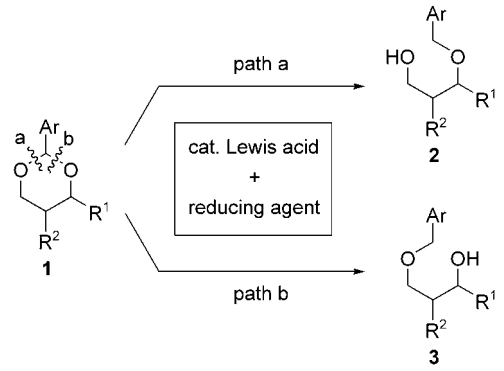
Synthetic Methods

$Cu(OTf)_2$ as an Efficient and Dual-Purpose Catalyst in the Regioselective Reductive Ring Opening of Benzylidene Acetals**

*Chi-Rung Shie, Zheng-Hao Tzeng, Suvarn S. Kulkarni, Biing-Jiun Uang, Ching-Yun Hsu, and Shang-Cheng Hung**

Regioselective ring opening of benzylidene acetals is one of the major challenges in carbohydrate and natural product syntheses.[1] Substituted and unsubstituted benzylidene acetals are valuable protecting groups to block 1,3-diols. Arylidene acetals **1** can be opened selectively under appropriate reaction conditions (Scheme 1) to yield primary **2** (path a) or

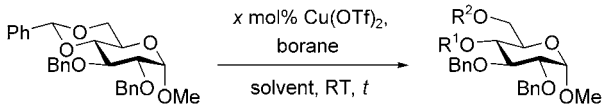


Scheme 1. Lewis acid catalyzed regioselective reductive ring opening of benzylidene acetals **1** to give primary alcohols **2** (path a) or secondary alcohols **3** (path b).

secondary alcohols **3** (path b). A number of effective reagents have been reported for the regioselective ring opening of 4,6-*O*-benzylidene acetals in hexopyranosides. Of these, AlH_3[2] and iBu_2AlH,[3] which are commonly used to cleave at the O6 position, often lack chemoselectivity when substrates contain base-sensitive functionalities. Alternatively, traditional acid-promoted reductive cleavage has been reported to open benzylidene acetals at either the O6[4] or O4 position.[4a,c,f,5] However, these traditional acids have to be used stoichiometrically or in excess and can lead to hydrolysis of the acetal ring as a major side reaction. Often when these protocols have been used, a mixture of regioisomers is obtained that can be difficult to purify by chromatographic techniques. The development of new Lewis acids as efficient catalysts for ring cleavage in a highly selective manner may offer a good solution (Scheme 1). No Lewis acid catalyzed ring openings of 4,6-*O*-benzylidene acetals at the O4 position have been published to date. So far only a reductive cleavage at O6 to the give corresponding 6-alcohol using borane and with $[V(O)(OTf)_2]$ (Tf = trifluoromethanesulfanyl) as the catalyst has been reported, and here the required amount of catalyst was 15 mol%.[6] Herein, we have developed $Cu(OTf)_2$ as an efficient and dual-purpose catalyst that can be used in catalytic quantities; it effects the regioselective reductive ring opening of benzylidene acetals at the O4 or O6 position by merely altering the reactivity of the reducing agent.

Compound **4** was selected for model studies. We examined the cleavage at O6 by employing various boranes in combination with $Cu(OTf)_2$ at room temperature; the results are outlined in Table 1. Initially, treatment of **4** with BH_3·THF in

Table 1: $Cu(OTf)_2$-catalyzed regioselective borane-reductive O6-ring opening of 4,6-*O*-benzylidene acetal **4** to the corresponding 6-alcohol **5** at room temperature.



Entry	*x*	Borane	Solv.	*t* [h]	Yield [%] 5	6
1	15	BH_3·THF[a]	CH_2Cl_2	0.75	94	0
2	15	BH_3·THF	–	0.75	92	0
3	10	BH_3·THF	–	1.5	93	0
4	5	BH_3·THF	–	2.5	95	0
5	1	BH_3·THF	–	27	70	0
6	5	BH_3·Me_2S[b]	–	10	78	3
7	5	BH_3·Me_3N	CH_2Cl_2	25	0	40
8	5	9-BBN[c]	–	27	40	0

[a] 1 M solution in THF. [b] 2 M solution in THF. [c] 0.5 M solution in THF, 9-BBN = 9-borabicyclo[3.3.1]nonane.

the presence of 15 mol% of catalyst in CH_2Cl_2 rapidly furnished the expected ring-opened product **5**[7] in excellent yield (entry 1, 45 min, 94%). Exclusion of CH_2Cl_2 gave similar results (entry 2, 92%). Lowering the concentration of catalyst to 10 mol% and 5 mol% (entries 3 and 4) led to similar selectivity and yields, while decreasing it to 1 mol% extended the reaction time and resulted in a drop in yield (entry 5).

We then tested various borane reagents in tandem with 5 mol% of $Cu(OTf)_2$ to study the effect of ligation and bulk

[*] C.-R. Shie, Z.-H. Tzeng, Prof. Dr. B.-J. Uang, Prof. Dr. S.-C. Hung
Department of Chemistry
National Tsing Hua University
Hsinchu 300 (Taiwan)
Fax: (+886) 3-571-1082
E-mail: schung@chem.sinica.edu.tw
Dr. S. S. Kulkarni, Prof. Dr. S.-C. Hung
Institute of Chemistry & Genomics Research Center
Academia Sinica
128 Academia Road, Section 2
Taipei 115 (Taiwan)
Dr. C.-Y. Hsu
Department of Chemical Engineering
Cheng-Shiu University
840 Cheng-Ching Road
Kaohsiung County 833 (Taiwan)

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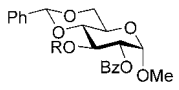
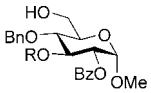
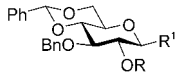
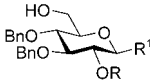
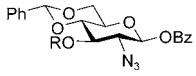
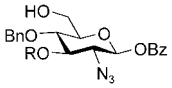
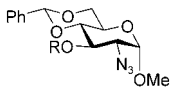
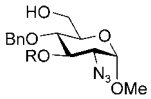
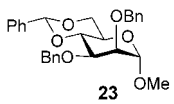
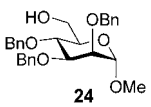
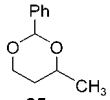
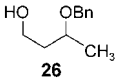
on the regiochemical outcome of the reactions. In entry 6, use of the $BH_3{\cdot}Me_2S$ complex with **4** afforded product **5** (78%) along with a minor 4-alcohol **6** (3%). Interestingly, the mode of regioselection was markedly shifted when $BH_3{\cdot}NMe_3$ was used as the reductant (entry 7); compound **6** was formed in 40% yield as the sole product, and some starting material was recovered (55%). A bulkier reagent, 9-borabicyclo[3.3.1]nonane (9-BBN), was sluggish to react (entry 8), and overnight stirring was needed to furnish **5** in a modest yield (40%) together with the hydrolyzed 4,6-diol (40%) and starting material (15%).

We then proceeded to investigate the compatibility of various substrates under these optimized conditions (1M $BH_3{\cdot}THF$ in THF, 5 mol% $Cu(OTf)_2$, without additional solvent, room temperature; Table 2). The 2-benzoyl-protected D-glucose derivative **7** successfully furnished the expected 4-benzyl-protected product **8** (entry 1, 4.5 h, 87%), while the 2,3-dibenzoyl-protected compound **9** gave the corresponding 6-alcohol **10**[4a] in 53% yield after 23 h (entry 2). When 15 mol% of $Cu(OTf)_2$ was used, the latter transformation was carried out over a short period (5 h), affording compound **10** in a high yield (entry 3, 91%). The electron-withdrawing groups in the substrates **7** and **9** made their reaction much slower than that of the 2,3-dibenzyl analogue **4** (0.75 h). The reaction rate is closely associated with the nucleophilicity of the oxygen atom at the C6 position and the Lewis acid catalyst. In the $LiAlH_4$–$AlCl_3$ system, the congestion of the protecting group at O3 in D-glucopyranosides plays an important role, and the presence of a bulkier substituent at C3 has been found to favor a higher proportion of O6-opened product.[2b] However, no such steric dependence was observed in our system, and only O4-benzyl ethers were obtained in high yields irrespective of their nature (H, Bn, or Bz).[4b] Similarly, the methyl β-pyranoside **11** (entry 4), β-thioglycoside **13** (entry 5), D-mannose-derived acetal **23** (entry 14), and non-sugar substrate **25** (entry 15) underwent a high-yielding facile ring fission to provide 6-OH derivatives **12**[8] (92%), **14** (93%), **24**[9] (84%), and **26**[10] (90%), respectively. In the D-glucosamine series, the β-benzoyl 3-benzyl-protected **15** led to the desired product **16** in 82% yield (entry 6). Its structure was determined by single-crystal X-ray structure analysis.[11] The 3-benzoyl analogue **17**, although sluggish to react under the optimized conditions (entry 7, 63%), did furnish the expected compound **18** rapidly and in excellent yield (90%) when 15 mol% of $Cu(OTf)_2$ was used (entry 8). When the α-form 3-benzyl **19** (entry 9) and 3-benzoyl **21** (entry 12) were employed, the expected ring-opened products **20** and **22** were obtained in 55 and 56% yields, respectively. Increasing the catalyst concentration to 15 mol% and the reaction temperature to 0°C improved the yield remarkably in case of the former (entry 11, 86%), whereas a substantial amount of the 4,6-diol (30%) from hydrolysis was present in the latter (entry 13, 57%).

Table 2: Reductive ring opening of various benzylidene acetals at the O6 position using $BH_3{\cdot}THF$ and *x* mol% of $Cu(OTf)_2$ as the catalyst.

Entry	Acetal	*x* [mol%]	*t* [h]	Product	Yield [%]
					
1	**7**: R = H	5	4.5	**8**: R = H	87
2	**9**: R = Bz	5	23	**10**: R = Bz	53
3	**9**	15	5	**10**	91
					
4	**11**: R = Bz, R^1 = OMe	5	4	**12**: R = Bz, R^1 = OMe	92
5	**13**: R = Bn, R^1 = STol	5	3.5	**14**: R = Bn, R^1 = STol	93
					
6	**15**: R = Bn	5	3	**16**: R = Bn	82
7	**17**: R = Bz	5	21	**18**: R = Bz	63
8	**17**	15	4.5	**18**	90
					
9	**19**: R = Bn	5	6.5	**20**: R = Bn	55
10	**19**	15	3.5	**20**	67
11	**19**	15[a]	14	**20**	86
12	**21**: R = Bz	5	5	**22**: R = Bz	56
13	**21**	15[a]	9	**22**	57
14	 **23**	5	3.5	 **24**	84
15	 **25**	5	1.5	 **26**	90

[a] The reaction was conducted in an ice bath. Bz = Benzoyl, Bn = benzyl, OMe = methoxy, Tol = tolyl.

With success in the $Cu(OTf)_2$-catalyzed borane-induced reductive O6-ring opening of benzylidene acetals, we then explored the catalytic properties of $Cu(OTf)_2$ for silane-induced reductive cleavage at the O4 position, including the effects of the solvent, silane agent, and catalyst concentration (Table 3). The catalyst was added at 0°C, and the reaction mixture was gradually warmed up to room temperature. When 1 mol% of $Cu(OTf)_2$ was used together with triethylsilane in CH_2Cl_2 (entry 1), the reaction took 15 h to provide the secondary alcohol **6**[5b] (62%) as the only regioisomer. A smaller reducing agent, Me_2EtSiH, offered a marginally improved yield of **6** in a much shorter reaction time (entry 2, 9 h, 65%). Employment of a more polar solvent like nitromethane speeded up the reaction of **4** with Et_3SiH (entry 3, 1 h) and Me_2EtSiH (entry 4, 1 h), which afforded **6** as the sole product in 60% and 68% yields, respectively. Although no other regioisomer was detected, hydrolysis of compound **4** to the corresponding 4,6-diol seemed to become a dominant factor limiting the yield. Less polar solvents, for example, THF and toluene, gave disappointing results. Nevertheless, reduction of **4** in acetonitrile using Et_3SiH (entry 5,

Table 3: $Cu(OTf)_2$-catalyzed reductive ring opening of compound **4** in various solvents with silanes to give the corresponding 4-alcohol **6**.

4 $\xrightarrow[\text{solvent, } 0\,^{\circ}C\rightarrow RT]{x\ \text{mol\%}\ Cu(OTf)_2,\ 2\ \text{equiv silane}}$ **5** + **6**

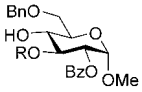
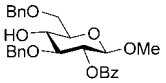
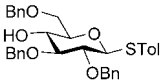
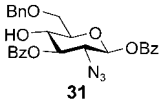
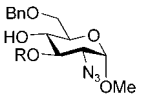
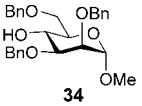
Entry	*x*	Silane	Solv.	*t* [h]	Yield [%]	
					5	**6**
1	1	Et_3SiH	CH_2Cl_2	15	0	62
2	1	Me_2EtSiH	CH_2Cl_2	9	0	65
3	1	Et_3SiH	CH_3NO_2	1	0	60
4	1	Me_2EtSiH	CH_3NO_2	1	0	68
5	1	Et_3SiH	CH_3CN	1	7	76
6	1	Me_2EtSiH	CH_3CN	0.5	0	84
7	0.5	Me_2EtSiH	CH_3CN	4	3	75
8	5	Me_2EtSiH	CH_3CN	0.5	3	80
9	10	Me_2EtSiH	CH_3CN	0.5	2	82

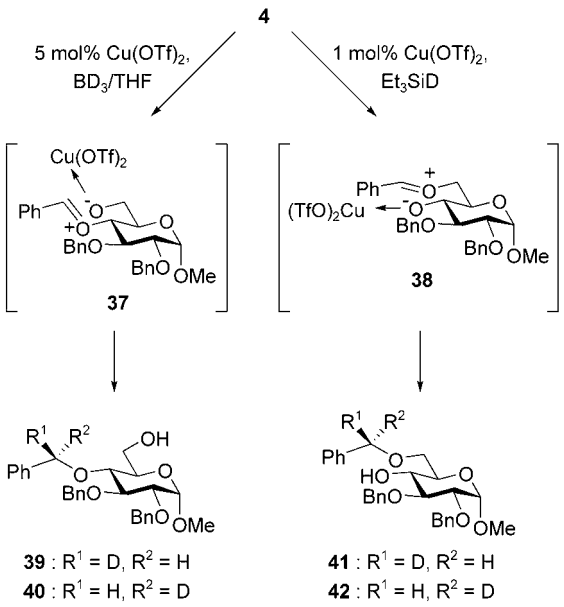
1 h) readily furnished the expected compound **6** (76%) along with the minor isomer **5** (7%), while Me_2EtSiH led to **6** in 84% yield (entry 6, 0.5 h), exclusively. In these cases the hydrolyzed product was recovered in up to 10% yield. In entry 7, when the catalyst concentration was halved, the transformation took place gradually (4 h) to afford compound **6** in 75% yield. In contrast, increasing the concentration of catalyst to 5 mol% or 10 mol% (entries 8 and 9) did not improve the yields of **6** (80–82%).

With these optimized reaction conditions (1 mol% $Cu(OTf)_2$, Me_2EtSiH, CH_3CN, 0°C→room temperature), we examined a number of α- and β-hexopyranosides bearing different protecting groups to check the generality of this protocol (Table 4). In entries 1–8, reactions of the D-glucose-derived benzoates **7** and **9**; β-glucopyranoside **11** and β-thioglycoside **13**; D-glucosamine-derived acetals **17**, **19**, and **21**; and D-mannopyranosyl sugar **23**[12] led to O4-opened products **27**–**34** in 71, 85, 74, 79, 87, 80, 83, and 70% yield, respectively. These experiments revealed that the electron-withdrawing group at the O3 position does not affect the reactivity of substrates, in contrast to the observations of the reductive O6-opening reactions with borane. In the case of the non-carbohydrate compound **25** (entry 9), regioisomeric benzyl ethers **26** (22%) and **35** (24%) were generated along with 1,3-dibenzyl ether **36** (36%) as the major product.

To examine the reaction pathway in greater depth, we performed two experiments using deuterated reducing agents (Scheme 2). Reductive ring opening of **4** with BD_3·THF furnished primary alcohols **39** and **40** in unequal proportions (5:1 ratio), as judged from the signals of the O4-benzylic protons in the ^1H NMR spectrum of the mixture with those of compound **5** (see the Supporting Information). The $Cu(OTf)_2$ catalyst may first coordinate with the more accessible O6 atom and lead to a zwitterionic species **37**, which can be reduced by the reactive borane reagent. The reaction essentially follows the S_N1 pathway, and the stereochemical bias is perhaps offered by the chirality at C4, which is reflected in the observed product ratio. On the other hand, the ring fission of **4** with Et_3SiD generated a 1:1 diastereomeric mixture of secondary alcohols **41** and **42**. The hindered O4-benzyl cation of the intermediate **37** cannot be reduced as the silane reagent is bulky and less reactive than borane and

Table 4: Regioselective reductive ring opening of various benzylidene acetals in acetonitrile employing Me_2EtSiH and with 1 mol% of $Cu(OTf)_2$ as the catalyst.

Entry	Acetal	*t* [h]	Product	Yield [%]
				
1	**7**	1	**27**: R = H	71
2	**9**	1	**28**: R = Bz	85
3	**11**	0.5	 **29**	74
4	**13**	1.5	 **30**	79
5	**17**	0.5	 **31**	87
				
6	**19**	1	**32**: R = Bn	80
7	**21**	0.5	**33**: R = Bz	83
8	**23**	1	 **34**	70
9	**25**	2	**26**: R^1 = H, R^2 = Bn	22
			35: R^1 = Bn, R^2 = H	24
			36: R^1 = R^2 = Bn	36



Scheme 2. The treatment of **4** with deuterated reducing agents. Bn = Benzyl.

an equilibrium is soon established between the O6- and O4-coordinated complexes, which leads to another zwitterionic species **38**. The silane agent can approach the intermediate **38** at the well-exposed O6-benzyl cation from either side to generate equal amounts of diastereomers.

In conclusion, we have successfully developed $Cu(OTf)_2$ as an excellent dual-purpose catalyst for highly regioselective reductive ring opening of various benzylidene acetals with BH_3 and Me_2EtSiH to furnish the corresponding primary and secondary alcohols, respectively. The reaction conditions are mild, and various protecting groups in the substrates are tolerated. The isotope studies provide the first experimental evidence that neither O6- nor O4-cleavage of the benzylidene ring proceeds through the S_N2 reaction pathway when borane or triethylsilane attacks the acetal carbon center.

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