Stripping off Water at Ambient **Temperature: Direct Atom-Efficient Acetal Formation between Aldehydes** and Diols Catalyzed by Water-Tolerant and Recoverable Vanadyl Triflate

Chien-Tien Chen,*,† Shiue-Shien Weng,† Jun-Qi Kao,† Chun-Cheng Lin,*,‡ and Mi-Dan Jan[‡]

Department of Chemistry, National Taiwan Normal University, and Institute of Chemistry, Academia Sinica, Taipei, Taiwan

chefv043@scc.ntnu.edu.tw

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ABSTRACT



Aromatic aldehydes can be readily protected as acetals with 1,2- and 1,3-diols by using vanadyl triflate as a catalyst in CH₃CN at ambient temperature. Carbohydrate-based 1,2- and 1,3-diols can similarly be protected in good to excellent yields. The catalyst can be readily recovered from the aqueous layer. In combination with vanadyl triflate-catalyzed sequential regioselective, reductive acetal opening and chemoselective acylations, the title method allows for differential functionalization of all four hydroxyl units in a given glucopyranoside.

Acetalization constitutes a fundamental technique for the protection of aldehydes and ketones with simple 1,2-ethaneor 1,3-propane-diol as well as the protection of functionalized 1,2- and 1,3-diols with simple aromatic aldehydes or acetone.1 Acetals tolerate a diverse array of nucleophilic and basic (including organometallic) reagents, as well as reductants and nonacidic oxidants.² In addition, chiral acetals are useful substrates in asymmetric synthesis.³ Conventionally, acetal formation at ambient temperature requires the use of

1,1-dimethoxyacetals as aldehyde precursors or orthoformates (HC(OR)₃) as dehydrating agents with concomitant generation of formate ester and release of ROH. Normally, the catalysts employed include HCl,4 p-TSA/TFA,5 Amberlyst-15,6 BF₃•Et₂O,7 metal halides (e.g., TiCl₄,⁸ ZrCl₄,⁹ LaCl₃,¹⁰

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[†] National Taiwan Normal University.

[‡] Institute of Chemistry, Academia Sinica.

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 WCl_{6} ,^{9a,11} FeCl₃,¹² and DCC/SnCl₄¹³), metal triflates (e.g., TMSOTf,¹⁴ Sc(NTf₂)₃,¹⁵ and Bi(OTf)₃¹⁶), and *N*-bromosuccinimide (NBS).¹⁷ Many of these are acidic in nature. Therefore, existing acid-sensitive groups such as THP ether and acetonide groups are not always fully compatible, and the catalysts cannot be recovered and reused. In addition, the preparation of the prerequisite 1,1-dimethoxyacetals somewhat limits their practical applications. In marked contrast, the direct condensation between the parent aldehydes and alcohols is much less used. A few methods such as the use of concentrated H₂SO₄ as a catalyst and dehydrating agent,¹⁸ or *p*-TSA in refluxed arenes,¹⁹ or stoichiometric ZnCl₂²⁰ have been documented, but the substrate scope is somewhat limited.

4,6-*O*-Benzylidene acetal-protected monosaccharides are important precursors in the synthesis of complex carbohydrates.²¹ So far, the most well-adopted procedure involves the use of a 1,1-dimethoxyacetal and the saccharide catalyzed by *p*-TSA or camphorsulfonic acid (CSA) in polar solvents. The direct condensation requires the use of ZnCl₂ in neat aldehyde.^{20,22} An ideal atom-efficient catalytic version of this process at ambient temperature remains to be realized.

For the past three years, we have unraveled several watertolerant vanadyl and other oxometallic species as recoverable, amphoteric catalysts for nucleophilic acyl substitutions (NAS) of anhydrides^{23a,b} and methyl esters^{23c} (including transesterification) with protic nucleophiles (alcohols, amines, and thiols); these catalysts have high functional group compatibility and chemoselectivity. In continuation of our work in this area of catalysis (including Mukaiyama aldol additions, oxidative couplings of 2-naphthols, and DNA photocleavages),²⁴ herein we describe a new moisturetolerant, environmentally benign protocol for the atom-

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efficient formation of acetals from aldehydes and diols catalyzed by vanadyl triflate.

The direct condensation between benzaldehyde derivatives and 1,2-ethandiol **2a** (1.1–1.2 equiv) was first tested as a model reaction with various vanadyl and oxometallic species (3–5 mol %) in CH₂Cl₂. Among them, only vanadyl triflate (VO(OTf)₂•*x*H₂O) could effect clean and complete conversion (in 20 min) at ambient temperature. The product **4a** was isolated in pure form (97% yield) by straight aqueous wash to remove both the catalyst and the residual diol (Scheme 1). Notably, such a simple and mild protocol was unprec-



edented with other metal-mediated catalysis. A couple of other more polar diol substrates such as 1-benzoylated glycerol **2b** and pentaerythritol **3** were further examined. These two cases were performed in CH₃CN due to the poor solubility of the substrates in CH₂Cl₂. The reactions were complete in 20–22 h, and the corresponding benzaldehyde acetals (**5** and **6**) were similarly isolated both in 92% yield.

With the preliminary success of using vanadyl triflate for the acetalization of benzaldehyde with simple diols, we turned our attention to functionalized monosaccharides as diol surrogates. *S*-Tolyl-thioglycoside **7** was first tested under previous standard reaction conditions (5 mol % VO(OTf)₂· xH₂O, 1.1–1.3 equiv of PhCHO). Among several different solvents examined, only CH₃CN led to satisfactory results due to the reasonably good substrate solubility and intact catalytic activity.²⁵

A series of monosaccharides (7-13) bearing *O*-, *S*-, and *Se*-glycosidic (OMe, S-Tol, SePh) bonds with varying C2substituents (OH, OBn, N₃, and NPhth) were further employed for the optimal catalytic protocol (Table 1). In all cases, the absolute configuration at the glycosidic positions was retained without any anomerization, bond cleavage, or oxidation of sulfides and selenides. The acetalization was completely regio- and chemoselective. Only 4,6-*O*-benzylidene products were obtained in D-gluco- (7–9) and D-galactopyranosides (10–12). No 3,4- or 2,3-*O*-benzylidene products were observed in the cases of 7a, 8–10a, 11a, and 12.

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^{(25) (}a) Solvent effects are as follows: CH₂Cl₂ (24 h, 32%), THF (24 h, 46%), dioxane (24 h, 51%). (b) A brief survey on the effects of vanadyl and oxometallic species on the test reaction in CH₃CN revealed that vanadyl triflate was the most reactive one. Other catalysts such as VO(OTs)₂·xH₂O (14 h, 71%), MoOCl₄ (14 h, 68%), and MoO₂Cl₂ (14 h, 75%) showed moderate activities.





On the other hand, competitive 2,3-*O*-benzylidene formation (5-7%) yield) could not be prevented due to the cis relationship of the 2,3-dihydroxyl unit in D-mannopyranosides (13). The desired 23 was thus obtained in 82% yield. Similar competitive acetal formation also occurred in more complicated structures such as 24 and 25 in Scheme 2. As expected, the 4,6-*O*-benzylidene product 26 was formed from 24, while 25 led to preferential formation of five-membered ring benzylidene product 27. The lower yield for 27 (73%) was due to the poorer solubility of 25 in CH₃CN.

The current direct condensation protocol tolerates a diverse array of functionalities, including residual free hydroxyl, benzyl ether (entries 5 and 14), *N*-phthalimido (*N*-Phth, entry





6), azido ($-N_3$, entries 20–22), (trifluoro)acetamido (-NHAc and $-NHC(O)CF_3$, Scheme 2), ester ($-CO_2Me$ and CO_2 -*tert*-Bu, Scheme 2), and carbamate groups (Fmoc, Scheme 2). So far, we have applied four different aromatic aldehydes of varying electronic demands for the current study. In general, the reactivity profile follows the order of benzal-dehyde and 4-acetoxybenzaldehyde > 4-anisaldehyde > 2-naphthaldehyde (entries 10 and 18).²⁶ The solid 2-naphthaldehyde is the least reactive one since it does not help in dissolving any saccharide substrates like other aldehydes.

Functionalized thioglycosides constitute a key template in carbohydrate chemistry. When activated by NIS-HOTf, MeOTf, and other suitable electrophilic activators (e.g., DMTST and IDCP),²⁷ functionalized thioglycosides serve as key building blocks for oligosaccharide synthesis via sequential O-glycosidic bond formation.²⁸ Since vanadyl triflate has been successfully applied to chemoselective NAS of anhydrides with alcohols and regioselective acetal opening,²⁹ a complete differentiation of all four hydroxyl groups may be possible when combined with the current catalytic acetal formation protocol. Therefore, the starting material **14a** was first treated with 2-methoxypropene (2-3 equiv)in the presence of catalytic camphorsulfonic acid (1 mol %) in anhydrous THF at ambient temperature.³⁰ This led to the 2,3-isopropylidene product 28 in 94% yield after recrystallization from ether (Scheme 3). Double reductive ring openings at both benzylidene and isopropylidene units in 28



by BH₃•THF complex catalyzed by vanadyl triflate at 0 °C led to regioselective ring opening product **29** in 86% yield.³¹ The remaining two hydroxyl groups in **29** were readily differentiated by sequential chemoselective acetylation (1.05–1.1 equiv of Ac₂O, 0 °C) and chloroacetylation (1.5 equiv of ClAc₂O, 40 °C) catalyzed by vanadyl triflate (5 mol %). The resulting fully functionalized thioglycoside **31** was provided in 88% yield. Each hydroxyl unit may be independently unmasked from the common oligosaccharide building block **31** by NaHCO₃/MeOH (ClAc at C3), NH₂-NH₂/HOAc (Ac at C6), H₂/Pd-C (Bn at C4),³² or CF₃CO₂H (*i*-Pr at C2) chemoselectively.³³

We have documented the first successful example of direct catalytic acetal formation between aromatic aldehydes with simple as well as functionalized diols derived from monosaccharides by vanadyl triflate. The new protocol is mild (ambient temperature) and regio- and chemoselective. No dehydrating agent or preformed 1,1-dimethoxyacetal reagent is required. Notably, the water-tolerant catalyst can be recovered easily from the aqueous layer after water removal. In combination with our recently developed catalytic acylation and regioselective acetal opening techniques, a handy four-step catalytic protocol has been established for the construction of a functional, hydroxyl group-differentiated thioglycoside serving as a universal oligosaccharide building block. The current and existing versatile vanadyl and oxometallic species-mediated catalyses augur well for their potential applications in carbohydrate chemistry.

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Supporting Information Available: Representative experimental procedures, spectral data, and ¹H and ¹³C NMR spectra of all end products **4a–c**, **5**, **6**, **14–23**, and **26–31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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