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FULL PAPER

# *N,N'*-Dimethylated Benzyloxytriazinedione: A Stable Solid Reagent for Acid-Catalyzed *O*-Benzylation

Hikaru Fujita, Satoshi Kakuyama, and Munetaka Kunishima*[a]

**Abstract:** *N,N'*-Dimethylated 6-(benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (DMBOT) has been developed as a triazinedione-based, stable solid reagent for acid-catalyzed *O*-benzylation. The *N,N'*-dimethyl groups were introduced on the basis of the design concept to fix the core triazinedione skeleton. The coproduct of DMBOT can be easily removed by simple washing. Various acid- and base-labile alcohols were *O*-benzylated using DMBOT in the presence of an acid catalyst. In particular, 2,6-di-*tert*-butylpyridinium trifluoromethanesulfonate, which is a mild, stable, and non-hygroscopic acid catalyst, can be utilized for the reaction of DMBOT. Compared to other reported methods, DMBOT afforded better results in several challenging *O*-benzylation under non-basic conditions.

## Introduction

Owing to its stability and mild deprotection conditions, the benzyl group is one of the most widely used alcohol-protecting groups.[1] Since typical Williamson ether synthesis requires strongly basic conditions, several reagents[2-4] such as benzyl trichloroacetimidate (BTCAI)[2] and 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate (Dudley reagent)[3] have been developed for *O*-benzylation under non-basic conditions. However, the handling of BTCAI is not satisfactory because it is a moisture- and heat-sensitive liquid.[5] Although Dudley reagent is stable enough to use in air, its reaction requires high temperatures (83−120 °C) to proceed. Therefore, the development of a milder *O*-benzylation method using an easy-to-handle reagent is still desirable.[6]

We previously reported a new acid-catalyzed *O*-benzylating reagents, 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT, Figure 1), which is a stable solid, and thus easy to handle.[7] The reaction using TriBOT involves 4,6-bis(benzyloxy)-1,3,5-triazin-2(1*H*)-one (DiBOT) and 6-(benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (MonoBOT) as reaction intermediates, and both of which are also capable of *O*-benzylation of alcohols.[8] Our recent study on the reactivity of TriBOT, DiBOT, and MonoBOT, whose triazine core skeletons are different from each other, revealed that MonoBOT has the highest ability of the generation of benzyl cation species ($Bn^+$), indicating that 1,3,5-triazine-2,4(1*H*,3*H*)-dione (triazinedione) is a promising core skeleton. On the basis of these findings, in this paper, we report the development of a new, highly reactive acid-catalyzed *O*-benzylating reagent based on the triazinedione skeleton.

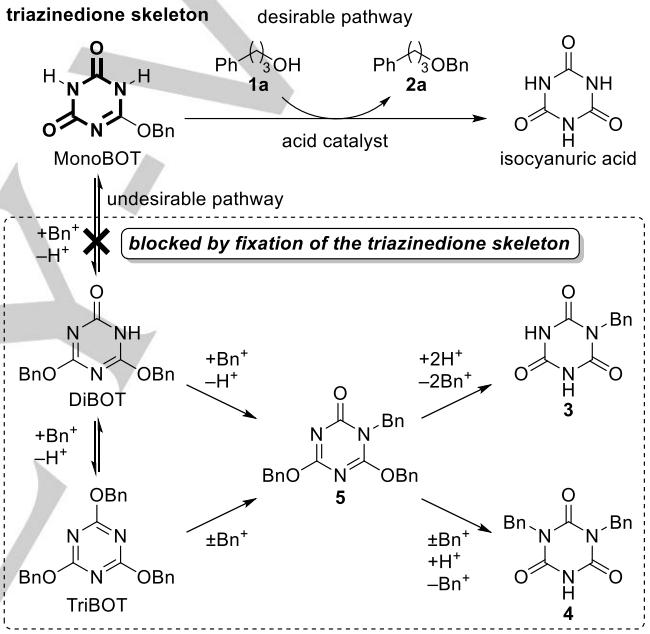


**Figure 1.** Desirable and undesirable pathways of acid-catalyzed *O*-benzylation using MonoBOT.

## Results and Discussion

*O*-Benzylation of 3-phenyl-1-propanol (**1a**) proceeded with 98% yield using MonoBOT (1.2 equiv) and TfOH (20 mol%) as an acid catalyst (entry 1 in Table 1, the desirable pathway in Figure 1).[8] Unfortunately, however, the use of milder acid catalysts resulted in lower yields of the corresponding benzyl ether **2a** (entries 2–5, 58–82%) with increased *N*-benzylated byproducts **3** and **4** (~28% and ~39% based on MonoBOT, respectively). When we monitored the time course of the reaction between **1a** and MonoBOT in the presence of TfOH (20 mol%), we found that about 20% of MonoBOT was converted to DiBOT rapidly in the early stage of the reaction (the undesirable pathway in Figure 1, details in Figure S1 in Supporting information). This conversion should be avoided because the reactivity of triazinone-based DiBOT is lower than that of MonoBOT. Moreover, non-reactive byproducts **3** and **4** can be formed via *N*-benzylated DiBOT (**5**).

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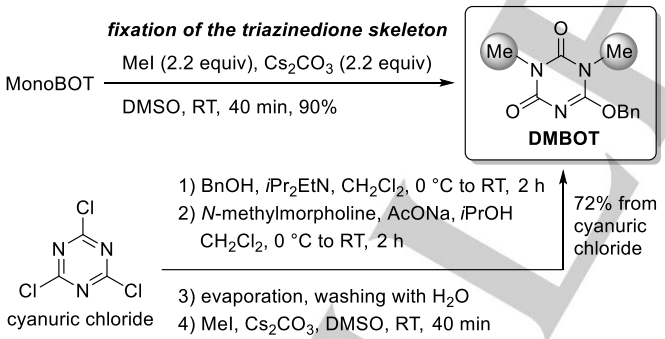
Since the use of milder acid catalysts increases the side reaction, *O*-benzylation with MonoBOT requires 20 mol% or more of TfOH. However, if the skeleton of MonoBOT can be firmly fixed as the triazinedione, the high reactivity of MonoBOT will be fully exhibited. On the basis of this concept, we newly designed *N*,*N*′-dimethylated benzyloxytriazinedione (DMBOT, Scheme 1). The *N*,*N*′-dimethyl groups of DMBOT play the role of "an anchor" to fix the core triazinedione scaffold, and thus they will block the undesirable conversion of the core skeleton into the triazinone caused by the two acidic protons of MonoBOT.

**Table 1.** Acid-catalyzed *O*-benzylation of **1a** using MonoBOT.

**1a** —(MonoBOT (1.2 equiv), acid catalyst; 1,4-dioxane, MS5A, RT)→ **2a** + **3** + **4**

| Entry | Acid catalyst [mol%] | Time [h] | **2a** [%][a] | **3** [%][a,b] | **4** [%][a,b] |
|---|---|---|---|---|---|
| 1[c] | TfOH [20] | 1.5 | 98 | 7 | 3 |
| 2 | TfOH [10] | 5 | 82 | –[d] | –[d] |
| 3 | TfOH [5] | 9 | 79 | 15 | 8 |
| 4 | $Sc(OTf)_3$ [20] | 24 | 73 | 28 | 13 |
| 5 | $BF_3{\cdot}Et_2O$ [20] | 4 | 58 | 13 | 39 |

[a] Calculated from $^1$H NMR analysis using an internal standard. [b] Yields based on benzyl groups (total 1.2 equiv = 120%). [c] Data from ref. 8. [d] Not determined.




**Scheme 1.** Synthesis of DMBOT.

The *N*,*N*′-dimethylation of MonoBOT afforded DMBOT (Scheme 1, 90% yield). More conveniently, the one-pot MonoBOT synthesis,[8] followed by *N*,*N*′-dimethylation, provided DMBOT (72% yield) from inexpensive cyanuric chloride. DMBOT is a stable crystalline solid, and thus it can be easily handled in air at room temperature. MonoBOT has limitation of the reaction solvents and the concentration, because its solubilities in aprotic solvents were low probably due to the hydrogen-bonding ability similar to isocyanuric acid.[9] In contrast, the solubilities of DMBOT were successfully much improved (details in Table S1 in Supporting Information).

Initially, *O*-benzylation of **1a** with DMBOT (1.2 equiv) was carried out at room temperature in 1,4-dioxane (0.1 M) in the presence of molecular sieves 5A (MS5A)[10] using TfOH as an acid catalyst (Table 2). Product **2a** was obtained in high yields in the presence of 20, 10, and 5 mol% of TfOH (entries 1−3, 93−97%). These results indicate that the *N*,*N*′-dimethyl groups of DMBOT effectively suppressed the side reaction observed in the reaction with MonoBOT. A similar result was observed when the substrate concentration was increased from 0.1 M to 0.3 M (entry 2 vs 4, respectively). Moreover, *O*-benzylation in the presence of only 1 mol% of TfOH at 60 °C was completed within 1.5 h (entry 5, 95%). The use of other ethereal solvents (entry 6, DME; entry 7, a 1:1 mixture of $Et_2O/CH_2Cl_2$) or other acid catalysts [entries 8−12, TMSOTf, $HBF_4{\cdot}Et_2O$, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$, and $Cu(OTf)_2$, respectively] were also effective (86−96%). It is worth noting that 2,6-di-*tert*-butylpyridinium trifluoromethanesulfonate (**6**), a compound that can be considered as partially neutralized TfOH, was also an efficient acid catalyst for DMBOT (entry 13, 97%). To the best of our knowledge, although **6** is a stable, non-hygroscopic and easy-to-handle solid,[11] it has never been used as an acid catalyst for *O*-benzylation of alcohols to date. In contrast to DMBOT, TriBOT was inert to **6** (entry 14), suggesting a higher reactivity of DMBOT when compared to that of TriBOT.

**Table 2.** Screening of reaction conditions.

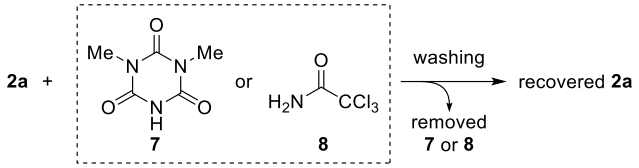
**1a** —(DMBOT (1.2 equiv), acid catalyst; solvent, MS5A, RT, time)→ **2a**

| Entry | Acid catalyst [mol%] | Solvent | Time [h] | Yield [%][a] |
|---|---|---|---|---|
| 1 | TfOH [20] | 1,4-dioxane[b] | 1.5 | 96 |
| 2 | TfOH [10] | 1,4-dioxane[b] | 5 | 93 |
| 3 | TfOH [5] | 1,4-dioxane[b] | 9 | 97 |
| 4 | TfOH [10] | 1,4-dioxane[c] | 4 | 97 (90)[d] |
| 5[e] | TfOH [1] | 1,4-dioxane[c] | 1.5 | 95 |
| 6 | TfOH [10] | DME[b] | 6 | 92 |
| 7 | TfOH [10] | $Et_2O/CH_2Cl_2$[c] | 17 | 90 |
| 8 | TMSOTf [10] | 1,4-dioxane[b] | 8 | 96 |
| 9 | $HBF_4{\cdot}Et_2O$ [10] | 1,4-dioxane[c] | 9 | 91 |
| 10 | $BF_3{\cdot}Et_2O$ [10] | 1,4-dioxane[c] | 24 | 86 |
| 11[e] | $Sc(OTf)_3$ [5] | 1,4-dioxane[c] | 3 | 93 |
| 12[e] | $Cu(OTf)_2$ [5] | 1,4-dioxane[c] | 3 | 91 |
| 13 | **6** [10] | 1,4-dioxane[c] | 6 | 97 |
| 14[f] | **6** [10] | 1,4-dioxane[c] | 6 | <1 |

[a] Calculated from $^1$H NMR analysis using an internal standard. [b] The substrate concentration was 0.1 M. [c] The substrate concentration was 0.3 M. [d] Isolated yield. [e] The reaction was conducted at 60 °C. [f] TriBOT (0.4 equiv) was used instead of DMBOT.

A coproduct, *N*,*N'*-dimethylisocyanuric acid (**7**, Table 3), is formed from DMBOT in a reaction[12] similar to that for trichloroacetamide (**8**) from BTCAI, and *N*-methylpyridone from Dudley reagent. Coproduct **7** can be removed by simple washing with a basic aqueous solution, because unlike *N*-methylpyridone, **7** has an acidic proton, with an acidity higher than that of **8**.[13] When a solution of **7** and **2a** (0.5 mmol each) in EtOAc (20 mL) was washed with saturated $NaHCO_3$ (Table 3, entry 1) or 1% $K_2CO_3$ (entry 2), almost all of **7** (97% or >98%, respectively) was successfully removed from **2a**. In contrast, **8** could not be removed by washing with these solutions (entries 3 and 4, 3% and 6%, respectively).[14] The easy removal of **7** greatly facilitates the purification of the product.[15]

**Table 3.** Removal of coproducts by washing.

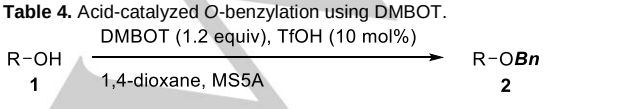


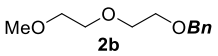
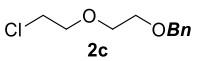
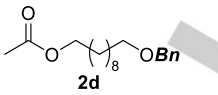
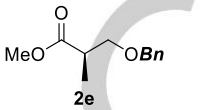
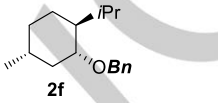
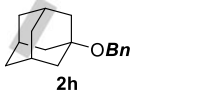
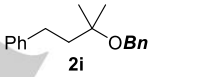

| Entry | Coproduct | Basic aqueous solution | Recovered **2a** [%][a] | Removed coproduct [%] |
|---|---|---|---|---|
| 1 | **7** | sat. $NaHCO_3$ | 99 | 97[b] |
| 2 | **7** | 1% $K_2CO_3$ | 99 | >98[b] |
| 3 | **8** | sat. $NaHCO_3$ | 98 | 3[c] |
| 4 | **8** | 1% $K_2CO_3$ | 98 | 6[c] |

[a] Calculated from $^1$H NMR analysis using an internal standard. [b] Calculated based on yields of recovered **7** determined from $^1$H NMR analysis using an internal standard. [c] Calculated based on isolated yields of recovered **8**.

As shown in Table 4,[16] the reactions between primary alcohols **1b**-**e** and DMBOT under the conditions of entry 4 in Table 2 provided benzyl ethers **2b**-**e** in high yields (entries 1−4, 87−94%). Neither the chloroalkyl group of **1c** nor the ester moieties of **1d** and **1e** were affected by the reaction. No racemization was observed during the reaction of **1e**. *O*-Benzylation of secondary alcohols **1f** and **1g** and tertiary alcohols **1h** and **1i** resulted in good yields (entries 5−8, 83−96%).[17] Interestingly, the use of **6** as a catalyst slightly improved the yield from 83% to 89% in the reaction with **1i** (entry 8 vs 9), which tends to undergo an elimination reaction under acidic conditions. This result suggests that **6** is more suitable than TfOH for the *O*-benzylation of an acid-labile alcohol.

**Table 4.** Acid-catalyzed *O*-benzylation using DMBOT.

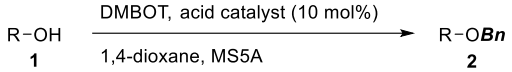


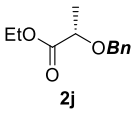
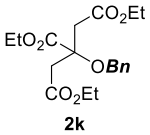
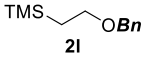
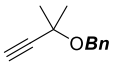
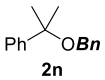

| Entry | Product | Time [h] | Yield [%][a] |
|---|---|---|---|
| 1 |  **2b** | 3.5 | 94 |
| 2 |  **2c** | 4 | 90 |
| 3 |  **2d** | 5 | 93 |
| 4 |  **2e** | 8.5 | 87[b] |
| 5 |  **2f** | 16 | 96 |
| 6 |  **2g** | 15 | 91 |
| 7 |  **2h** | 13 | 90 |
| 8[c] |  **2i** | 3 | 83 |
| 9[c,d] | **2i** | 3 | 89 |

[a] Isolated yield. [b] No racemization was observed. [c] The reaction was conducted at 50 °C using DMBOT (1.5 equiv). [d] Acid catalyst **6** (10 mol%) was used instead of TfOH.

To evaluate the usefulness of DMBOT, we conducted an *O*-benzylation reactions between DMBOT and several alcohols (Table 5).[16] These reactions did not proceed with high yields when BTCAI or Dudley reagent was used. *O*-Benzylation of chiral lactate ester **1j** proceeded with 62−70% yield when BTCAI and TfOH (entry 1, reported method) were utilized.[20,21] Furthermore, triethyl citrate (**1k**) underwent *O*-benzylation with only 5% yield when BTCAI and TfOH were used (entry 2, reported method). In contrast, the reaction of **1j** and **1k** using DMBOT and TfOH, proceeded to afford 88% (entry 1, without racemization) and 55% (entry 2)[22] yields, respectively. No evidence of the desired product (**2l**) was observed in the reaction of **1l** with BTCAI and TfOH (entry 3, reported method). However, **2l** was successfully obtained with 73% yield when DMBOT was used with **6** (entry 3).[23] The use of Dudley reagent for the *O*-benzylation of the acid-labile tertiary alcohols **1m** and **1n** resulted in 59% and 44% yields of **2m** and **2n**, respectively (entries 4 and 5, respectively; reported method). Moreover, when DMBOT and **6** were used, the yields of both **2m** and **2n** improved significantly (entries 4 and 5, 70% and 65% yields, respectively).

**Table 5.** Comparison of challenging *O*-benzylation using DMBOT, BTCAI, or Dudley Reagent.




| Entry | Product | DMBOT [equiv] | Acid catalyst | *T* [°C] | Time [h] | Yield [%][a] | Reported method |
|---|---|---|---|---|---|---|---|
| 1 |  **2j** | 1.2 | TfOH | 50 | 4 | 88[b] | BTCAI (1.2 equiv), TfOH (15 mol%), cyclohexane/$CH_2Cl_2$, RT, 18 h, 62%[c]; BTCAI (1.2 equiv), TfOH (20 mol%), cyclohexane/$CH_2Cl_2$, RT, 2.5 h, 70%[d] |
| 2 |  **2k** | 1.2 | TfOH | 50 | 11 | 55 | BTCAI (1.2 equiv), TfOH (15 mol%), cyclohexane/$CH_2Cl_2$, RT to 38 °C, 2.5 h, 5%[e] |
| 3 |  **2l** | 2 | **6** | RT | 12 | 73 | BTCAI (2 equiv), TfOH (50 mol%), RT, 2 h, decomposition[f] |
| 4 |  **2m** | 2 | **6** | 50 | 5.5 | 70 | Dudley reagent (2 equiv), MgO (2 equiv), $PhCF_3$, 120 °C (MW), 20 min, 59%[g] |
| 5 |  **2n** | 2 | **6** | 50 | 3 | 65 | Dudley reagent (2 equiv), MgO (2 equiv), $PhCF_3$, 83 °C, 24 h, 44%[f] |

[a] Isolated yield. [b] No racemization was observed. [c] Data from ref. 18. [d] Data from ref. 19. [e] Data from ref. 2c. [f] Data from ref. 3b. [g] Data from ref. 3f.

## Conclusions

In conclusion, we have designed and synthesized DMBOT on the basis of the concept of the triazinedione fixation with *N*,*N*′-dimethyl groups. Owing to the fixed triazinedione skeleton, DMBOT successfully showed high reactivity and suppressed byproducts formation. Various alcohols with acid- and base-labile functionalities were *O*-benzylated using DMBOT in the presence of TfOH. Furthermore, an easy-to-handle organic salt **6**, whose acidity is weaker than TfOH, was also an effective acid catalyst for DMBOT. In the challenging *O*-benzylation processes of several alcohols, DMBOT gave better results than those of BTCAI and Dudley reagent. DMBOT has high practicability because of its favorable physical properties (*i.e.* high stability and solubility) and the coproduct removability.

## Experimental Section

**General methods:** NMR spectra were determined on a JEOL JNM-ECS400 spectrometer [$^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz)] or a JEOL JNM-ECA600 [$^1$H NMR (600 MHz), $^{13}$C NMR (150 MHz)]. Chemical shifts for $^1$H NMR are reported in parts per million (*δ*) relative to tetramethylsilane as the internal standard. Coupling constant (*J*) are reported in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Chemical shifts for $^{13}$C NMR are reported in parts per million (*δ*) relative to the solvent [$CDCl_3$, *δ* 77.16; $(CD_3)_2SO$, *δ* 39.52]. IR spectra were recorded on a Horiba FT-720 FREEXACT-II spectrophotometer and were reported in wavenumbers ($cm^{-1}$). Mass spectra were measured on JMS-T100TD (DART-MS) and Micromass Zq2000 spectrometer (ESI-MS). Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm, silica gel 60 $F_{254}$. Preparative TLC separations were performed on Merck analytical plates (0.50 or 1.0 mm) precoated with silica gel 60 $F_{254}$. Flash chromatography separations were performed on Kanto Chemical Silica Gel 60 N (spherical, neutral, 40–100 mesh) unless otherwise noted. Recycling preparative HPLC was performed with Japan Analytical Industry LC-928 equipped with GPC columns Jaigel-1H and 2H. Reagents were commercial grades and were used without any purification unless otherwise noted. Dehydrated $Et_2O$, DMSO and $CH_2Cl_2$ were purchased from commercial sources. DME and 1,4-dioxane was purchased from commercial sources and distilled over sodium metal before use. MonoBOT[8] and **6**[24] were prepared according to the reported procedure. All reactions sensitive to oxygen or moisture were conducted under a nitrogen atmosphere.

**6-(Benzyloxy)-1,3-dimethyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (DMBOT)**

Synthesis from cyanuric chloride: To a solution of cyanuric chloride (368.8 mg, 2.00 mmol) and benzyl alcohol (0.31 mL, 3.0 mmol) in $CH_2Cl_2$ (4.00 mL) was added ethyldiisopropylamine (359 μL, 2.06 mmol) at 0 °C. After stirred for 1 h, the mixture was allowed to warm to RT. After stirred for additional 1 h, the mixture was cooled to 0 °C. Sodium acetate (492.2 mg, 6.00 mmol), isopropyl alcohol (4.00 mL), and *N*-methylmorpholine (110 μL,

1.00 mmol) was added at 0 °C. The mixture was stirred for 1 h at 0 °C and for 1 h at RT. After aqueous HCl (6 M, 0.33 mL) was added at 0 °C, the mixture was concentrated under reduced pressure. The residue was washed with cold water. Cesium carbonate (1.95 g, 6.00 mmol), DMSO (4.00 mL), and methyl iodide (374 μL, 6.00 mmol) was added at RT. After stirred for 40 min, the mixture was diluted with EtOAc (20 mL) and washed with water (40 mL) and brine (20 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 2:1) to afford DMBOT (358.0 mg, 72%) as a crystalline solid.

Synthesis from MonoBOT: To a suspension of MonoBOT (109.6 mg, 0.500 mmol) and cesium carbonate (358 mg, 1.10 mmol) in DMSO (1.00 mL) was added methyl iodide (68.5 μL, 1.10 mmol) at RT. After stirred for 40 min, the reaction mixture was diluted with EtOAc (10 mL) and washed with water (30 mL × 2) and brine (30 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to afford DMBOT (111.2 mg, 90%) as a crystalline solid. M.p. 109–110 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.47–7.37 (m, 5H), 5.49 (s, 2H), 3.37 (s, 3H), 3.36 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 158.9, 154.6, 151.2, 134.0, 129.2, 128.9, 128.8, 71.8, 29.4, 29.3; IR (KBr): 3060, 2956, 1739, 1671, 1616, 1600, 1583, 1500, 1435, 1225; HRMS (DART): *m*/*z*: Calcd for $C_{12}H_{14}N_3O_3$ ($[M+H]^+$): 248.1035, Found: 248.1051; elemental analysis calcd (%) for $C_{12}H_{13}N_3O_3$: C 58.29, H 5.30, N 17.00; found: C 58.23, H 5.48, N 17.02.

**Benzyl 3-phenylpropyl ether (2a):**[25] To a mixture of **1a** (54.5 μL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol), and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 4 h, the reaction mixture was quenched with pyridine (32.0 μL), diluted with EtOAc (20 mL), and filtered to remove MS5A. The filtrate was washed with 1% (w/w) aqueous $K_2CO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) followed by recycling preparative HPLC to afford **2a** (81.0 mg, 90%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.39–7.12 (m, 10H), 4.51 (s, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.94 (tt, *J* = 6.4, 7.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 142.1, 138.7, 128.6, 128.5, 128.4, 127.8, 127.7, 125.9, 73.1, 69.6, 32.5, 31.5; LRMS (DART): *m*/*z* 227 ($[M+H]^+$).

**Benzyl 2-(2-methoxyethoxy)ethyl ether (2b):**[26] To a solution of **1b** (47.1 μL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 3.5 h, the reaction mixture was quenched with pyridine (32.0 μL), diluted with EtOAc (10 mL) and filtered to remove MS5A. The filtrate was washed with water (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 4:1) to afford **2b** (79.0 mg, 94%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–7.20 (m, 5H), 4.57 (s, 2H), 3.70–3.60 (m, 6H), 3.58–3.53 (m, 2H), 3.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.4, 128.5, 127.9, 127.7, 73.4, 72.1, 70.8, 70.7, 69.6, 59.2; LRMS (DART): *m*/*z* 211 ($[M+H]^+$).

**Benzyl 2-(2-chloroethoxy)ethyl ether (2c):**[7a,26] To a solution of **1c** (42.2 μL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 4 h, the reaction mixture was diluted with EtOAc (10 mL), and filtered to remove MS5A. The filtrate was washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 17:3) and preparative TLC (hexane/EtOAc = 4:1) to afford **2c** (76.9 mg, 90%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.25 (m, 5H), 4.58 (s, 2H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.72–3.67 (m, 2H), 3.66–3.61 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.2, 128.5, 127.9, 127.8, 73.5, 71.5, 70.9, 69.5, 42.9 LRMS (DART): *m*/*z* 215 ($[M+H]^+$).

**1-Acetoxy-10-(benzyloxy)decane (2d):**[7a] To a solution of **1d** (86.5 mg, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 5 h, the reaction mixture was diluted with EtOAc (10 mL), filtered to remove MS5A. The filtrate was washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) and preparative TLC (hexane/EtOAc= 9:1) to afford **2d** (114.1 mg, 93%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–7.23 (m, 5H), 4.50 (s, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.05 (s, 3H), 1.67–1.55 (m, 4H), 1.40–1.23 (m, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 171.4, 138.8, 128.5, 127.8, 127.6, 73.0, 70.6, 64.8, 29.9, 29.62, 29.58, 29.4, 28.7, 26.3, 26.0, 21.2; LRMS (DART): *m*/*z* 307 ($[M+H]^+$).

**Methyl (2*R*)-3-(benzyloxy)-2-methylpropionate (2e):**[27] To a solution of **1e** (44.2 μL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 8.5 h, the reaction mixture was diluted with EtOAc (10 mL), filtered to remove MS5A. The filtrate was washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford **2e** (72.4 mg, 87%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.23 (m, 5H), 4.52 (s, 2H), 3.70 (s, 3H), 3.66 (dd, *J* = 7.3, 9.2 Hz, 2H), 3.49 (dd, *J* = 5.5, 9.2 Hz, 1H), 2.85–2.73 (m, 1H), 1.18 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.5, 138.3, 128.5, 127.74, 127.71, 73.2, 72.1, 51.9, 40.3, 14.1; LRMS (DART): *m*/*z* 209 ($[M+H]^+$).

**(1*R*, 2*S*, 5*R*)-(−)-*O*-Benzylmenthol (2f):**[28] To a solution of **1f** (62.5 mg, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (6.7 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 16 h, the reaction mixture was quenched with pyridine (16.0 μL), diluted with EtOAc (10 mL) and filtered to remove MS5A. The filtrate was washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$ = 3:1) to afford **2f** (94.5 mg, 96%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.46–7.15 (m, 5 H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.17 (td, *J* = 4.1, 10.6 Hz, 1H), 2.40–2.24 (m, 1H), 2.24–2.11 (m, 1H), 1.72–1.58 (m, 2H), 1.45–1.22 (m, 2H), 1.11–0.77 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 139.3, 128.4, 128.0, 127.5, 78.9, 70.6, 48.5, 40.4, 34.7, 31.7, 25.6, 23.2, 22.5, 21.2, 16.2; LRMS (DART): *m*/*z* 247 ($[M+H]^+$).

**Benzyl 1-phenylethyl ether (2g):**[7a] To a solution of **1g** (48.4 μL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (33.3 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 μL, 0.040 mmol) at RT. After stirred for 15 h, the reaction mixture was quenched with pyridine (32.0 μL), diluted with EtOAc (10 mL) and filtered to remove MS5A. The filtrate was washed with water (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/$Et_2O$/EtOAc = 47:2:1) and recycling preparative HPLC to afford **2g** (77.2 mg, 91%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–7.23 (m, 10H), 4.50 (q, *J* = 6.4 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 2H), 4.30 (d, *J* = 11.9 Hz, 2H), 1.48 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 143.8, 138.8, 128.6, 128.5, 127.9, 127.7, 127.6, 126.5, 77.4, 70.4, 24.4; LRMS (DART): *m*/*z* 213 ($[M+H]^+$).

**1-Adamantyl benzyl ether (2h):**[3b] To a solution of **1h** (60.9 mg, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (33.3 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 µL, 0.040 mmol) at RT. After stirred for 13 h, the reaction mixture was quenched with pyridine (32.0 µL), diluted with EtOAc (10 mL) and filtered to remove MS5A. The filtrate was washed with water (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 97:3) and preparative TLC (hexane/acetone = 30:1) to afford **2h** (87.2 mg, 90%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–7.16 (m, 5H), 4.51 (s, 2H), 2.18 (s, 3H), 1.91–1.80 (m, 6H), 1.71-1.59 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 140.3, 128.4, 127.6, 127.2, 72.9, 62.4, 41.9, 36.6, 30.7 LRMS (DART): *m*/*z* 243 ([M+H]$^+$).

**Benzyl 2-methyl-4-phenylbutan-2-yl ether (2i):**[4k] To a mixture of **1i** (51.0 µL, 0.300 mmol), DMBOT (111.3 mg, 0.450 mmol), and MS5A (5.0 mg) in 1,4-dioxane (1.00 mL, 0.3 M) was added **6** (10.2 mg, 0.030 mmol) at RT. The reaction mixture was heated to 50 °C for 3 h. After cooled to RT, the reaction mixture was quenched with $NEt_3$ (6.3 µL), diluted with EtOAc (5 mL) and filtered to remove MS5A. The filtrate was washed with 1% (w/w) aqueous $K_2CO_3$ (5 mL) and brine (5 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/acetone = 40:1) followed by recycling preparative HPLC to afford **2i** (67.6 mg, 89%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.41–7.14 (m, 10H), 4.47 (s, 2H), 2.76–2.69 (m, 2H), 1.93–1.84 (m, 2H), 1.33 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 143.0, 139.9, 128.50, 128.47, 128.45, 127.4, 127.3, 125.8, 75.1, 63.8, 42.6, 30.5, 25.9; LRMS (DART): *m*/*z* 255 ([M+H]$^+$).

**Ethyl (2*S*)-(benzyloxy)propanoate (2j):**[4k] To a solution of **1j** (34.1 µL, 0.300 mmol), DMBOT (89.0 mg, 0.360 mmol) and MS5A (15.0 mg) in 1,4-dioxane (1.00 mL, 0.3 M) was added TfOH (2.6 µL, 0.030 mmol) at RT. The reaction mixture was heated to 50 °C for 4 h. After cooled to RT, the reaction mixture was diluted with EtOAc (20 mL), filtered to remove MS5A. The filtrate was washed with sat. aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc= 19:1) and preparative TLC (hexane/EtOAc = 19:1 × 2) to afford **2j** (54.7 mg, 88%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.40–7.22 (m, 5H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.29–4.15 (m, 2H), 4.05 (q, *J* = 6.9 Hz, 1H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.30 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 173.4, 137.7, 128.6, 128.1, 128.0, 74.2, 72.1, 61.0, 18.9, 14.4; LRMS (DART-MS): *m*/*z* 209 ([M+H]$^+$).

**2-Benzyloxy-1,2,3-propanetricarboxylic acid triethyl ester (2k):**[2c] To a solution of **1k** (96.9 µL, 0.400 mmol), DMBOT (118.7 mg, 0.480 mmol) and MS5A (33.3 mg) in 1,4-dioxane (1.33 mL, 0.3 M) was added TfOH (3.5 µL, 0.040 mmol) at RT. The reaction mixture was heated to 50 °C for 11 h. After cooled to RT, the reaction mixture was diluted with EtOAc (10 mL), filtered to remove MS5A. The filtrate was washed with 1%(w/w) aqueous $K_2CO_3$ (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) and followed by recycling preparative HPLC to afford **2k** (80.1 mg, 55%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.42–7.15 (m, 5H), 4.58 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 4H), 3.25 (d, *J* = 15.6 Hz, 2H), 3.09 (d, *J* = 15.6 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.7, 170.0, 137.8, 128.4, 127.8, 127.7, 78.9, 66.9, 61.8, 60.9, 39.5, 14.3; LRMS (DART): *m*/*z* 367 ([M+H]$^+$).

**Benzyl 2-(trimethylsilyl)ethyl ether (2l):**[6] To a mixture of **1l** (36.7 µL, 0.300 mmol), DMBOT (148.4 mg, 0.600 mmol), and MS5A (5.0 mg) in 1,4-dioxane (1.00 mL, 0.3 M) was added **6** (10.2 mg, 0.030 mmol) at RT. After stirred for 12 h, the reaction mixture was quenched with $NEt_3$ (6.3 µL), diluted with EtOAc (5 mL) and filtered to remove MS5A. The filtrate was washed with 1% (w/w) aqueous $K_2CO_3$ (5 mL) and brine (5 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/acetone = 40:1) to afford **2l** (45.8 mg, 73%) as a clear colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.37–7.23 (m, 5H), 4.49 (s, 2H), 3.58 (t, *J* = 8.1 Hz, 2H), 1.00 (t, *J* = 8.1 Hz, 2H), 0.02 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 138.9, 128.5, 127.7, 127.5, 72.5, 67.8, 18.4, −1.2; LRMS (ESI): *m*/*z* 231 ([M+Na]$^+$).

**Benzyl 2-methylbut-3-yn-2-yl ether (2m):**[3f] To a mixture of **1m** (29.2 µL, 0.300 mmol), DMBOT (148.4 mg, 0.600 mmol), and MS5A (5.0 mg) in 1,4-dioxane (1.00 mL, 0.3 M) was added **6** (10.2 mg, 0.030 mmol) at RT. The reaction mixture was heated to 50 °C for 5.5 h. After cooled to RT, the reaction mixture was quenched with $NEt_3$ (6.3 µL), diluted with EtOAc (5 mL) and filtered to remove MS5A. The filtrate was washed with 1% (w/w) aqueous $K_2CO_3$ (5 mL) and brine (5 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/acetone = 40:1) to afford **2m** (36.3 mg, 70%) as a clear colorless oil. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.39–7.30 (m, 4H), 7.29–7.23 (m, 1H), 4.64 (s, 2H), 2.47 (s, 1H), 1.56 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 139.0, 128.4, 127.9, 127.5, 86.2, 72.4, 70.6, 66.7, 29.0; LRMS (DART): *m*/*z* 175 ([M+H]$^+$).

**Benzyl 2-phenylpropan-2-yl ether (2n):**[3b] To a mixture of **1n** (40.9 mg, 0.300 mmol), DMBOT (148.4 mg, 0.600 mmol), and MS5A (5.0 mg) in 1,4-dioxane (1.00 mL, 0.3 M) was added **6** (10.2 mg, 0.030 mmol) at RT. The reaction mixture was heated to 50 °C for 3 h. After cooled to RT, the reaction mixture was quenched with $NEt_3$ (6.3 µL), diluted with EtOAc (5 mL) and filtered to remove MS5A. The filtrate was washed with 1% (w/w) aqueous $K_2CO_3$ (5 mL) and brine (5 mL), dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/acetone = 40:1) to afford **2n** (43.8 mg, 65%) as a clear colorless oil. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.52−7.48 (m, 2H), 7.40−7.20 (m, 8H), 4.24 (s, 2H), 1.64 (s, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 146.3, 139.5, 128.43, 128.41, 127.6, 127.3, 127.1, 126.0, 77.3, 65.2, 28.7; LRMS (ESI): *m*/*z* 249 ([M+Na]$^+$).

***N*,*N*'-Dimethylisocyanuric acid (7):**[29] Crystalline solid; $^1$H NMR [400 MHz, $(CD_3)_2SO$]: $\delta$ = 11.6 (br s, 1H), 3.10 (s, 6H); $^{13}$C NMR [100 MHz, $(CD_3)_2SO$]: $\delta$ = 150.5, 149.0, 28.1; LRMS (DART): *m*/*z* 158 ([M+H]$^+$).

**2,2,2-Trichloroacetamide (8):**[30] Crystalline solid; $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 6.58 (br s, 1H), 5.81 (br s, 1H); $^{13}$C NMR [100 MHz, $(CD_3)_2SO$]: $\delta$ = 163.0, 93.1; LRMS (DART): *m*/*z* 163 ([M+H]$^+$).

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[9] C.-K. Lam, S. C.-K. Hau, C.-W. Yau, T. C. W. Mak, *Cryst. Growth Des.* **2016**, *16*, 759-773.

[10] Addition of powdered MS5A as a dehydrating agent decreased formation of dibenzyl ether, which probably derives from residual moisture (ref. 7a). Nevertheless, in some cases, repeated purification with recycling preparative HPLC or preparative TLC was necessary to complete removal of a trace amount of dibenzyl ether from a product.

[11] A. Zhdanko, M. E. Maier, *ACS Catal.* **2014**, *4*, 2770-2775.

[12] The coproduct **7** was isolated in 94% yield (based on DMBOT) under the reaction conditions of entry 4 in Table 2.

[13] The p$K_a$ values of **8** were reported as 11.2 and 12. a) T. J. Donohoe, C. J. R. Bataille, P. Innocenti, *Org. React.* **2012**, *76*, 1-48; b) B. C. Duffy, K. T. Howard, J. D. Chisholm, *Tetrahedron Lett.* **2015**, *56*, 3301-3305. The acidity of **7** would be similar to that of isocyanuric acid (p$K_a$ of 6.85 for the first deprotonation). For the p$K_a$ value of isocyanuric acid, see: S. Aoki, M. Shiro, T. Koike, E. Kimura, *J. Am. Chem. Soc.* **2000**, *122*, 576-584.

[14] Removal of **8** by washing with 2 M NaOH was reported. See: ref. 13b and K. T. Howard, B. C. Duffy, M. R. Linaburg, J. D. Chisholm, *Org. Biomol. Chem.* **2016**, *14*, 1623-1628.

[15] Problems during purification caused by the contamination of **8** formed from trichloroacetimidate-based reagents were reported in some cases. a) J. Thierry, C. Yue, P. Potier, *Tetrahedron Lett.* **1998**, *39*, 1557-1560; b) D. Enders, S. von Berg, B. Jandeleit, *Org. Synth.* **2003**, *78*, 177; c) N. Barroca-Aubry, M. Benchekroun, F. Gomes, D. Bonnaffé, *Tetrahedron Lett.* **2013**, *54*, 5118-5121; d) P. Cao, Z.-J. Li, W.-W. Sun, S. Malhotra, Y.-L. Ma, B. Wu, V. S. Parmar, *Nat. Prod. Bioprospect.* **2015**, *5*, 37-45.

[16] The benzyl groups introduced in the reaction are indicated in bold and italic face in Tables 4 and 5.

[17] *O*-Benzylation of secondary and tertiary alcohols **2f**-**i** with DMBOT proceeded at a slower rate than that of primary alcohols **2a**-**e**. The reason for this is unclear at present.

[18] F. Sakai, N. Seki, Y. Tenda, H. Yamazaki, C. Miyamoto, M. Kuno, H. Okumura, K. Nakamura, Patent WO0126605, 2001.

[19] P. Van de Weghe, C. Bied, J. Collin, J. Marçalo, I. Santos, *J. Organomet. Chem.* **1994**, *475*, 121-126.

[20] The use of BTCAI (2 equiv) afforded **2j** in 69−90% yield. See: ref. 15b and a) Y. Ito, Y. Kobayashi, T. Kawabata, M. Takase, S. Terashima, *Tetrahedron* **1989**, *45*, 5767-5790; b) R. Riclea, B. Aigle, P. Leblond, I. Schoenian, D. Spiteller, J. S. Dickschat, *ChemBioChem* **2012**, *13*, 1635-1644.

[21] It has been reported that methyl (*R*)-lactate, a chiral ester similar to **1j**, was *O*-benzylated with 79% yield when Dudley reagent (3 equiv, prepared *in situ*) was used (ref. 3d).

[22] The $^1$H NMR spectra of the crude products contained a considerable number of diarylmethylene peaks (3.9−4.1 ppm), suggesting that the *O*-benzylation of **1k** was in competition with Friedel-Crafts benzylation at the benzyl group of **2k**.

[23] The reaction of **1l** with Dudley reagent was reported to proceed to complete conversion with no evidence of decomposition. However, the yield was not reported (ref. 3b)

[24] G. A. Crispino, R. Breslow, *J. Org. Chem.* **1992**, *57*, 1849-1855.

[25] H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981-13996.

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[30] I. N. Stepanenko, B. Cebrián-Losantos, V. B. Arion, A. A. Krokhin, A. A. Nazarov, B. K. Keppler, *Eur. J. Inorg. Chem.* **2007**, 400-411.

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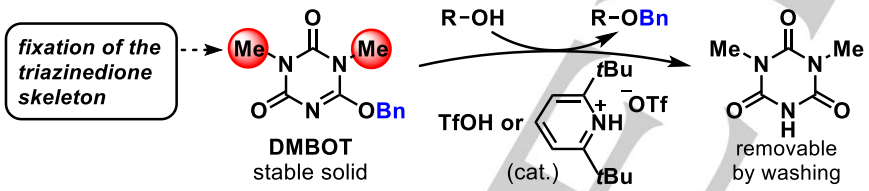


A triazinedione-based acid-catalyzed *O*-benzylating reagent, DMBOT, has been developed. The fixation of the triazinedione skeleton of DMBOT with *N*,*N*′-dimethyl groups as "an anchor" was essential to mild reaction conditions and high yields of benzyl ethers. DMBOT has high practicability because (1) it is a stable solid in air at room temperature, and (2) the coproduct can be easily removed by simple washing.

**Benzylating Reagent**

*H. Fujita, S. Kakuyama, M. Kunishima**

***Page No. – Page No.***

***N*,*N*′-Dimethylated Benzyloxytriazinedione: A Stable Solid Reagent for Acid-Catalyzed *O*-Benzylation**

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