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Indium(III)trifluoromethanesulfonate as a mild, efficient catalyst for the formation of acetals and ketals in the presence of acid sensitive functional groups

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Abstract

Aldehydes and ketones, including acetophenone and benzophenone, are readily protected under mild, neutral conditions in the presence of various alcohols or orthoformates and catalytic amounts of indium(III) trifluoromethanesulfonate (<0.8 mol %) under either room temperature or mild heating conditions to give the corresponding cyclic and acyclic acetals and ketals in good to excellent yields. Acid sensitive functional groups, *N*-Boc, THP, and TBDMS do not undergo competitive deprotection under the reported conditions.

1. Introduction

The use of cyclic and acyclic acetals and ketals for the protection of aldehydes and ketones is well established in the literature. The selective protection and deprotection of functional groups plays an important role in many multistep synthetic strategies.[1] Traditional methods[1] for the formation of acetals and ketals involve condensation of an aldehyde or ketone with an alcohol or diol using acid catalysis with the concurrent removal of water. These conditions are incompatible with common protecting groups such as *N*-Boc protected amines or silyl protected alcohols. Examples of these include dry HCl in alcoholic solvent,[2] dry methanol, $(MeO)_3CH$, and *p*-TsOH,[3] or Amberlyst-15.[4] Recently, a number of mild reaction protocols have been developed and disclosed for the formation of acetals under neutral, or near neutral conditions. These include $LaCl_3$/$(MeO)_3CH$,[5] various clays,[6] $Sc(OTf)_3$/$(MeO)_3CH$,[7] $InCl_3$,[8] $CeCl_3$/$(MeO)_3CH$,[9] $Bi(OTf)_3$,[10] I_2,[11] $TiCl_4$/NEt_3,[12] Cu(II)BF_4/$(MeO)_3CH$,[13] decaborane,[14] $LiBF_4$/$(MeO)_3CH$,[15] and *N*,*N*′-bis[3,5-bis (trifluoromethyl)phenyl]thiourea.[16] Despite the large body of work in this area, these procedures suffer from one or more drawbacks, including limited substrate scope, uncommon reagents and/or catalysts and moderate product yields. In particular, general, mild methods to protect unreactive ketones in the presence of acid labile functionalities are lacking and would be highly desirable.

Indium(III) trifluoromethanesulfonate (indium triflate) has recently been shown to be a versatile reagent for organic synthesis.[17] Work by ourselves[18,19] and others[20] have established indium(III) salts as exceptionally useful and mild Lewis acid catalysts for a wide range of organic transformations. We have recently reported[19] the rapid indium triflate-catalyzed deprotection of acetals and ketals in acetone under mild, neutral conditions to give the corresponding carbonyl compounds in high yield. Of particular importance was the stability of several acid labile protecting groups, *N*-*tert*-butyl carbamate (Boc), THP, and TBDMS under the reaction conditions. The recent disclosure by Graham[21,22] that indium triflate can catalyze the formation of acetals and ketals prompts us to report on our work in this area. Considering the significant interest in Lewis acid catalyzed reactions over the last several years[23] and the stability of acid sensitive groups in the presence of indium triflate,[19] we set out to complete a comprehensive study of carbonyl compounds, which included these common

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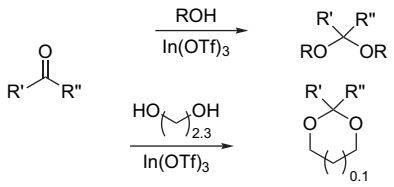
protecting groups. We herein report our findings utilizing indium triflate as an efficient Lewis acid catalyst for the acetalization/ketalization of carbonyl compounds including heretofore problematic substrates (Scheme 1).



Scheme 1.

2. Results and discussion

We herein report three effective protocols that facilitate the protection of carbonyl compounds as either their cyclic or acyclic acetals and ketals using methanol, ethanol or a variety of diols, and a catalytic amount of indium triflate. These methods are robust, straightforward, and scalable. There is no need for the use of anhydrous solvents or inert atmosphere. In general, there is no need for chromatographic purification. To demonstrate the practicality of this methodology, several reactions were conducted on multi-gram scale.

Reactive aldehydes (Table 1, entries 1–7) were rapidly converted under mild conditions to their corresponding acetals in high yield with either methanol or ethanol and less than 1 mol % of indium triflate. ^{1}H NMR analysis of the crude reaction mixtures generally showed quantitative conversion of starting aldehyde to the dialkyl acetal.

The acetalization of benzaldehyde **1** (Table 1, entries 1–3) reveals two issues that needed to be addressed; incomplete acetal formation and partial deacetalization during workup and isolation. We first set out to optimize conversion to the diethyl acetal. A maximum formation of **2a** (91%) was observed after 3 h at room temperature (Table 1, entry 1). Neither additional catalyst (2–5 mol %), increased reaction time (up to 8 h), nor increased reaction temperature (50 °C) led to an improvement in the yield of **2a**. Addition of triethyl orthoformate (TEOF, 1.0 equiv) to the reaction mixture resulted in complete conversion of **1** to **2a** (98%, Table 1, entry 2).

Having optimized the conversion of **1** to **2a**, we set out to reduce the deacetalization observed during isolation. While ^{1}H NMR analysis of the crude reaction mixture shows a 98% conversion of **1** to **2a**, upon concentration of the reaction mixture, only an 88% isolated yield was achieved (Table 1, entry 2). This degradation was directly attributed[24] to the presence of indium triflate in the reaction mixture. We reasoned that, if the indium could be sequestered prior to concentration, product decomposition would be minimized. Our extensive experience in parallel synthesis and purification led us to examine several potential acid scavenging resins (MP–Carbonate, PS–Trisamine, PS–Aminomethyl, and PVP resins) with PS–Trisamine being the most effective reagent for the removal of indium triflate and trace, unreacted aldehyde. This scavenging protocol resulted in the isolation of analytically pure acetal after removal of the resin by filtration and concentration of the reaction mixture under reduced pressure. To our knowledge, this represents the first example of PS–Trisamine being used as a scavenging resin for indium triflate from a reaction mixture. PS–Trisamine has the added benefit of being an aldehyde scavenger as well. Preparation and isolation of **2a** was increased from 79% to essentially quantitative yield (Table 1, entries 1–3) resulting from the addition of TEOF and PS–Trisamine resin. Due to the ease of use and increased purity of final compounds, PS–Trisamine resin was routinely used for the preparation of other acetals with excellent results (Table 1, entries 6 and 7).

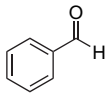
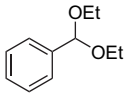
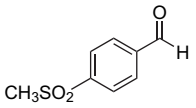
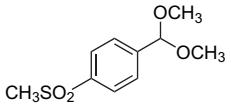
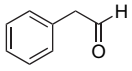
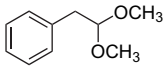
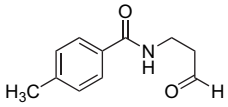
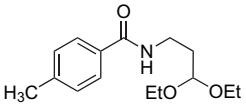
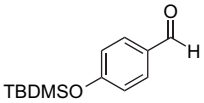
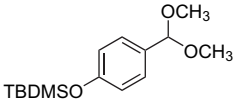
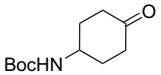
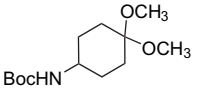
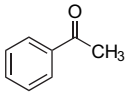
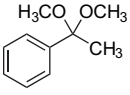
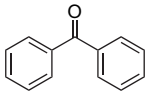
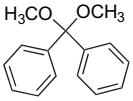
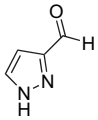
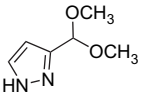
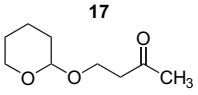
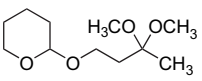
As expected, more vigorous reaction conditions were necessary to facilitate the acetalization of less reactive carbonyls, such as 1*H*-pyrazole-3-carboxaldehyde **17**, acetophenone **13**, and benzophenone **15**. Acetalization of **17** (Table 1, entry 13) was achieved by heating the reaction mixture at 50 °C for 12 h to give 3-(dimethoxymethyl)-1*H*-pyrazole **18** in high yield.[25] Acetophenone and benzophenone, when treated with methanol and indium triflate, either at room temperature or under microwave irradiation (140 °C for 20 min), did not result in significant ketal formation. Addition of trimethyl orthoformate (1.0 equiv) and the application of either microwave heating (140 °C, 10 min) or traditional heating (50 °C, 6 h) gave dimethyl ketals **14a** and **16a** in high yield (Table 1, entries 9–11). As was observed for **2a**, addition of PS–Trisamine resin was critical for the isolation of **14a** and **16a**, both of which underwent significant deacetalization in the absence of the acid scavenging procedure. These experimental protocols represent a significant advancement in the synthesis of cyclic ketals as compared to the work of Graham,[21] which resulted in only low (~30%) conversion of **13** to **14a** and made no mention of benzophenone as a substrate.

The formation of cyclic acetals and ketals was readily achieved by treating carbonyl compounds and indium triflate with a variety of diols in refluxing benzene with azeotropic removal of water (Table 2). Reactions were typically complete within 3–8 h. These cyclic acetals and ketals were isolated in high yield and purity after normal phase chromatography, without the need for acid scavenging. Of particular note are the excellent yields obtained for acetophenone and benzophenone (Table 2, entries 9–10).

An important requirement in many synthetic protocols is the chemoselective protection/deprotection of a variety of functional groups. The ability to selectively protect carbonyl moieties in the presence of other common protecting groups (Boc, TBDMS, THP, etc.) is highly desirable. We have previously reported the stability of the Boc, TBDMS, and THP groups to indium triflate-catalyzed deprotection of acetals and ketals in acetone.[19] Based on these results, we sought to expand the scope of substrates that have typically been employed for carbonyl protection to include these important protecting groups as well.

Our results clearly show that indium triflate is the reagent of choice when other protecting groups are present. The ubiquitous amine protecting group *N*-Boc is stable to our reaction

Table 1
Indium triflate-catalyzed acetalization and ketalization of carbonyl compounds

Entry	Substrate	Conditions[a]	Product[c]	Yield[d] (%)
1	 **1**	A 3 h	 **2a**	79 91[e]
2	**1**	B 3 h	**2a**	88 98[e]
3	**1**	C 3 h	**2a**	98
4	 **3**	A 3 h	 **4a**	94
5	 **5**	A 3 h	 **6**	84
6	 **7**	D 3 h	 **8**	98
7	 **9**	D 2 h	 **10a**	98
8	 **11**	D 2 h	 **12a**	97
9	 **13**	C 6 h, 50 °C	 **14a**	91
10	**13**	C[b] 10 min, 140 °C	**14a**	89
11	 **15**	C 6 h, 50 °C	 **16a**	97
12	**15**	C[b] 10 min, 140 °C	**16a**	94
13	 **17**	A 12 h, 50 °C	 **18**	82 99[e]
14	 **19**	B[f] 45 min	 **20**	97[e]

[a] All reactions conducted at room temperature with an indium triflate catalyst loading of 0.8 mol % unless otherwise noted. Conditions: (A) ROH; (B) ROH, trialkyl orthoformate (1.0 equiv); (C) ROH, trialkyl orthoformate (1.0 equiv), PS–Trisamine resin; (D) ROH, PS–Trisamine resin.
[b] Reaction conducted under microwave heating conditions.
[c] All products were characterized by mass, ^{1}H and ^{13}C NMR spectroscopies.
[d] Isolated yield unless otherwise noted.
[e] Yield determined by ^{1}H NMR analysis of crude reaction mixture before purification.
[f] Trimethyl orthoformate (2.0 equiv) added.

Table 2
Indium triflate-catalyzed formation of cyclic acetals and ketals

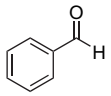
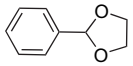
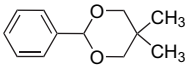
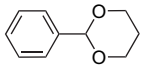
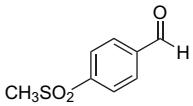
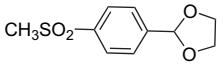
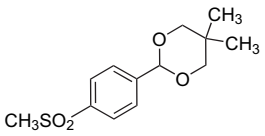
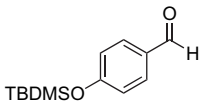
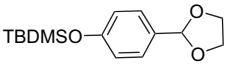
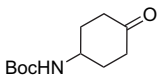
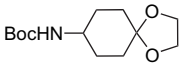
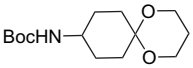
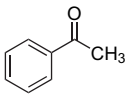
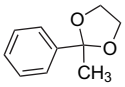
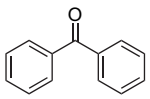
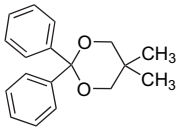
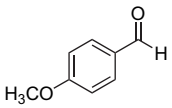
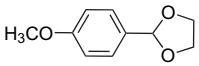
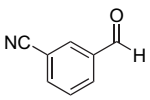
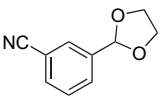
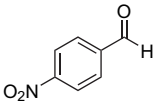
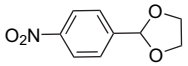
Entry	Substrate	Conditions[a]	Product[b]	Yield[c] (%)
1	 **1**	3 h, reflux	 **2b**	92
2	**1**	6 h, reflux	 **2c**	96
3	**1**	6 h, reflux	 **2d**	98
4	 **3**	6 h, reflux	 **4b**	89
5	**3**	8 h,reflux	 **4c**	89
6	 **9**	4 h, reflux	 **10b**	98
7	 **11**	3 h, reflux	 **12b**	91
8	**11**	3 h, reflux	 **12c**	99
9	 **13**	8 h, reflux	 **14b**	99
10	 **15**	8 h, reflux	 **16b**	98
11	 **21**	3 h, reflux	 **22**	85
12	 **23**	8 h, reflux	 **24**	95

Table 2 (*continued*)

Entry	Substrate	Conditions[a]	Product[b]	Yield[c] (%)
13	 **25**	3 h, reflux	 **26**	90

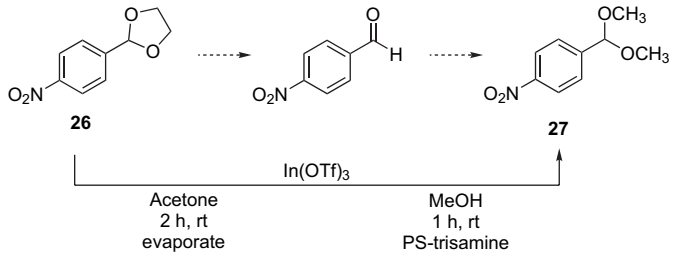
[a] All reactions were conducted in benzene at reflux with azeotropic removal of water and an indium triflate catalyst loading of 0.2 mol % unless otherwise noted.
[b] All products were characterized by mass, ^{1}H and ^{13}C NMR spectroscopies.
[c] Isolated yield.

conditions (Table 1, entry 8; Table 2, entries 7–8). No Boc deprotection is observed. Additionally, the common alcohol protecting groups TBDMS and THP ethers are stable (Table 1, entries 7, 14; Table 2, entry 6). Specifically, 4-(*tert*-butyldimethyl-silyloxy) benzaldehyde **9** was cleanly converted to both the dimethylacetal **10a** and 1,3-dioxolane **10b** in excellent yield. As a comparison, Sato and co-workers recently reported the $LiBF_4$ catalyzed conversion of **9** to **10a** in 92% yield.[15] In addition to a poorer yield, their method is not applicable to the formation of other acetals, such as **10b** (Table 2, entry 6). Other reported conditions for the formation of **10b** claim only 72% yield.[26]

Using the indium triflate methodology reported herein, *tert*-butyl-4-oxocyclohexyl carbamate **11** was converted to the corresponding dimethylketal **12a**, 1,3-dioxolane **12b**, and 1,3-dioxane **12c** analogs in high yield. To the best of our knowledge, this is the first report of the protection of this pharmacologically important building block. Under our reaction conditions, no loss of the Boc protecting group was observed.

Previously, it has been reported that the TBDMS and CO_2Et moieties are stable to $InCl_3$ catalyzed acetalization/ketalization;[8] however no mention was made of the Boc protecting group. In our hands, treatment of *tert*-butyl-4-oxocyclohexyl carbamate **11** with ethylene glycol and indium(III) chloride as reported led to an intractable reaction mixture. In addition to the desired product **12b** (~50% yield), unreacted starting material **11** (~20%), Boc-deprotected starting material (~15%), and Boc-deprotected-**12b** (~15%) were identified. Considering the importance of the Boc protecting group in organic synthesis, the procedures we report herein using indium triflate as the Lewis acid catalyst offers a significant advantage over previously reported methods.

The THP group has been previously reported[27] as unstable in the presence of methanol/water and $In(OTf)_3$ over 6–12 h. Under our reaction conditions, the THP group has proven to be stable (Table 1, entry 14). At room temperature the reaction of **19** cleanly proceeded to give **20** in excellent yield within 45 min. We ascribe our observed stability of the THP group to the anhydrous conditions utilized for the acetalization and the rapid rate of acetal formation.



Scheme 2.

Coupling the utility of indium triflate to catalyze both the protection and deprotection[19] of carbonyl compounds by simply changing the reaction solvent between methanol and acetone, we sought to illustrate the one-pot, two-step transacetalization of **26** to **27** (Scheme 2). Within 2 h at room temperature, 2-(4-nitrophenyl)-1,3-dioxolane **26** underwent complete deacetalization with catalytic indium triflate in acetone. Subsequent protection of the resulting aldehyde was achieved by removal of the acetone under reduced pressure and redissolving the reaction mixture in methanol without additional indium triflate. After 1 h, PS–Trisamine resin was added, the reaction mixture stirred for 0.5 h and filtered giving **27** (93%, two steps) without the need to isolate the intermediate aldehyde.

3. Conclusion

We have developed a highly effective indium triflate catalyst system for the formation of cyclic and acyclic acetals and ketals. Our indium triflate system has a number of distinct advantages over other catalyst systems. It is commercially available, inexpensive, non-toxic, air stable, and water stable. It is highly active (less than 1 mol % is required for rapid reaction) and easily removed with PS–Trisamine resin. No special precautions need to be taken with respect to experimental conditions. We routinely run these protections in reagent grade solvent, open to the atmosphere. Another advantage is the ease of catalyst removal with PS–Trisamine prior to product isolation, which facilitates increased, often quantitative, yields. Substrates possessing acid labile protecting groups (Boc, TBDMS, and THP) chemoselectively generate the corresponding acetal/ketal compounds while keeping the protecting groups intact additionally, our method is effective for the protection of unreactive hindered and aromatic ketones, such as acetophenones and benzophenones. The described methods can readily be scaled to multi-gram reactions. Many examples involving simple aldehydes and ketones proceed at room temperature. Less reactive substrates can be cleanly protected with the addition of trialkyl orthoformates and mild microwave or traditional heating. In our hands, chromatographic purification

of the products is seldom necessary. Many of these protection reactions need only to be concentrated to dryness prior to utilization directly in the next step of a synthetic sequence. Indium triflate is the reagent of choice for this protection protocol due to its commercial availability, low toxicity, low cost, high turn-over rate, and ease of handling.

4. Experimental section

4.1. General

All solvents and reagents were obtained from commercial sources and used without further purification. Reactions were monitored by LC–MS and were recorded on a single quadropole mass-spectrometer (AUC 254 nm and 210 nm) using a 5 μm C8(2) column (100×4.60 mm). Two mobile phases (A: 99.98% water, 0.02% TFA; B: 99.98% acetonitrile, 0.02% TFA) were used as a gradient 5% B to 95% B over 6.0 min and 5% B for 2.0 min with a flow rate of 2.0 mL/min. ^{1}H (300 MHz) and ^{13}C (125 MHz) NMR spectra were recorded in 5 mm tubes in $CDCl_3$ or CD_3OD. Chemical shifts are reported in δ units (ppm) downfield from TMS as an internal standard. All microwave-heated reaction mixtures were conducted in a Personal Chemistry, Emrys Creator microwave reactor fitted with an IR sensor for continuous monitoring of reaction temperature.

All known compounds were identified based on their reported ^{1}H and ^{13}C NMR spectroscopic data as compared to authentic samples. Identity was verified by comparison with authentic samples of commercially available material. The following commercially available reagents were either starting materials or used to identify reaction products: **1**, **2a**, **2b**, **2c**, **2d**, **3**, **4b**, **5**, **6**, **9**, **11**, **13**, **14a**, **15**, **16a**, **17**, **18**, **21**, **22**, **23**, **24**, **25**, **26**, **27**.

4.2. Typical procedure

4.2.1. General procedure for the protection of aldehydes and ketones with ROH and indium triflate—method A

To a 50 mL round-bottomed flask was added the carbonyl compound (2.0 mmol) in methanol or ethanol (30 mL) to which was added indium triflate (0.8 mol %). The reaction mixture was stirred at room temperature, monitored for completion by HPLC (AUC, 220 and 254 nm) and TLC analyses and concentrated to dryness under reduced pressure. The crude products were typically pure enough to be used without further purification. Alternatively, the crude reaction product was purified by column chromatography using silica gel (40 g) with hexanes/ethyl acetate (20:1–5:1 gradient) as the eluent system.

4.2.2. General procedure for the protection of aldehydes and ketones with ROH, $HC(OR)_3$, and indium triflate—method B

Prepared according to method A with the addition of trialkyl orthoformate (1.0 equiv) to the reaction mixture.

4.2.3. General procedure for the protection of aldehydes and ketones with ROH, $HC(OR)_3$, indium triflate, and PS–Trisamine—method C

To a 50 mL round-bottomed flask was added either aldehyde or ketone (2.0 mmol), trialkyl orthoformate (1.0 equiv), and alcohol (30 mL) to which was added indium triflate (0.8 mol %). The reaction mixture was stirred at room temperature, monitored for completion by both HPLC (AUC, 220 and 254 nm) and TLC analyses. PS–Trisamine resin (0.400 g) was added to the reaction mixture, stirred for 30 min, filtered and concentrated to dryness under vacuum. The crude products were typically pure enough to be used without further purification.

4.2.4. General procedure for the protection of aldehydes and ketones with ROH, indium triflate and PS–Trisamine—method D

Prepared according to method A. Upon reaction completion as determined by both HPLC (AUC, 220 and 254 nm) and TLC analyses, PS–Trisamine resin (0.400 g) was added to the reaction mixture, stirred for 30 min, filtered and concentrated to dryness under vacuum. The crude products were typically pure enough to be used without further purification.

4.2.5. General procedure for the microwave assisted protection of acetophenone and benzophenone with $HC(OR)_3$, indium triflate and PS–Trisamine

To a 30 mL glass microwave reactor vessel was added the appropriate ketone (2.0 mmol), methanol (20 mL), and trimethyl orthoformate (1.0 equiv) to which was added indium triflate (0.8 mol %) (alternatively, ethanol and triethyl orthoformate were used to generate the diethyl acetals and ketals). The vial was sealed with a Teflon-lined cap, heated to 140 °C for 10 min and the reaction progress was monitored by both HPLC (AUC, 220 and 254 nm) and TLC analyses. Upon completion of the reaction, the reaction mixture was cooled to room temperature, PS–Trisamine resin (0.400 g) was added to the reaction mixture, stirred for 30 min, filtered and concentrated to dryness under vacuum. The crude products were purified by column chromatography using silica gel (40 g) and hexanes/ethyl acetate (20:1–5:1 gradient) as the eluent system.

4.2.6. General procedure for the indium triflate-catalyzed formation of cyclic acetals and ketals

To a 50 mL round-bottomed flask fitted with a Dean–Stark trap was added either aldehyde or ketone (8.5 mmol), benzene (40 mL), and the appropriate diol (2.0 equiv) to which was added the indium triflate (0.2 mol %). Reactions were heated at reflux and monitored by both HPLC (AUC, 220 and 254 nm) and TLC analyses. Upon completion of the reaction, the reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The crude residue was purified by column chromatography using silica gel (40 g) with hexanes/ethyl acetate (20:1 to 5:1 gradient) as the eluent system.

4.3. Characterization data

4.3.1. (Diethoxymethyl)benzene (**2a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J=7.6 Hz, 2H), 7.41–7.30 (m, 3H), 5.51 (s, 1H), 3.69–3.48 (m, 4H), 1.24 (t, J=7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 129.7, 128.2, 126.6, 101.6, 61.0, 15.2.

4.3.2. 2-Phenyl-1,3-dioxolane (**2b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.41–7.35 (m, 3H), 5.82 (s, 1H), 4.18–4.08 (m, 2H), 4.07–3.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 129.1, 128.3, 126.4, 103.7, 65.3.

4.3.3. 5,5-Dimethyl-2-phenyl-1,3-dioxane (**2c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.48 (m, 2H), 7.41–7.30 (m, 3H), 5.40 (s, 1H), 3.78 (d, J=11.2 Hz, 2H), 3.66 (d, J=10.5 Hz, 2H), 1.30 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.9, 128.3, 126.2, 101.8, 77.7, 30.25, 23.1, 21.9.

4.3.4. 2-Phenyl-1,3-dioxane (**2d**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.40–7.29 (m, 3H), 5.51 (s, 1H), 4.31–4.23 (m, 2H), 4.05–3.94 (m, 2H), 2.32–2.14 (m, 1H), 1.49–1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.8, 128.3, 126.0, 101.7, 67.4, 25.8.

4.3.5. 1-(Dimethoxymethyl)-4-(methylsulfonyl)benzene (**4a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J=8.5 Hz, 2H), 7.67 (d, J=8.1 Hz, 2H), 5.46 (s, 1H), 3.34 (s, 6H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 140.6, 127.8, 127.3, 101.9, 52.8, 44.5; HREI-MS m/z: found 231.0698 ($C_{10}H_{14}O_4S$ requires 231.0691).

4.3.6. 2-(4-(Methylsulfonyl)phenyl)-1,3-dioxolane (**4b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J=8.5 Hz, 2H), 7.69 (d, J=8.2 Hz, 2H), 5.89 (s, 1H), 4.21–3.98 (m, 4H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 141.1, 127.54, 127.46, 102.5, 65.5, 44.5; HREI-MS m/z: found 229.0534 ($C_{10}H_{12}O_4S$ requires 229.0534).

4.3.7. 5,5-Dimethyl-2-(4-(methylsulfonyl)phenyl)-1,3-dioxane (**4c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, J=8.5 Hz, 2H), 7.73 (d, J=8.2 Hz, 2H), 5.46 (s, 1H), 3.80 (d, J=11.2 Hz, 2H), 3.67 (d, J=11.2 Hz, 2H), 3.02 (s, 3H), 1.28 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 140.8, 127.4, 127.3, 100.2, 77.7, 44.6, 30.3, 22.9, 21.8; HREI-MS m/z: found 271.1007 ($C_{13}H_{18}O_4S$ requires 271.1004).

4.3.8. (2,2-Dimethoxyethyl)benzene (**6**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 5H), 4.55 (t, J=5.6 Hz, 1H), 3.34 (s, 6H), 2.92 (d, J=5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 129.4, 128.3, 126.4, 105.4, 53.4, 39.7.

4.3.9. N-(3,3-Diethoxypropyl)-4-methylbenzamide (**8**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J=8.2 Hz, 2H), 7.22 (d, J=7.9 Hz, 2H), 6.98 (br s, 1H), 4.64 (t, J=5.0 Hz, 1H), 3.77–3.67 (m, 2H), 3.62–3.47 (m, 4H), 2.39 (s, 3H), 1.98–1.90 (m, 2H), 1.24 (t, J=7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 141.6, 131.9, 129.1, 126.8, 103.1, 62.2, 35.9, 32.8, 21.4, 15.4; HREI-MS m/z: found 266.1764 ($C_{15}H_{23}NO_3$ requires 266.1756).

4.3.10. tert-Butyl(4-(dimethoxymethyl)phenoxy)dimethylsilane (**10a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J=8.4 Hz, 2H), 6.64 (d, J=8.6 Hz, 2H), 5.15 (s, 1H), 3.12 (s, 6H), 0.79 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 130.6, 128.1, 127.9, 119.7, 115.0, 103.2, 52.6, 25.7, 18.2, −4.2.

4.3.11. (4-(1,3-Dioxolan-2-yl)phenoxy)(tert-butyl)dimethylsilane (**10b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.13 (m, 2H), 6.69–6.60 (m, 2H), 5.55 (s, 1H), 4.02–3.89 (m, 2H), 3.89–3.77 (m, 2H), 0.79 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 130.5, 127.8, 120.0, 103.8, 65.3, 25.7, 18.2, −4.4.

4.3.12. tert-Butyl-4,4-dimethoxycyclohexylcarbamate (**12a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (br s, 1H), 3.52 (br s, 1H), 3.18 (s, 3H), 3.15 (s, 3H), 1.89–1.35 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 99.1, 79.2, 48.5, 47.8, 47.4, 30.5, 29.1, 28.4; HREI-MS m/z: found 282.1688 ($C_{13}H_{24}NO4Na$ requires 282.1681).

4.3.13. tert-Butyl-1,4-dioxaspiro[4.5]decan-8-ylcarbamate (**12b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (br m, 1H), 3.93 (s, 4H), 3.51 (br m, 1H), 1.94 (m, 2H), 1.47–1.89 (m, 7H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 108.0, 79.2, 64.3, 64.2, 48.1, 33.1, 30.2, 28.4; HREI-MS m/z: found 257.1625 ($C_{13}H_{23}NO_4$ requires 257.1627).

4.3.14. tert-Butyl-1,5-dioxaspiro[5.5]undecan-9-ylcarbamate (**12c**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (br s, 1H), 3.98–3.80 (m, 4H), 3.51 (br s, 1H), 2.17 (d, J=8.7 Hz, 2H), 1.91–1.78 (m, 2H), 1.78–1.63 (m, 2H), 1.59–1.31 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 96.9, 79.2, 59.6, 59.2, 48.6, 30.9, 28.7, 28.4, 25.6; HREI-MS m/z: found 272.1859 ($C_{14}H_{25}NO_4$ requires 272.1862).

4.3.15. (1,1-Dimethoxyethyl)benzene (**14a**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.40–7.27 (m, 3H), 3.19 (s, 6H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 128.1, 127.5, 126.2, 101.7, 48.9, 26.1.

4.3.16. 2-Methyl-2-phenyl-1,3-dioxolane (**14b**)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.38–7.24 (m, 3H), 4.11–3.97 (m, 2H), 3.85–3.71 (m, 2H), 1.66

(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 128.2, 127.8, 125.3, 108.8, 64.4, 27.6; HREI-MS *m/z*: found 165.0922 ($C_{10}H_{12}O_2$ requires 165.0915).

*4.3.17. Dimethoxydiphenylmethane (**16a**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.47 (m, 4H), 7.35–7.17 (m, 6H), 3.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 127.9, 127.4, 126.9, 102.8, 49.3.

*4.3.18. 5,5-Dimethyl-2,2-diphenyl-1,3-dioxane (**16b**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.48 (m, 4H), 7.38–7.21 (m, 6H), 3.61 (s, 4H), 0.99 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 128.3, 127.8, 126.7, 100.9, 72.1, 30.2, 22.6; HREI-MS *m/z*: found 269.1545 ($C_{18}H_{20}O_2$ requires 269.1541).

*4.3.19. 3-(Dimethoxymethyl)-1H-pyrazole (**18**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.10 (br s, 1H), 7.59 (d, J=2.1 Hz, 1H), 6.36 (d, J=1.9 Hz, 1H), 5.60 (s, 1H), 3.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 132.1, 103.6, 98.9, 52.6; HREI-MS *m/z*: found 143.0821 ($C_6H_{10}N_2O_2$ requires 143.0820).

*4.3.20. 4-(Tetrahydro-2H-pyran-2-yloxy)butan-2-one (**19**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, J=3.5 Hz, 1H), 4.03–3.96 (m, 1H), 3.89–3.81 (m, 1H), 3.72–3.65 (m, 1H), 3.56–3.45 (m, 1H), 2.71 (t, J=6.3 Hz, 2H), 2.20 (s, 3H), 1.83–1.66 (m, 2H), 1.59–1.48 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 99.1, 62.7, 62.4, 43.7, 30.6, 30.5, 25.4, 19.5.

*4.3.21. 2-(3,3-Dimethoxybutoxy)tetrahydro-2H-pyran (**20**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (t, J=3.5 Hz, 1H), 3.88–3.79 (m, 1H), 3.64–3.56 (m, 2H), 3.54–3.46 (m, 1H), 3.34 (s, 6H), 1.87 (t, J=7.4 Hz, 2H), 1.82–1.65 (m, 2H), 1.58–1.47 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.9, 101.4, 63.2, 59.2, 50.7, 40.2, 31.7, 26.6, 21.9, 20.5.

*4.3.22. 2-(4-Methoxyphenyl)-1,3-dioxolane (**22**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J=8.5 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 5.76 (s, 1H), 4.16–4.07 (m, 2H), 4.07–3.98 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 130.0, 127.9, 113.8, 103.7, 65.2, 55.3; HREI-MS *m/z*: found 181.0859 ($C_{10}H_{12}O_3$ requires 181.0864).

*4.3.23. 3-(1,3-Dioxolan-2-yl)benzonitrile (**24**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73–7.64 (m, 2H), 7.49 (t, J=7.8 Hz, 1H), 5.83 (s, 1H), 4.16–4.09 (m, 2H), 4.08–4.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 132.7, 130.9, 130.2, 129.2, 118.6, 112.6, 102.3, 65.5; HREI-MS *m/z*: found 176.0707 ($C_{10}H_9NO_2$ requires 176.0711).

*4.3.24. 2-(4-Nitrophenyl)-1,3-dioxolane (**26**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J=8.8 Hz, 2H), 7.66 (d, J=8.5 Hz, 2H), 5.90 (s, 1H), 4.16–4.05 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 144.9, 127.4, 123.6, 102.3, 65.5; HREI-MS *m/z*: found 196.0609 ($C_9H_9NO_4$ requires 196.0610).

*4.3.25. 1-(Dimethoxymethyl)-4-nitrobenzene (**27**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J=8.8 Hz, 2H), 7.65 (d, J=8.3 Hz, 2H), 5.48 (s, 1H), 3.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 145.1, 127.8, 123.4, 101.6, 52.7.

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2a, methanol, 1% indium triflate, and PS–Trisamine resin (30 min), filtration and concentration to dryness showed no deacetalization product. Other resins investigated with poor results included PS–DIEA (diisopropylethyl amine), PS–pyridine and MP–carbonate.

25. ^{1}H NMR yield of crude reaction mixture indicates 98% conversion to **12**. Unlike other substrates that were subjected to deacetalization in the absence of PS–Trisamine scavenging at the conclusion of the reaction, the lower isolated yield of **12** (80%) was due to attempted isolation after silica gel purification.
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