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A Simple and Versatile Method for the Formation of Acetals/Ketals Using Trace Conventional Acids

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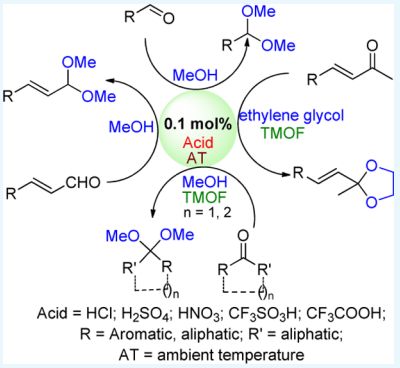
Supporting Information

ABSTRACT: An important and surprising finding that the acetalization and ketalization of aldehydes and ketones with alcohols, respectively, proceed smoothly in the presence of 0.1 mol % acid, without removing water, has been presented. This process has many merits, such as commercial available catalysts with low cost and low loadings (as low as 0.03 mol %), quite a broad substrate scope (including various aldehydes, ketones, acid-sensitive substrates, and diols), a wide range of reaction temperature (−60 to 50 °C), high yields, large-scale preparation, environmental friendliness, and simple work-up procedure. This new protocol has also been successfully applied to protect the important organic compounds, such as 1,3-diols, 1,2-diols, acid-sensitive substrates, glucose, and 1,3-dicarbonyl compounds.



1. INTRODUCTION

A protective group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in the course of the preparation of multifunctional complex organic molecules. It plays an important role in organic, medicinal, carbohydrate, and drug design chemistry. As Wuts pointed out, organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products; thus, the development of new methods for functional group protection and deprotection continues.[1] Acetalization/ketalization is one of the most useful methods for the protection of aldehydes/ketones, which are extensively encountered in organic synthesis.[2,3] The acetals/ketals are traditionally generated by treating aldehydes/ketones with alcohols in the presence of typical acid catalysts (such as dry HCl, H_2SO_4, trifluoroacetic acid, and p-toluenesulfonic acid), which are often corrosive.[4−7] In addition, the acidic environment is incompatible with the acid-sensitive groups of the substrates, such as N-Boc-protected amines, silyl-protected alcohols, alkenes, and alkynes.[8] Especially, the acetals/ketals are also highly unstable because of the reversible reactions to the hemiacetals/hemiketals and the starting carbonyls; as a result, to avoid shifting the equilibrium back to the reactants, the byproduct water has to be removed by additional physical and chemical means.[8] A series of Lewis acids,[9−17] other homogeneous catalysts,[18−23] different metal complexes of Pt(II), Pd(II), and Rh(II),[24−28] and various heterogeneous catalysts[29−36] have been reported to catalyze the acetal/ketal protection of carbonyl compounds. Recently, a few more successful and efficient acetalization/ketalization reactions have also been reported: (1) Connon designed a series of aprotic salts (pyridinium salt derivatives, dialkyltriazolium salts, and imidazolium salts) capable of behaving as Brønsted acids for chemoselective acetalization of aldehydes;[37−40] (2) Azzena developed a novel acetalization/ketalization formation process of aliphatic and aromatic aldehydes/ketones with diols employing ammonium salts as acidic catalysts, using cyclopentyl methyl ether as a solvent under Dean−Stark conditions;[41] (3) Ying's group developed a mesoporous polymelamine−formaldehyde polymer as an efficient catalyst for chemoselective acetalization of aldehydes;[42] and (4) very recently, graphitic-C_3N_4 has been shown to catalyze photoacetalization of aldehydes/ketones with alcohols to acetals/ketals in high yields using visible light under ambient conditions.[43] Although acetalization has been widely reported and well-investigated, the recent reports also suffered from lack of generality because of the following drawbacks: limited substrate scope, use of toxic or expensive reagents, high reaction temperature, stoichiometric amounts of catalysts, poor chemoselectivity and atom-economy, the need for excess amounts of drying agents, long reaction times, low yields, high costs, tedious workup, and so forth. Consequently, most of the reported methods had inevitably lowered the overall synthetic efficiency. Up to now, the application of acetalization/ketalizationin chemical industries, including pharmaceuticals, agrochemicals, and intermediates, has been hampered by the lack of general methods. Therefore, the development of alternative technologies that are greener, safer, and more environmentally friendly is highly desirable.

Can we find a simple molecule which acts like an enzyme for the acetalization of aldehydes/ketones? If this was possible, it would represent a remarkable synthetic alternative to many

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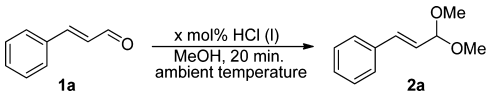
established acetalizations. In particular, such processes would overcome the abovementioned catalyst limitations/problems and allow the cost-effective manufacture of acetals or ketals in chemicals and pharmaceutical industries on an industrial scale. As we know, to increase the electrophilicity of the carbonyl carbon in the acetalization/ketalization process, acids are required to promote the reactions by forming oxonium ions. However, the alcohols would also be protonated in the presence of excess acids, dramatically decreasing the nucleophilicity of the alcohols. In addition, the excess acids may also cause the hydrolysis of acetals/ketals to aldehydes/ketones. Therefore, we envisioned that the acid loadings would be crucial for the generation of acetal/ketal products.

2. RESULTS AND DISCUSSION

To verify the feasibility of our proposal, acetalization of *trans*-cinnamaldehyde with methanol was chosen as the model reaction using different loadings of concentrated hydrochloric acid (12 mol/L) at ambient temperature. The results are summarized in Table 1 and Figure 1. Surprisingly, the formation of dimethyl acetal proceeded quite well in 20 min even with 0.005 mol % hydrochloric acid *without removing the water* (Table 1, entry 1). The conversion was significantly improved by increasing the acid loadings (entry 2), and excellent data were observed by using a range of acid loadings from 0.03 to 30 mol % (entries 3−14). However, the formation of acetal decreased as the acid loadings continued to increase (entries 15−18), and only 6% conversion was observed by using 600 mol % acid, probably because the alcohols were also protonated resulting in decreased nucleophilicity in the presence of excess acid (entry 19). In addition, the hydrolysis of acetals might also become a serious problem and the acetalization conversions decreased. It should be noted that no cis−transisomerization was observed during our investigation.[44] We further explored the reaction with 0.1 mol % hydrochloric acid at different temperatures. It was found that the temperature has little effect on the reactions, and excellent conversions were also obtained ranging from 50 to −60 °C (entries 20−24). For example, hydrochloric acid exhibited a very high catalytic activity when the domino reaction was carried out at 50 °C, and excellent conversion was obtained in 3 min with 0.1 mol % hydrochloric acid (entry 20); the reaction time should be extended at lower temperature (entry 24). Although the reported methods pointed out that the acetalization reaction was sensitive to water, the reaction proceeded smoothly without any effect on the reaction rate and conversion even when the concentration of HCl decreased from 12 to 4 mol/L (entries 25 and 26), indicating that the loadings of the acid catalyst should be more crucial for the formation of acetal products.

Table 1. Screenings of the Acid Loadings[a]



entry	loading (mol %)	conv. (%)[b]	entry	loading (mol %)	conv. (%)[b]
1	0.005	68	14	30	91
2	0.01	76	15	60	89
3	0.03	91	16	100	84
4	0.05	93	17	120	78
5	0.10	95	18	300	59
6	0.20	94	19	600	6
7	0.25	94	20[c]	0.10	93
8	0.30	95	21[d]	0.10	93
9	0.5	92	22[e]	0.10	96
10	1.0	92	23[f]	0.10	93
11	3.0	92	24[g]	0.10	91
12	6.0	92	25[h]	0.10	92
13	12	91	26[i]	0.10	91

[a]Unless otherwise specified, a mixture of aldehydes **1** (2 mmol) and hydrochloric acid in methanol was stirred at an ambient temperature for 20 min. [b]Determined by gas chromatography (GC) analyses of the crude reaction mixture. [c]At 50 °C for 3 min. [d]At 30 °C for 10 min. [e]At 0 °C for 2 h. [f]At −20 °C for 2 h. [g]At −60 °C for 24 h. [h]8 mol/L HCl was used. [i]4 mol/L HCl was used.

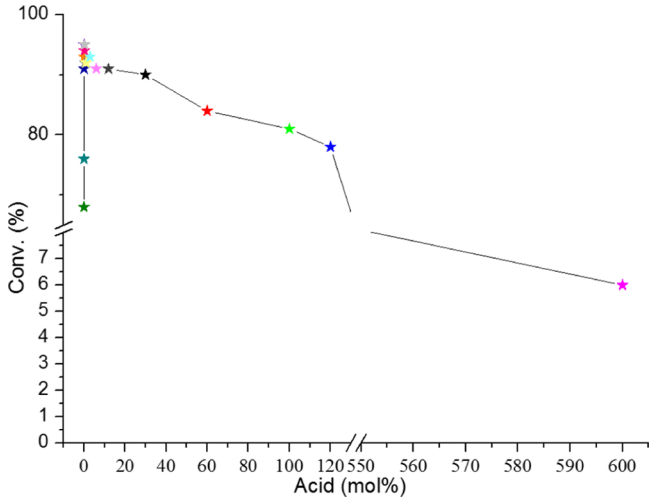


Figure 1. Conversion plot for acetalization of *trans*-cinnamaldehyde with different acid loadings. See Table 1 for reaction conditions.

Subsequently, our attention turned to evaluate its general utility in the acetalization of other aldehydes. A wide range of aldehydes **1** were treated with methanol at an ambient temperature, catalyzed by 0.1 mol % hydrochloric acid. As shown in Table 2, several points are noteworthy: (1) All acetalization reactions proceeded smoothly with excellent conversions and yields (entries 1−18). (2) The scope of the acetalization reactions was proven to be quite broad. Various aldehydes, such as *substituted cinnamaldehydes* (entries 1−5), *aliphatic α β-unsaturated aldehydes* (entry 6), *aryl aldehydes* (entries 7−12), *and aliphatic aldehydes* (entries 15 and 16), could be transformed into the corresponding acetals with excellent conversions and isolated yields. In addition, the heteroaromatic aldehydes, such as 2-furaldehyde and 2-thiophenecarboxaldehyde (entries 13 and 14) as well as the cyclic aldehyde (entry 17), could be successfully employed to afford excellent yields. Especially, bisaldehyde **1r** also furnished bisacetal **2r** in an excellent yield. (3) In general, the substituents on the aryl ring of aromatic aldehydes had little effect on the efficiency of the acetalization reaction. However, cinnamaldehydes with electron-donating groups showed a relatively low activity, and trimethylorthoformate (TMOF) had to be added to improve the conversion (entry 3). (4) Most of the aldehydes underwent nearly quantitative acetalization at 0.1 mol % catalyst loading in a short reaction time, and the products could be purified by a simple extraction. (5) The reaction is not confined to methanolysis. The protection of benzaldehyde as a

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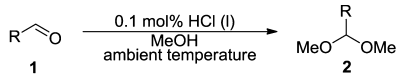
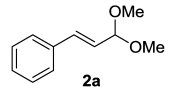
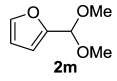
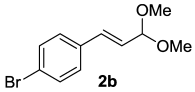
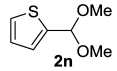
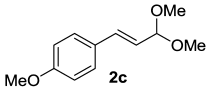
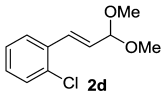
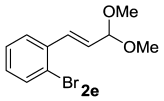
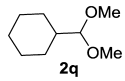
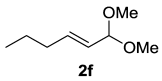
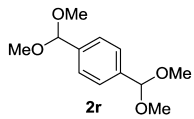
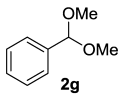
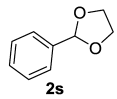
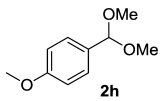
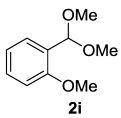
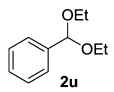
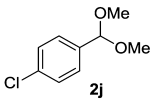
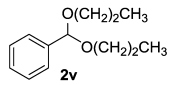
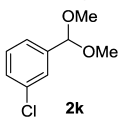
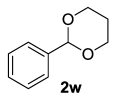
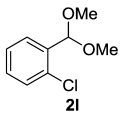
Table 2. Acetalization of Various Aldehydes with Methanol Catalyzed by 0.1 mol % Hydrochloric Acid[a]



Entry	2	Conv.(%)[b]	Yield(%)[c]	Entry	2	Conv.(%)[b]	Yield(%)[c]
1[d]	 2a	95(92)[e]	93(91)[e]	13[g]	 2m	100	97
2[f]	 2b	94	90	14[g]	 2n	100	96
3[f,g]	 2c	87	83	15[g]	$CH_3(CH_2)_5CH(OMe)_2$ 2o	95	93
4[d]	 2d	97	94	16[g]	$CH_3(CH_2)_7CH(OMe)_2$ 2p	98	95
5[d]	 2e	97	94	17[g]	 2q	100	96
6[g]	 2f	94	90	18[g]	 2r	93	90
7[g]	 2g	95	93	19[g,h]	 2s	100	97
8[g]	 2h	100	99	20[g,h]	 2t	99	95
9[g]	 2i	99	97	21[i]	 2u	100	98
10[g]	 2j	100	99	22[j]	 2v	100	98
11[g]	 2k	100	97	23[k]	 2w	100	97
12[g]	 2l	100	98				

[a]Unless otherwise specified, a mixture of aldehydes **1** (2 mmol) and 0.1 mol % hydrochloric acid in methanol was stirred at an ambient temperature for 30 min. [b]Determined by GC analyses of the crude reaction mixture. [c]Isolated yield. [d]For 30 min. [e]Scaled up by 200 times. [f]1.2 equiv of TMOF was added. [g]For 24 h. [h]Ethylene glycol was used as the solvent. [i]Ethanol was used as the solvent. [j]*n*-Propanol was used as the solvent. [k]1,3-Propanediol was used as the solvent.

stable five-membered cyclic 1,3-dioxolane also proceeded smoothly under identical reaction conditions to afford products with excellent conversions (entries 19 and 20). (6) Other alcohols, such as ethanol, *n*-propanol, and 1,3-diols, were also effective for the acetalization (entries 21−23). (7) To investigate the scalability of this protocol, the acetalization reaction of cinnamaldehyde with methanol was scaled up by 200 times in comparison with the reaction shown in Table 2, entry 1. The reaction was also effective and could conveniently prepare the acetal on a gram scale (>5 g) with slightly inferior conversion.

Ketalization usually requires an elevated temperature or water needs to be removed under Dean−Stark conditions to avoid shifting the equilibrium back to the reactants. Therefore,

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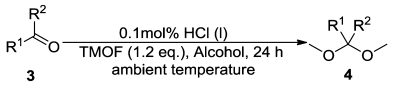
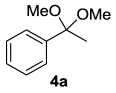
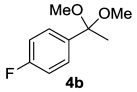
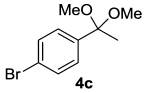
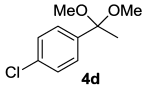
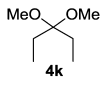
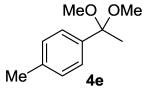
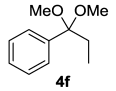
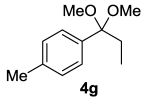
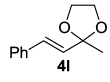
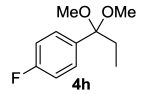
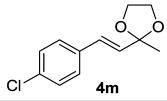
Table 3. Ketalization of Various Ketones with Alcohol Catalyzed by 0.1 mol % Hydrochloric Acid[a]



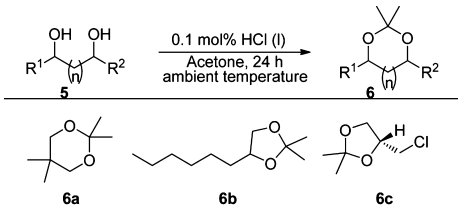
Entry	4	Conv. (%)[b]	Yield (%)[c]	Entry	4	Conv. (%)[b]	Yield (%)[c]
1[d]	 4a	100	99	9[f]	 4i	97	93
2[d]	 4b	100	99	10[e, g]	 4j	99	95
3[d]	 4c	100	98	11[e]	 4j'	96	94
4[d]	 4d	99	96	12[e, g]	 4k	98[g]	94
5[e]	 4e	95	91	13[e, h]	 4k'	97	94
6[d]	 4f	99	97				
7[e]	 4g	95	92	14[e, h]	 4l	99	95
8[d]	 4h	100	99	15[e,h,i]	 4m	100	96

[a]Unless otherwise specified, a mixture of ketones **1** (2 mmol), $CH(OCH_3)_3$ (2.4 mmol) and 0.1 mol % hydrochloric acid in methanol was stirred at an ambient temperature for 12 h. [b]Determined by GC analyses of the crude reaction mixture. [c]Isolated yield. [d]12 h. [e]For 24 h. [f]For 30 min. [g]At 40 °C. [h]Ethylene glycol was used as the solvent. [i]THF was used as the solvent.

the development of a greener, safer, and environmentally friendly method for ketalization still represents a major challenge in organic synthesis. Encouraged by the successful results described above, we turned our attention to the possible ketalization reactions of ketones, taking acetophenone **3a** and methanol as the model compounds under the optimized conditions; a low conversion (7%) was observed after 30 min, even when the reaction time was extended to 24 h. Fortunately, a quantitative conversion of the ketone was achieved when 1.2 equiv of TMOF was added in 12 h (Table 3, entry 1). Subsequently, a series of ketones were applied to establish the scope and generality of the protocol, and the corresponding ketals **4** were produced in high conversions/yields (entries 1−15). The aromatic ketones **3** with electron-donating groups such as a methyl group showed a relatively low activity, and the reaction time was extended to 24 h (entries 5 and 7). On the other hand, the aromatic ketones **3** with electron-withdrawing groups such as F, Cl, and Br ones showed a higher activity, giving almost quantitative ketal products (entries 2−4 and 8). The cyclic and acyclic aliphatic ketones also exhibited a high reactivity (entries 9−13). Interestingly, when methanol was replaced with ethylene glycol, 1,3-dioxolanes **4j′**, **4k′** were also obtained with excellent conversions/yields (entries 11 and 13). We also investigated the reactions of conjugated enone systems, and excellent conversions/yields were obtained without forming oxy-Michael/ketal derivatives (entries 14 and 15).[45−49]

The diols or polyols are widely encountered in carbohydrates, macrolides, pharmaceutical agents, and nucleosides, leading to the development of a number of new methods for these functional groups protection. Dioxolanes and dioxanes are the most common protective groups for diols. Gratifyingly, 0.1 mol % hydrochloric acid readily promoted the ketalization of a range of diols with acetone (Scheme 1). 1,3-Diols, such as

Scheme 1. Ketalization of Acetone with 1,3-Diols and 1,2-Diols



glycol **5a**, was transformed to the dioxanes in a high yield, as well as the 1,2-diols (e.g. 1,2-octanediol **5b**) and *R*-(−)-3-chloro-1,2-propanediol **5c** were transformed to the dioxolanes in high yields, usually without further purification. These studies demonstrate the high efficiency and the wide synthetic utility of the current catalytic protocol.

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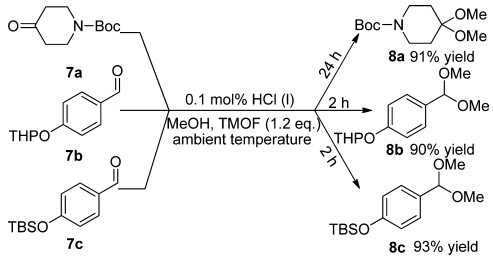
The compatibility of this method with other acid-sensitive substrates, such as N-Boc-protected amines **7a**, silyl-protected alcohols **7c**, and tetrahydropyranyl-protected alcohols **7b**, was also established. As exemplified in Scheme 2, the acetalization/

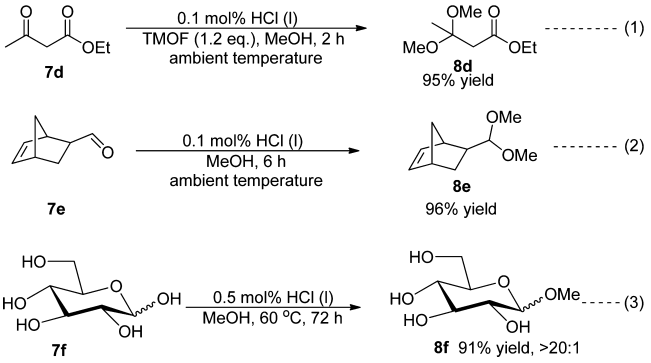
Scheme 2. Acetalization/Ketalization of Acid-Sensitive Substrates with Methanol



ketalization of aldehydes/ketones with methanol to form dimethyl acetals/ketals proceeded well with 0.1 mol % hydrochloric acid, also without affecting the abovementioned groups.

To further demonstrate its potential applications, this method was applied for the protection of other important carbonyl compounds (Scheme 3). Ethyl acetoacetate **7d**, which

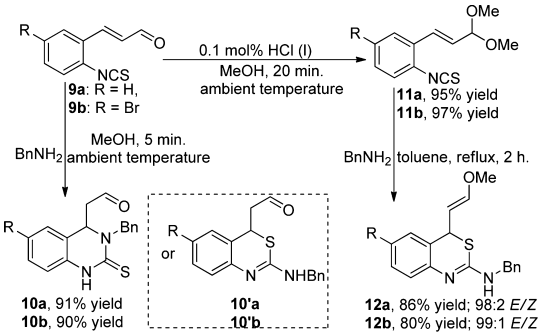
Scheme 3. Acetalization/Ketalization of Other Important Carbonyl Compounds with Alcohol



is used as one of the most important chemical intermediates in the production of a wide variety of compounds, was transformed to dimethyl ketal **8d** in a good yield under mild conditions, while TMOF should be added (eq 1). 5-norbornene-2-carboxaldehyde **7e**, which contained a double bond, could be successfully employed to afford the corresponding acetal **8e** in an excellent yield, while the double bond remained intact (eq 2). The acetalization/ketalization of glucose is very important in carbohydrate chemistry. However, the methylation of D-glucose was usually treated with $SOCl_2$,[50] AcCl,[51] Ac_2O/BF_3,[52] and Amberlyst-15.[53] To our delight, direct treatment of D-glucose **7f** with 0.5 mol % hydrochloric acid in methanol at 60 °C for 72 h gave methyl D-glucopyranoside **8f** in 91% yield (eq 3).

To further assess the usefulness of our protocol, the applications of this acetalization protocol in heterocyclic compounds synthesis were also investigated. As described in Scheme 4, two possible structural isomers (**10** and **10′**) would be obtained by treatment of *o*-isothiocyanato-(*E*)-cinnamaldehydes **9** with primary amines. Interestingly, only 3,4-dihydroquinazolines **10** were exclusively obtained when the reaction was performed in methanol under an ambient

Scheme 4. Applications of This Acetalization Protocol in Heterocyclic Compound Synthesis



temperature. However, when the *o*-isothiocyanato-(*E*)-cinnamaldehydes were treated with hydrochloric acid (0.1 mol %) in methanol, they could be transformed into their corresponding acetals **11** in excellent isolated yields. Subsequently, the S-terminus of thiourea, not the N-terminus of thiourea, served as a nucleophilic site to react with the *γ*-position of *β*,*γ*-unsaturated dimethylacetal, following elimination a methoxyl group to afford the cyclizing product 4*H*-3,1-benzothiazine derivative **12** with excellent selectivity in refluxing toluene.

In addition, other strong inorganic acids (e.g., H_2SO_4 and HNO_3) as well as the strong organic acids (e.g., CF_3COOH and CF_3SO_3H) also exhibited a high catalytic activity for the acetalization of cinnamaldehyde with methanol at a low acid loading under an ambient temperature, and excellent conversions were obtained in 20 min (Table 4, entries 1−4). As expected, the weak acids, such as acetic acid and *p*-nitrobenzoic acid (PNBA), showed poor catalytic activity (entries 5 and 6).

Table 4. Other Acids for the Acetalization

Entry	Acid	Conv. (%)[b]	Entry	Acid	Conv. (%)[b]
1	H_2SO_4	93	4	CF_3SO_3H	93
2	HNO_3	92	5	HAc	24
3	CF_3COOH	93	6	PNBA	4

entry	acid	conv (%)[b]	entry	acid	conv (%)[b]
1	H_2SO_4	93	4	CF_3SO_3H	93
2	HNO_3	92	5	HAc	24
3	CF_3COOH	93	6	PNBA	4

3. CONCLUSIONS

In conclusion, we have presented a greener, safer, more efficient and environmentally friendly procedure for the acetalization/ketalization of aldehydes and ketones. Most of the catalyst problems for acetalization/ketalization have been overcome, and these are the important points: (1) The main advantage of this process is the use of very low catalyst loadings (0.1 mol %), and the acid loadings varying from 0.03 to 30 mol % have marginal effect on the catalytic activity and conversion; (2) The acetalization/ketalization protocol is insensitive to water, and there is no need to remove water by additional physical and chemical means; (3) The acetalization/ketalization process is relatively insensitive to temperature. (4) The reaction scope is much broader than previous reports. Whether aldehydes (such as *α*,*β*-unsaturated aldehydes, aryl aldehydes, and aliphatic

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aldehydes) or ketones (such as aromatic ketones, cyclic ketones, conjugated enones, and aliphatic ketones) or even the diols (such as 1,2-diols and 1,3-diols), excellent results were generally obtained. (5) The acetalization/ketalization protocol is compatible with acid-sensitive substrates, such as N-Boc-protected amines, silyl-protected alcohols, and alkenes; (6) The reaction was proven effectively and conveniently to prepare the acetals on a gram scale (>5 g) with slightly inferior conversion; (7) The work-up procedure is remarkably simple, and the products do not require further purification in most cases; (8) The strong inorganic acids, as well as the strong organic acids, also exhibited high catalytic activity for the acetalization; (9) The acetalization/ketalization protocol has been successfully applied to construct heterocyclic compounds and protect the complex organic molecules. The broad reaction scope and remarkable versatility will enable us to tackle a broad spectrum of aldehydes/ketones/diols for the production of acetals/ketals with satisfied results. These new and important findings will have a promising prospective in industrial applications because of its considerably low catalyst loading, cost effectiveness, ease of handling, environmental friendliness, high conversions, and compatibility with acid-sensitive substrates. We anticipate that this protocol would arouse more interest in the chemistry of acetalization/ketalization and their further applications.

4. EXPERIMENTAL SECTION

4.1. General Methods. Nuclear magnetic resonance (NMR) spectra were recorded with tetramethylsilane as the internal standard. Thin-layer chromatography was performed on glass-backed silica plates. Column chromatography was performed using silica gel (150−200 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 600 MHz, and ^{13}C NMR spectra were recorded at 150 MHz. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) or dimethyl sulfoxide (DMSO) (δ = 2.50 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) or DMSO resonance (δ = 39.5 ppm) for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were measured with an ion trap mass spectrometer.

4.1.1. General Procedure for the Acetalization. A mixture of aldehyde **1** (0.3 mmol) and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 30 min. Then 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.1.1. (E)-(3,3-Dimethoxyprop-1-en-1-yl)benzene (**2a**).* 50 mg, 93% yield, colorless oily liquid. The NMR spectra of **2a** were consistent with those previously reported.[5] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.42−7.39 (m, 2H), 7.32 (m, 2H), 7.28−7.24 (m, 1H), 6.72 (d, J = 16.2 Hz, 1H), 6.16 (dd, J = 16.2, 4.9 Hz, 1H), 4.96 (dd, J = 4.9, 1.2 Hz, 1H), 3.38 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.1, 133.6, 128.6, 128.6, 128.2, 126.8, 126.8, 125.7, 103.0, 52.8, 52.8.

*4.1.1.2. (E)-1-Bromo-4-(3,3-dimethoxyprop-1-en-1-yl)-benzene (**2b**).* 69 mg, 90% yield, colorless oily liquid. The NMR spectra of **2b** were consistent with those previously reported.[5] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46−7.43 (m, 2H), 7.28−7.25 (m, 2H), 6.66 (d, J = 16.2 Hz, 1H), 6.14 (dd, J = 16.2, 4.8 Hz, 1H), 4.95 (dd, J = 4.8, 1.2 Hz, 1H), 3.37 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 135.1, 132.4, 132.4, 131.8, 129.8, 128.3, 126.6, 122.0, 102.7, 52.8, 52.8. ESI-HRMS: calcd for $C_{11}H_{13}BrO_2$ + H, 257.0177; found, 257.0182.

*4.1.1.3. (E)-1-(3,3-Dimethoxyprop-1-en-1-yl)-4-methoxy-benzene (**2c**).*[12] 52 mg, 83% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35 (m, 2H), 6.86 (m, 2H), 6.66 (d, J = 16.1 Hz, 1H), 6.02 (dd, J = 16.1, 5.0 Hz, 1H), 4.93 (dd, J = 5.0, 1.1 Hz, 1H), 3.80 (s, 3H), 3.37 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 159.6, 133.1, 128.9, 128.0, 128.0, 123.4, 114.0, 114.0, 103.3, 55.3, 52.8, 52.8.

*4.1.1.4. (E)-1-Chloro-2-(3,3-dimethoxyprop-1-en-1-yl)-benzene (**2d**).* 60 mg, 94% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.54 (m, 1H), 7.37−7.35 (m, 1H), 7.25−7.18 (m, 2H), 7.11 (d, J = 16.1 Hz, 1H), 6.13 (dd, J = 16.1, 5.0 Hz, 1H), 4.98 (d, J = 4.9 Hz, 1H), 3.40 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 134.4, 133.5, 129.9, 129.8, 129.1, 128.5, 127.1, 126.9, 102.9, 52.9, 52.9. ESI-HRMS: calcd for $C_{11}H_{13}ClO_2$ + H, 213.0682; found, 213.0689.

*4.1.1.5. (E)-1-Bromo-2-(3,3-dimethoxyprop-1-en-1-yl)-benzene (**2e**).* 72 mg, 94% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.54 (m, 2H), 7.29−7.25 (m, 1H), 7.14−7.10 (m, 1H), 7.07 (d, J = 16.0 Hz, 1H), 6.09 (dd, J = 16.1, 5.0 Hz, 1H), 4.97 (dd, J = 5.0, 1.2 Hz, 1H), 3.40 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.2, 133.0, 132.5, 129.4, 128.7, 127.6, 127.3, 124.0, 102.8, 52.9, 52.9. ESI-HRMS: calcd for $C_{11}H_{13}BrO_2$ + H, 257.0177; found, 257.0190.

*4.1.1.6. (E)-1,1-Dimethoxyhex-2-ene (**2f**).* 39 mg, 90% yield, colorless oily liquid. The NMR spectra of **2f** were consistent with those previously reported.[57] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.83 (m, 1H), 5.46 (m, 1H), 4.73 (d, J = 5.4 Hz, 1H), 3.32 (s, 6H), 2.09−2.04 (m, 2H), 1.48−1.40 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 135.6, 126.5, 103.5, 52.6, 52.6, 34.2, 22.0, 13.7.

*4.1.1.7. (Dimethoxymethyl)benzene (**2g**).* 42 mg, 93% yield, colorless oily liquid. The NMR spectra of **2g** were consistent with those previously reported.[12,34] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.45 (m, 2H), 7.37 (m, 2H), 7.34−7.30 (m, 1H), 5.39 (s, 1H), 3.33 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.1, 128.5, 128.5, 128.2, 126.7, 126.7, 103.2, 52.7, 52.7.

*4.1.1.8. 1-(Dimethoxymethyl)-4-methoxybenzene (**2h**).* 54 mg, 99% yield, colorless oily liquid. The NMR spectra of **2h** were consistent with those previously reported.[22,34] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37 (m, 2H), 6.89 (m, 2H), 5.35 (s, 1H), 3.81 (s, 3H), 3.31 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 159.7, 130.4, 128.0, 113.5, 103.1, 55.3, 52.6, 52.6.

*4.1.1.9. 1-(Dimethoxymethyl)-2-methoxybenzene (**2i**).* 51 mg, 97% yield, colorless oily liquid. The NMR spectra of **2i** were consistent with those previously reported.[58] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.52 (m, 1H), 7.30 (m 1H), 6.97 (m, 1H), 6.89 (m, 1H), 5.68 (s, 1H), 3.85 (s, 3H), 3.36 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 157.1, 129.7, 127.3, 126.0, 120.2, 110.6, 99.0, 55.6, 53.5, 53.5.

*4.1.1.10. 1-Chloro-4-(dimethoxymethyl)benzene (**2j**).* 55 mg, 99% yield, colorless oily liquid. The NMR spectra of **2j** were consistent with those previously reported.[12] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40−7.37 (m, 2H), 7.35−7.33 (m, 2H), 5.37 (s, 1H), 3.31 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 136.6, 134.3, 128.4, 128.4, 128.2, 128.2, 102.3, 52.6, 52.6.

*4.1.1.11. 1-Chloro-3-(dimethoxymethyl)benzene (**2k**).* 54 mg, 97% yield, colorless oily liquid. The NMR spectra of **2k** were consistent with those previously reported.[59] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48−7.45 (m, 1H), 7.34−7.31 (m, 1H), 7.31−7.28 (m, 2H), 5.36 (s, 1H), 3.32 (s, 6H). ^{13}C NMR (151

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MHz, $CDCl_3$) δ: 140.2, 134.3, 129.5, 128.6, 127.0, 124.9, 102.1, 52.6, 52.6.

*4.1.1.12. 1-Chloro-2-(dimethoxymethyl)benzene (**2l**).* 55 mg, 98% yield, colorless oily liquid. The NMR spectra of **2l** were consistent with those previously reported.[59] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.62 (m, 1H), 7.38−7.35 (m, 1H), 7.30−7.25 (m, 2H), 5.63 (s, 1H), 3.39 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 135.3, 133.2, 129.8, 129.6, 128.1, 126.6, 101.0, 53.8, 53.8.

*4.1.1.13. 2-(Dimethoxymethyl)furan (**2m**).* 41 mg, 97% yield, colorless oily liquid. The NMR spectra of **2m** were consistent with those previously reported.[12,34] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41 (dd, J = 1.7, 0.8 Hz, 1H), 6.42 (d, J = 3.3 Hz, 1H), 6.37 (dd, J = 3.2, 1.8 Hz, 1H), 5.44 (s, 1H), 3.35 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 150.9, 142.5, 110.1, 108.5, 98.0, 52.8, 52.8.

*4.1.1.14. 2-(Dimethoxymethyl)thiophene (**2n**).* 46 mg, 96% yield, colorless oily liquid. The NMR spectra of **2n** were consistent with those previously reported.[60] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 7.08 (dt, J = 3.5, 1.0 Hz, 1H), 7.01 (dd, J = 5.0, 3.5 Hz, 1H), 5.64 (d, J = 0.7 Hz, 1H), 3.37 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 141.5, 126.7, 125.7, 125.5, 100.1, 52.6, 52.6.

*4.1.1.15. 1,1-Dimethoxyheptane (**2o**).* 45 mg, 93% yield, colorless oily liquid. The NMR spectra of **2o** were consistent with those previously reported.[12] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.37 (t, J = 5.8 Hz, 1H), 3.32 (s, 6H), 1.63−1.56 (m, 2H), 1.35−1.26 (m, 8H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 104.6, 52.5, 52.5, 32.5, 31.8, 29.1, 24.6, 22.6, 14.0.

*4.1.1.16. 1,1-Dimethoxynonane (**2p**).* 54 mg, 95% yield, colorless oily liquid. The NMR spectra of **2p** were consistent with those previously reported.[6] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.36 (t, J = 5.8 Hz, 1H), 3.31 (s, 6H), 1.62−1.56 (m, 2H), 1.34−1.23 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 104.6, 52.6, 52.6, 32.5, 31.9, 29.5, 29.5, 29.2, 24.6, 22.7, 14.1.

*4.1.1.17. (Dimethoxymethyl)cyclohexane (**2q**).* 46 mg, 96% yield, colorless oily liquid. The NMR spectra of **2q** were consistent with those previously reported.[6] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.99 (d, J = 7.2 Hz, 1H), 3.33 (s, 6H), 1.75 (m, 4H), 1.67−1.56 (m, 2H), 1.26−1.17 (m, 2H), 1.17−1.11 (m, 1H), 0.99 (tt, J = 12.6, 6.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 108.5, 53.5, 53.5, 40.0, 28.0, 28.0, 26.4, 25.8, 25.8.

*4.1.1.18. 1,4-Bis(dimethoxymethyl)benzene (**2r**).* 61 mg, 90% yield, colorless oily liquid. The NMR spectra of **2r** were consistent with those previously reported.[6] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46 (s, 4H), 5.40 (s, 2H), 3.32 (s, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.3, 138.3, 126.6, 126.6, 126.6, 126.6, 102.9, 102.9, 52.7, 52.7, 52.7, 52.7.

*4.1.1.19. 2-Phenyl-1,3-dioxolane (**2s**).* 44 mg, 97% yield, colorless oily liquid. The NMR spectra of **2s** were consistent with those previously reported.[12] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.54−7.50 (m, 2H), 7.44−7.39 (m, 3H), 5.85 (s, 1H), 4.17 (dd, J = 8.7, 5.1 Hz, 2H), 4.07 (dd, J = 8.7, 5.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 137.9, 129.2, 128.4, 128.4, 126.5, 126.5, 103.8, 65.3, 65.3.

*4.1.1.20. 2-Octyl-1,3-dioxolane (**2t**).* 53 mg, 95% yield, colorless oily liquid. The NMR spectra of **2t** were consistent with those previously reported.[12] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.83 (t, J = 4.9 Hz, 1H), 3.98−3.93 (m, 2H), 3.86−3.82 (m, 2H), 1.67−1.62 (m, 2H), 1.41 (m, 2H), 1.29 (m, 12H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 104.7, 64.8, 64.8, 33.9, 31.9, 29.6, 29.5, 29.2, 24.1, 22.7, 14.1.

*4.1.1.21. (Diethoxymethyl)benzene (**2u**).* 53 mg, 98% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48 (d, J = 7.8 Hz, 2H), 7.36 (dd, J = 11.3, 4.2 Hz, 2H), 7.33−7.29 (m, 1H), 5.51 (s, 1H), 3.62 (ddt, J = 8.0, 7.1, 4.0 Hz, 2H), 3.57−3.51 (m, 2H), 1.24 (td, J = 7.0, 1.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 139.1, 128.3, 128.2, 128.2, 126.7, 126.7, 101.6, 61.0, 61.0, 15.2, 15.2.

*4.1.1.22. (Dipropoxymethyl)benzene (**2v**).* 62 mg, 99% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.51 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.36−7.32 (m, 1H), 5.55 (s, 1H), 3.54 (dt, J = 9.3, 6.7 Hz, 2H), 3.46 (dt, J = 9.3, 6.7 Hz, 2H), 1.70−1.64 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 139.1, 128.2, 128.1, 128.1, 126.7, 126.7, 101.5, 67.1, 67.1, 23.0, 23.0, 10.8, 10.8.

*4.1.1.23. 2-Phenyl-1,3-dioxane (**2w**).* 48 mg, 97% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48 (dd, J = 8.1, 1.2 Hz, 2H), 7.38−7.31 (m, 3H), 5.50 (s, 1H), 4.29−4.24 (m, 2H), 4.02−3.96 (m, 2H), 2.23 (dtt, J = 13.4, 12.5, 5.0 Hz, 1H), 1.44 (dtt, J = 13.5, 2.6, 1.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.7, 128.9, 128.3, 128.3, 126.0, 126.0, 101.7, 67.4, 61.9, 25.8.

4.1.2. General Procedure for the Ketalization. A mixture of ketone **3** (0.3 mmol), 1.2 equiv of TMOF, and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 12 h. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.2.1. (1,1-Dimethoxyethyl)benzene (**4a**).* 49 mg, 99% yield, colorless oily liquid. The NMR spectra of **4a** were consistent with those previously reported.[8] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49 (m, 2H), 7.36−7.31 (m, 2H), 7.28−7.24 (m, 1H), 3.18 (s, 6H), 1.53 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 142.9, 128.1, 128.1, 127.5, 126.3, 126.3, 101.7, 48.9, 48.9, 26.1.

*4.1.2.2. 1-(1,1-Dimethoxyethyl)-4-fluorobenzene (**4b**).* 55 mg, 99% yield, colorless oily liquid. The NMR spectra of **4b** were consistent with those previously reported.[61] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49−7.44 (m, 2H), 7.02 (m, 2H), 3.17 (s, 6H), 1.52 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 163.06 (s), 161.43 (s), 128.1, 128.0, 114.9, 114.7, 101.4, 48.9, 48.9, 26.1.

*4.1.2.3. 1-Bromo-4-(1,1-dimethoxyethyl)benzene (**4c**).* 72 mg, 98% yield, colorless oily liquid. The NMR spectra of **4c** were consistent with those previously reported.[61] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48−7.45 (m, 2H), 7.39−7.35 (m, 2H), 3.16 (s, 6H), 1.50 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 142.0, 131.2, 131.2, 128.2, 128.2, 121.7, 101.3, 49.0, 49.0, 26.0.

*4.1.2.4. 1-Chloro-4-(1,1-dimethoxyethyl)benzene (**4d**).* 58 mg, 96% yield, colorless oily liquid. The NMR spectra of **4d** were consistent with those previously reported.[62] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46−7.41 (m, 2H), 7.34−7.29 (m, 2H), 3.17 (s, 6H), 1.51 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 141.5, 133.4, 128.2, 128.2, 127.8, 127.8, 101.3, 49.0, 49.0, 26.0.

*4.1.2.5. 1-(1,1-Dimethoxyethyl)-4-methylbenzene (**4e**).* 49 mg, 91% yield, colorless oily liquid. The NMR spectra of **4e** were consistent with those previously reported.[61] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40−7.35 (m, 2H), 7.15 (m, 2H), 3.17 (s, 6H), 2.34 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (151 MHz,

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$CDCl_3$) δ: 140.0, 137.2, 128.8, 128.8, 126.2, 126.2, 101.7, 48.9, 48.9, 26.2, 21.1.

*4.1.2.6. (1,1-Dimethoxypropyl)benzene (**4f**).* 52 mg, 97% yield, colorless oily liquid. The NMR spectra of **4f** were consistent with those previously reported.[62] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.49 (m, 2H), 7.40−7.36 (m, 2H), 7.33−7.29 (m, 1H), 3.19 (s, 6H), 1.95 (q, J = 7.5 Hz, 2H), 0.62 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 140.7, 128.6, 128.0, 127.8, 127.5, 127.1, 104.2, 48.6, 48.6, 29.9, 7.7.

*4.1.2.7. 1-(1,1-Dimethoxypropyl)-4-methylbenzene (**4g**).* 54 mg, 92% yield, colorless oily liquid. The NMR spectra of **4g** were consistent with those previously reported.[62] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33 (m, 2H), 7.15 (m, 2H), 3.15 (d, J = 5.9 Hz, 6H), 2.35 (s, 3H), 1.89 (q, J = 7.5 Hz, 2H), 0.59 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 137.7, 137.1, 128.6, 128.6, 127.0, 127.0, 104.2, 48.5, 48.5, 29.9, 21.1, 7.8.

*4.1.2.8. 1-(1,1-Dimethoxypropyl)-4-fluorobenzene (**4h**).* 59 mg, 99% yield, colorless oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.47−7.42 (m, 2H), 7.04 (m, 2H), 3.16 (s, 6H), 1.91 (q, J = 7.5 Hz, 2H), 0.60 (t, J = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 163.1, 161.4, 136.5, 128.8, 114.7, 114.6, 103.9, 48.5, 48.5, 29.9, 7.7. ESI-HRMS: calcd for $C_{11}H_{15}FO_2$ + H, 199.1134; found, 199.1141.

*4.1.2.9. 1,1-Dimethoxycyclohexane (**4i**).* 40 mg, 93% yield, colorless oily liquid. The NMR spectra of **4i** were consistent with those previously reported.[13,28] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.18 (s, 6H), 1.67−1.60 (m, 4H), 1.50 (dt, J = 11.9, 6.0 Hz, 4H), 1.40 (dd, J = 11.3, 5.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 100.0, 47.3, 47.3, 32.7, 32.7, 25.6, 22.8, 22.8.

*4.1.2.10. 1,1-Dimethoxycyclopentane (**4j**).* 37 mg, 95% yield, colorless oily liquid. The NMR spectra of **4j** were consistent with those previously reported.[22,28] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.21 (s, 6H), 1.79−1.74 (m, 4H), 1.67−1.64 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 112.2, 49.3, 49.3, 34.2, 34.2, 23.2, 23.2.

*4.1.2.11. 1,4-Dioxaspiro[4.4]nonane (**4j′**).* 36 mg, 94% yield, colorless oily liquid. The NMR spectra of **4j′** were consistent with those previously reported.[19] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.90 (s, 4H), 1.81−1.75 (m, 4H), 1.72−1.66 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 118.5, 64.2, 64.2, 35.9, 35.9, 23.5, 23.5.

*4.1.2.12. 3,3-Dimethoxypentane (**4k**).* 37 mg, 94% yield, colorless oily liquid. The NMR spectra of **4k** were consistent with those previously reported.[61] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.16 (s, 6H), 1.60 (q, J = 7.5 Hz, 4H), 0.82 (t, J = 7.5 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 104.1, 47.6, 47.6, 24.2, 24.2, 7.9, 7.9.

*4.1.2.13. 2,2-Diethyl-1,3-dioxolane (**4k′**).* 37 mg, 94% yield, colorless oily liquid. The NMR spectra of **4k′** were consistent with those previously reported.[63] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.94 (s, 4H), 1.63 (q, J = 7.5 Hz, 4H), 0.90 (t, J = 7.5 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 112.3, 65.0, 65.0, 29.4, 29.4, 8.0, 8.0.

*4.1.2.14. (E)-2-Methyl-2-styryl-1,3-dioxolane (**4l**).* 54 mg, 95% yield, colorless oily liquid. The NMR spectra of **4l** were consistent with those previously reported.[61] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39 (m, 2H), 7.31 (m, 2H), 7.26−7.22 (m, 1H), 6.70 (d, J = 16.0 Hz, 1H), 6.15 (d, J = 16.0 Hz, 1H), 4.02−3.91 (m, 4H), 1.56 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 129.8, 129.7, 129.7, 128.6, 128.6, 127.9, 126.8, 126.8, 107.7, 64.7, 64.7, 25.3.

*4.1.2.15. (E)-2-(4-Chlorostyryl)-2-methyl-1,3-dioxolane (**4m**).* 65 mg, 96% yield, colorless oily liquid. The NMR spectra of **4m** were consistent with those previously reported.[64] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.33−7.30 (m, 2H), 7.29−7.26 (m, 2H), 6.65 (d, J = 16.0 Hz, 1H), 6.13 (d, J = 16.0 Hz, 1H), 4.03−3.98 (m, 2H), 3.97−3.92 (m, 2H), 1.55 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 134.7, 133.5, 130.5, 128.8, 128.8, 128.5, 128.0, 128.0, 107.5, 64.7, 64.7, 25.2.

4.1.3. General Procedure for the Ketalization of Acetone with Diols. A mixture of diol **5** (0.3 mmol), acetone (4 mL), and 0.1 mol % hydrochloric acid was stirred at an ambient temperature for 24 h. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.3.1. 2,2,5,5-Tetramethyl-1,3-dioxane (**6a**).* 39 mg, 91% yield, colorless oily liquid. The NMR spectra of **6a** were consistent with those previously reported.[13] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.50 (s, 4H), 1.42 (s, 6H), 0.96 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 97.6, 70.6, 70.6, 30.0, 23.8, 23.8, 22.5, 22.5.

*4.1.3.2. 4-Hexyl-2,2-dimethyl-1,3-dioxolane (**6b**).* 52 mg, 93% yield, colorless oily liquid. The NMR spectra of **6b** were consistent with those previously reported.[65] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.04−3.99 (m, 1H), 3.97−3.44 (m, 2H), 1.62−1.40 (m, 2H), 1.36 (m, 3H), 1.30 (s, 3H), 1.28−1.17 (m, 8H), 0.83 (t, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 108.5, 76.1, 69.4, 33.6, 31.7, 29.3, 26.9, 25.7, 25.7, 22.5, 14.0.

*4.1.3.3. (R)-4-(Chloromethyl)-2,2-dimethyl-1,3-dioxolane (**6c**).* 41 mg, 90% yield, colorless oily liquid. The NMR spectra of 6c were consistent with those previously reported.[65] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.31 (m, 1H), 4.12−3.88 (m, 2H), 3.58−3.47 (m, 2H), 1.46−1.43 (m, 3H), 1.36 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 110.1, 75.4, 67.5, 44.5, 26.9, 25.3.

*4.1.4. Synthesis of Tert-Butyl 4,4-Dimethoxypiperidine-1-carboxylate (**8a**).* A mixture of aldehyde **7a** (0.3 mmol), 1.2 equiv of TMOF, and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 30 min. Then 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.4.1. tert-Butyl 4,4-dimethoxypiperidine-1-carboxylate (**8a**).* 67 mg, 91% yield, colorless oily liquid. The NMR spectra of **8a** were consistent with those previously reported.[54] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.45−3.38 (m, 4H), 3.19 (s, 6H), 1.70 (s, 4H), 1.45 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 154.6, 98.4, 79.3, 47.4, 47.4, 32.2, 32.2, 32.2, 32.2, 28.3, 28.3, 28.3.

*4.1.4.2. Synthesis of 2-(4-(Dimethoxymethyl)phenoxy)-tetrahydro-2H-pyran (**8b**).* A mixture of aldehyde **7b** (0.3 mmol), 1.2 equiv of TMOF, and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 30 min. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.4.3. 2-(4-(Dimethoxymethyl)phenoxy)tetrahydro-2H-pyran (**8b**).* 68 mg, 90% yield, colorless oily liquid. The NMR spectra of **8b** were consistent with those previously reported.[55] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35 (m, 2H), 7.07−7.01 (m, 2H), 5.42 (t, J = 3.2 Hz, 1H), 5.34 (s, 1H),

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3.89−3.56 (m, 2H), 3.30 (s, 6H), 2.04−1.56 (m, 2H), 1.87−1.83 (m, 2H), 1.71−1.62 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 157.2, 131.2, 127.8, 127.8, 116.0, 116.0, 103.0, 96.3, 62.0, 52.6, 52.6, 30.4, 25.2, 18.8.

4.1.5. A Mixture of Aldehyde ***7c****.* TMOF (0.3 mmol, 1.2 equiv) and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 30 min. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.5.1. tert-Butyl(4-(dimethoxymethyl)phenoxy)-dimethylsilane (****8c****).* 79 mg, 93% yield, colorless oily liquid. The NMR spectra of **8c** were consistent with those previously reported.[56] H NMR (600 MHz, $CDCl_3$) δ: 7.33 (m, 2H), 6.86 (m, 2H), 5.37 (s, 1H), 3.34 (s, 6H), 1.01 (s, 9H), 0.22 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 155.8, 130.9, 127.9, 127.9, 119.8, 119.8, 103.2, 52.7, 52.7, 25.7, 25.7, 25.7, 18.2, −4.4, −4.4.

*4.1.6. Synthesis of Ethyl 3,3-Dimethoxybutanoate (****8d****).* A mixture of aldehyde **7d** (0.3 mmol), 1.2 equiv of TMOF, and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at an ambient temperature for 30 min. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.6.1. Ethyl 3,3-Dimethoxybutanoate (****8d****).* 50 mg, 95% yield, colorless oily liquid. The NMR spectra of **8d** were consistent with those previously reported.[28] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.16 (q, J = 7.1 Hz, 2H), 3.23 (s, 6H), 2.66 (s, 2H), 1.47 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 169.6, 99.8, 60.5, 48.3, 48.3, 42.3, 21.8, 14.1.

*4.1.7. Synthesis of (1R,4R)-5-(Dimethoxymethyl)bicyclo-[2.2.1]hept-2-ene (****8e****).* A mixture of aldehyde **7e** (0.3 mmol) and 0.1 mol % hydrochloric acid in methanol (4 mL) was stirred at ambient temperature for 30 min. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.7.1. (1R,4R)-5-(Dimethoxymethyl)bicyclo[2.2.1]hept-2-ene (****8e****).* 48 mg, 96% yield, colorless oily liquid. The NMR spectra of **8e** were consistent with those previously reported.[50] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.17−6.13 (m, 1H), 6.09−5.97 (m, 1H), 4.20−3.76 (m, 1H), 3.36 (d, J = 17.5 Hz, 3H), 3.30 (d, J = 16.4 Hz, 3H), 2.90−2.77 (m, 2H), 2.42−1.83 (m, 1H), 1.71−0.80 (m, 1H), 1.42 (m, 1H), 1.33 (s, 1H), 1.28 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 137.6, 136.4, 107.9, 52.9, 52.9, 49.4, 43.9, 42.2, 41.3, 28.6.

4.1.8. Synthesis of ***8f****.* A mixture of D-glucose **7f** (3 mmol) and 0.5 mol % hydrochloric acid in methanol (40 mL) was stirred at 60 °C for 72 h, after which 1.0 mol % $NaHCO_3$ was added, and the solution was stirred for 20 min. The solution was filtered and then concentrated in vacuo. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using CH_2Cl_2−MeOH (7:1) in 1% triethylamine to obtain the product as a white solid. The NMR spectra of **8f** were consistent with those previously reported.[50]

53 mg, 91% yield, colorless oily liquid. ^{1}H NMR (400 MHz, D_2O) δ: 4.69 (d, J = 27.4 Hz, 5H), 3.80 (d, J = 16.9 Hz, 2H), 3.65 (d, J = 7.8 Hz, 2H), 3.57−3.44 (m, 2H), 3.30 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ: 100.7, 72.4, 70.4, 69.7, 66.6, 60.8, 54.5.

*4.1.9. Synthesis of 2-(3-Benzyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetaldehydes (****10****).* A mixture of *o*-isothiocyanato-(*E*)-cinnamaldehyde **9** (0.3 mmol) and benzylamine (0.36 mmol) was stirred in methanol (2.0 mL) at room temperature for 5 min; then, flash chromatography on silica gel (25% ethyl acetate/petroleum ether) gave **10** as a white solid.

*4.1.9.1. 2-(3-Benzyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetaldehyde (****10a****).* 81 mg, 91% yield, white solid, mp 66−69 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.59 (s, 1H), 9.31 (s, 1H), 7.36 (m, 2H), 7.30 (m, 3H), 7.24−7.19 (m, 1H), 7.01 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 15.2 Hz, 1H), 5.08 (dd, J = 8.2, 4.0 Hz, 1H), 4.70 (d, J = 15.2 Hz, 1H), 2.93 (dd, J = 17.8, 8.2 Hz, 1H), 2.78 (dd, J = 17.8, 3.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.5, 177.8, 135.8, 134.2, 129.1, 128.9, 128.9, 128.1, 127.9, 127.9, 125.7, 124.1, 121.3, 113.8, 55.2, 53.2, 48.3. ESI-HRMS: calcd for $C_{17}H_{16}N_2OS$ + H, 297.1058; found, 297.1054.

*4.1.9.2. 2-(3-Benzyl-6-bromo-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetaldehyde (****10b****).* 101 mg, 91% yield, white solid, mp 77−80 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.61 (s, 1H), 9.27 (s, 1H), 7.37−7.29 (m, 6H), 7.18 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 5.88 (d, J = 15.1 Hz, 1H), 5.05 (dd, J = 8.1, 4.0 Hz, 1H), 4.67 (d, J = 15.1 Hz, 1H), 2.93 (dd, J = 18.2, 8.2 Hz, 1H), 2.80 (dd, J = 18.2, 4.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 198.0, 177.7, 135.6, 133.3, 132.1, 129.0, 129.0, 128.6, 128.3, 128.0, 123.2, 116.2, 115.4, 55.2, 52.5, 48.2, 29.7. ESI-HRMS: calcd for $C_{17}H_{15}BrN_2OS$ + H, 375.0161; found, 375.0155.

*4.1.10. Synthesis of (E)-1-(3,3-Dimethoxyprop-1-en-1-yl)-2-isothiocyanatobenzenes (****11****).* A mixture of *o*-isothiocyanato-(*E*)-cinnamaldehyde **9** (0.3 mmol) and 0.1 mol % hydrochloric acid in methanol (2 mL) was stirred at an ambient temperature for 20 min. Then, 0.15 mol % $NaHCO_3$ was added and stirred for a few minutes. After that, the organic layer was concentrated in vacuo, and column purification on silica gel was performed using hexane−ethyl acetate in 1% triethylamine to obtain the product and its isolated yield.

*4.1.10.1. (E)-1-(3,3-Dimethoxyprop-1-en-1-yl)-2-isothiocyanatobenzene (****11a****).* 67 mg, 95% yield, yellow oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.55−7.50 (m, 1H), 7.27−7.23 (m, 3H), 7.00−6.93 (m, 1H), 6.21 (dd, J = 16.1, 4.9 Hz, 1H), 4.98 (dd, J = 4.9, 1.2 Hz, 1H), 3.41 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 132.4, 129.4, 129.3, 129.0, 129.0, 128.0, 128.0, 127.4, 126.6, 102.8, 53.1, 53.1. ESI-HRMS: calcd. for $C_{12}H_{13}NO_2S$ + H, 236.0740; found, 236.0738.

*4.1.10.2. (E)-4-Bromo-2-(3,3-dimethoxyprop-1-en-1-yl)-1-isothiocyanatobenzene (****11b****).* 91 mg, 97% yield, yellow oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.64 (d, J = 2.2 Hz, 1H), 7.36 (dd, J = 8.5, 2.2 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 16.1 Hz, 1H), 6.20 (dd, J = 16.1, 4.7 Hz, 1H), 4.99 (dd, J = 4.7, 1.1 Hz, 1H), 3.40 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 138.2, 134.1, 131.9, 130.7, 129.5, 128.6, 126.8, 126.8, 121.0, 102.3, 53.0, 53.0. ESI-HRMS: calcd. for $C_{12}H_{12}BrNO_2S$ + H, 313.9845; found, 313.9845.

*4.1.11. Synthesis of (E)-N-Benzyl-4-(2-methoxyvinyl)-4H-Benzo[d][1,3]thiazin-2-amines (****12****).* The above compound **11** was dissolved in toluene (1 mL). The mixture was refluxed for

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2 h; then, flash chromatography on silica gel (25% ethyl acetate/petroleum ether) gave **12** as a white solid.

*4.1.11.1. (E)-N-Benzyl-4-(2-methoxyvinyl)-4H-benzo[d]-[1,3]thiazin-2-amine (**12a**).* 80 mg, 86% yield, yellow oily liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37−7.31 (m, 4H), 7.29−7.23 (m, 2H), 7.17 (dd, J = 7.8, 1.0 Hz, 1H), 7.14−7.11 (m, 1H), 7.05 (t, J = 7.4, 1.3 Hz, 1H), 6.37 (d, J = 12.6 Hz, 1H), 4.94 (dd, J = 12.6, 8.7 Hz, 1H), 4.73 (s, 2H), 4.62 (d, J = 8.7 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ: 150.1, 145.2, 138.6, 128.7, 128.7, 128.3, 128.3, 128.0, 128.0, 127.6, 127.6, 125.8, 125.0, 123.6, 101.8, 56.3, 46.5, 43.2. ESI-HRMS: calcd for $C_{18}H_{18}N_2OS$ + H, 311.1213; found, 311.1208. E/Z = 98:2.

*4.1.11.2. (E)-N-Benzyl-6-bromo-4-(2-methoxyvinyl)-4H-benzo[d][1,3]thiazin-2-amine (**12b**).* 93 mg, 80% yield, yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.31 (m, 5H), 7.30−7.23 (m, 2H), 7.03 (d, J = 8.4 Hz, 1H), 6.40 (d, J = 12.5 Hz, 1H), 4.88 (dd, J = 12.5, 8.9 Hz, 1H), 4.71 (s, 2H), 4.58 (d, J = 8.8 Hz, 1H), 3.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.7, 138.3, 131.2, 128.7, 128.7, 128.5, 128.5, 127.9, 127.9, 127.6, 127.6, 126.5, 125.6, 115.9, 100.8, 56.5, 46.5, 42.8. ESI-HRMS: calcd for $C_{18}H_{17}N_2OS$ + H, 389.0318; found, 389.0310. E/Z = 99:1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00159.

Scanned copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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