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# A Simple and Versatile Method for the Synthesis of Acetals from Aldehydes and Ketones Using Bismuth Triflate

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Acetals are obtained in good yields by treatment of aldehydes and ketones with trialkyl orthoformate and the corresponding alcohol in the presence of 0.1 mol % $Bi(OTf)_3 \cdot 4H_2O$. A simple procedure for the formation of acetals of diaryl ketones has also been developed. The conversion of carbonyl compounds to the corresponding 1,3-dioxolane using ethylene glycol is also catalyzed by $Bi(OTf)_3 \cdot 4H_2O$ (1 mol %). Two methods, both of which avoid the use of benzene, have been developed.

## Introduction

Aldehydes and ketones are frequently protected as acetals in the course of a total synthesis.[1a−c] In addition, acetals can be converted to a variety of other useful functional groups and hence serve as useful intermediates in synthesis.[1d,e] Thus, conversions of carbonyl compounds to the corresponding acyclic and cyclic acetals (1,3-dioxolanes) are important synthetic transformations that have received much attention. Acetalization is typically carried out by treatment of the carbonyl compound with the alcohol and/or the corresponding orthoformate in the presence of an acid catalyst. Some methods for the formation of dimethyl acetals include dry HCl in $CH_3OH$,[2] $LaCl_3/CH_3OH/(CH_3O)_3CH$,[3] DCC−$SnCl_4$,[4] $(CH_3)_3SiOCH_3/Me_3SiOTf$,[5] $(CH_3O)_3CH$/*p*-TsOH,[6] $CH_3OH/(CH_3O)_4Si$/dry HCl,[7] and $CH_3OH/PhSO_2NHOH$.[8] Fewer methods are known for the synthesis of diethyl acetals. These include $(CH_3CH_2O)_3CH$/HCl,[9] $(CH_3CH_2O)_3CH/FeCl_3$ in refluxing ethanol,[10] $(CH_3CH_2O)_3CH$/Amberlyst,[11] DDQ,[12] and $ZrCl_4$.[13] The formation of 1,3-dioxolanes (cyclic acetals) is usually carried out using ethylene glycol in the presence of an acid catalyst.[14] Several other methods that do not require protic acid catalysis have also been developed.[15] In addition, mild methods for the formation of acetals under almost neutral conditions have also been developed.[16] The synthesis of dialkyl acetals from diaryl ketones is more difficult, and the standard acetalization conditions generally do not work with diaryl ketones. Triflic acid (20 mol %) has been shown to be a useful catalyst for synthesis of diaryl ketones.[17] Many of the existing methods for acetalization suffer from certain drawbacks and often use reagents that are toxic and corrosive. For example, $TiCl_4$, $BF_3.Et_2O$, $CF_3SO_3H$, and TMSOTF are rather corrosive. In addition, few of these methods have broad applicability.

Due to our continued interest in the use of bismuth compounds as environmentally friendly reagents for organic synthesis, we undertook a study of the utility of bismuth triflate as a catalyst for acetal formation. Herein we report that bismuth triflate (0.1−1.0 mol %) is a versatile and robust catalyst for acetal formation. The highly catalytic nature of this reagent and its wide applicability should make this procedure an attractive alternative to existing methods for acetal formation.

† Both students contributed equally to the project.

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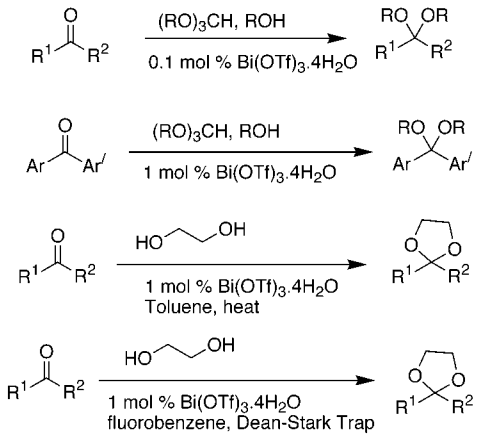
**SCHEME 1**




Bismuth compounds have attracted recent attention due to their low toxicity, low cost, and good shelf life.[18,19] We recently reported the use of bismuth triflate as a catalyst for rearrangement of epoxides to aldehydes and ketones,[20] formation of acylals,[21] and deprotection of acetals.[22] Bismuth triflate has also been used as a catalyst for Friedel−Crafts acylations,[23] sulfonylations,[24] Diels−Alder reactions,[25] and aza-Diels−Alder reactions.[26]

## Results and Discussion

Herein we report a mild and general procedure for the conversion of aldehydes and ketones to the corresponding acetals in good yields using bismuth triflate (0.1−1.0 mol %) as a catalyst (Scheme 1). The catalyst is very versatile and works well for the synthesis of dimethyl acetals, diethyl acetals as well as 1,3-dioxolanes from a variety of aldehydes and ketones.

Although bismuth triflate is not commercially available, it can be easily synthesized in large quantities at a relatively low cost.[27] A wide variety of aldehydes and ketones underwent smooth reaction to give the corresponding acetal in good yield (Table 1). The experimental procedure for synthesis of acetals is straightforward and involves heating the aldehyde or ketone as a solution in trialkylorthoformate (1.5 equiv) and the corresponding alcohol (8 equiv) in the presence of 0.1 mol % $Bi(OTf)_3 \cdot 4H_2O$. Smooth reaction was observed at room temperature but, not surprisingly, at a considerably slower rate. Unlike triflic acid or other air-sensitive Lewis acids such as $BF_3 \cdot Et_2O$ or $TiCl_4$, bismuth triflate is a relatively stable, easy to handle solid that is insensitive to small amounts of air and moisture. While acetal formation was observed in the presence of the catalyst and trialkylorthoformate alone, the addition of the alcohol accelerated the rate of the reaction. When the reaction was attempted using the catalyst and alcohol alone (no trialkylorthoformate), significant acetal formation was not observed. The addition of molecular sieves or a drying agent such as anhydrous magnesium sulfate did not accelerate the reaction significantly. Aromatic aldehydes with both activating and deactivating groups (entries 1−4), conjugated aldehydes (entries 5 and 6), and aliphatic aldehydes (entries 7 and 8) underwent smooth transformation to the corresponding acetal in good yield. In almost all cases, the crude product was found to be >98% pure (determined by GC and $^1H$ and $^{13}C$ NMR). Commercial citral (entry 6), available as a mixture of *E*/*Z* isomers, was subjected to the reaction conditions and, it was found that the double bond in citral did not undergo isomerization during acetal formation. This indicates that the reaction conditions are relatively mild and not sufficiently acidic to cause isomerization of the double bond. The conversion of ketones (entries 9−11) to the corresponding acetal was also successfully carried out. While a large number of methods exist for synthesis of dimethyl acetals, fewer methods are available for synthesis of diethyl acetals. One reported method that is catalytic in nature uses DDQ as the catalyst.[12] DDQ, however, is rather toxic and corrosive, and hence it is desirable to have safer alternatives. Using bismuth triflate as a catalyst (0.1 mol %), we were able to synthesize a variety of diethyl acetals (entries 12−16) in good yields. The best yields were obtained using 2.4 equiv of triethylorthoformate and 6.2 equiv of ethanol.

Diaryl ketones are quite resistant to the standard conditions for acetalization, and hence indirect routes to their preparation have been developed. For example, the dimethyl acetals of 4,4′-dichlorobenzophenone and 4,4′-dimethoxybenzophenone have been prepared by alkoxy−halogen exchange from the corresponding dihalodiarylmethanes.[28] To study the versatility of bismuth triflate, we extended our methodology to a series of benzophenones (Table 2). Gratifyingly, the corresponding acetals were obtained in excellent yields with only 1.0 mol % bismuth triflate. When the substituted benzophenones were insoluble in methanol/trimethyl orthoformate, nitromethane was used as a cosolvent. A wide variety of substituted benzophenones underwent smooth reaction to give both dimethyl and diethyl acetals. However, fluorenone (entry 7) failed to give the corresponding acetal. It has been reported that even with 20 mol % triflic acid as a catalyst, the acetalization of fluorenone was not successful.[17]

The standard method for synthesis of 1,3-dioxolanes consists of heating a mixture of the carbonyl compound

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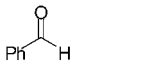
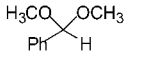
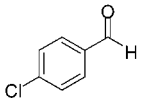
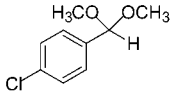
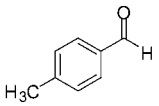
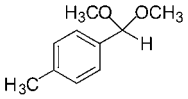
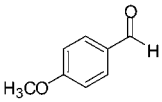
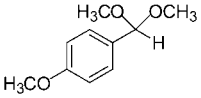
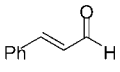
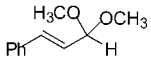
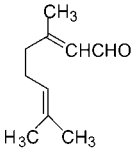
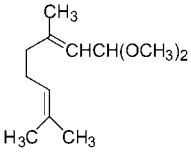
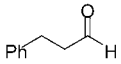
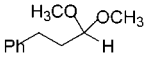
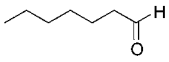
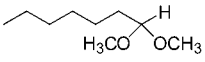
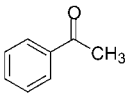
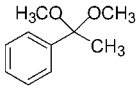
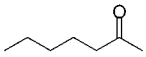
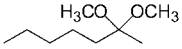
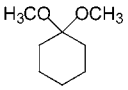
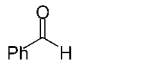
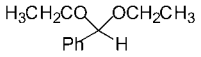
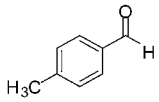
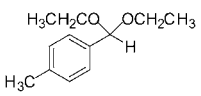
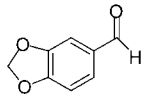
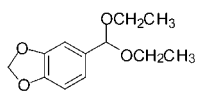
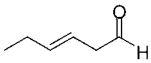
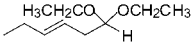
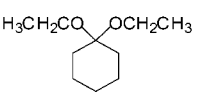
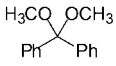
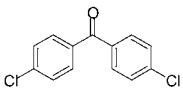
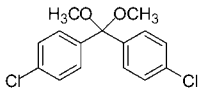
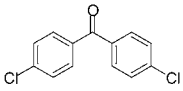
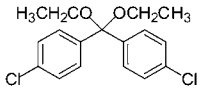
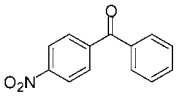
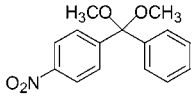
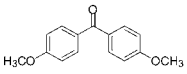
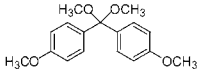
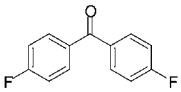
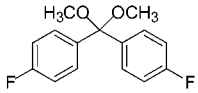
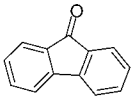
**TABLE 1. Formation of Acyclic Acetals from Aldehydes and Ketones Using $Bi(OTf)_3 \cdot 4H_2O$**

| Entry[a] | Substrate | Orthoformate and Alcohol | Time[b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|
| 1[30] |  | $(CH_3O)_3CH/CH_3OH$ | 1 h |  | 82[d] |
| 2[8] |  | $(CH_3O)_3CH/CH_3OH$ | 3 h |  | 90 |
| 3[8] |  | $(CH_3O)_3CH/CH_3OH$ | 2 h |  | 92 |
| 4[30] |  | $(CH_3O)_3CH/CH_3OH$ | 24 h |  | 68 |
| 5[30] |  | $(CH_3O)_3CH/CH_3OH$ | 2 h |  | 98 |
| 6[30] |  | $(CH_3O)_3CH/CH_3OH$ | 1 h, rt |  | 93[d] |
| 7 |  | $(CH_3O)_3CH/CH_3OH$ | 4 h |  | 85[e] |
| 8[30] |  | $(CH_3O)_3CH/CH_3OH$ | 2 h |  | 75[d, i] |
| 9 |  | $(CH_3O)_3CH/CH_3OH$ | 3 h |  | 94[f, d] |
| 10 |  | $(CH_3O)_3CH/CH_3OH$ | 2 h |  | 94[g] |
| 11[8] |  | $(CH_3O)_3CH/CH_3OH$ | 3.25 h, rt |  | 87[d, h] |
| 12[31] |  | $(CH_3CH_2O)_3CH$ $CH_3CH_2OH$ | 2 h |  | 92 |
| 13[12] |  | $(CH_3CH_2O)_3CH$ $CH_3CH_2OH$ | 2 h |  | 80[e] |
| 14[32] |  | $(CH_3CH_2O)_3CH$ $CH_3CH_2OH$ | 1.5 h |  | 76 |
| 15 |  | $(CH_3CH_2O)_3CH$ $CH_3CH_2OH$ | 17 h, rt |  | 77[h, d] |
| 16[12] |  | $(CH_3CH_2O)_3CH$ $CH_3CH_2OH$ | 2 h, rt |  | 73 |

[a] Superscripted numbers accompanying entry numbers refer to literature references for the product. [b] All reactions were carried out at reflux temperatures unless otherwise mentioned. [c] Refers to the yield of the isolated product. The crude product was estimated to be ≥98% pure unless otherwise mentioned. [d] Product is commercially available. [e] Purified by flash chromatography. [f] Contains 5% SM. [g] Contains 2% triethyl orthoformate. [h] Contains 5% triethyl orthoformate. [i] Purified by Kugelrohr distillation.

**TABLE 2. Formation of Acyclic Acetals from Diaryl Ketones Using $Bi(OTf)_3 \cdot 4H_2O$**

| Entry[a] | Substrate | Orthoformate and Alcohol | Time[b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|
| 1[17] |  | $(CH_3O)_3CH/CH_3OH$ | 24 h |  | 97 |
| 2[17] |  | $(CH_3O)_3CH/CH_3OH$ | 24 h |  | 95 |
| 3[17] |  | $(CH_3CH_2O)_3CH/$ $CH_3CH_2OH$ | 24 h |  | 98 |
| 4[d] |  | $(CH_3O)_3CH/CH_3OH$ , | 28 h |  | 83 |
| 5[17e] |  | $(CH_3O)_3CH/CH_3OH$ | 42 h |  | 80 |
| 6[17] |  | $(CH_3O)_3CH/CH_3OH$ | 24 h |  | 94 |
| 7 |  | $(CH_3O)_3CH/CH_3OH$ | 24 h | NR | |

[a] Superscripted numbers against entry numbers refer to literature references for the product. [b] All reactions were carried out at reflux temperature. [c] Refers to the yield of crude product unless otherwise mentioned. Purity of the crude product was estimated to be ≥98% by $^1H$ and $^{13}C$ NMR spectroscopy. [d] Nitromethane was used a cosolvent. [e] Purified by flash chromatography.

in ethylene glycol and removing the water as an azeotrope with benzene. This method is not particularly suitable for small-scale synthesis and also uses the carcinogenic solvent benzene. We have developed two practical methods for the synthesis of 1,3-dioxolanes (Table 3). In one method (method A), toluene is used as a solvent and 1.0 mol % $Bi(OTf)_3 \cdot 4H_2O$ serves as the catalyst. Under these conditions, at 110 °C, the reactions reached >95% conversion and the pure dioxolane was then isolated by flash chromatography. The advantage of this method is that no Dean−Stark trap is needed, making the procedure suitable for small-scale reactions. A search for a substitute for the highly toxic solvent benzene led to fluorobenzene (which, unlike benzene, is not classified as a carcinogen) as the solvent of choice for removal of the water formed as an azeotrope (method B). Again the reaction was catalyzed by as little as 1.0 mol % $Bi(OTf)_3 \cdot 4H_2O$. As in the synthesis of dialkyl acetals, the addition of molecular sieves did not increase the percent conversion or yield.

## Conclusions

Bismuth triflate (0.1−1.0 mol %) has been shown to be a versatile and robust catalyst for the synthesis of dimethyl and diethyl acetals as well as 1,3-dioxolanes from a wide variety of aldehydes and ketones. The procedure also works very well with diaryl ketones, which are often resistant to the standard acetalization conditions. The highly catalytic nature of this reagent coupled with its low cost, noncorrosive nature, ease of handling, and wide applicability should make this method for synthesis of acetals particularly attractive.

## Experimental Section

Methanol was dried over magnesium metal.[29] Fluorobenzene, trimethylorthoformate, and triethylorthoformate were

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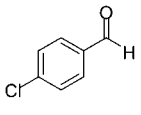
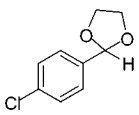
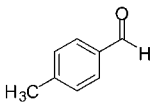
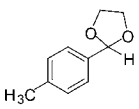
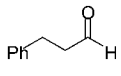
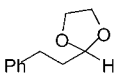
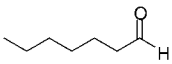
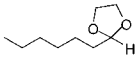
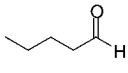
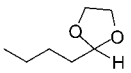
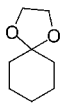
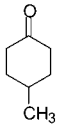
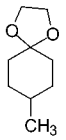
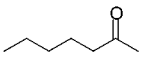
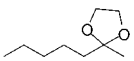
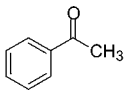
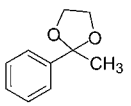
(30) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc. Chem. Commun.* **1978**, 976.
(31) Heywood, D. L.; Phillips, B. *J. Org. Chem.* **1960**, *25*, 1699.
(32) Yamato, M.; Hashigaki, K.; Kokubu, N.; Tashiro, T.; Tsuruo, T. *J. Med. Chem.* **1986**, 29, 1202.
(33) Reddy, B. M.; Reddy, V. R.; Giridhar, D. *Synth. Commun.* **2001**, *31*, 1819.
(34) Suzuki, T.; Oriyama, T. *Synth. Commun.* **1999**, *29*, 1263.
(35) Wang, W.-B.; Shi, L.-L.; Huang, Y.-Z. *Tetrahedron Lett.* **1990**, *46*, 3315.
(36) Carbera, A.; Vázquez, D.; Velasco, L.; Salmón, M.; Arias, J. L. *J. Mol. Catal.* **1992**, *75*, 101.
(37) Gihani, M. E.; Heaney, H. *Synlett* **1993**, 583.

**TABLE 3. Formation of 1,3-Dioxolanes from Aldehydes and Ketones**

| Entry[a] | Substrate | Product | Method | Time | % Conversion[b] | Yield[c] (%) |
|---|---|---|---|---|---|---|
| 1[f] |  |  | A[d] | 4 h | 93 | 71 |
| | | | B | 1.5 | 98 | 73 |
| 2[33] |  |  | A | 4.5 | 94 | 72 |
| | | | B | 5 | 99 | 76 |
| 3[34] |  |  | A | 9.5 | 82 | 50 |
| | | | B | 5 | 93 | 75 |
| 4[34] |  |  | B | 2 h | 96 | 68 |
| 5[35] |  |  | A[d] | 1 h | 90 | 56 |
| | | | B | 1h | 96 | 77 |
| 6[36] |  |  | B | 5 h | 90 | 69[e] |
| 7[f] |  |  | A | 4.5 | 87 | 70 |
| | | | B | 3.5 | 99 | 82 |
| 8[37] |  |  | B | 19 h | 98 | 70 |
| 9[38] |  |  | B | 13 h | 98 | 76 |
| 10[33] |  |  | B | 13.5 | 99.6 | 79 |

[a] Superscripted numbers against entry numbers refer to literature references for the product. [b] Determined by GC analysis of the reaction mixture. [c] Refers to the yield of pure (≥98%), isolated product after purification by flash chromatography. [d] Relative to the aldehyde, 2 equiv of 2,2-dimethoxypropane was added as a water scavenger. [e] Product was found to be ≥98% pure by $^1$H and $^{13}$C NMR. GC analysis, however, showed the product to be 90% pure. [f] Product is commercially available.

used as received. Ethylene glycol was dried over 4 Å sieves before use. Commercially available 200 proof ethanol was dried over anhydrous magnesium sulfate prior to use. Reactions were heated at the indicated temperature using a temperature-controlled oil bath.

**Representative Procedure for Synthesis of Dimethyl and Diethyl Acetals.** A solution of *p*-chlorobenzaldehyde (3.00 g, 21.3 mmol) and trimethylorthoformate (3.39 g, 31.95 mmol) in methanol (7.0 mL) was stirred as bismuth triflate (14.0 mg, 0.0213 mmol, 0.1 mol %) was added. The resulting mixture was heated at reflux for 3 h and then cooled to room temperature. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was stirred well and extracted with ether (2 × 20 mL). The combined organic layers were washed with water (3 × 15 mL) and saturated aqueous NaCl (15 mL). The organic layer was dried ($Na_2SO_4$), and the solvents were removed on a rotary evaporator to yield 3.56 g (89%) of a colorless oil (>99% pure by GC and $^1$H and $^{13}$C NMR) that was identified as the corresponding dimethyl acetal by $^1$H and $^{13}$C NMR spectroscopy.

**Representative Procedure for Synthesis of Acetals from Diaryl Ketones.** A mixture of 4,4′-difluorobenzophenone (1.00 g, 4.58 mmol) in methanol (3 mL) and trimethylorthoformate (3.16 g, 3.3 mL, 29.8 mmol) was stirred at room temperature as bismuth triflate (30 mg, 0.0458 mmol, 1.0 mol %) was added. As the mixture was heated, a solution resulted

(38) Fadel, A.; Yefsah, R.; Salaun, J. *Synthesis* **1987**, 37.

that was further heated at reflux for 24 h and allowed to cool to room temperature. The solution was then poured onto 10% aqueous $NaHCO_3$ (15 mL), which resulted in precipitation of a solid. The mixture was cooled in ice, and the solid formed was collected by suction filtration and dried in a vacuum desiccator to afford 1.14 g (94%) of white crystals. The product has been reported in the literature, but $^{13}C$ NMR data has not been previously reported: $^{13}C$ NMR (67.5 MHz, $CDCl_3$) $\delta$ 49.2, 102.2, 114.8 (d, $J_{CF} = 21.1$ Hz), 128.7 (d, $J_{CF} = 8.3$ Hz), 138.19 (d, $J_{CF} = 3.1$ Hz), 162.2 (d, $J_{CF} = 244.9$ Hz).

**Dimethyl Acetal of 4-Nitrobenzophenone.** A mixture of 4-nitrobenzophenone (2.00 g, 8.80 mmol) in methanol (4.5 g, 5.7 mL, 0.141 mol) and trimethylorthoformate (6.07 g, 6.3 mL, 57.2 mmol) was stirred at room temperature as bismuth triflate (57.8 mg, 0.0880 mmol, 1.0 mol %) was added. The resulting mixture was heated at reflux, and nitromethane (5 mL) was added until a solution resulted. The solution was refluxed for 24 h and allowed to cool to room temperature. It was then poured onto 10% aqueous $NaHCO_3$ solution (15 mL), and the mixture was extracted with $CH_2Cl_2$ (2 × 20 mL). The combined organic layers were washed with $H_2O$ (2 × 15 mL) and saturated NaCl (15 mL), dried ($Na_2SO_4$), and concentrated on a rotary evaporator to give 2.00 g (83%) of off-white crystals: IR (KBr) 2967, 2834, 1559, 1343, 1212, 1090 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 3.13 (s, 6 H), 7.24 (m, 3 H), 7.45 (m, 2 H), 7.67 (m, 2 H), 8.4 (m, 2 H); $^{13}C$ NMR $\delta$ 49.3, 102.1, 123.2, 126.6, 127.8, 127.9, 128.2, 140.8, 147.1, 149.5; mp 61−63 °C. Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.84; H, 5.55; N, 5.17.

**Synthesis of 1,3-Dioxolanes (Method A).** A mixture of *p*-chlorobenzaldehyde (3.00 g, 21.34 mmol), ethylene glycol (5.30 g, 85.4 mmol), and toluene (6 mL) was stirred at room temperature as $Bi(OTf)_3 \cdot 4H_2O$ (0.140 g, 0.213 mmol, 1.0 mol %) was added. The mixture was heated under $N_2$ at 110 °C in an oil bath. After 4.5 h, the mixture was poured onto 10% aqueous $NaHCO_3$ (25 mL) and extracted with ether (45 mL). The organic layer was then washed with $H_2O$ (4 × 30 mL), saturated NaCl (30 mL), dried ($Na_2SO_4$), and concentrated on a rotary evaporator to yield 3.72 g of an oil that was purified by flash chromatography on 300 g of silica to yield 2.83 g (72%) of a clear liquid that was consistent with the expected dioxolane (>98% pure as confirmed by GC analysis and $^1H$ and $^{13}C$ NMR spectroscopy).

**Synthesis of 1,3-Dioxolanes (Method B).** A round-bottom flask was charged with *p*-chlorobenzaldehyde (3.00 g, 21.34 mmol), fluorobenzene (10 mL), ethylene glycol (10.60 g, 0.171 mol), and bismuth triflate (0.140 g, 0.213 mmol, 1.0 mol %). The flask was equipped with a Dean−Stark trap, and the well-stirred mixture was heated at 110 °C using an oil bath. After 5 h, the mixture was poured on to 10% aqueous $NaHCO_3$ solution (30 mL) and extracted with ether (3 × 40 mL). The organic layer was then washed with $H_2O$ (4 × 30 mL) and saturated NaCl (30 mL), dried, and concentrated on a rotary evaporator to yield 3.00 g (76%) of a colorless oil that was consistent with the expected dioxolane (>98% pure as confirmed by GC and $^1H$ and $^{13}C$ NMR spectroscopy).

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