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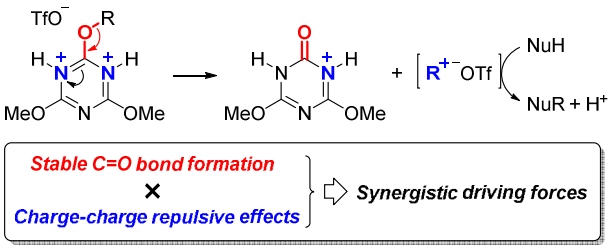


ABSTRACT

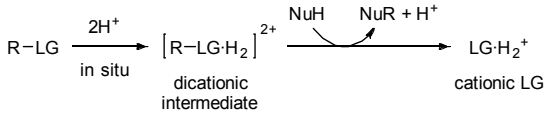
A new triazine-based cationic leaving group has been developed for the acid-catalyzed alkylation of *O*- and *C*-nucleophiles. There are two synergistic driving forces, namely, stable C=O bond formation and charge-charge repulsive effects, involved in the rapid generation of the carbocation species in the presence of trifluoromethanesulfonic acid (~200 mol%). Considerable rate acceleration of benzylation, allylation, and *p*-nitrobenzylation was observed as compared to the reactions with less than 100 mol% of the acid catalyst. The triazine-based leaving group showed superior *p*-nitrobenzylation yield and stability in comparison to common leaving groups, trichloroacetimidate and bromide. A plausible reaction mechanism (the cationic leaving group pathway) was proposed on the basis of mechanistic and kinetic studies, NMR experiments, and calculations.

INTRODUCTION

To date, a large number of leaving groups (LGs) have been developed because of the fundamental importance of substitution reactions in organic chemistry.[1] Most of the reported LGs are either anionic or neutral. Cationic LGs[2–4] have also been reported in studies relating to the decomposition reactions of dicationic compounds.[5] However, their application to organic synthesis is limited because the dicationic precursors are generally unstable and difficult to prepare in advance. Instead, the in situ activation of LGs by diprotonation is a rational and useful method to form cationic LGs from easy-to-handle, neutral precursors (Scheme 1). The strong driving force of bond cleavage to separate dications into monocations is known as the charge-charge repulsive effect of diprotonated intermediates called superelectrophiles.[6] Successful applications of such LG activation were reported for halogenation[7,8] and Friedel-Crafts type reactions,[9,10] whose proposed or possible reaction mechanisms involved the formation of

cationic LGs (Figure 1).[11] However, these reactions were carried out using a large excess (typically the solvent) of a strong acid or a superacid. Furthermore, such cationic LGs only cleaved weak nitrogen-halogen (Cl, Br, or I) bonds or provided carbocations stabilized by heteroatoms such as acylium ions and isocyanate cations ($O=C=NR_2^+$). Also, the nucleophiles in such reactions were limited to aromatic compounds and alkenes. In order to overcome these issues, we propose herein a new concept of cationic LGs, which exhibit an additional driving force to facilitate the formation of the carbocation species.

Scheme 1. In situ activation of a LG by diprotonation followed by substitution with a nucleophile to form a cationic LG



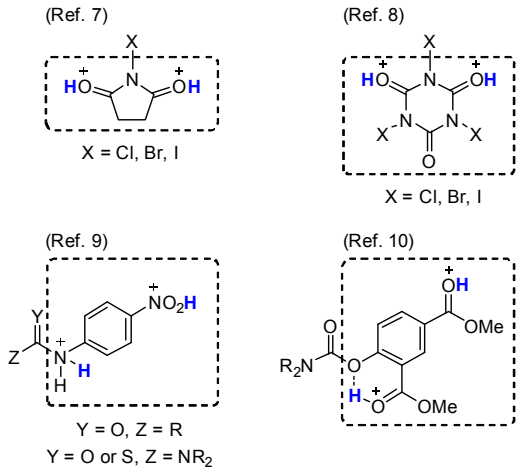
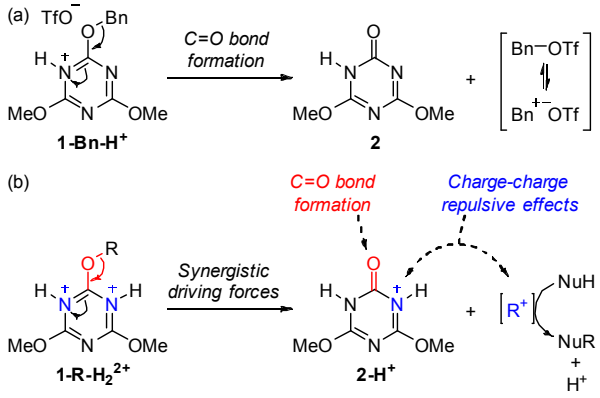


Figure 1. Previously reported dicationic intermediates activated in situ. Proposed cationic LGs are indicated in dashed squares.

We have developed a series of triazine-based alkylating reagents, which generate a variety of carbocation species under acidic conditions.[12] Stable C=O bond formation (10–11 kcal/mol stabilization)[13] in the LGs is considered to be a key driving force of these reactions. For example, **1-Bn-H**$^+$, formed by the monoprotonation of 2-benzyloxy-4,6-dimethoxy-1,3,5-triazine (**1-Bn**), afforded neutral triazine-based LG **2** and a benzyl cation species, probably benzyl trifluoromethanesulfonate, with a half-life of 42 min at 25 °C (Scheme 2a).[12d] Similar stable bond formation has also been utilized as a driving force for well-designed LGs.[14] Thus, we conceived that the diprotonated alkoxytriazines **1-R-H$_2$**$^{2+}$ would exhibit a synergistic combination of driving forces, namely, stable C=O bond formation and charge-charge repulsive effects (Scheme 2b). We found that this double acceleration leads to a rapid generation of highly reactive carbocation species without the need for heteroatom stabilization from stable precursors (2-alkoxy-4,6-dimethoxy-1,3,5-triazine, **1-R**) in the presence of only less than two equivalents of a superacid catalyst. Alcohols, carboxylic acids, and an aromatic compound were chosen as nucleophiles for

alkylation with this carbocation species. Mechanistic and kinetic studies, NMR experiments, and calculations rationalized the design concept of the triazine-based cationic LGs, and provided us insights into the reaction mechanism.

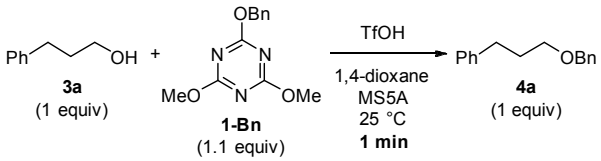
Scheme 2. Synergistic Driving Forces of a Triazine-Based Cationic LG



RESULTS AND DISCUSSION

Acid-Catalyzed Alkylation Using Triazine-Based Reagents. We first carried out *O*-benzylation of alcohol **3a** in 1,4-dioxane using **1-Bn** in the presence of trifluoromethanesulfonic acid (TfOH) at 25 °C. Powdered molecular sieves 5A were added as a dehydrating agent to remove residual moisture.[12a] Interestingly, when 200 mol% of TfOH (182 mol% based on **1-Bn**) was used, the *O*-benzylation was complete *within a minute* and afforded the corresponding benzyl ether **4a** in 84% yield (Table 1, entry 1).[15] In contrast, almost no reaction took place with 100 mol% (91 mol% based on **1-Bn**) of TfOH in 1 min (entry 2). These results suggested that the reaction mechanism was dependent on the amount of TfOH.

Table 1. Acid-Catalyzed Benzylation of 3a Using 1-Bn



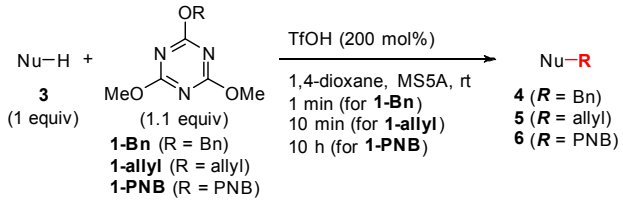
entry	TfOH (mol%)	**4a** (%)[a]	recovered **3a** (%)[a]
1	200	84	1
2	100	1	99

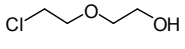
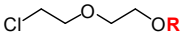
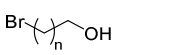
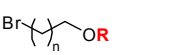
[a] Calculated from ^{1}H NMR analysis using an internal standard.

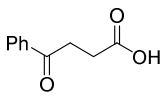
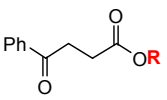
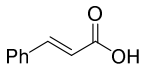
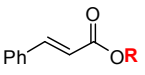
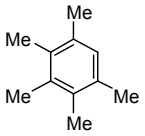
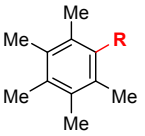
We applied the reaction conditions with **1-Bn** and TfOH (200 mol%) to various nucleophiles (Table 2). Chloroalkyl, bromoalkyl, and fluorous alcohols (**3b**, **3c**, and **3e**, respectively) were *O*-benzylated in high yields (89–90%, entries 1–3). The *O*-benzylation of aliphatic and conjugated carboxylic acids (**3f** and **3g**, respectively) afforded the corresponding benzyl esters **4f** and **4g** in 86% yield (entries 4 and 5). Furthermore, the *C*-benzylation of

pentamethylbenzene (**3h**) also proceeded smoothly (94% yield, entry 6). Similar *O*- and *C*-allylation reactions were conducted using 2-allyloxy-4,6-dimethoxytriazine (**1-allyl**) in the presence of TfOH (200 mol%). As a result, allyl haloalkyl ethers (**5b**, **5d**, and **5e**; entries 1–3), allyl esters (**5f** and **5g**, entries 4 and 5), and allylpentamethylbenzene (**5h**, entry 6) were obtained in good to high yields (71–95%) within 10–20 min. Long-chain bromoalkyl alcohol **3d** was used for the *O*-allylation instead of **3c** to increase the boiling point of the product. The lower isolated yields of **5b** and **5e** in comparison to their NMR yields (84% vs 90% of **5b**; 71% vs 88% of **5e**) were attributed to their volatility. Furthermore, it was possible to introduce the *p*-nitrobenzyl (PNB) group in the nucleophiles by using 2-(*p*-nitrobenzyl)oxy-4,6-dimethoxytriazine (**1-PNB**) and TfOH (200 mol%). Similarly, PNB ethers (**6b**, **6c**, and **6e**; entries 1–3), PNB esters (**6f** and **6g**, entries 4 and 5), and pentamethyl(*p*-nitrobenzyl)benzene (**6h**, entry 6) were obtained in good to high yields (76–97%), although 10 h were required for the completion of the reactions. As shown in entry 1, when 100 mol% of TfOH was used for the *O*-allylation (or *O*-*p*-nitrobenzylation) of **3b** with **1-allyl** (or **1-PNB**), only 1% of the corresponding allyl (or PNB) ether **5b** (or **6b**) was obtained in 10 min (or 10 h). Again, these results imply a change in the reaction mechanism depending on the amount of TfOH. The successful alkylation of arene **3h** (entry 6) suggested that benzyl, allyl, and PNB cations were the intermediates of the reactions with **1-Bn**, **1-allyl**, and **1-PNB**, respectively. The increasing order of the reaction times, i.e., 1 min for benzylation < 10–20 min for allylation < 10 h for *p*-nitrobenzylation, reflected the order of stability of the corresponding carbocations.[16,17]

Table 2. Introduction of Benzyl, Allyl, and *p*-Nitrobenzyl (PNB) Groups to Various Nucleophiles Using 1-Bn, 1-allyl, and 1-PNB in the Presence of TfOH (200 mol%)



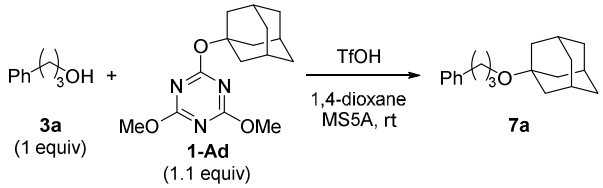
entry	nucleophile	product	yield of **4** (%)[a]	yield of **5** (%)[a]	yield of **6** (%)[a]
1	 **3b**		**4b** 90	**5b** 84[b] (90)[c] 1[c,d]	**6b** 95 1[c,d]
2	 **3c** (n = 1), **3d** (n = 11)		**4c** (n = 1) 89	**5d** (n = 11) 87[e]	**6c** (n = 1) 97
3	 **3e**		**4e** 90	**5e** 71[b] (88)[c]	**6e** 91

4	 **3f**		**4f** 86[f]	**5f** 76[f,g]	**6f** 84
5	 **3g**		**4g** 86[h]	**5g** 74[g,h]	**6g** 76
6	 **3h**		**4h** 92	**5h** 95	**6h** 94

[a] Isolated yields. [b] Isolated yields were lower than the NMR yields because of the volatility of the products. [c] Calculated from ^{1}H NMR spectroscopic analysis using an internal standard. [d] TfOH (100 mol%) was used. [e] Reaction time was 20 min. [f] 1.3 equivalents of **1-Bn** or **1-allyl** were used. [g] Molecular sieves (3Å) were used. [h] 1.2 equivalents of **1-Bn** or **1-allyl** were used.

Next, we conducted the acid-catalyzed *O*-1-adamantylation of **3a** using 2-(1-adamantyl)oxy-4,6-dimethoxy-1,3,5-triazine (**1-Ad**) (Table 3). The corresponding 1-adamantyl ether **7a** was obtained in high yield in the presence of both 100 and 200 mol% of TfOH (90%, entry 1; 92%, entry 2). In contrast to the alkylation reactions shown in Table 2, the increased amount of TfOH had little influence on the reaction time (7.5 h, entry 1; 3 h, entry 2). Entry 3 shows the incomplete formation of **7a** at 25 min with TfOH (200 mol%). However, careful monitoring of the reaction revealed the rapid disappearance of **1-Ad** in the presence of TfOH (200 mol%), and the slow formation of **7a** from **3a** and a moderately stable intermediate, probably 1-adamantyl trifluoromethanesulfonate[18] (Figure 2, details in Figures S1 and S2). A gradual decrease in the amount of **1-Ad** was observed when 100 mol% of TfOH was used. In contrast, it disappeared almost completely within 30 s in the presence of 200 mol% of TfOH. Therefore, a change in the reaction mechanism was also evident in the case of the reaction with **1-Ad**. The substitution at 1-adamantyl group is considered to be a suitable model to study typical S_N1 behavior since β-elimination or rear-side nucleophilic attack is not allowed.[19] Thus, these results suggest that the carbocation species forms from **1-R** via an S_N1 mechanism in the presence of an excess amount of TfOH.

Table 3. Acid-Catalyzed *O*-1-Adamantylation Using 1-Ad



entry	TfOH (mol%)	time	yield of **7a** (%)

1	100	7.5 h	90[a]
2	200	3 h	92[b]
3	200	25 min	78[a]

[a] Calculated from ^{1}H NMR spectroscopic analysis using an internal standard. [b] Isolated yield.

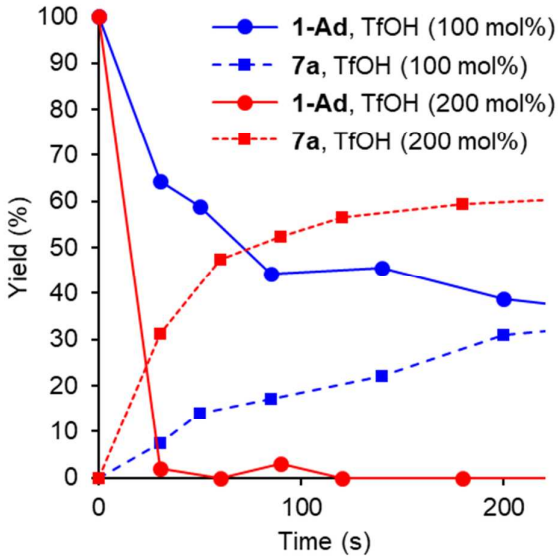


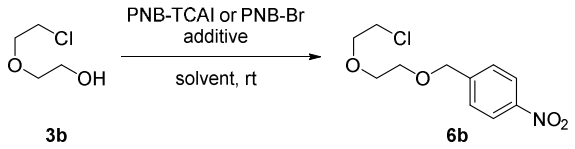
Figure 2. Time course of **1-Ad** and **7a** in acid-catalyzed *O*-1-adamantylation of **3a** with 100 or 200 mol% of TfOH. Reaction conditions: **3a** (50 mM, 1 equiv), **1-Ad** (1 equiv), TfOH (100 or 200 mol%), 1-chlorooctane (internal standard, 1 equiv), 1,4-dioxane, rt. Aliquots were withdrawn from the reaction mixture at indicated time and treated with an excess amount of EtOH containing ^{i}Pr$_2$EtN.

Comparison of the Triazine-Based LG with Other LGs. To demonstrate the synthetic utility of alkylation with the triazine-based reagents described above, we compared their reactivity and stability with those of other common alkylating reagents, namely, alkyl 2,2,2-trichloroacetimidate (R-TCAI) and alkyl bromide (R-Br).

O-p-Nitrobenzylation. Interestingly, the *O*-*p*-nitrobenzylation of an alcohol with PNB-TCAI has been seldom reported despite the usefulness of PNB as a protecting group.[20] In fact, only one report referred to this reaction briefly, but the experimental details were not described.[21] We attempted the TfOH-catalyzed *O*-*p*-nitrobenzylation of **3b** with PNB-TCAI (Table 4). It was found that the yields of **6b** under these conditions were moderate (40% in CH_2Cl_2, entry 1; 72% in 1,4-dioxane, entry 2) even though the reactions were performed in the presence of TfOH (20 mol%). When the amount of TfOH was increased to 200 mol%, the yield did not improve (64%, entry 3). In these cases, various amounts of *O*-trichloroacetimidoyl and trichloroacetyl products of **3b** (respectively, 12–23% in total, details are given in Table S1) were observed as by-products. Owing to these competing side reactions, it was difficult to achieve high yields in *O*-*p*-nitrobenzylation with PNB-TCAI. An alternative method to introduce the PNB group is the combination of PNB-Br and a silver salt such as Ag_2O. These conditions are chosen because Williamson ether synthesis cannot to be applied as a result of the decomposition of PNB-Br under strongly basic conditions.[20] Chloroalkyl alcohol **3b** was converted to **6b** with PNB-Br/Ag_2O in 87% yield (entry 4). However, the

reaction of bromoalkyl alcohol **3c** led to poor yield of the product (13%, entry 5). Therefore, it is worth noting that the reaction of **1-PNB** with TfOH allowed the introduction of the PNB group to base- and silver-sensitive alcohols **3b** and **3c**, and excellent yields (95 and 97%, entries 1 and 2 in Table 2, respectively) were attainable.

Table 4. *O*-*p*-Nitrobenzylation Using *p*-Nitrobenzyl 2,2,2-Trichloroacetimidate (PNB-TCAI) and *p*-Nitrobenzyl Bromide (PNB-Br)



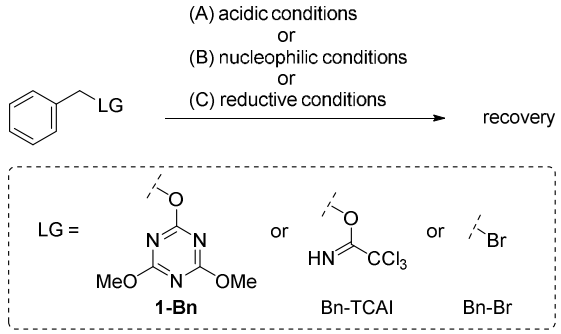
3b **6b**

entry	reagent, additive	solvent	time (h)	yield (%)[a]
1	PNB-TCAI (1.1 equiv) TfOH (20 mol%)	CH_2Cl_2	32	40
2	PNB-TCAI (1.1 equiv) TfOH (20 mol%)	1,4-dioxane[b]	6.5	73 (72)[c]
3	PNB-TCAI (1.1 equiv) TfOH (200 mol%)	1,4-dioxane[b]	0.5	64
4	PNB-Br (1.2 equiv) Ag_2O (1.2 equiv)	CH_2Cl_2	24	87
5[d]	PNB-Br (1.2 equiv) Ag_2O (1.2 equiv)	CH_2Cl_2	24	13

[a] Calculated from ^{1}H NMR spectroscopic analysis using an internal standard. [b] Molecular sieves (5Å) were added. [c] Isolated yield. [d] Alcohol **3c** was used instead of **3b** to obtain PNB ether **6c**.

Stability. As shown in Tables 2 and 3, the triazine-based LGs showed remarkable reactivity in the presence of an excess amount of TfOH. On the other hand, they were found to be highly stable under other more common conditions. Table 5 summarizes the results of the experiments demonstration the inertness of the triazine-based LGs. The benzyl derivatives, namely, **1-Bn**, Bn-TCAI, and Bn-Br, were exposed to (A) acidic ($TsOH\cdot H_2O$ (0.5 equiv), CH_2Cl_2/MeOH, rt, 5 min), (B) nucleophilic [Et_2NH (2.5 equiv), CH_2Cl_2, rt, 1 h], and (C) reductive [Zn (5 equiv), NH_4Cl (5 equiv), EtOH, reflux, 5 min] conditions, respectively.[22] In these experiments, **1-Bn** was recovered almost quantitatively in all cases (96–98% recovery, entry 1). In contrast, considerable decomposition was observed for Bn-TCAI and Bn-Br. While Bn-TCAI was resistant to condition (B) (96% recovery), it decomposed to benzyl alcohol almost completely under conditions (A) and (C) (entry 2). On the other hand, Bn-Br was partially stable under condition (A) (63% recovery), although it did not survive under conditions (B) and (C) (entry 3). Thus, it was evident that the triazine-based LGs had superior stability in comparison to TCAI and bromide, providing practicability for handling and possibility of acting as protecting groups of carbocation species for selective transformations.

Table 5. Stability of LGs under the Acidic, Nucleophilic, and Reductive conditions.



entry	starting material	conditions	recovery (%)[a]
1	**1-Bn**	A[b]	98
		B[c]	96
		C[d]	96
2	Bn-TCAI	A[b]	trace[e]
		B[c]	96
		C[d]	n.d.[f,g]
3	Bn-Br	A[b]	63
		B[c]	trace[h]
		C[d]	n.d.[g]

[a] Calculated from ^{1}H NMR spectroscopic analysis using an internal standard. [b] Acidic conditions: TsOH·H_2O (0.5 equiv), CH_2Cl_2/MeOH (1:1, 0.2 M), rt, 5 min. [c] Nucleophilic conditions: Et_2NH (2.5 equiv), CH_2Cl_2 (0.2 M), rt, 1 h. [d] Reductive conditions: Zn (5 equiv), NH_4Cl (5 equiv), EtOH (0.5 M), reflux, 5 min. [e] Benzyl alcohol was obtained in 83% yield. [f] Benzyl alcohol was obtained in 96% yield. [g] Not detected. [h] Benzyldiethylamine was obtained in 86% yield.

Mechanistic Studies. *NMR analysis*. To observe the protonation behavior of the triazine-based LGs by TfOH, we performed ^{13}C NMR analysis (NoD-NMR) in 1,4-dioxane using 2,4,6-trimethoxy-1,3,5-triazine (**1-Me**) as a model compound. Figure 3 plots the chemical shifts of the methyl group in **1-Me** (1 equiv) versus the amount of TfOH (0–500 mol%). A linear downfield shift from 55.0 to 58.6 ppm was observed when the concentration of TfOH was less than 100 mol%. This downfield shift was linear and gradual (58.6136 to 58.7572 ppm) in the range of 105–500 mol% TfOH. This gradual shift (0.1436 ppm) is significant because only a small change (± 0.0062 ppm at the maximum) was detected in the carbon chemical shifts of dodecane, which was used as a control during the addition of TfOH (0–500 mol%) under the same conditions (details are given in Table S3). The downfield shifts of **1-Me** can be explained by the quantitative formation of **1-Me-H**$^+$ by monoprotonation with TfOH (< 100 mol%) and the subsequent equilibration to the diprotonated form **1-Me-H$_2$**$^{2+}$ with an excess of TfOH (> 100 mol%).[23]

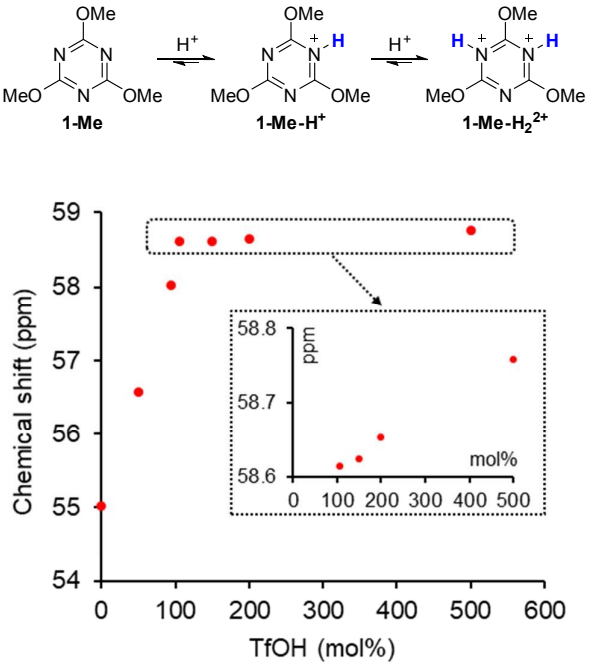
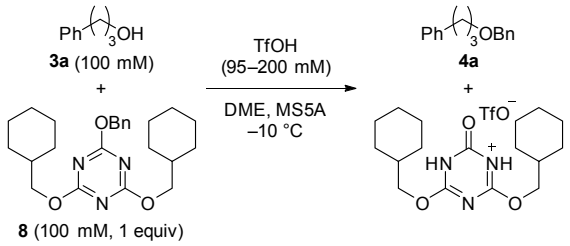


Figure 3. NMR spectroscopic analysis of the protonation of **1-Me** with TfOH.

Kinetic Study. We studied the kinetics of the *O*-benzylation of **3a** (100 mM) using benzyloxytriazine **8** (100 mM) in the presence of various amounts of TfOH (95–200 mM (or mol% based on **8**)) to gain insights into the mechanism of the reaction (Table 6). This kinetic study was performed at −10 °C to decrease the reaction rate to a measurable degree. 1,2-Dimethoxyethane (DME) (m.p. −58 °C) was used as a solvent instead of 1,4-dioxane (m.p. 12 °C) because DME has similar properties to those of 1,4-dioxane; it dissolves TfOH well and shows favorable solvent effects in the acid-catalyzed *O*-benzylation.[12a] Compound **8** possesses lipophilic cyclohexylmethyl groups instead of methyl groups, which increase its solubility in DME. First-order kinetics were observed for the decrease in the [**8**-**H**$^+$] concentration with any [TfOH].[24,25] The observed first-order kinetic constants (k_{obs}) are summarized in Table 6 (entries 1–5). It was concluded that the trifluoromethanesulfonate anion (TfO^-) did not affect the rate-determining step because the addition of $TfON^nBu_4$ had no effect on the reaction rate (entry 3 vs 6). This result also indicated that the influence of ionic strength could be ignored. Figure 4 clearly shows that k_{obs} increased sharply when [TfOH] > 100 mM (i.e., concentration of TfOH was greater than 100 mol%), which supported the formation of a dicationic intermediate. The reaction rate in the case of [TfOH] = 200 mM was more than 800 times faster than that the reaction with [TfOH] = 95 mM. Interestingly, a careful analysis revealed that the increase in the value of k_{obs} could be correlated with the square of [$TfOH_{ex}$]. Here, [$TfOH_{ex}$] is defined by [TfOH] − 100 mM and represents the concentration of an excess amount of TfOH over **8** (listed in Table 6). The likely linear relationship between [$TfOH_{ex}$]^2 and k_{obs} (r^2 = 0.975) is shown in Figure 5.[26] This correlation may suggest that two molecules of $TfOH_{ex}$ are involved in the transition state.

Table 6. Observed First-Order Rate Constants of TfOH-Catalyzed *O*-Benzylation with 8



entry	TfOH (mM or mol%)	$TfOH_{ex}$ (mM or mol%)	k_{obs} (10^{-3} min^{-1})[a]	relative rate
1	95	-	0.0831 ± 0.0343	1.00
2	110	10	1.42 ± 0.54	17.1
3	140	40	13.6 ± 1.2	164
4	170	70	34.3 ± 4.5	413
5	200	100	66.6 ± 6.1	801
6[b]	140	40	13.7	165

[a] Rate constants (k_{obs}) were determined by HPLC analysis using *p*-nitrotoluene as an internal standard. Measurement of k_{obs} was repeated three times each except for entry 6. [b] $TfON^nBu_4$ (100 mM) was added.

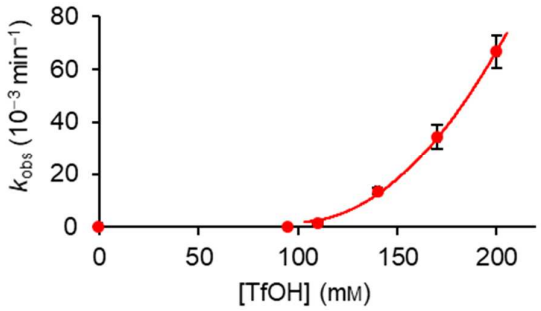


Figure 4. Dependence of k_{obs} on [TfOH] for the TfOH-catalyzed *O*-benzylation with **8**.

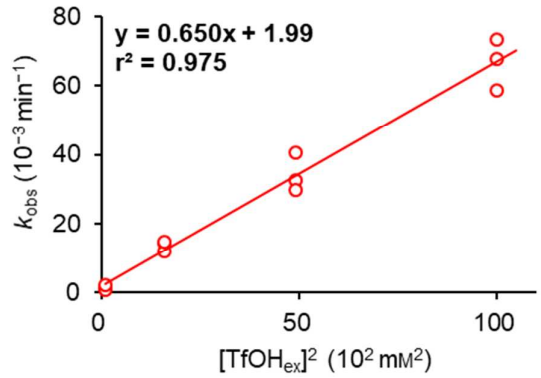


Figure 5. Linear relationship between $[TfOH_{ex}]^2$ and k_{obs}.

Calculations. Since results depicted in Figure 3 suggested the formation of a dicationic species of **1-Me**, we calculated the energy differences between *N*- or *O*-protonated mono/dication of **1-Me** in 1,4-dioxane using protonated 1,4-dioxane as a proton donor (Figures 6 and 7, B3LYP/6-31+G(d,p)). As shown in Figure 6, it was evident that the *N*-protonation of the triazine nitrogen provided significant stabilization (−20.5 kcal/mol). This is in agreement with the quantitative formation of **1-Me-H**$^+$ by TfOH shown in Figure 3. In contrast, the *O*-protonation of **1-Me** was a disfavored process (**1-Me-H**$^+$ **(*O*)**, +12.1 kcal/mol). Calculations for the dications of **1-Me** are shown in Figure 7. The most stable dication was the *N*,*N*′-diprotonated **1-Me-H$_2$**$^{2+}$ (+15.1 kcal/mol). This result indicated that the further protonation of **1-Me-H**$^+$ to form **1-Me-H$_2$**$^{2+}$ was disfavored (+35.6 kcal/mol). The other possible dications (**1-Me-H$_2$**$^{2+}$ **(*OO*)**, **1-Me-H$_2$**$^{2+}$ **(*o-NO*)**, and **1-Me-H$_2$**$^{2+}$ **(*p-NO*)**) had higher energies than that of **1-Me-H$_2$**$^{2+}$ (37.7–66.9 kcal/mol).

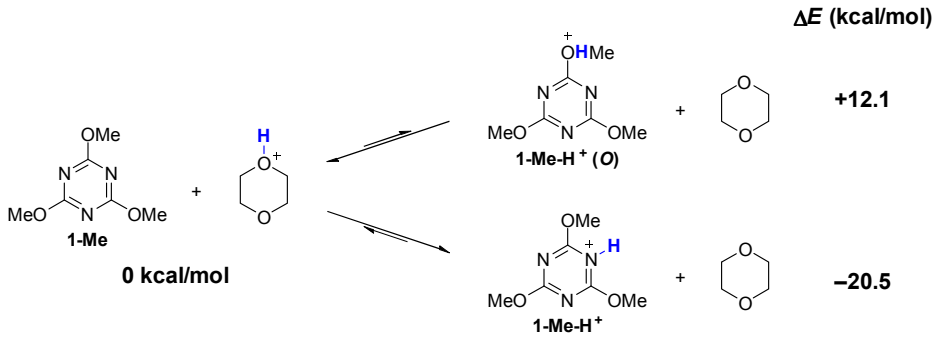


Figure 6. Calculated energy differences (kcal/mol) of the *N*- or *O*-protonated monocation of **1-Me** (B3LYP/6-31+G(d,p), in 1,4-dioxane).

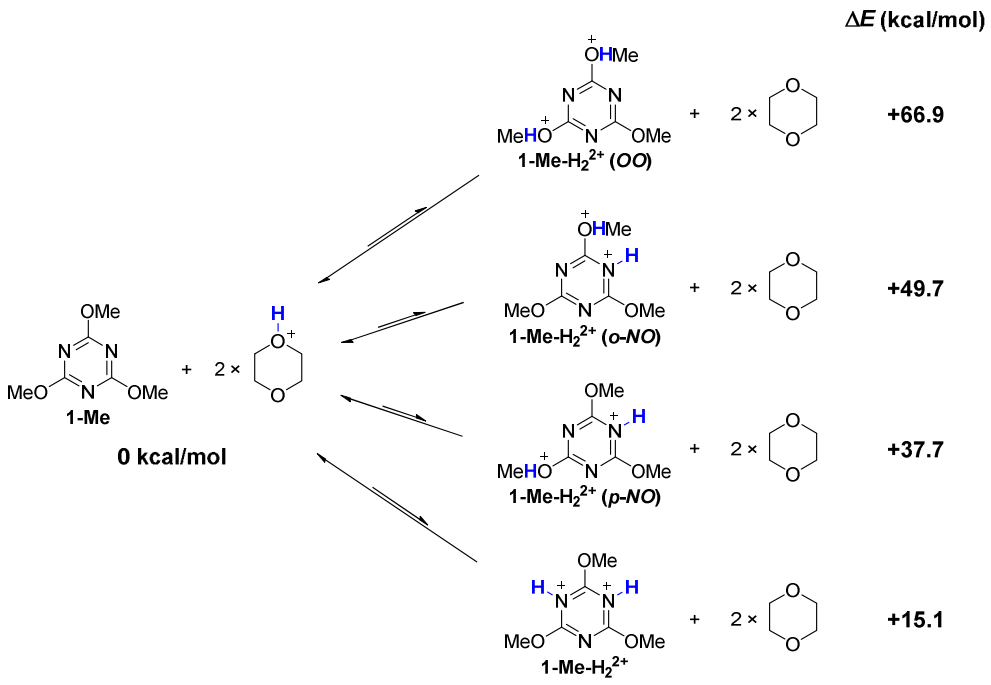
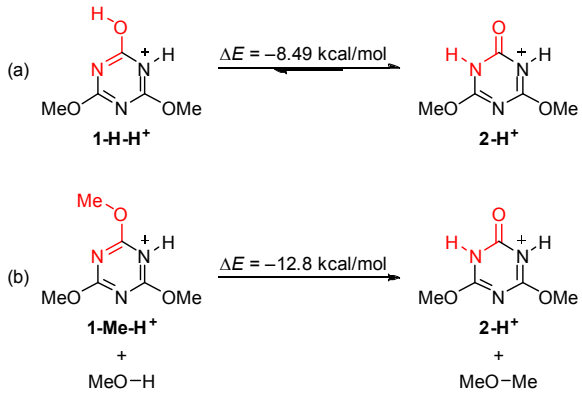


Figure 7. Calculated energy differences (kcal/mol) of the *N*- or *O*-protonated dications of **1-Me** (B3LYP/6-31+G(d,p), in 1,4-dioxane).

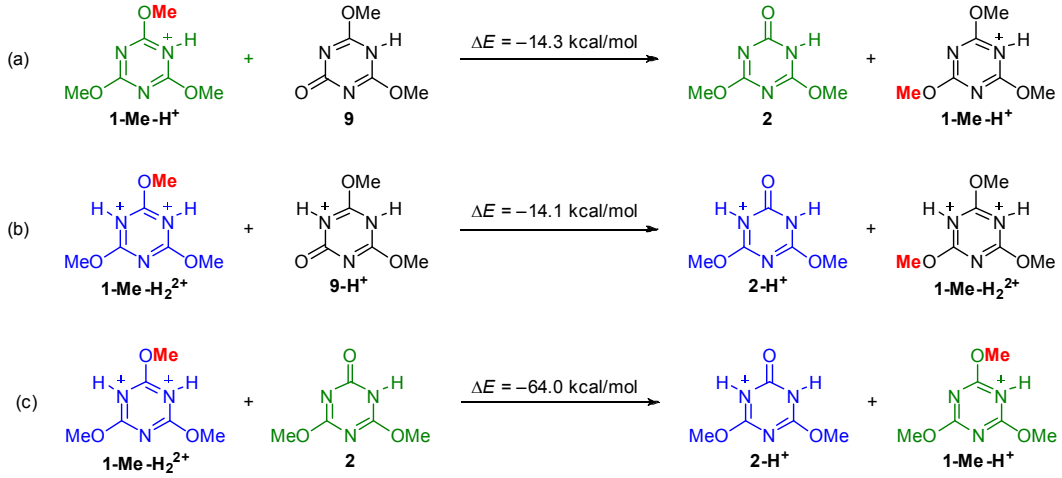
The tautomerization energy from **1-H-H**$^+$ to **2-H**$^+$ was calculated to be −8.49 kcal/mol in 1,4-dioxane, which reflected the stability of the C=O bond in **2-H**$^+$ (Scheme 3a). Furthermore, the model reaction between **1-Me-H**$^+$ and methanol to give **2-H**$^+$ and dimethyl ether was calculated to be a favored process in 1,4-dioxane (−12.8 kcal/mol, Scheme 3b). Therefore, the C=O bond formation in cationic LG **2-H**$^+$ can be an effective driving force for the generation of carbocation species from **1-R-H**$^+$, similar to that in a triazine-based neutral LG.[13]

Scheme 3. Calculated Energy differences of (a) the tautomerization of 1-H-H$^+$ to 2-H$^+$ and (b) the model reaction between 1-Me-H$^+$ and methanol to give 2-H$^+$ and dimethyl ether (B3LYP/6-31+G(d,p), in 1,4-dioxane)



Further calculations were performed to compare the driving forces in isodesmic reactions of triazine compounds, where a methyl cation was hypothetically exchanged (Scheme 4). The favored reaction in Scheme 4a (–14.3 kcal/mol) predicted the formation of the neutral LG **2** from **1-Me-H**$^+$ rather than that of **9**, which is an tautomer of **2**. Similarly, the formation of the cationic LG **2-H**$^+$ from **1-Me-H$_2$**$^{2+}$ was calculated to be more favored than that of **9-H**$^+$ (–14.1 kcal/mol, Scheme 4b). A large energy difference (–64.0 kcal/mol) was found in the methyl cation exchange between **1-Me-H$_2$**$^{2+}$ and **2** to give **2-H**$^+$ and **1-Me-H**$^+$ (Scheme 4c). This stabilization (–64.0 kcal/mol) overwhelms the energy difference of the second protonation process calculated in Figures 6 and 7 (**1-Me-H**$^+$ to **1-Me-H$_2$**$^{2+}$, +35.6 kcal/mol). Therefore, the reaction affording the triazine-based cationic LG (**1-Me-H$_2$**$^{2+}$ to **2-H**$^+$) would be favored over the formation of the neutral LG (**1-Me-H**$^+$ to **2**). Charge-charge repulsive effects can explain the large driving force of the formation of **2-H**$^+$.

Scheme 4. Calculated Isodesmic Reactions for the Hypothetical Methyl Cation Exchange Between (a) 1-Me-H$^+$ and 9, (b) 1-Me-H$_2$$^{2+}$ and 9-H$^+$, and (c) 1-Me-H$_2$$^{2+}$ and 2 (B3LYP/6-31+G(d,p), in 1,4-dioxane)



Reaction Mechanisms. On the basis of the above considerations, we proposed a plausible reaction mechanism of TfOH-catalyzed alkylation with **1-R** (Figure 8). As a large K_1 was indicated by the model experiments and calculations (Figures 3 and 6), protonation of **1-R** by TfOH was considered to proceed quantitatively to give the monocation/TfO$^-$ salt **9**. This salt generated the neutral LG **2** along with the corresponding carbocation species, probably alkyl triflate (ROTf), which may form carbocation (R$^+$—OTf) depending on the ionizing ability of the R group (neutral LG pathway). If an excess amount of TfOH was used, the equilibrium (K_2) would lead to the second protonation of **1-R**. Although the reason for the likely second-order kinetic dependence of k_{obs} on [TfOH$_{ex}$] (Figure 5) is unclear, a possible explanation is the dimerization of TfOH$_{ex}$ to the (TfOH$_{ex}$)$_2$ species (K_3).[27] This interpretation has been previously proposed to explain the similar second-order kinetic behavior of TfOH-mediated dealkylative lactonization.[28] If the second protonation by (TfOH$_{ex}$)$_2$ to afford the dication salt **10** is necessary for the formation of ROTf along with cationic LG **2-H**$^+$ and the regenerated TfOH$_{ex}$ (cationic LG pathway), the rate law for the decrease in concentration of **9** is given by Eq. 1. This is because **9** is consumed via both neutral and cationic LG pathways.

$$-\frac{\mathrm{d}[\mathbf{9}]}{\mathrm{d}t} = \frac{\mathrm{d}[\mathrm{ROTf}]}{\mathrm{d}t}$$
$$= k_\mathrm{n}[\mathbf{9}] + k_\mathrm{c}[\mathbf{10}]$$
$$= \left(k_\mathrm{n} + k_\mathrm{c}K_2K_3[\mathrm{TfOH}_\mathrm{ex}]^2\right)[\mathbf{9}] \#(1)$$

Since there are three basic nitrogen atoms in the 1,3,5-triazine ring, the monocation and dication of **1-R** should have regioisomers, including the less active forms as shown in Figure 9 (see discussion of model compounds in Scheme 4). Nevertheless, similar to the previous analysis of acid-catalyzed *O*-benzylation with benzyloxytriazines,[12d] we treated them as a mixture of the regioisomers because this protonation equilibrium is inevitable. Only the active regioisomers of **9** and **10** are shown in Figure 8. In the case of R = Bn, [$\mathrm{TfOH}_\mathrm{ex}$] should be constant throughout the reaction because $\mathrm{TfOH}_\mathrm{ex}$ is regenerated rapidly by the fast reaction between BnOTf and a nucleophile. Therefore, the decrease in [**9**] follows first-order kinetics, where k_obs is equal to $k_\mathrm{n} + k_\mathrm{c}K_2K_3[\mathrm{TfOH}_\mathrm{ex}]^2$. The kinetic parameters of the *O*-benzylation studied in Table 6 are given by the slope and the *y*-intercept in Figure 5, respectively: $k_\mathrm{n} = 1.99 \times 10^{-3}$ min^{-1} (–10 °C) and $k_\mathrm{c}K_2K_3 = 6.50 \times 10^{-6}$ $\mathrm{min}^{-1}\mathrm{mM}^{-2}$ (–10 °C). Similar to the benzylation reaction, nucleophile alkylation with ROTf would be faster than its formation when R = allyl or PNB. In contrast, alkylation is slower when R = 1-adamantyl, as discussed for Figure 2.

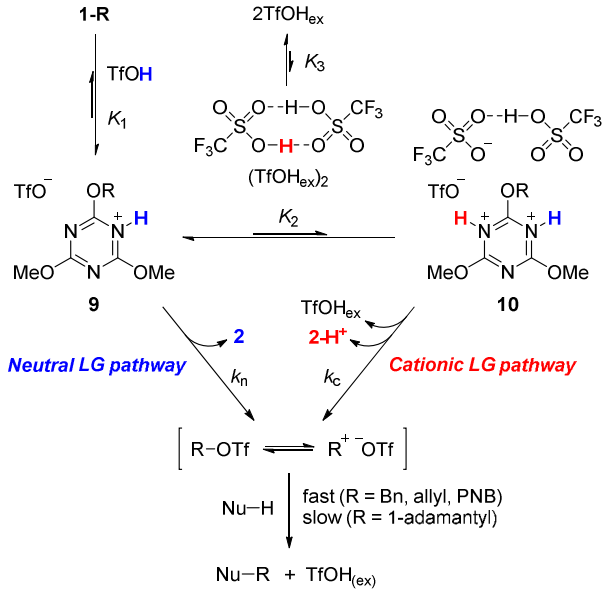


Figure 8. Plausible reaction mechanisms.

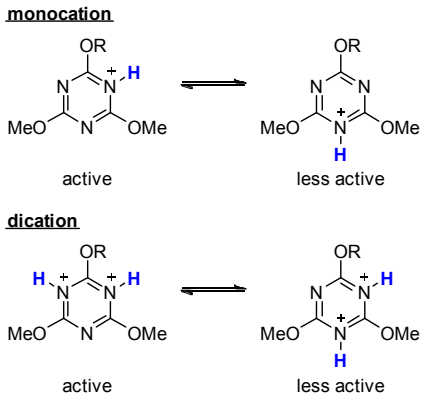


Figure 9. The regioisomers of the monocation and dication of **1-R**.

The neutral LG pathway is operative in the presence of less than 100 mol% of TfOH, while the cationic LG pathway predominates when only a small amount of TfOH (~ 200 mol%) is added. This "switching" of the reaction mechanism is an interesting property of the triazine-based LGs.[29]

CONCLUSION

We have developed a new, triazine-based cationic LG **2-H**$^+$ for acid-catalyzed alkylation in the presence of TfOH (~200 mol%). Alkyl groups such as benzyl, allyl, PNB, and 1-adamantyl were introduced to the *O*- and *C*-nucleophiles in good to high yields. The reaction times were dramatically shorter than the alkylation reactions with < 100 mol% of TfOH, except for the case of *O*-1-adamantylation. Advantages of the triazine-based cationic LGs over TCAI and Br were demonstrated by comparing the ease of *O*-*p*-nitrobenzylation and stability. The formation of the dicationic intermediate **1-R-H$_2$**$^{2+}$ was supported by NMR experiments and theoretical calculations. Kinetic studies using a model compound clarified the remarkable acceleration of the formation of the benzyl cation species in the presence of an excess amount of TfOH. A new reaction mechanism, i.e., the cationic LG pathway, was suggested on the basis of mechanistic studies. We have proposed that the origin of the rapid formation of carbocation species from **1-R-H$_2$**$^{2+}$ can be rationalized by the synergistic combination of two driving forces in **2-H**$^+$, namely, stable C=O bond formation and charge-charge repulsive effects. These driving forces were evaluated by calculations of the model compounds. The concept of the cationic LG described here expands the utility of 1,3,5-triazines and allows us to apply this new strategy for substitution reactions in organic synthesis.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a JEOL JNM-ECS400 spectrometer [^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 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. Chemical shifts for ^{13}C NMR are reported in parts per million (δ) relative to the solvent [$CDCl_3$, δ 77.16]. Chemical shifts for ^{19}F NMR are reported in parts per million (δ) relative to α,α,α-trifluorotoluene [$CDCl_3$, δ −62.82]. 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 JMS-700(2) (EI-MS). Analytical thin layer chromatography (TLC) was performed using glass plates precoated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm). Preparative TLC separations were performed using glass plates precoated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm). Flash chromatography was performed using silica gel (spherical, neutral, 40–100 mesh). Recycling preparative HPLC was performed with Japan Analytical Industry LC-928 equipped with GPC columns Jaigel-1H and 2H. All reactions sensitive to oxygen or moisture were conducted under a nitrogen atmosphere. Reagents were commercial grades and were used without any purification unless otherwise noted. TfOH (>98.0% purity), dehydrated 1,4-dioxane, CH_2Cl_2, THF, and MeOH were purchased from commercial sources and used without further purification. DME and ethyldiisopropylamine were purchased from commercial sources and distilled before use. Cyanuric chloride and 2-chloro-4,6-dimethoxy-1,3,5-triazine were recrystallized from hexane/chloroform before use. Known compounds [**1-Bn**, **1-Me**, and 2-chloro-4,6-bis(cyclohexylmethoxy)-1,3,5-triazine] were prepared as described in the literature.[12d]

*Benzyl 2-(2-chloroethoxy)ethyl ether (**4b**)*.[12a] TfOH (52.7 μL, 0.60 mmol) was to a mixture of **3b** (31.7 μL, 0.30 mmol), **1-Bn** (81.6 mg, 0.33 mmol), and MS5A (5 mg) in 1,4-dioxane (1.00 mL) at room temperature. After 1 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford a clear colorless oil (57.7 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.25 (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 ($CDCl_3$, 100 MHz): δ 138.3, 128.5, 127.9, 127.8, 73.5, 71.5, 70.9, 69.5, 42.9. LRMS (DART-TOF): m/z 215 ($[M + H]^+$).

*Benzyl 2-bromoethyl ether (**4c**)*.[12a] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3c** (21.4 μL, 0.30 mmol), **1-Bn** (81.6 mg, 0.33 mmol), and MS5A (10 mg) in 1,4-dioxane (1.00 mL) at room temperature. After 1 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford a clear colorless oil (57.1 mg, 89%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.40–7.25 (m, 5H), 4.59 (s, 2H), 3.79 (t, J = 6.2 Hz, 2H), 3.49 (t, J = 6.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 137.9, 128.6, 128.0, 127.9, 73.3, 70.1, 30.6. LRMS (DART-TOF): m/z 215 ($[M + H]^+$).

Benzyl 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluorodecyl ether (4e). TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3e** (139.2 mg, 0.30 mmol), **1-Bn** (81.6 mg, 0.33 mmol), and MS5A (5 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 1 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford a clear colorless oil (150.4 mg, 90%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49–7.25 (m, 5H), 4.55 (s, 2H), 3.77 (t, J = 6.5 Hz, 2H), 2.50–2.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.7, 128.7, 128.0, 127.8, 120.5–105.6 (perfluorocarbons), 73.5, 62.2 (t), 31.7 (t). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −80.8, −113.4, −121.8, −122.0, −122.8, −123.7, −126.2. Anal. Calcd for $C_{17}H_{11}F_{17}O$: C, 36.84; H, 2.00.

Found: C, 37.10; H, 2.20. HRMS (double-focusing, EI) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{11}F_{17}O$ 554.0538. Found: 554.0526. IR ($CHCl_3$): 1603, 1259, 1240, 1195, 1178, 1151 cm^{-1}.

*Benzyl 3-benzoylpropionate (**4f**)*.[12c] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3f** (53.5 mg, 0.30 mmol), **1-Bn** (96.4 mg, 0.39 mmol), and MS5A (5 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 1 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford a pale yellow oil (69.6 mg, 86%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00–7.95 (m, 2H), 7.59–7.54 (m, 1H), 7.49–7.44 (m, 2H), 7.39–7.25 (m, 5H), 5.15 (s, 2H), 3.34 (t, J = 6.6 Hz, 2H), 2.83 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.2, 172.9, 136.7, 136.0, 133.4, 128.8, 128.7, 128.37, 128.35, 128.2, 66.7, 33.5, 28.4. LRMS (DART-TOF): *m*/*z* 269 ($[M + H]^+$).

*Benzyl (E)-cinnamate (**4g**)*[12c] TfOH (105.3 μL, 1.2 mmol) was added to a mixture of **3g** (88.9 mg, 0.60 mmol), **1-Bn** (178.0 mg, 0.72 mmol), and MS5A (10 mg) in 1,4-dioxane (1.00 mL) at room temperature. After 1 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with 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) to afford a clear pale yellow oil (122.5 mg, 86%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, J = 16.0 Hz, 1H), 7.59–7.48 (m, 2H), 7.46–7.30 (m, 8H), 6.49 (d, J = 16.0 Hz, 1H), 5.26 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0, 145.3, 136.2, 134.5, 130.5, 129.0, 128.8, 128.43, 128.40, 128.3, 118.0, 66.5. LRMS (DART-TOF): *m*/*z* 239 ($[M + H]^+$).

*Benzylpentamethylbenzene (**4h**)*.[12a] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3h** (44.5 mg, 0.30 mmol), **1-Bn** (81.6 mg, 0.33 mmol), and MS5A (10 mg) in 1,4-dioxane (1.00 mL) at room temperature. After 1 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 9:1) to afford a white solid (66 mg, 92%). Mp 111–112 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.11 (m, 3H), 7.03 (d, J = 7.4 Hz, 2H), 4.11 (s, 2H), 2.27 (s, 3H), 2.24 (s, 6H), 2.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.8, 133.9, 133.3, 132.9, 132.6, 128.5, 128.1, 125.7, 36.3, 17.1, 17.01, 17.00. LRMS (DART-TOF): *m*/*z* 239 ($[M + H]^+$).

*2-Allyloxy-4,6-dimethoxy-1,3,5-triazine (**1-Allyl**)*.[30] *N*-Methylmorpholine (1.10 mL, 10 mmol) was added to a suspension of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.756 g, 10.0 mmol) and ethyldiisopropylamine (2.09 mL, 12.0 mmol) in allyl alcohol (10.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and room temperature for 0.5 h. The reaction mixture was quenched with AcOH (0.57 mL) and concentrated under reduced pressure. The residue was dissolved in hexane/EtOAc (1:1, 10 mL). The solution was washed with 10% aqueous citric acid (10 mL) followed by brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 4:1) followed by recrystallization from hexane to afford a white solid (1.79 g, 91%). Mp 36 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.06 (m, J = 17.4, 10.6, 5.5 Hz, 1H), 5.42 (d, J = 17.4, 1H), 5.30 (d, J = 10.6 Hz, 1H), 4.92 (d, J = 5.5 Hz, 2H), 4.03 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 173.6, 172.9, 131.7, 119.1, 69.0, 55.5. LRMS (DART-TOF): *m*/*z* 198 ($[M + H]^+$).

*Allyl (2-(2-chloroethoxy)ethyl ether (**5b**)*.[31] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3b** (31.7 μL, 0.30 mmol), **1-allyl** (65.1 mg, 0.33 mmol), and MS5A (5 mg) in 1,4-dioxane (0.50 mL) was added at room temperature. After 10 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford a clear colorless oil (41.5 mg, 84%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.92 (ddt, J = 18.0, 10.0, 4.8 Hz, 1H), 5.28 (ddt, J = 18.0, 1.6, 1.6 Hz, 1H), 5.19 (ddt, J = 10.7, 1.6, 1.6 Hz, 1H), 4.04 (ddd, J = 4.8, 1.6, 1.6 Hz, 2H), 3.77 (t, J = 5.9 Hz, 2H), 3.71–3.67 (m, 2H), 3.66–3.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 134.8, 117.4, 72.4, 71.6, 70.9, 69.5, 42.8. LRMS (DART-TOF): m/z 165 ($[M + H]^+$).

Allyl 12-bromododecyl ether (5d). TfOH (35.1 μL, 0.40 mmol) was added to a mixture of **3d** (53.0 mg, 0.20 mmol), **1-allyl** (43.4 mg, 0.22 mmol), and MS5A (3.3 mg) in 1,4-dioxane (0.33 mL) at room temperature. After 20 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 49:1) to afford a clear colorless oil (53.3 mg, 87%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.92 (ddt, J = 17.2 , 10.7, 5.5 Hz, 1H), 5.27 (dd, J = 17.2, 1.4 Hz, 1H), 5.25 (dd, J = 10.7, 1.4 Hz, 1H), 3.96 (d, J = 5.5 Hz, 2H), 3.42 (t, J = 6.9 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 1.90–1.80 (m, 2H), 1.62–1.54 (m, 2H), 1.46–1.38 (m, 2H), 1.37–1.10 (m, 14H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 135.3, 116.8, 72.0, 70.7, 34.2, 33.0, 29.9, 29.71, 29.68, 29.66, 29.64, 29.57, 28.9, 28.3, 26.3. Anal. Calcd for $C_{15}H_{29}BrO$: C, 59.01; H, 9.57. Found: C, 58.97; H, 9.84. HRMS (DART-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{30}BrO$ 305.1480. Found: 305.1508. IR ($CHCl_3$): 2929, 2856, 1464, 1095 cm^{-1}.

*Allyl 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluorodecyl ether (**5e**)*.[32] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3e** (139.2 mg, 0.30 mmol), **1-allyl** (65.1 mg, 0.33 mmol), and MS5A (5 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 10 min, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford a clear colorless oil (107.2 mg, 71%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.90 (ddt, J = 18.0, 9.9, 4.8 Hz, 1H), 5.30 (ddt, J = 18.0, 1.5, 1.5 Hz, 1H), 5.22 (ddt, J = 9.9, 1.5, 1.5 Hz, 1H), 4.01 (ddd, J = 4.8, 1.5, 1.5 Hz, 2H) , 3.73 (t, J = 6.8 Hz, 2H), 2.42 (tt, J = 18.8, 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.3, 121.6–106.8 (perfluorocarbons), 117.6, 72.3, 62.1 (t), 31.7 (t). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −80.8, −113.5, −121.8, −122.0, −122.8, −123.7, −126.2. LRMS (DART-TOF): m/z 505 ($[M + H]^+$).

*Allyl 3-benzoylpropionate (**5f**)*.[33] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3f** (53.5 mg, 0.30 mmol), **1-allyl** (76.9 mg, 0.39 mmol), and MS3A (5 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 10 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to afford a pale yellow oil (49.6 mg, 76%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.98 (d, J = 7.9 Hz, 2H), 7.57 (t, J = 7.9 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 5.93 (ddt, J = 17.3, 10.6, 5.8 Hz, 1H), 5.33 (dd, J = 17.3, 1.7 Hz, 1H), 5.24 (dd, J = 10.6,

1.7 Hz, 1H), 4.62 (d, J = 5.8 Hz), 3.33 (t, J = 6.5 Hz, 2H), 2.81 (t, J = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 198.1, 172.7, 136.7, 133.4, 132.3, 128.8, 128.2, 118.4, 65.5, 33.5, 28.3. LRMS (DART-TOF): m/z 219 ($[M + H]^+$).

*Allyl (E)-cinnamate (**5g**)*.[34] TfOH (52.7 μL, 0.6 mmol) was added to a mixture of **3g** (44.4 mg, 0.30 mmol), **1-allyl** (71.0 mg, 0.36 mmol), and MS3A (25 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 10 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford a clear colorless oil (41.8 mg, 74%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.72 (d, J = 15.8 Hz, 1H), 7.56–7.50 (m, 2H), 7.42–7.36 (m, 3H), 6.47 (d, J = 15.8 Hz, 1H), 6.00 (ddt, J = 17.0, 11.4, 5.8 Hz, 1H), 5.38 (dt, J = 17.0, 1.4 Hz), 5.28 (dt, J = 11.4, 1.4 Hz, 1H), 4.72 (ddd, J = 5.8, 1.4, 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 166.8, 145.2, 134.5, 132.4, 130.5, 129.0, 128.2, 118.4, 118.0, 65.4; LRMS (DART-TOF): m/z 189 ($[M + H]^+$).

*Allylpentamethylbenzene (**5h**)*.[35] TfOH (52.7 μL, 0.60 mmol) was added to a mixture of **3h** (44.5 mg, 0.30 mmol), **1-allyl** (65.1 mg, 0.33 mmol), and MS5A (5 mg) in 1,4-dioxane (0.50 mL) at room temperature. After 10 min, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to afford a white solid (53.5 mg, 95%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.93 (ddt, J = 17.4, 9.8, 4.8 Hz, 1H), 5.00 (ddt, J = 9.8, 1.8, 1.8 Hz, 1H), 4.88 (ddt, J = 17.4, 1.8, 1.8 Hz), 3.45 (ddd, J = 4.8, 1.8, 1.8 Hz, 2H), 2.24 (s, 3H), 2.23 (s, 6H), 2.22 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 136.4, 133.4, 133.0, 132.5, 132.4, 115.0, 34.8, 17.0, 16.9, 16.6. LRMS (DART-TOF): m/z 189 ($[M + H]^+$).

2,4-Dimethoxy-6-(*p*-nitrobenzyloxy)-1,3,5-triazine (1-PNB). Ag_2O (139.0 mg, 0.60 mmol) was added to a solution of *p*-nitrobenzyl alcohol (76.6 mg, 0.500 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (105.3 mg, 0.600 mmol) in CH_2Cl_2 (10.0 mL) at room temperature. After stirred at 35 °C for 66 h, the reaction mixture was directly purified by column chromatography (CH_2Cl_2/EtOAc = 19:1) to afford colorless crystals (141.7 mg, 97%). Mp 174.8−176.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27−8.21 (m, 2H), 7.66−7.60 (m, 2H), 5.55 (s, 2H), 4.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 172.9, 147.9, 142.8, 128.5, 124.0, 68.3, 55.7. Anal. Calcd for $C_{12}H_{12}N_4O_5$: C, 49.32; H, 4.14; N, 19.17. Found: C, 48.92; H, 4.14; N, 19.01. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_{12}H_{13}N_4O_5$ 293.0886. Found: 293.0888. IR (KBr): 1562, 1363, 1335, 1134, 1111 cm^{-1}.

(2-(2-Chloroethoxy)ethyl *p*-nitrobenzyl ether (6b). TfOH (87.8 μL, 1.0 mmol) was added to a mixture of **3b** (52.8 μL, 0.50 mmol), **1-PNB** (160.7 mg, 0.55 mmol), and MS5A (8.3 mg) in 1,4-dioxane (0.83 mL) at room temperature. After 10 h, the reaction mixture was diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (5 mL) followed by brine (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1:1) to afford a clear pale brown oil (123.4 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.17 (m, 2H), 7.56−7.50 (m, 2H), 4.69 (s, 2H), 3.79 (t, J = 5.8 Hz, 2H), 3.77−3.69 (m, 4H), 3.66 (t, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.1, 127.8, 123.7, 72.1, 71.5, 70.8, 70.3, 42.9. Anal. Calcd for $C_{11}H_{14}ClNO_4$: C, 50.88; H, 5.43; N, 5.39. Found: C, 50.73; H, 5.39; N, 5.42. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_{11}H_{15}ClNO_4$ 260.0690. Found: 260.0712. IR ($CHCl_3$): 2866, 1608, 1531, 1346, 1105, 860 cm^{-1}.

*2-Bromoethyl p-nitrobenzyl ether (**6c**)*.[36] TfOH (87.8 μL, 1.0 mmol) was added to a mixture of **3c** (35.6 μL, 0.50 mmol), **1-PNB** (160.7 mg, 0.55 mmol), and MS5A (8.3 mg) in 1,4-dioxane (0.83 mL) at room temperature. After 10 h, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (5 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (5 mL) followed by brine (5 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 19:1) to afford a clear pale yellow oil (126.1 mg, 97%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.21 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 4.70 (s, 2H), 3.87 (t, J = 5.8 Hz, 2H), 3.54 (s, J = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 147.6, 145.5, 127.8, 123.8, 71.9, 70.7, 30.3. LRMS (DART-TOF): m/z 260 ($[M + H]^+$).

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluorodecyl *p*-nitrobenzyl ether (6e). TfOH (26.3 μL, 0.30 mmol) was added to a mixture of **3e** (69.6 mg, 0.15 mmol), **1-PNB** (48.2 mg, 0.165 mmol), and MS5A (2.5 mg) in 1,4-dioxane (0.25 mL) at room temperature. After 10 h, the reaction mixture was quenched with 2,6-lutidine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/acetone = 4:1) to afford a crystalline solid (81.5 mg, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 4.65 (s, 2H), 3.84 (t, J = 6.4 Hz, 2H), 2.49 (tt, J = 18.4, 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 145.3, 127.8, 123.9, 120.4–107.5 (perfluorocarbons), 72.1, 63.0, 31.7. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −80.8, −113.4, −121.7, −122.0, −122.8, −123.7, −126.2. Anal. Calcd for $C_{17}H_{10}F_{17}NO_3$: C, 34.07; H, 1.68; N, 2.34. Found: C, 33.73; H, 1.79; N, 2.64. HRMS (double-focusing, EI) m/z: $[M]^+$ Calcd for $C_{17}H_{10}F_{17}NO_3$ 599.0389. Found: 599.0392. IR (KBr): 2360, 1606, 1522, 1373, 1356, 1250, 1203, 1151, 1108 cm^{-1}.

*p-Nitrobenzyl 3-benzoylpropionate (**6f**)*.[37] TfOH (87.8 μL, 1.00 mmol) was added to a mixture of **3f** (89.1 mg, 0.50 mmol), **1-PNB** (160.7 mg, 0.55 mmol), and MS5A (8.3 mg) in 1,4-dioxane (0.83 mL) at room temperature. After 10 h, the reaction mixture was quenched with NEt_3, diluted with EtOAc (3 mL), and filtered. The filtrate was washed with aqueous 1 M HCl (3 mL) followed by brine (3 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$ = 1:1) to afford a white solid (132.1 mg, 84%). Mp 73–74 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.22 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 8.6, 2H), 7.48 (t, J = 7.6 Hz, 2H), 5.25 (s, 2H), 3.36 (t, J = 6.5 Hz, 2H), 2.86 (t, J = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 198.0, 172.6, 147.8, 143.4, 136.5, 133.5, 128.8, 128.4, 128.2, 123.9, 65.1, 33.4, 28.3. LRMS (DART-TOF): m/z 314 ($[M + H]^+$).

*p-Nitrobenzyl (E)-cinnamate (**6g**)*.[38,39] TfOH (26.3 μL, 0.30 mmol) was added to a mixture of **3g** (22.2 mg, 0.15 mmol), **1-PNB** (48.2 mg, 0.165 mmol), and MS5A (2.5 mg) in 1,4-dioxane (0.25 mL) at room temperature. After 10 h, the reaction mixture was quenched with pyridine, diluted with EtOAc (10 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford a white solid (33.3 mg, 78%). Mp 117 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.24 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 16.1 Hz, 1H), 7.57 (d, J = 8.6 Hz, 2H), 7.56–7.52 (m, 2H), 7.45–7.35 (m, 3H), 6.51 (d, J = 16.1 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.6, 147.8, 146.2, 143.5, 134.2, 130.8, 129.1, 128.5, 128.3, 124.0, 117.2, 64.9; LRMS (DART-TOF): m/z 284 ($[M + H]^+$).

*Pentamethyl(p-nitrobenzyl)benzene (**6h**)*.[40] TfOH (87.8 μL, 1.00 mmol) was added to a mixture of **3h** (74.1 mg, 0.50 mmol), **1-PNB** (160.7 mg, 0.55 mmol), and MS5A (8.3 mg) in 1,4-dioxane (0.83 mL) at room temperature. After 10 h, the reaction mixture was quenched with NEt_3, diluted with EtOAc (3 mL), and filtered. The filtrate was washed with aqueous 1 M HCl (3 mL) followed by brine (3 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/$CHCl_3$ = 1:1) to afford a white solid (133.1 mg, 94%). Mp 131–132 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.09 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 4.20 (s, 2H), 2.28 (s, 3H), 2.25 (s, 6H), 2.14 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 149.0, 146.4, 134.1, 133.0, 132.7, 132.3, 128.8, 123.8, 36.4, 17.2, 17.05, 17.02. LRMS (DART-TOF): m/z 284 ([M + H]$^+$).

2-(1-Adamantyloxy)-4,6-dimethoxy-1,3,5-triazine (1-Ad). Cyanuric chloride (1.84 g, 10 mmol) was added to a suspension of 1-adamantanol (1.52 g, 10 mmol) and *n*-BuLi (2.6 M in hexane, 3.85 mL, 10 mmol) in THF (50 mL) was added at −10 °C. The reaction mixture was stirred at room temperature for 2 h and at reflux temperature for 45 min, and then cooled to 0 °C. Ethyldiisopropylamine (5.18 mL, 30 mmol), MeOH (50 mL), and *N*-methylpyrrolidine (317 μL, 3.0 mmol) was added. After stirred for 23 h at room temperature, the reaction mixture was concentrated to half volume under reduced pressure. After addition of aqueous 10% citric acid (50 ml), the mixture was extracted with EtOAc (300 mL). The organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 17:3) followed by recrystallization from $CHCl_3$/MeOH to afford the a colorless crystalline solid (2.28 g, 78%). Mp 180–181 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00 (s, 6H), 2.33 (m, 6H), 2.23 (m, 3H), 1.70 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 172.4, 83.9, 55.3, 41.4, 36.3, 31.2. Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.59; H, 7.24; N, 14.35. HRMS (DART-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{22}N_3O_3$ 292.16612. Found: 292.16424. IR ($CHCl_3$): 2916, 2856, 1570, 1558, 1466, 1431, 1381, 1360, 1298, 1221, 1140, 1111 cm^{-1}.

1-Adamantyl 3-phenylpropyl ether (7a). TfOH (87.8 μL, 1.00 mmol) was added to a mixture of **3a** (68.1 μL, 0.50 mmol), **1-Ad** (160.2 mg, 0.55 mmol), and MS5A (50 mg) in 1,4-dioxane (10.0 mL) at room temperature. After 3 h, the reaction mixture was quenched with pyridine, diluted with EtOAc (50 mL), and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (50 mL) followed by brine (40 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 2:1) to afford a clear colorless oil (124.0 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33–7.12 (m, 5H), 3.42 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 7.8 Hz, 2H), 2.19–2.08 (m, 3H), 1.85 (tt, J = 7.8, 6.4 Hz, 2H), 1.74 (m, 6H), 1.62 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 128.6, 128.4, 125.8, 72.0, 59.0, 41.8, 36.7, 32.6, 32.3, 30.7; Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.19; H, 9.85. HRMS (DART-TOF) m/z: Calcd for $C_{19}H_{27}O$ ([M+H]$^+$): 271.20619, Found: 271.20374; IR ($CHCl_3$): 3045, 2912, 2854, 1454, 1249, 1115, 1088 cm^{-1}.

General Procedure for TfOH-Catalyzed *O*-1-Adamantylation Using 1-Ad. TfOH (100 or 200 mol%, 50 or 100 mM) was added to a mixture of **3a** (1 equiv, 50 mM), **1-Ad** (1 equiv, 50 mM), and 1-chlorooctane (internal standard, 1 equiv, 50 mM) in 1,4-dioxane at room temperature. Aliquots were withdrawn from the reaction mixture at indicated time and treated with an excess amount of EtOH containing ethyldiisopropylamine to convert 1-adamantyl trifluoromethanesulfonate to 1-adamantyl ethyl ether. The yields were determined by ^{1}H NMR spectroscopic analysis using the internal standard.

p-Nitrobenzyl 2,2,2-trichloroacetimidate (PNB-TCAI).[41] 1,8-Diazabicyclo[5.4.0]undec-7-ene (7.5 μL, 0.050 mmol) was added to a solution of *p*-nitrobenzyl alcohol (382.9 mg, 2.50 mmol) and trichloroacetonitrile (1.25 mL, 12.5 mmol) in CH_2Cl_2 (2.50 mL) at room temperature. After 6 h, 1,8-diazabicyclo[5.4.0]undec-7-ene (11.2 μL, 0.075 mmol) was added. After additional 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 6:1) followed by recrystallization from hexane/$CHCl_3$ to afford colorless crystals (735.2 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 8.28−8.23 (m, 2H), 7.63−7.59 (m, 2H), 5.45 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2, 147.9, 142.9, 128.0, 124.0, 91.0, 69.2. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_9H_8N_2O_3Cl_3$ 296.9601. Found: 296.9581. IR (KBr): 3319, 2945, 1664, 1514, 1344, 1296, 1101, 1013, 800 cm^{-1}.

2-(2-Chloroethoxy)ethyl 2,2,2-trichloroacetimidate. 1,8-Diazabicyclo[5.4.0]undec-7-ene (11.2 μL, 0.075 mmol) was added to a solution of **3b** (158 μL, 1.50 mmol) and trichloroacetonitrile (0.75 mL, 7.5 mmol) in CH_2Cl_2 (1.50 mL) at 0 °C. After 30 min, 1,8-diazabicyclo[5.4.0]undec-7-ene (22.4 μL, 0.15 mmol) was added. After additional 20 min, the reaction mixture was quenched with AcOH (14 μL), and then concentrated under reduced pressure. The residue was purified by column chromatography (hexane/CH_2Cl_2, 1:1) to afford a clear colorless oil (326.1 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 4.49−4.44 (m, 2H), 3.90−3.85 (m, 2H), 3.82 (t, J = 5.8 Hz, 2H), 3.64 (t, J = 5.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.9, 91.4, 71.6, 68.83, 68.81, 42.9. Anal. Calcd for $C_6H_9Cl_4NO_2$: C, 26.80; H, 3.37; N, 5.21. Found: C, 26.70; H, 3.34; N, 5.11. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_6H_{10}Cl_4NO_2$ 267.9466. Found: 267.9487. IR ($CHCl_3$): 3342, 2962, 1666, 1309, 1090, 650 cm^{-1}.

2-(2-Chloroethoxy)ethyl 2,2,2-trichloroacetate. Pyridine (266 μL, 3.30 mmol) was added to a solution of **3b** (317 μL, 3.00 mmol) and trichloroacetic anhydride (603 μL, 3.30 mmol) in THF (6.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 20 min. The reaction mixture was diluted with hexane (6 mL), filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to afford a clear colorless oil (658.7 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.55−4.51 (m, 2H), 3.87−3.83 (m, 2H), 3.80 (t, J = 5.7 Hz, 2H), 3.63 (t, J = 5.7 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.1, 89.8, 71.6, 68.5, 68.2, 42.8. Anal. Calcd for $C_6H_8Cl_4O_3$: C, 26.70; H, 2.99. Found: C, 26.50; H, 3.03. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_6H_9Cl_4O_3$ 268.9306. Found: 268.9313. IR ($CHCl_3$): 2870, 1766, 1261, 1138, 1028, 827 cm^{-1}

General Procedure for the Stability Comparison of LGs under the Acidic Conditions. *p*-Toluenesulfonic acid monohydrate (0.5 equiv) was added to a solution of the benzyl derivative [**1-Bn**, Bn-TCAI, or Bn-Br (0.1–0.2 mmol, 1 equiv)] in CH_2Cl_2/MeOH (1:1, 0.5 M) at room temperature. After stirred for 5 min, the reaction mixture was quenched with triethylamine (1 equiv), passed through silica gel (EtOAc as an eluent), and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR spectroscopic analysis using 6-methylcoumarin as an internal standard.

General Procedure for the Stability Comparison of LGs under the Nucleophilic Conditions. Diethylamine (2.5 equiv) was added to a solution of the benzyl derivative [**1-Bn**, Bn-TCAI, or Bn-Br (0.1–0.2 mmol, 1 equiv)] in CH_2Cl_2 (0.2 M) at room temperature. After stirred for 1 h, the reaction mixture passed through silica gel (EtOAc as an eluent) and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR spectroscopic analysis using 6-methylcoumarin as an internal standard.

General Procedure for the Stability Comparison of LGs under the Reductive Conditions. A mixture of the benzyl derivative [**1-Bn**, Bn-TCAI, or Bn-Br (0.25 mmol, 1 equiv)], zinc (81.7 mg, 1.25 mmol, 5 equiv), and ammonium chloride (66.9 mg, 1.25 mmol, 5 equiv) in EtOH (0.50 mL, 0.5 M) was heated at reflux for 5 min. After cooled to room temperature, the mixture was passed through silica gel (EtOAc as an eluent) and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR spectroscopic analysis using 6-methylcoumarin as an internal standard.

General Procedure for NMR Spectroscopic Analysis of the Protonation of 1-Me with TfOH. TfOH (0, 50, 95, 105, 150, 200, or 500 mol%) and **1-Me** (1 equiv, 40 mM) were dissolved in 1,4-dioxane (600 μL). The solution was used for ^{13}C NMR spectroscopic analysis (NoD-NMR, 600 MHz, 20 °C).

2-(Benzyloxy)-4,6-bis(cyclohexylmethoxy)-1,3,5-triazine (8). *N*-Methylimidazole (40 μL, 0.50 mmol) was added to a solution of 2-chloro-4,6-bis(cyclohexylmethoxy)-1,3,5-triazine (1.70 g, 5.00 mmol),[12d] benzyl alcohol (2.57 mL, 25.0 mmol), and ethyldiisopropylamine (958 μL, 5.50 mmol) in THF (10.0 mL) at room temperature. The reaction mixture was heated at reflux for 35 h and then cooled to room temperature. The mixture was diluted with Et_2O (20 mL), and washed with H_2O (100 mL), 1 M aqueous HCl (10 mL), and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 20:1) followed by recrystallization from hexane to afford colorless crystals (1.85 g, 88%). Mp 113.5−116.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47−7.42 (m, 2H), 7.39−7.30 (m, 3H), 5.44 (s, 2H), 4.18 (d, J = 6.2 Hz, 2H), 1.87−1.64 (m, 12H), 1.32−1.13 (m, 6H), 1.07−0.97 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.4, 173.0, 135.6, 128.6, 128.5, 73.8, 69.9, 37.2, 29.8, 26.5, 25.8. Anal. Calcd for $C_{24}H_{33}N_3O_3$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.31; H, 8.07; N, 10.25. HRMS (DART-TOF): $[M + H]^+$ Calcd for $C_{24}H_{34}N_3O_3$ 412.2600. Found: 412.2617. IR (KBr): 2925, 2852, 1568, 1448, 1340, 1140 cm^{-1}.

General Procedure for the Kinetic Study of *O*-Benzylation Using 8. TfOH (33.4, 38.6, 49.1, 59.7, or 70.2 μL; 95, 110, 140, 170, or 200 mol%; 0.381−0.800 mmol) was added to a solution of **8** (164.6 mg, 0.400 mmol, 1 equiv), **3a** (54.5 μL, 0.400 mmol, 1 equiv), *p*-nitrotoluene (16.5 mg, 0.120 mmol, 0.3 equiv) and MS5A (20.0 mg) in DME (4.00 mL) at −10 ± 0.5 °C. Aliquots (40 μL) were withdrawn from the reaction mixture at intervals, diluted with pyridine solution (8 mM, 2.0 mL) in H_2O−MeCN (1:3), and filtered. HPLC analysis was performed using a gradient solvent system of H_2O/MeCN (4:1 to 1:4) and *p*-nitrotoluene as an internal standard. In the case of entry 6 in Table 6, the reaction was carried out in the presence of TfON^nBu_4 (1 equiv).

Calculations. All calculations were performed using Gaussian09.[42] Energy minimum was obtained without any constraints by density functional theory (DFT) calculation with the B3LYP functional and the 6-31+G(d,p) basis set in 1,4-dioxane using the conductor-like polarizable continuum model (CPCM). Vibrational frequency calculations confirmed that there is no imaginary frequency for the energy-minimum geometries. In addition, the relative energies were corrected for the zero-point energy.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge on the ACS Publications website. Kinetics and compuational details, ^{1}H and ^{13}C NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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(25) Similar to the previous kinetic study (Ref. 12d), [**8**-**H**$^+$] was estimated as [**8**]$_{obs}$ − 5 mM when [TfOH] is 95 mM, where [**8**]$_{obs}$ is the concentration of **8** observed in HPLC analysis, and represents the sum of [**8**] and [**8**-**H**$^+$] in the reaction mixture. As the reaction proceeded very slowly in the case of [TfOH] = 95 mM, only the early stage of the reaction (~20% conversion) was analyzed. Nevertheless, the reaction was considered as a first-order reaction

because we have previously reported the first-order kinetics of **1-Bn-H**$^+$ in the presence of 95 mol% of TfOH. In the case of 110–200 mM of [TfOH], [**8-H**$^+$] was estimated as [**8**]$_{obs}$ because **8** would be completely protonated by TfOH.

(26) The coefficient of determination (r^2) between k_{obs} ([TfOH] > 100 mM) and [TfOH$_{ex}$], [TfOH$_{ex}$]^3, or [TfOH$_{ex}$]^4 was lower than that of [TfOH$_{ex}$]^2 (0.902–0.944 vs 0.975, details are given in Figures S9–11). In addition, their y-intercepts (–10.7, 7.35, and 10.4 in the case of [TfOH$_{ex}$], [TfOH$_{ex}$]^3, and [TfOH$_{ex}$]^4, respectively) were not close to 0.0831, which is k_{obs} in the case of [TfOH] = 95 mol%. Therefore, a linear relationship between k_{obs} and [TfOH$_{ex}$], [TfOH$_{ex}$]^3, or [TfOH$_{ex}$]^4 is unlikely.

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