# Quaternary Ammonium-Supported Scavenger Reagents for Acids and Electrophiles

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The present article describes how we devised new quaternary ammonium-supported quench reagents (TAMA-Cl and BAX-sulfate) for scavenging acids and excess electrophiles from crude reaction mixtures. TAMA-Cl is liquid at room temperature, but is very glutinous and has to be used in aqueous solution. It removes unchanged electrophiles very efficiently. An aqueous preparation of TAMA-Cl may be easily added in automated syntheses, and high-throughput phase-separation techniques should allow purification of scavenger-containing reaction mixtures. However, workup with TAMA-Cl is more complex than simple filtration. Recognizing this major advantage of solid-phase syntheses, we designed BAX-sulfate, a highly crystalline scavenger reagent that allows reaction workup to be simplified to a single filtration and evaporation of solvent. BAX-sulfate reacts with electrophiles, quenches acids and precipitates quantitatively when diethyl ether is added. It even precipitates from methanol solutions. With BAX-sulfate the workup stage uses simple filtration to make crude separations.



## Introduction

Solid-phase organic synthesis is routinely used for the preparation of combinatorial libraries of small organic molecules. The clear advantage of this biphasic method is in the area of purification, as simple filtration generally leads to the desired products in high purity. However, excess of reagents is usually necessary to drive the reaction to completion and preparation of a target compound on a solid support may require up to two additional steps compared to the same synthesis in solution, one to anchor the starting material to the resin bead and another to cleave the product from the solid support.

Therefore, there has been concomitant growth of solution-phase preparations of chemical libraries.[1,2] Quench reagents have been conceived so that in the development of new technologies there is a reduced need for chromatographic purifications.[3−5] These scavenger resins offer the convenience of solution-phase reactions with the advantages of solid-phase techniques. However, there is considerable scope for improvement. Most of these compounds are reticulated polystyrene resins and the major drawbacks of these supported scavengers are their high cost, the large amount generally required to clean up a typical reaction product and long reaction times arising from the solid/liquid interface reactions. Moreover, these Merrifield-type resins are hydrophobic and their use is restricted to solvents with good swelling properties such as DMF, dichloromethane, or THF.

To address these issues, several groups have developed alternative nonpolymeric phase labels for quench reagents.[6] Some water-soluble[7] and some fluorous tag-bound scavengers,[8,9] as well as a polyaromatic-supported scavenger reagent[10] have been designed to circumvent these limitations. More recently, Wilcox has described the first photoactivable precipiton-supported isocyanate and has demonstrated that it could be used successfully as a selective scavenger reagent for amines.[11] Some 2-substituted-5-norbornenes have also been used to quench electrophiles. A ring-opening metathesis polymerization applied to the crude reaction mixture generates a polymer that can be precipitated with specific solvents, leaving the desired products essentially pure.[12,13]

Our basic idea was to replace the polymeric core of polystyrene-supported dendrimer-like scavenger reagents[14] by a specific functional group of low molecular weight. Using this strategy, we hoped to build an efficient, very high-loading scavenger reagent. This report describes the synthesis of new quaternary ammonium salts bearing amino functionalities, and demonstrates how they can be used to remove electrophiles.

## Results and Discussion

Our synthesis of electrophile-scavenging quaternary ammonium salt **3** employs methylation of Boc-protected tris(2-aminoethyl)amine (**1**) (Boc = *tert*-butoxycarbonyl) (Scheme 1).[15] The progress of the methylation reaction was

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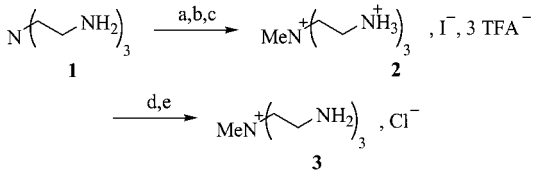
monitored by reversed-phase high-pressure liquid chromatography. This reaction was completed within 3 d with a four-fold excess of methyl iodide in a sealed reaction vessel. This quaternary ammonium salt was purified by diluting the crude reaction mixture with ethyl acetate and extracting with deionized water. It is interesting that, although triply Boc-protected, this ammonium salt is hydrophilic enough to be extracted by water from an organic solvent. The Boc groups were subsequently removed using trifluoroacetic acid (TFA), and after evaporation of excess reagent, the $I^-$/tris(trifluoroacetate) salt **2** was obtained in quantitative yield in essentially pure form.




a) $Boc_2O$, NaOH, $H_2O$, dioxane (84%); b) MeI, $CH_3CN$ (93%); c) TFA/$CH_2Cl_2$ (quant.); d) Amberlite IRA400 (90%); e) NaOH (3 equiv.) (89%)

Scheme 1

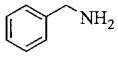
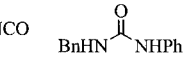
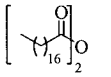
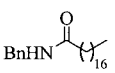
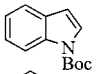
Filtration through an anion-exchange resin (Amberlite IRA400, $Cl^-$ form) allowed us to isolate the compound in which counterions were quantitatively replaced by chloride ions, as indicated by $^{13}C$ NMR spectroscopy. The final stage of the scheme requires deprotonation of the terminal ammonium salts. This was effected using sodium hydroxide, as insoluble sodium chloride formed in this reaction could be easily separated from the desired product by trituration with ethyl alcohol. Filtration and concentration of the filtrate afforded the desired tris(2-aminoethyl)(methyl)ammonium chloride (TAMA-Cl, **3**) in pure form. Owing to its low molecular mass (196.7 $g \cdot mol^{-1}$) and dense functionalization, **3** is to the best of our knowledge the highest loaded supported scavenger reagent known so far, bearing 15.3 mmol of reactive amino groups per gram of compound.

However, this quench reagent was difficult to manipulate because of its high viscosity. Since we could reasonably expect it would be hygroscopic, we decided to use it in aqueous solution, and therefore dissolved it in water at a concentration of 0.87 M. We chose water because it does not evaporate easily, which implies that solution concentration would be reliable over time. Furthermore, water is the cheapest and safest solvent and although it is not miscible with most organic solvents, amines dissolved in water are known to react readily with electrophiles in organic phases.

Starting from benzylamine and indole, an array of amides, carbamates, ureas, and sulfonamides was synthesized using excess electrophiles (1.5 equiv.) and eventually triethylamine when required (Table 1, Entries 3 and 7). Subsequent removal of the remaining electrophiles from solution using triamine **3** afforded the products in excellent yields and purities.

One equiv. of TAMA-Cl (i.e. 3 equiv. of amino groups) per equivalent of excess electrophilic reagent was used to trap the unchanged electrophile. Two different simple procedures were attempted for removal of the quaternary ammonium-bound amino scavenger and its derivatives resulting from the trapping of excess electrophiles. First, we found that washing crude reaction mixtures with water afforded the pure desired products in the organic layer (Table 1, Method A). Secondly, we found that drying crude mixtures with sodium sulfate and filtering through a short pad of silica gel (solvent: EtOAc) also gave the expected products electrophile-free in very high yields (Table 1,

Table 1. Electrophile trapping with TAMA-Cl and BAX-sulfate from crude reaction mixture

| Entry | Substrate | Electrophile | Product | Remaining electrophile *before scavenging* | Remaining electrophile *after scavenging*[a] | Isolated yield[b] | Estimated purity (NMR)[c] |
|---|---|---|---|---|---|---|---|
| 1 |  | $Boc_2O$ | BnNHBoc | 0.45 equiv. | not detected | 98% | > 90 % |
| 2 | | $Ac_2O$ | BnNHAc | 0.48 equiv. | " | 87% | " |
| 3 | | TsCl | BnNHTs | 0.50 equiv. | " | 91% | " |
| 4 | | PhNCO |  | 0.50 equiv. | " | 92% | " |
| 5 | |  |  | 0.40 equiv. | "[d] | not determined | 57 % |
| 6 |  | $Boc_2O$ |  | 0.45 equiv. | " | 89% | > 90 % |
| 7 | | TsCl |  | 0.48 equiv. | " | 95% | " |

[a] With TAMA-Cl: Method A (adding ethyl acetate and washing three times with water) or method B [drying with sodium sulfate and filtering through a short pad of silica (solvent: EtOAc)] gave the same results. With BAX-sulfate: Method C [addition of diethyl ether ($CDCl_3/Et_2O$, 1:1) and filtration] gave identical results in terms of purity. [b] All yields are isolated yields of TAMA-Cl-purified material. Yields with BAX-sulfate are identical within the uncertainty range. [c] Purity was estimated at above 90% when no trace of side product was detected by $^1H$ NMR spectroscopy. [d] Contaminated with a stearic acid derivative. Yield was not calculated because of the large proportion of contaminant remaining.

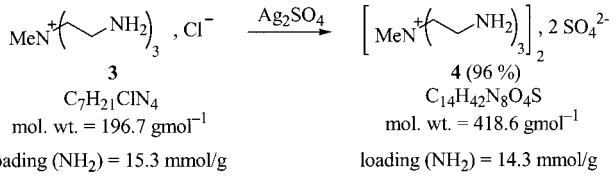
  

Method B). The two methods turned out to be equally efficient. Purities were assumed to be above 90% when no trace of side-products was detected by $^1$H NMR spectroscopy. In most cases, no further purification was required for organic synthesis purposes.

Only in one case (Table 1, Entry 5) was the resulting amide still contaminated, probably with a stearate salt. However, $^1$H NMR spectroscopy indicated that neither stearic anhydride nor derivatives of TAMA-Cl were left, and the rather polar contaminant was easily removed by chromatography. Entry 5 was the only example where further purification was necessary. Since no residual carboxylate was detected for acetic anhydride scavenging (Table 1, Entry 2), short-chain carboxylic acids may also be trapped by this triamine.

Such aqueous preparations of TAMA-Cl may be easily added in automated syntheses, and high-throughput phase-separation techniques should allow purification of scavenger-containing reaction mixtures. However, reaction workup is not as straightforward as simple filtration. Recognizing this major advantage of solid-phase synthesis, we set out to devise another scavenger reagent with which the reaction workup could be simplified to a single filtration and evaporation of solvent.

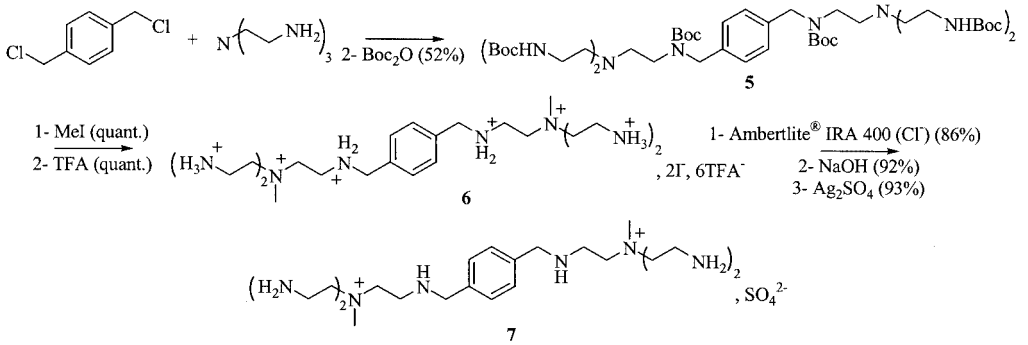
In 1999, Perrier et al. described a new strategy to use aromatic amines as support for solution-phase organic synthesis and found that protonation with sulfuric acid provided the best behaved solids.[16] On the basis of this work, we considered using the divalent sulfate counterion instead of $Cl^-$. Therefore, scavenger **3** was treated with a saturated aqueous solution of exactly 0.5 equiv. of silver sulfate (Scheme 2). The amount of silver chloride formed suggested that the exchange was quantitative. Insoluble silver chloride was removed by filtration, and lyophilization led to the expected quench reagent **4** in quantitative yield. Although this compound was indeed solid immediately after lyophilization, it became sticky almost at once after being removed from vacuum. Attempts to use it as a scavenger reagent demonstrated that its derivatives do separate from reaction mixtures when diethyl ether is added, but stay at the bottom of the flask in the form of a sticky residue that cannot be collected by filtration. Extraction with water or filtration though silica gel did provide the reaction product in pure form. However, it is clear that this quench reagent is no better than the previous one.




Scheme 2

With the idea of building a scavenger reagent that would be more prone to precipitation and would be almost as highly loaded as our first one, we decided to prepare the larger and somewhat more rigid α,α′-bis{2-[bis(2-aminoethyl)(methyl)ammonio]ethylamino}-*p*-xylene dichloride (BAX-2Cl; Scheme 3).

Our synthesis involved grafting the tetraamine onto α,α′-dichloro-*p*-xylene. The crude reaction mixture was Boc-protected, and purification afforded the desired branched hexacarbamate **5** in 52% yield over two steps. After methylation, the Boc protecting groups were removed using TFA, and after evaporation of excess reagent, the 2I$^-$/hexakis(trifluoroacetate) salt was obtained in excellent yield in pure form. The chloride form was obtained by anion exchange to facilitate purification after deprotonation, and treatment with aqueous sodium hydroxide afforded the desired scavenger reagent. However, we found that this derivative did not crystallize readily and we were only able to obtain it in solid form after careful purification by preparative reversed-phase high-pressure liquid chromatography. Recognizing that synthesis of scavengers should be straightforward and economically viable, we looked for alternative counterions. Treatment with 0.5 equiv. of silver sulfate generated the corresponding BAX-sulfate (**7**), which was found to be highly crystalline and apparently not very hygroscopic.



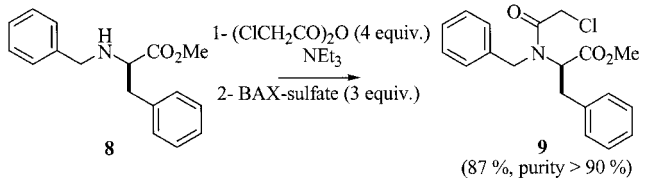

α,α′-bis(2-{[bis(2-aminoethyl)methyl]ammonio}ethylamino)-*p*-xylene sulfate
(BAX-sulfate, mol. wt. = 520.7 gmol$^{-1}$, loading = 11.5 mmol/g)

Scheme 3

This derivative is only soluble in water and to a lesser extent in methanol. Its amino groups loading is 11.5 $mmol \cdot g^{-1}$. Like polymer-supported scavenger reagents, it reacts readily with electrophiles and acids at the solid/liquid interface. In fact, its ability to remove excess of electrophiles was first put to the test of purification of all the reaction mixtures listed in Table 1. The same levels of purity, and essentially the same yields, were obtained as with quench reagent **3** dissolved in water. However, in this case the scavenger reagent and its derivatives were removed by simple filtration after addition of diethyl ether to ensure quantitative precipitation ($CDCl_3/Et_2O$, 1:1).

An example of the application of BAX-sulfate in synthesis is shown in Scheme 4. While working on a medicinal chemistry project, we were interested in generating a solution-phase library of *N*-(chloroacetyl) *N*-substituted amino acids. However, the reaction proceeded very slowly with 1 equiv. of electrophile and generally stopped at about 50% conversion. Therefore, amine **8** and a three-fold excess of anhydride were allowed to react for 2 h in dichloromethane. The quaternary ammonium quenching agent was then added to scavenge the excess anhydride (1 mol-equiv. relative to the excess anhydride). The scavenging reaction was allowed to proceed overnight at ambient temperature. Addition of diethyl ether ensured complete precipitation of ionic species, which were removed by filtration. This simple workup procedure gave the product in very high yield and in excellent purity (> 90% by $^1H$ NMR).[17] Indeed, we were able to use this product without further purification in the next step of our synthesis.




Scheme 4

We then decided to test our new reagent for precipitation from methanol. Known relative proportions of *p*-toluenesulfonic acid and pentamethylbenzene as an NMR internal standard were combined in methanol. Quenching with 0.5 equiv. of BAX-sulfate (3 equiv. of amino groups) resulted in the formation of a cloudy solution. Dilution with diethyl ether led to the formation of a well-behaved precipitate that could be collected by filtration. Diethyl ether was added for good measure to ensure that no traces of scavenger derivatives remained in solution (diethyl ether/methanol, 1:1). Concentration of the filtrate and $^1H$ NMR spectroscopic analysis demonstrated that pentamethylbenzene was isolated without any detectable trace of contaminant (i.e. $pTsO^-$ salts and derivatives of the scavenger reagent).

## Conclusion

In summary, we have prepared two complementary quaternary ammonium-supported polyamines (TAMA-Cl and BAX-sulfate) which have found applications as high-loading scavenger reagents for quenching acids and excess of electrophiles from crude reaction mixtures. It is noteworthy that in the case of scavengers the number of equivalents should be calculated on a molar basis. As a result, approximately one third to one quarter the weight of scavenger was required to achieve a scavenging efficiency similar to high-loading commercially available resins (typically loaded at about 3 $mmol \cdot g^{-1}$).

High-loading scavenger reagents offer the advantage of producing less waste while facilitating product purifications. Relative to traditional polymer-supported scavengers, these ones use even less solvent, require less material, and eliminate undesired contaminants equally well, even from methanolic solutions, which is something that hydrophobic polystyrene-based resins cannot do. The workup stage uses simple phase-separation techniques such as extraction, filtration and evaporation of solvent to make crude separations.

If BAX-sulfate was to be used in industry, the first step of the synthesis would certainly need to be improved and $Cl^-/SO_4^{2-}$ exchange would have to be performed without silver sulfate. However, based upon the success of these simple test examples, it seems reasonable to conceive of traditional solution-phase multistep syntheses with quaternary ammonium-supported scavenger purifications. Thus, ammonium-supported quenching could be applied to the preparation of chemical libraries in solution.

## Experimental Section

**General Remarks:** $^1H$ NMR spectra were recorded at 200 or 300 MHz and $^{13}C$ NMR spectra at 75.5 or 100.6 MHz as indicated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane, and coupling constants (*J*) are in Hz; s, singlet; q, quadruplet; m, multiplet. All solvents were dried and distilled by standard techniques. Analytical HPLCs were run with a Nulceosil C18 column (250 × 4.6 mm). A polarity gradient water/acetonitrile (100:0 to 0:100) was applied for 20 min immediately after injection. Acetonitrile and water contained 0.1% TFA. Detailed experimental procedures relating to synthesis and use of TAMA-Cl have been published previously.[15]

**Boc-Protected α,α′-Bis{2-[bis(2-aminoethyl)amino]ethylamino}-*p*-xylene 5:** 1,4-Bis(chloromethyl)benzene (1.0 g, 5.7 mmol) was added to a solution of tris(2-aminoethyl)amine (5.1 mL, 34.2 mmol) in dichloromethane (2 mL). The reaction mixture was stirred for 24 h at room temperature, then DMAP (70 mg, 0.57 mmol) and $Boc_2O$ (24.6 g, 113 mmol) were added at 0 °C. The mixture was warmed to room temperature, stirred for another 24 h, concentrated and then purified by column chromatography (hexane/EtOAc, 6:4) to give **5** (2.95 g, 52% over two steps) as a colourless oil. $^1H$ NMR ($CDCl_3$, 200 MHz, ppm): δ = 1.45 (br. s, 54 H), 2.53 (br. s, 12 H), 3.14 (br. s, 8 H), 3.27 (br. s, 4 H), 4.43 (br. s, 4 H),

7.12 (br. s, 4 H). $^{13}$C NMR ($CDCl_3$, 100.6 MHz, ppm): δ = 14.6 ($CH_3$), 21.5 ($CH_3$), 28.9 ($CH_3$), 38.9 ($CH_2$), 45.1 ($CH_2$), 45.4 ($CH_2$), 50.9 ($CH_2$), 52.4 ($CH_2$), 53.0 ($CH_2$), 53.8 ($CH_2$), 54.2 ($CH_2$), 60.8 ($CH_2$), 79.4 (C), 80.6 (C), 127.8 (CH), 128.3 (CH), 137.8 (C), 156.4 (C), 156.7 (C), 171.6 (C). MS (FAB+, GT matrix): *m/z* (%) = 995 [$MH^+$] (62), 895 (11), 447 (49). HRMS: calcd. for $C_{50}H_{90}N_8O_{12}$ *m/z* = 995.6756 [$MH^+$], found 995.6683.

**Boc-Protected BAX-2I:** Methyl iodide (1.25 mL, 20 mmol) was added to a solution of diamine **5** (5 g, 5.03 mmol) in acetonitrile (10 mL). The reaction vessel was sealed. The progress of the reaction was monitored by reversed-phase HPLC. After 3 d at room temperature, HPLC showed complete disappearance of a peak at $t_R$ = 11.02 min and the emergence of a new signal at $t_R$ = 10.67 min. Concentration allowed isolation of the desired product in pure form (6.38 g, quant.). $^1$H NMR ($CDCl_3$, 200 MHz, ppm): δ = 1.39 (br. s, 54 H), 3.28 (br. s, 6 H), 3.61 (m, 24 H), 4.85 (br. s, 4 H), 5.84 (br. s, 4 H), 7.29 (s, 4 H). $^1$H NMR ([$D_4$]MeOH, 200 MHz, ppm): δ = 1.47 (br. s, 54 H), 3.23 (s, 6 H), 3.51 (br. s, 20 H), 3.80 (br. s, 4 H), 4.55 (s, 4 H), 7.37 (s, 4 H). $^{13}$C NMR ([$D_4$]MeOH, 100.6 MHz, ppm): δ = 22.7 and 27.7 ($CH_3$), 34.2 ($CH_2$), 40.5 and 40.9 ($CH_2$), 49.2 ($CH_3$), 50.2 and 51.1 ($CH_2$), 58.8 and 59.2 ($CH_2$), 61.0 ($CH_2$), 80.0 (C), 81.5 and 82.1 (C), 128.0 and 128.3 (CH), 137.5 (C), 155.8 and 156.1 (C), 157.1 (C).

**BAX-2I·6TFA (6):** Boc-protected BAX-2I (6.38 g, 4.99 mmol) was treated with 50% TFA in dichloromethane (10 mL) for 2 h. Solvent and excess reagent were then removed under reduced pressure to give the desired product in pure form (6.80 g, 100%). $^1$H NMR ($D_2O$, 200 MHz, ppm): δ = 2.96 (s, 6 H), 3.22−3.50 (m, 18 H), 3.91 (s, 4 H), 7.05 (s, 4 H). $^{13}$C NMR ($D_2O$, 100.6 MHz, ppm): δ = 32.2 ($CH_2$), 39.6 ($CH_2$), 49.6 ($CH_3$), 52.5 ($CH_2$), 57.2 ($CH_2$), 58.3 ($CH_2$), 116.0 (q, *J* = 291 Hz, C), 130.7 (CH), 131.5 (C) 162.4 (q, *J* = 36 Hz, C).

**BAX-2Cl·6HCl:** BAX-2I.6TFA (**6**) (6.80 g, 4.99 mmol) was dissolved in distilled water (20 mL) and loaded onto a column of Amberlite IRA 400 (13 g, 3.8 mequiv. $Cl^-$/g, 50 mmol). The column was eluted very slowly with water. The collected aqueous phase was concentrated by rotary evaporation then lyophilized to give the desired octaammonium salt (3.08 g, 86%). $^1$H NMR ($D_2O$, 200 MHz, ppm): δ = 3.37 (s, 6 H), 3.56−3.64 (m, 8 H), 3.70−3.92 (m, 16 H), 4.34 (s, 4 H), 7.53 (s, 4 H). $^{13}$C NMR ($D_2O$, 75.5 MHz, ppm): δ = 32.6 ($CH_2$), 39.9 ($CH_2$), 50.0 ($CH_3$), 51.4 ($CH_2$), 57.4 ($CH_2$), 58.5 ($CH_2$), 131.0 (CH), 131.7 (C).

**BAX-2Cl:** A solution of sodium hydroxide (1.22 g, 30.6 mmol) in distilled water (5 mL) was added to BAX-2Cl·6HCl (3.57 g, 5.11 mmol). After concentration, the residue was triturated with ethanol and insoluble sodium chloride was removed by filtration. The filtrate was concentrated to give the desired product (2.32 g, 93%) as a viscous pale-yellow oil. $^1$H NMR ([$D_4$]MeOH, 200 MHz, ppm): δ = 3.03−3.13 (m, 12 H), 3.20 (s, 6 H), 3.38−3.54 (m, 12 H), 3.82 (s, 4 H), 7.38 (s, 4 H). $^{13}$C NMR ([$D_4$]MeOH, 75.5 MHz, ppm): δ = 34.8 ($CH_2$), 42.0 ($CH_2$), 49.2 ($CH_3$), 52.7 ($CH_2$), 61.4 ($CH_2$), 63.6 ($CH_2$), 128.3 (CH), 138.6 (C).

**BAX-Sulfate (7):** A saturated solution of silver sulfate (1.35 g, 4.34 mmol) in distilled water (170 mL) was added to a solution of BAX-2Cl (2.15 g, 4.34 mmol) in distilled water (3 mL). The aqueous solution became immediately cloudy, and 75% of its volume was removed by evaporation. Insoluble silver chloride was removed by filtration. The filtrate was lyophilized to give the desired product (2.10 g, 93%) as a slightly grey solid (m.p. 145 °C). $^1$H NMR ($D_2O$, 300 MHz, ppm): δ = 3.03−3.17 (m, 20 H), 3.33−3.45 (m, 14 H), 3.83 (s, 4 H), 7.45 (s, 4 H). $^{13}$C NMR ($D_2O$, 75.5 MHz, ppm): δ = 35.0 ($CH_2$), 40.7 ($CH_2$), 49.6 ($CH_2$), 52.4 ($CH_3$), 60.4 ($CH_2$), 62.7 ($CH_2$), 129.3 (CH), 138.4 (C) ppm. HRMS: calcd. for $C_{22}H_{48}N_8$ *m/z* = 212.2001 [$M^{2+}$/2], found 212.2018.

**General Procedure for Electrophile Scavenging with BAX-Sulfate** (Table 1): The electrophile (1.5 equiv.) was added to a solution of benzylamine or indole (1 equiv.) and triethylamine when needed (Entries 3 and 7) in dichloromethane. At the end of the reaction (typically 1 h), BAX-sulfate (0.25 equiv., 3 equiv. of amino groups per excess electrophile) was added and the reaction mixture was allowed to stand overnight at room temperature. Addition of diethyl ether (diethyl ether/dichloromethane, 1:1), filtration, and evaporation of the solvents allowed isolation of the desired products in excellent yields pure enough for organic chemistry purposes (except with stearic anhydride as electrophile, Entry 5).

***N*-Benzyl-*N*-(α-chloroacetyl)phenylalanine Methyl Ester (9):** α-Chloroacetic anhydride (22.5 mg, 0.316 mmol) and triethylamine (11 mL, 0.079 mmol) were successively added to a solution of *N*-benzyl-phenylalanine methyl ester (21.2 mg, 0.079 mmol) in $CDCl_3$. HPLC indicated that the reaction was complete within 3 h. BAX-sulfate (120 mg, 0.237 mmol) was then added and the reaction mixture was stirred overnight at room temperature. Diethyl ether (1 mL) was added, the reaction mixture was filtered, and the precipitate was washed with more diethyl ether (2 × 1 mL). Concentration provided the desired product containing no detectable trace of either α-chloroacetic anhydride derivatives or BAX-sulfate derivatives (24 mg, 87%). $^1$H and $^{13}$C NMR spectra are identical to those previously described in the literature.[17]

**Quenching of TsOH in Methanol:** *p*-Toluenesulfonic acid monohydrate (38.2 mg, 0.20 mmol) and pentamethylbenzene (20 mg, 0.134 mmol) were dissolved in deuterated methanol (1 mL). BAX-sulfate (53 mg, 0.10 mmol, 0.75 equiv./1 equiv.TsOH) was added. After 1 h of stirring at room temperature, diethyl ether (1 mL) was added and the precipitate was removed by filtration and washed with more diethyl ether (3 mL). After concentration, $^1$H NMR spectroscopy indicated that TsOH had been quantitatively sequestered by BAX-sulfate.

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