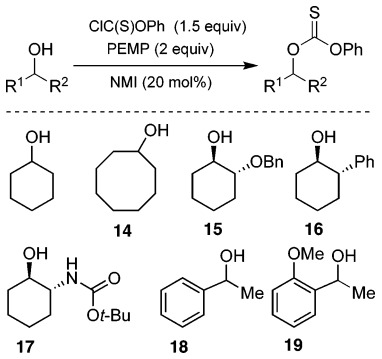
(21) (a) Guibe-Jampel, E.; Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, 1021−1027. (b) Pandit, N. K.; Connors, K. A. *J. Pharm. Sci.* **1982**, *71*, 485−491. (c) Breslow, R. *J. Mol. Catal.* **1994**, *91*, 161−174.

(22) (a) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402−4404. (b) Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M.; Vacca, J. P.; Jane deSolms, S.; Huff, J. R. *J. Chem. Soc., Perkin Trans.* **1989**, *1*, 1423−1429.

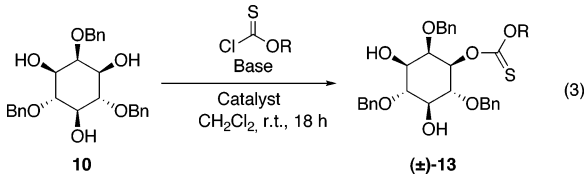
(23) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012−6028.

(24) Ferro, V.; Mocerino, M.; Stick, R. V.; Tilbrook, D. M. G. *Aust. J. Chem.* **1988**, *41*, 813−815.

CHART 1. Substrates for Which No Reaction Was Observed within 24 h under the Catalytic Conditions

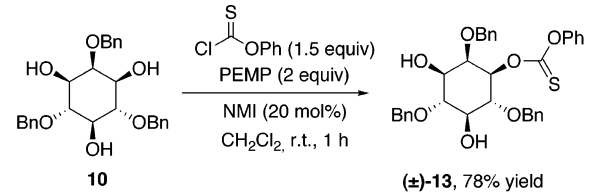


robust catalytic conditions were identified when 1,2,2,6,6-pentamethylpiperidine (PEMP) was employed as a base in combination with NMI as a catalyst. PEMP alone was found to afford no background rate under the conditions we explored (entry 4); use of PEMP in combination with 20 mol % NMI, on the other hand, led to 90% conversion to (±)-**13** within 18 h (entry 5); a combination of PEMP and 20 mol % DMAP led to a slightly less efficient reaction (76% conversion; entry 6). As shown in entries 7−10, PEMP was found to be superior to a range of other bases in combination with NMI as a catalyst. The thionoformate was also varied (entries 11−13), which leads to comparable results.

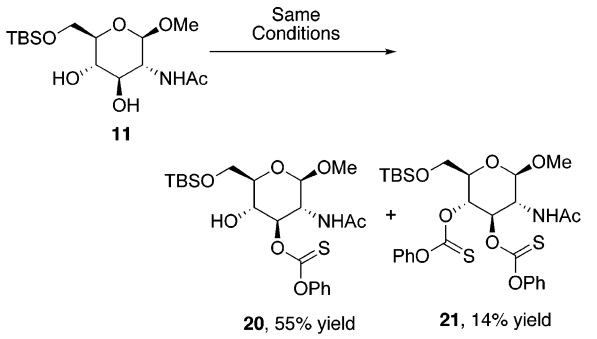


(3)

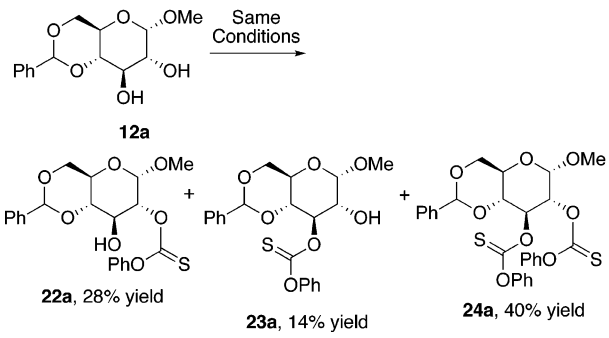
With seemingly robust conditions identified for NMI-catalyzed thionoformate transfer in hand (Table 1, entry 5; eq 3), we sought to examine the scope for a wide variety of substrates. Surprisingly, as shown in Chart 1, the conditions were strikingly specific for carbohydrate derivatives. Examination of seven "simple" substrates revealed that compounds such as cyclohexanol and **14**−**19** underwent no reaction under the identical conditions that led to efficient formation of (±)-**13**. Indeed, inositol derivative (±)-**13** could be obtained in 78% isolated yield within 1 h of reaction time under the preparative, catalytic conditions (eq 4). Glucosamine derivative **11** is efficiently converted to a 4:1 mixture of the corresponding mono- and bis(thionoformates) **20** and **21** in 69% combined yield (eq 5). Glucose derivative **12a** is converted to an 82% combined, isolated yield of thionoformates **22a**, **23a**, and **24a** within 1 h under the identical conditions (eq 6).



(4)



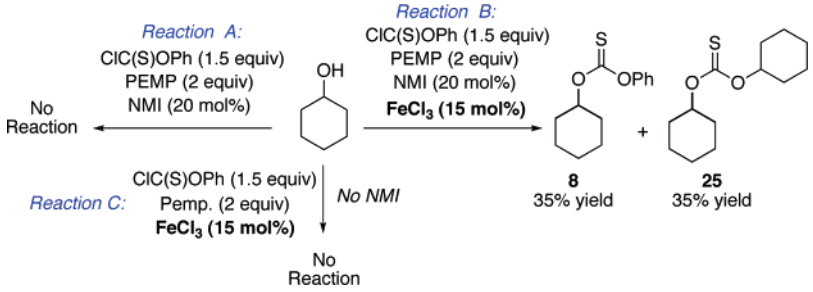
(5)



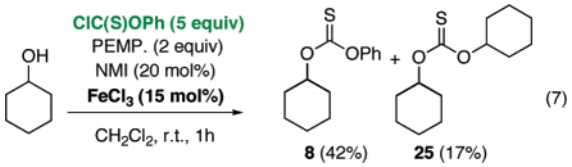
(6)

Identification of an $FeCl_3$ Effect. To address the lack of generality of the PEMP/NMI conditions, we began to explore additives that might accelerate the reactions of recalcitrant substrates. Among the hypotheses we explored was the idea that phenyl chlorothionoformate could be activated through the use of a co-catalytic amount of a Lewis acid. Indeed, we found that incorporation of a substoichiometic amount of $FeCl_3$ (15 mol %) led to a dramatic increase in the rate of the reactions in the presence of PEMP (2 equiv) and NMI (20 mol %). Whereas no reaction was observed with cyclohexanol in the presence of phenyl chlorothionoformate and PEMP/NMI (Scheme 4, Reaction A), rapid consumption of cyclohexanol was observed when $FeCl_3$ (15 mol %) was introduced (Scheme 4, Reaction B). In terms of control experiments, no reaction was observed in the corresponding reaction when cyclohexanol was exposed to phenyl chlorothionoformate, PEMP, and $FeCl_3$ in the absence of catalytic NMI (Scheme 4, Reaction C). Of further note, in the rapid reaction containing each of the catalytic additives, monoaddition product **8** is not the sole significant product. In

SCHEME 4



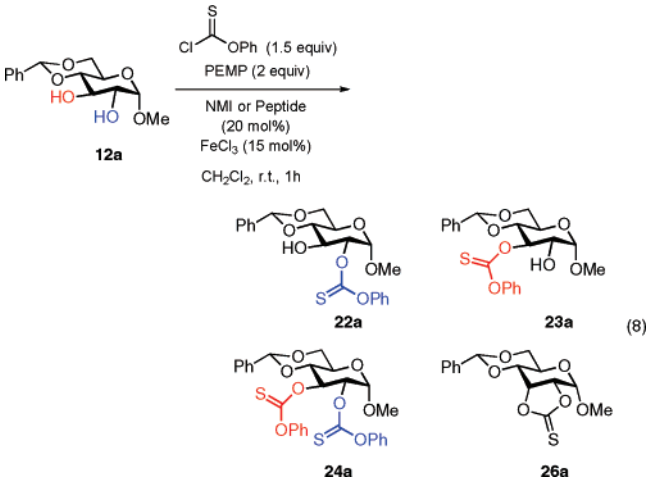
fact, over-addition product **25** is also observed (70% combined yield), with compound **8** and **25** being formed in a 1:1 ratio. However, the amount of the over-addition product may be decreased by using a larger excess of phenyl chlorothionoformate, as is exemplified in eq 7. Similar results were obtained with cyclooctanol, whereas other "simple" alcohols such as **15** and **16** turned out to be less reactive, requiring 50 mol % $FeCl_3$ and refluxing dichloromethane for 5 h to give the desired thiocarbonylation products.



(7)

At this stage, it is too preliminary to state definitively what the role of the $FeCl_3$ co-catalyst is for these more rapid thionoformylation reactions. Among the potential roles we have considered are (a) that $FeCl_3$ activates phenyl chlorothionoformate in analogy to its role in Friedel−Crafts chemistry (e.g., Figure 1, complex **A** or complex **B**);[25] (b) that NMI−$FeCl_3$ complexes are formed that in turn activate the reagent (e.g., Figure 1, complex **C**); (c) that substrate-metal alkoxides are formed that perturb reactivity (e.g., Figure 1, complex **D**).[26] These mechanistic possibilities are not easily resolved and will be the subject of future studies in our laboratory.

Case Studies in Regioselective Polyol Thiocarbonylation and Deoxygenation. Given the role of deoxysugars in numerous natural products,[27] we chose several simple carbohydrate derivatives as a testing ground for the application of these catalytic thiocarbonylation conditions to site-selective deoxygenations. Our studies began with an examination of α-methyl glucoside **12a** (eq 8), and the goal of identifying two sets of catalytic conditions: one that would favor the formation of the mono-functionalized 2-thiocarbonate **22a** and an orthogonal catalytic reaction that would favor the regioisomer, 3-thiocarbonate **23a**. Of course, we were keenly aware of the possibility of overfunctionalization to give bis(thiocarbonate) **24a** and also the possible formation of cyclic thiocarbonate **26a**.



(8)

(25) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457−476.
(26) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643−663.
(27) See ref 2.

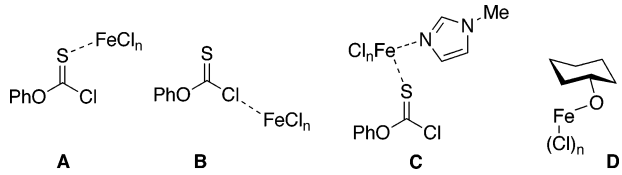
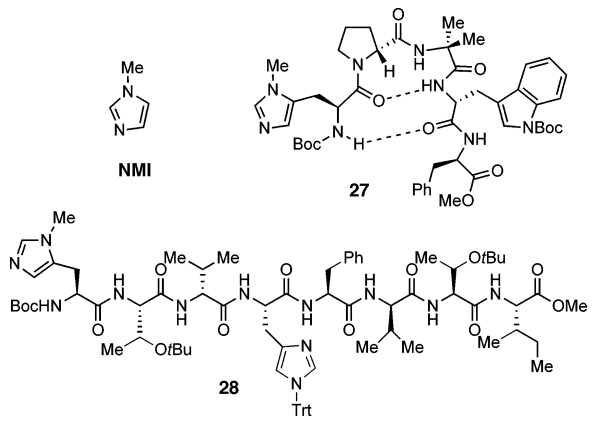


FIGURE 1. Some potential modes of $FeCl_3$ activation of thionoformylation reactions.

CHART 2. Catalysts Employed in the Thiocarbonylation Reaction



Any study of regiochemical functionalization also requires a set of minimal control experiments that document (a) the inherent preferences in the hierarchical reactivity within the substrate and (b) the potential for thermodynamic equilibration of products such as **22a**−**24a** and **26a** under the reaction conditions. In the studies we describe below, each case includes a delineation of a hierarchical reactivity of the regiotopic hydroxyl groups in the presence of a given set of reaction conditions. Typically, these involve the use of NMI and $FeCl_3$, each in substoichiometric quantity, in the presence of a stoichiometric quantity of PEMP. Subsequently, we present the perturbation of the inherent product distribution (defined by the outcome with NMI/$FeCl_3$-PEMP), to give different product ratios as a function of the NMI-embedded peptide structure (e.g., **27** versus **28**; Chart 2). In the following cases, isolation of the pure mono(thiocarbonates) and resubmission to the reaction conditions revealed them to be non-interconverting under the reaction conditions. As a result, the data presented seem to reflect kinetic selectivities for the site-selective derivatizations we studied. Gratifyingly, in each of the cases we examined, we were able to identify catalyst-dependent reversals of inherent site-selectivity, a manifestation of the ability of these reaction conditions to exhibit kinetic selectivity.

Thus, our investigation of regioselective thiocarbonylation of **12a** began with a documentation of the "inherent" regioselectivity under the optimized conditions and under conditions of various control experiments. As shown in Table 2, entries 1 and 2, the inherent NMI-catalyzed ratio of products appears to be ∼2:1, either when the reaction is monitored by ^{1}H NMR (entry 1) or when ratios are assessed by quantitative product isolation by careful silica gel chromatography (entry 2). As in our earlier studies, $FeCl_3$ alone does not promote the reaction (entry 3). The inherent selectivity under the NMI/$FeCl_3$ conditions is somewhat different. As illustrated in entries 4 and 5,

TABLE 2. Regioselectivity in the Thiocarbonylation of 4,6-Benzylidene α-Methyl Glucoside (eq 8) [a]

Entry	Catalyst	**12a** (%)	**22a** (%)	**23a** (%)	**22a** : **23a**	**24a** (%)	**26a** (%)
1[b]	NMI (20 mol%)	4	32	14	2.3 : 1	50	-
2[c]	NMI (20 mol%)		28	14	2 : 1	40	6
3	$FeCl_3$ (15 mol%)	No Reaction					
4[b]	NMI (20 mol%) + $FeCl_3$ (15 mol%)	10	30	30	1 : 1	28	2
5[c]	NMI (20 mol%) + $FeCl_3$ (15 mol%)		26	26	1 : 1	20	16
6[b]	**27** (20 mol%)	14	70	6	11.7 : 1	10	-
7[b]	**27** (20 mol%) + $FeCl_3$ (15 mol%)	40	53	7	7.6 : 1	-	-
8[cd]	**27** (20 mol%)		67	3	22 : 1	10	7
9[b]	**28** (20 mol%)	17	42	25	1.7 : 1	16	-
10[c]	**28** (20 mol%) + $FeCl_3$ (15 mol%)	40	11	47	1 : 4	-	2
11[ce]	**28** (20 mol%) + $FeCl_3$ (15 mol%)		8	53	1 : 6.6	5	8

[a] All reactions were conducted in the presence of PEMP (2 equiv) and run according to the standard conditions described in Experimental Section. [b] Conversion determined by ^{1}H NMR. [c] Isolated yield after flash chromatography. [d] The reaction was conducted at −40 °C, 5 h. [e] The reaction was conducted at −25 °C, 5 h.

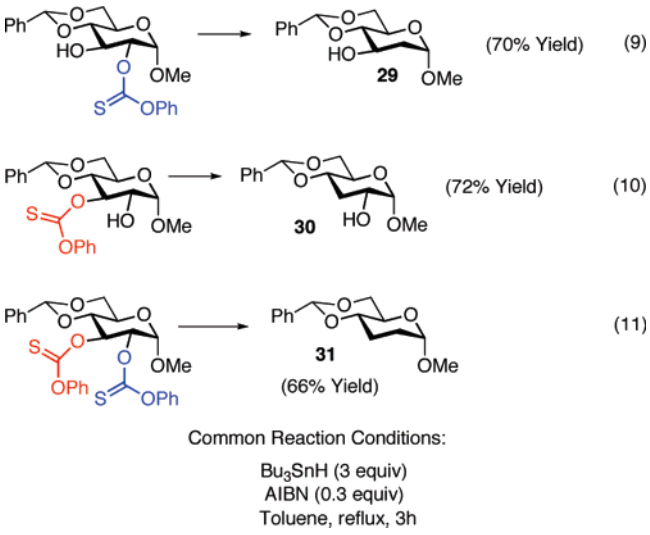
under these conditions **22a** and **23a** appear in essentially a 1:1 ratio. In each of the reactions containing NMI, a substantial amount of the over-addition product **24a** is also observed. Nonetheless, the equivalence in reactivity of the 2- and 3-positions of **12a** under these conditions sets the stage for diverting the product distribution in either direction, as a function of the NMI-embedded peptide structure.[28] Our choice of peptides for screening derives from our historical catalyst libraries that we have amassed over several years of study. In particular, catalyst libraries have been assembled from both designed libraries and random libraries that we prepared for various projects involving alcohol derivatization.[29] Notably, catalyst **27** contributes to an enhancement of the 2-substituted product **22a**, whether $FeCl_3$ is excluded as a co-catalyst (**22a**:**23a** = 11.7:1, entry 6) or whether it is included (7.6:1, entry 7). Furthermore, when this reaction is conducted at −40 °C, the 2-substituted product **22a** is formed in a 22:1 ratio, and may be isolated in 67% yield (entry 8).

A peptide-dependent *reversal* in regioselectivity was observed when peptide **28** was used as a co-catalyst in place of **27**. Interestingly, the reversal was only observed when the peptide-$FeCl_3$ co-catalyst combination was employed. When catalyst **28** is used exclusively, a **22a**:**23a** ratio of 1.7:1 is observed (entry 9). In the presence of $FeCl_3$, however, the ratio reverses to 1:4 (entry 10) and is amplified to 1:6.6 when the reaction is conducted at low temperature, enabling isolation of **23a** in 53% yield under these conditions (entry 11). These results represented an encouraging illustration of the possibility of controlling the regiochemical outcome of these thiocarbonylations as a function of the specific catalytic conditions. Moreover, contrasting entries 7 and 11 illustrates the potential for different regioselectivity outcomes that are fully attributable to the chiral, functionality-rich environment provided by the peptide structure.

(28) After screening about 100 peptides of different length and structure, we found pentapeptide **27** and octapeptide **28** showed the most regiodivergent behavior in the thiocarbonylation of α-methyl glucoside **12**.

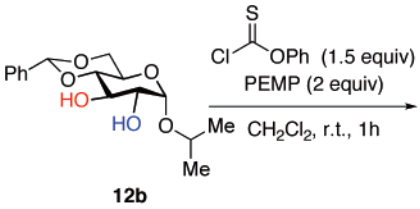
(29) A representative comparison of such libraries may be found in the following article: Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. *J. Org. Chem.* **2001**, *66*, 5522−5527.

We note parenthetically that each of the compounds prepared with the site-selective thiocarbonylations is readily converted to the deoxygenated species using a common set of standard Barton−McCombie reaction conditions. Thus, deoxysugars **29**−**31** are readily obtained by this method (eqs 9−11).

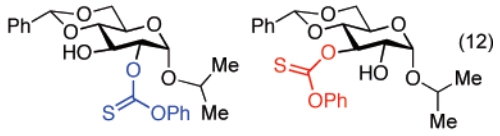


In an effort to establish the generality of this first-generation set of conditions, we explored several other simple derivatives of glucose. Thus, the thiocarbonylation on the α-isopropyl glucoside **12b** gave essentially the same product distribution as the corresponding α-methyl derivative **12a**: peptide **27** enhanced the reactivity for the 2 position to give **22b** preferentially, whereas peptide **28**, in combination with $FeCl_3$, reversed the product distribution to favor the 3-thiocarbonyl derivative **23b** (eq 12).

Clearly, in the absence of a detailed role of the peptide structure in translating stereochemical information to the substrate, screening of diverse peptide catalyst libraries is one



12b



(12)

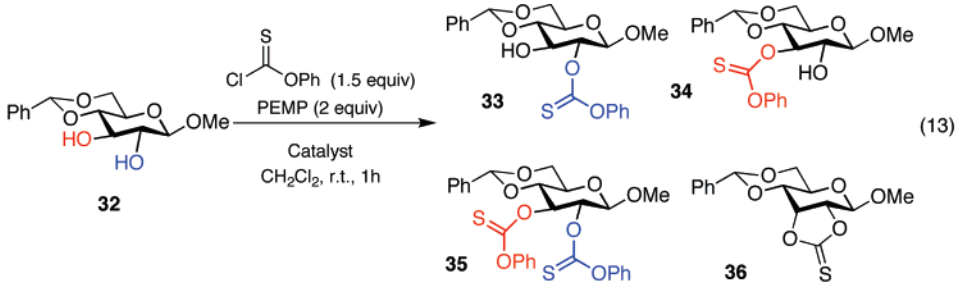
Catalyst	22b		23b
NMI (20 mol%)	2	:	1
27 (20 mol%)	7.4	:	1
28 (20 mol%)+ $FeCl_3$ (15 mol%)	1	:	3

way forward in finding analogous reversals of kinetic regioselectivity. One such study of interest includes the simple β-methyl glucoside **32**, which provides a direct comparison to our study of α-anomer **12a**. As shown in eq 13, the issues are similar in terms of the potential for a complex product distribution, with derivatives **33**−**36** possible. With the β-anomer, the inherent product distribution for the formation of 2- versus 3-mono-(thiocarbonates) (i.e., **33**:**34**) is 1:2 under catalysis by NMI in the absence of $FeCl_3$, and a similar ratio (1:1.6) is observed in the presence of both NMI and $FeCl_3$ (Table 3, entries 1 and 2). In this case, our "hit" peptides for the α-glucoside were less successful in terms of regioselectivity. Entry 3 shows that peptide catalyst **27**, in the absence of $FeCl_3$, provides a modest preference for 3-thiocarbonate **34** (1:1.5). Alternatively, peptide **28** provides a modest preference for 2-thiocarbonate **33** (1.5:1; entry 5). In both cases, the inclusion of $FeCl_3$ in the reaction mixture provides subtle modulation of ratios, but the effects overall with β-glucoside **32** are small. It is possible that a more comprehensive screen of peptide co-catalysts could provide a more dramatic result. In the context of the present study, it may suffice to say that the differentiation of β-glucosides of glucose, with the 4-position protected, may provide a particular challenge to regioselective catalysis in this "all-equatorial" array.

Finally, we decided to investigate the reactivity in a more complex setting. To compare with the glucose derivatives previously studied, we synthesized the 4,6-*O*-benzylidene-1′,6′-bis-*O*-*tert*-butyldiphenylsilyl protected sucrose derivative **37** (eq 14).[30] As shown in Table 4, with NMI as catalyst, the 3′-position is slightly more reactive than the 2-position on the hexose ring (entry 1). Notably, the 3-position of the glucose ring is substantially less reactive still. A brief screen of peptide catalysts and conditions revealed that the potential exists for modulating the site-selectivity of these thiocarbonylations. For example, when peptide **27** is employed as a catalyst, modest 2:1 preference for reaction of the 2-position of the glucoside is favored to deliver **38** as the major product (entry 2). In contrast, peptide **28** reverses the site-selectivity to the 3-position of the fructoside to favor **39** in a ratio of 1:2 (entry 3). While the reversal is modest in these cases, we suspect that a more extensive screening of catalysts and conditions could lead to more dramatic reversals in terms of magnitude.

Notably, sucrose derivatives **38** and **39** were readily deoxygenated to give deoxy-sucrose derivatives **40** and **41** (eqs 15 and 16). Such sequences may provide straightforward access to deoxygenated disaccharide derivatives with enhanced efficiencies in comparison to the corresponding reactions wherein a single catalyst is employed to obtain a given product distribution.

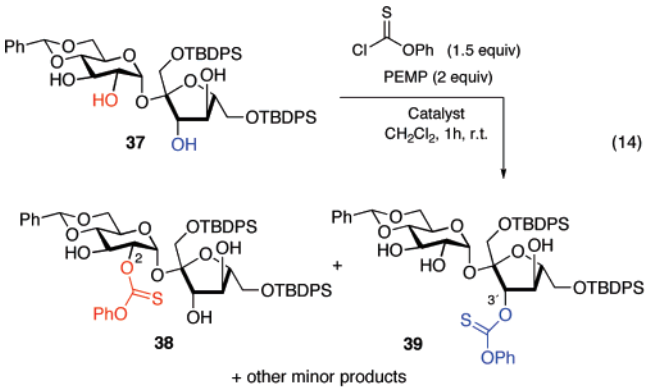
TABLE 3. Regioselectivity in the Thiocarbonylation of 4,6-Benzylidene β-Methyl Glucoside[a,b]



Entry	Catalyst	**32** (%)	**33** (%)	**34** (%)	**33** : **34**	**35** (%)	**36** (%)
1	NMI (20 mol%)	-	7	13	1 : 2	76	4
2	NMI (20 mol%) + $FeCl_3$(15 mol%)	5	11	18	1 : 1.6	38	28
3	**27** (20 mol%)	-	18	27	1 : 1.5	25	30
4	**27** (20 mol%) + $FeCl_3$(15 mol%)	9	33	23	1.4 : 1	7	29
5	**28** (20 mol%)	7	14	10	1.5 : 1	36	33
6	**28** (20 mol%) + $FeCl_3$(15 mol%)	15	10	18	1 : 2	4	54

[a] All reactions were conducted in the presence of PEMP and run according to the standard conditions described in Experimental Section. **27**: BOC-Pmh-DPro-Aib-DTrp(Boc)-DPhe-OMe. **28**: BOC-Pmh-Thr(tBu)-DVal-His(trt)-DPhe-DVal-Thr(tBu)-Ile-OMe. [b] Conversion determined by ^{1}H NMR.

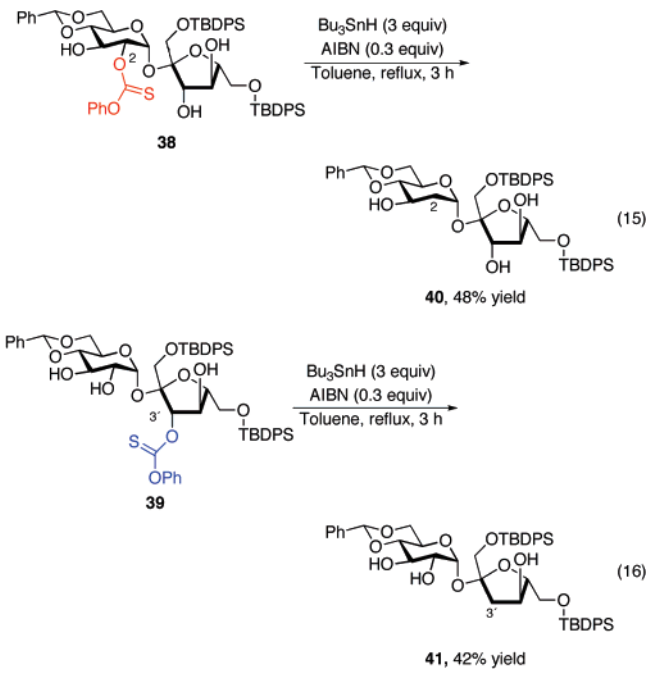
TABLE 4. Regioselectivity in the Thiocarbonylation of Sucrose Derivative 37[a]



(14)

Entry	Catalyst	38 : 39	Yield (38 + 39)[b]
1	NMI (20 mol%)	1 : 1.6	39
2	**27** (20 mol%)	2 : 1	66
3	**28** (20 mol%) + $FeCl_3$(15 mol%)	1 : 2	40

[a] All reactions were conducted in the presence of PEMP and run according to the standard conditions described in the Experimental Section. **27**: BOC-Pmh-DPro-Aib-DTrp(Boc)-DPhe-OMe. **28**: BOC-Pmh-Thr(t-Bu)-DVal-His(trt)-DPhe-DVal-Thr(t-Bu)-Ile-OMe. [b] Isolated yield after flash chromatography.



(15)

(16)

Conclusions

In these studies of site-selective thiocarbonylation, we have established a number of important milestones. Initially, we identified a reliable reagent combination that leads to consistent and efficient thiocarbonylation reactions using phenyl chlorothionoformate as a reagent and a combination of NMI and $FeCl_3$ (each in substoichiometric quantities) as co-catalysts. Importantly, we then showed that site-selectivity of thiocarbonylation may be modulated in a catalyst-dependent fashion, and in particular, peptidic structures containing the *N*-alkylimidazole substructure are critical variables in screening and optimization. Furthermore, in selected cases, we showed that one could observe reversals of inherent selectivity such that *catalyst control* rather than *substrate control* only could be utilized to deliver alternative major products in the polyol settings. Such reactions hold the potential to reduce the chemist's dependence on protecting groups by designing direct thiocarbonylation-deoxygenation sequences that may be of interest in synthetic and medicinal chemistry applications.

The mechanistic basis of these reversals is a frontier activity in the developing area of asymmetric catalysts that modulate regioselectivity. We have taken important first steps in our studies of chiral, peptide-based asymmetric catalysts.[31] That these new protocols include a significant, metal-based co-catalyst increases the complexity of these catalytic reactions in significant ways. The elucidation of how peptide-based systems function in the presence of additives like $FeCl_3$ is an exciting challenge that we are now addressing in our laboratory.

Experimental Section

General Procedures for the Thiocarbonylation Reaction. General Procedure A. Phenyl chlorothionoformate (1.5 equiv), 1,2,2,6,6-pentamethyl piperidine (2.0 equiv), and *N*-methylimidazole or a peptide catalyst (0.20 equiv) were added sequentially to a flame-dried 10-mL round-bottom flask containing a solution of alcohol, diol, or polyol (1.0 equiv) in anhydrous dichloromethane (1 mL). The reaction (yellow or brown) solution was stirred at room temperature for 1 h, then quenched with 1 mL of methanol, and concentrated under reduced pressure. The mixture of reaction products was isolated by silica gel flash chromatography.

General Procedure B. Phenyl chlorothionoformate (1.5 equiv), 1,2,2,6,6-pentamethyl piperidine (2.0 equiv), *N*-methylimidazole or a peptide catalyst (0.20 equiv), and $FeCl_3$ (0.15 equiv) were added sequentially to a flame-dried 10-mL round-bottom flask containing a solution of alcohol, diol, or polyol (1.0 equiv) in anhydrous dichloromethane (1 mL). The reaction (yellow or brown) mixture was stirred at room temperature for 1 h, then quenched with 1 mL of methanol, and concentrated under reduced pressure. The mixture of reaction products was isolated by silica gel flash chromatography.

NOTE: Optimized reaction conditions are described for each respective substrate. Unless otherwise noted, reactions were run according to conditions (General Procedure A or B) described above.

4, 6-*O*-Benzylidene 2-Mono(thiocarbonate) α-Methyl Glucoside 22a. General Procedure A for thiocarbonylation was followed; glucose derivative **12a** (40 mg, 0.14 mmol) was employed as starting material with peptide **27** (25 mg, 0.028 mmol), phenyl chlorothionoformate (28 μL, 0.21 mmol), and 1,2,2,6,6-pentamethyl piperidine (51 μL, 0.28 mmol) in CH_2Cl_2 (1.5 mL); and the reaction was allowed to stir for 5 h at −40 °C. Purification through silica gel flash chromatography (7:1 to 2:1 hexanes−EtOAc) afforded a 22:1 product ratio of **22a**:**23a**. Both **22a** (39 mg, 67%) and **23a** (2.0 mg, 3%) were isolated as white solids. In addition, minor amounts of **24a** (8 mg, 10%) and **26a** (3 mg, 7%) were also isolated, each as a white solid.

Data for 22a. The spectral data for compound **22a** matched that which had been previously reported.[32]

4,6-*O*-Benzylidene 3-Mono(thiocarbonate) α-Methyl Glucoside, 23a. General Procedure B for thiocarbonylation was followed; glucose derivative **12a** (30 mg, 0.11 mmol) was employed as starting material with peptide **28** (32 mg, 0.022 mmol), phenyl

(30) (a) Karl, H.; Lee, C. K.; Khan, R. *Carbohydr. Res.* **1982**, *101*, 31−38. (b) Adinolfi, M.; De Napoli, L.; Di Fabio, G.; Iadonisi, A.; Montesarchio, D. *Org. Biomol. Chem.* **2004**, *2*, 1879−1886.

(31) (a) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824−2827. (b) See ref. 12.

(32) Petráková, E.; Glaudemans, C. P. J. *Glycoconjugate J.* **1994**, *11*, 17−22.

chlorothionoformate (22 μL, 0.165 mmol), 1,2,2,6,6-pentamethyl piperidine (40 μL, 0.22 mmol), and $FeCl_3$ (2.7 mg, 0.0165 mmol) in CH_2Cl_2 (1.0 mL); and the reaction was allowed to stir for 5 h at −25 °C. Purification through silica gel flash chromatography (7:1 to 2:1 hexanes−EtOAc) afforded a 1:6.6 product ratio of **22a**:**23a**. Both **22a** (4.0 mg, 8%) and **23a** (24 mg, 53%) were isolated as white solids. In addition, minor amounts of **24a** (3 mg, 5%) and **26a** (3 mg, 8%) were also isolated, each as a white solid.

Data for 23a. Mp 97−101 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51−7.49 (m, 2H), 7.41−7.27 (m, 6H), 7.12−7.10 (m, 2H), 5.98 (t, J = 9.5 Hz, 1H), 5.56 (s, 1H), 4.89 (d, J = 3.5 Hz, 1H), 4.35 (dd, J = 4.7, 10.4 Hz, 1H), 3.98−3.91 (m, 2H), 3.83−3.77 (m, 2H), 3.52 (s, 3H), 2.31 (d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.8, 153.5, 136.9, 129.4, 129.1, 128.2, 126.5, 126.2, 101.5, 100.1, 82.1, 78.7, 71.9, 68.9, 62.7, 55.7, 53.4; IR (film, cm^{-1}) 3457, 2917, 1483, 1283, 1201, 1070, 1050; TLC R_f 0.22 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +84.1 (*c* 1.0, $CHCl_3$); HRMS calcd for $[C_{21}H_{23}O_7S\ H]^+$ requires *m*/*z* 419.1165; found 419.1167 (ESI+).

4,6-*O*-Benzylidene 2,3-Bis(thiocarbonate) α-Methyl Glucoside, 24a. Mp 58−60 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.39 (m, 2H), 7.33−7.13 (m, 9H), 7.03−7.01 (m, 2H), 6.95−6.93 (m, 2H), 6.22 (t, J = 9.6 Hz, 1H), 5.57 (dd, J = 3.8, 9.5 Hz, 1H), 5.48 (s, 1H), 5.17 (d, J = 3.8 Hz, 1H), 4.27 (dd, J = 4.7, 10.3 Hz, 1H), 3.97 (dt, J = 4.7, 10.0 Hz, 1H), 3.83 (t, J = 9.6 Hz, 1H), 3.74 (t, J = 10.2 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 194.3, 153.5, 153.4, 136.7, 129.6, 129.4, 129.1, 128.2, 126.8, 126.6, 126.2, 121.8, 121.7, 101.7, 96.9, 79.6, 79.1, 78.5, 68.8, 62.4, 55.7; IR (film, cm^{-1}) 2918, 1487, 1454, 1272, 1225, 1192, 1148, 1123; TLC R_f 0.56 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ −30.5 (*c* 1.0, $CHCl_3$); HRMS calcd for $[C_{28}H_{27}O_8S_2\ H]^+$ requires *m*/*z* 555.1147; found 555.1145 (ESI+).

Compound 26a. The spectral data for compound **26a** matched that which had been previously reported.[33]

General Procedure for the Deoxygenation Reaction. To a solution of the corresponding mono- or bis(thiocarbonate) (1 equiv) in toluene (4 mL) were added tributyltin hydride (3 equiv) and AIBN (0.3 equiv), and the mixture was heated at reflux for 3 h. Solvent was then removed under reduced pressure, and the resulting residue was purified by silica gel flash chromatography (3:1 to 2:1, hexanes−EtOAc).

Compound 29. General Procedure for deoxygenation was followed, and glucose derivative **22a** (54 mg, 0.13 mmol) was employed as starting material with AIBN (6.4 mg, 0.039 mmol) and tributyltin hydride (100 μL, 0.39 mmol). Compound **29** was isolated as a white solid (24 mg, 70%). The spectral data for compound **29** matched that which had been previously reported.[34]

Compound 30. General Procedure for deoxygenation was followed, and glucose derivative **23a** (50 mg, 0.12 mmol) was employed as starting material with AIBN (6.0 mg, 0.036 mmol) and tributyltin hydride (95.0 μL, 0.36 mmol). Compound **30** was isolated as a white solid (23 mg, 72%). The spectral data for compound **30** matched that which had been previously reported.[35]

Compound 31. General Procedure for deoxygenation was followed, and glucose derivative **24a** (79 mg, 0.14 mmol) was employed as starting material with AIBN (7.0 mg, 0.042 mmol) and tributyltin hydride (110 μL, 0.42 mmol). Compound **31** was isolated as a white solid (23 mg, 66%).

Data for 31. Mp 199−202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.48 (m, 2H), 7.39−7.34 (m, 3H), 5.57 (s, 1H), 4.70 (d, J = 3.3 Hz, 1H), 4.22 (dd, J = 4.5, 10.1 Hz, 1H), 3.83 (dt, J = 4.8, 9.7 Hz, 1H), 3.72 (t, J = 10.2 Hz, 1H), 3.63−3.57 (m, 1H), 3.38 (s, 3H), 2.02−1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 129.0, 128.3, 126.2, 101.9, 97.9, 78.3, 69.6, 64.8, 54.6, 29.5, 24.0; IR (film, cm^{-1}) 2946, 2901, 2868, 1377, 1123, 1095, 1054, 997, 919, 694; TLC R_f 0.44 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +93.5 (*c* 0.62, $CHCl_3$); HRMS calcd for $[C_{14}H_{18}O_4\ Na]^+$ requires *m*/*z* 273.1103; found 273.1112 (ESI+).

Acknowledgment. This work is supported by the NIH (GM-068649). M.S.-R. would like to thank the *Ministerio de Educación y Ciencia* of Spain for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds **8**, (±)-**13**, **20**, **21**, **22b**−**24b**, **26b**, **33**, **34**, **35**, **36**, **38**, and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702334Z

(33) Tsuda, Y.; Noguchi, S.; Kanemitsu, K.; Sato, Y.; Kakimoto, K.; Iwakura, Y.; Hosoi, S. *Chem. Pharm. Bull.* **1997**, *45*, 971−980.

(34) Minami, A.; Eguchi, T. *J. Am. Chem. Soc*. **2007**, *129*, 5102−5107.

(35) Lee, E.; McArdle, P.; Browne, P.; Gavin, N. *Carbohydr. Res.* **1989**, *191*, 351−356.