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Chemoselective N-Difluoromethylation of Functionalized Tertiary Amines

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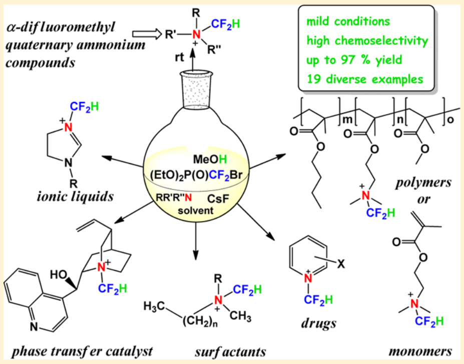
Supporting Information

ABSTRACT: A practical, convenient, and general method for the difluoromethylation of tertiary amines, using diethyl bromodifluoromethylphosphonate and fluoride, is described. This commercially available phosphonate smoothly reacts with a fluoride ion to liberate a difluorocarbene intermediate that in the presence of a proton source and a tertiary amine generates the corresponding α-difluoromethylammonium compound in good to excellent yields. Despite the involvement of a difluorocarbene intermediate, this difluoromethylation occurs almost exclusively on the nitrogen atom with diverse molecular structures, including drugs, surfactants, chiral phase transfer catalysts, polymers, ionic liquids, and other fine chemicals. A preliminary assessment of the effects that an α-difluoromethyl groupT has on hydrogen bonding and log$P$ of quaternary ammonium salts is also described.



INTRODUCTION

Synthesis of organic compounds containing fluorine atoms has become one of the more important issues in the field of organic synthesis because of the central role fluorinated functions play as bioisosteres in medicinal chemistry, leading to changes in affinity, metabolic stability, hydrophobicity, and bioavailability of various bioactive compounds.[1,2] Apart from the pharmaceutical domain, in the world of organic synthesis, the incorporation of a fluorine atom is also frequently employed for various other applications to modify both chemical and physical properties of molecules.[3] Among various fluorinated moieties, difluoromethyl ($-CF_2H$) is one of the most promising.[4] Therefore, it is not surprising that considerable efforts are being made in order to develop new strategies for incorporating this important group into a wide scope of substrates.[5]

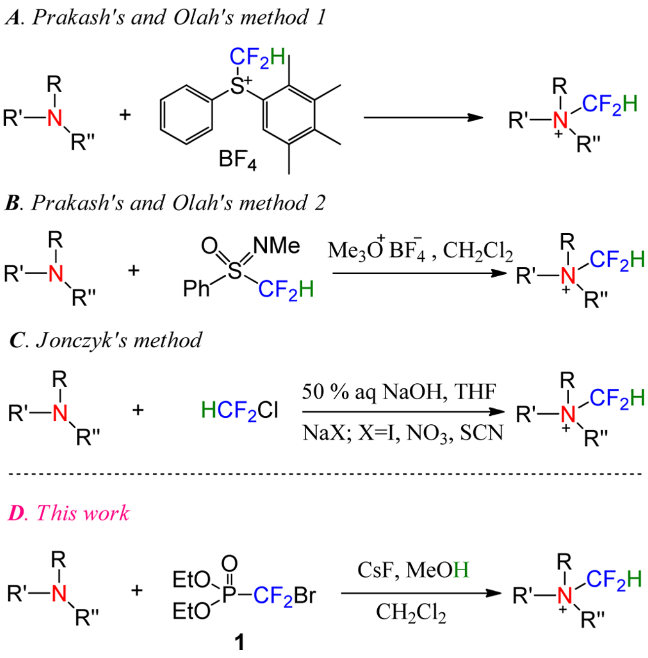


Figure 1. Methods for the synthesis of difluoromethyltrialkylammonium salts.

Quaternary ammonium salts are a well-known and abundant family of compounds used in medical applications, cosmetics, agriculture, chemical catalysis, and so on.[6] Since the charged moiety is responsible for the unique properties of these compounds, the influence of a difluoromethyl group adjacent to the cationic center may be of interest. In recent years, three practical methods for the synthesis of simple difluoromethyltrialkylammonium salts were reported (Figure 1A–C).[7−9] In methods A and B, reactive electrophilic difluoromethylation reagents that are not commercially available are used, and in method C, the ozone-depleting chlorofluorocarbon CHF_2Cl (Freon R-22) is used as a difluorocarbene precursor under strong basic conditions. Important ammonium compounds such as drugs, chiral phase transfer catalysts, monomers, polymers, and so on usually contain other reactive/sensitive functional groups that may be unstable under the reaction conditions of these methods. Therefore, the development of a practical and chemoselective difluoromethylation method for tertiary amines is still a significant challenge. Herein, we wish to

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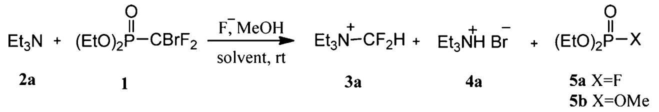
Table 1. Selected Optimization Conditions for the Difluoromethylation of Triethylamine



$$Et_3N + (EtO)_2P(O){-}CBrF_2 \xrightarrow[\text{solvent, rt}]{F^-,\ MeOH} Et_3\overset{+}{N}{-}CF_2H + Et_3\overset{+}{N}H\ \overset{-}{Br} + (EtO)_2P(O){-}X$$

2a **1** **3a** **4a** **5a** X=F **5b** X=OMe

entry	F^- source (equiv)	H^+ source (1.1 equiv)	solvent	t^a (h)	products (%)[b] **3a**	 **4a**	 **5a**	 **5b**[c]
1	TMAF (1)	MeOH		1	87	13	55	44
2	TBAF (1)	MeOH		1	77	23	63	21
3	TBAF (0.05)	MeOH		1	78	22	5	71
4	Resin-F (1)	MeOH		24	24	76	22	76
5	Resin-F (0.05)	MeOH		3.5	85	15	16	73
6	Resin-F (0.05)	2-PrOH		1	63	37	11[d]	58[d]
7	Resin-F (0.05)	*t*-BuOH		1	57	43	17[d]	47[d]
8	Resin-F (0.05)	H_2O		1	50	50	25[d]	48[d]
9	Resin-F (1)	MeOH	DCM	24	70	[e]		92
10	Resin-F (0.05)	MeOH	DCM	3.5	85	15	2	95
11	CsF (1)	MeOH		5	100			81
12	CsF (1)	MeOH	DCM	3.5	93	[e]		89
13	CsF (0.05)	MeOH	DCM	3.5	90	10		83
14	none	MeOH		1.5	90	10	22	75
15	none	MeOH	DCM	4.5	91	9		100

[a] Time for full conversion. [b] Products **3a** and **4a** were determined by ^1H NMR; products **5a** and **5b** were determined by ^{31}P NMR. [c] In some cases, these percents contain diethylphosphate as minor product. [d] The appropriate phosphate was observed. [e] **2a** was observed.

disclose our results on a facile and highly chemoselective difluoromethylation of tertiary amines to α-difluoromethylammonium compounds using the commercially available diethyl bromodifluoromethylphosphonate (**1**) (Figure 1D). We will show that despite the fact that the mechanism of this difluoromethylation involves the difluorocarbene intermediate, it occurs almost exclusively on the nitrogen atom, even in molecules containing hydroxyl, alkynyl, or alkenyl groups.

■ RESULTS AND DISCUSSION

In previous work, we have shown that phosphonate **1** is an efficient difluorocarbene precursor for difluoromethylation of phenols and thiophenols under strong basic conditions. Unfortunately, these conditions were found to be inapplicable for other interesting functions, inter alia, amines.[5c] We hypothesized that cleaving the P−C bond using the appropriate fluoride ion[10−12] instead of a hydroxide would give a difluorocarbene under mild nonhydrolytic conditions, and that this intermediate would react selectively with a tertiary amine free base to give the difluoromethylammonium product upon protonation. Indeed, we have found that phosphonate **1** reacts completely and rapidly with various fluorides, which in the presence of triethylamine and a proton source yield the desired product difluoromethyltriethylammonium bromide (**3a**). Selected optimization conditions for the difluoromethylation of triethylamine are tabulated in Table 1. Initially, using tetramethylammonium fluoride (TMAF) and methanol yielded **3a** (87%) and the undesired side products triethylamine hydrobromide (**4a**, 13%) together with the main phosphorus byproducts **5a** (55%) and **5b** (44%) (entry 1). Replacing TMAF with TBAF·H_2O somewhat increased the relative amounts of both side products **4a** and **5a** (entry 2), yet a significant decrease in the relative amount of fluorophosphate **5a** was observed when a catalytic amount of TBAF·H_2O was used (entry 3). Charged side products such as **4a** directly decrease the reaction yield and pose difficulties in the isolation of **3a** at neutral pH. In addition, phosphate triester **5b** is considered as environmentally benign and safe, while fluorophosphate **5a** has moderate toxicity.[13] Therefore, our goal in the optimization study was to completely eliminate **4a** and **5a** as side products and to facilitate the isolation of the desired difluoromethylammonium bromide salt from other charged starting materials or side products. In an attempt to use a solid support to facilitate effective separation of the ammonium product from the fluoride source, we proceeded to investigate the reaction using polystyrene-supported ammonium fluoride[14] (Resin-F). With one fluoride equivalent of nonswelled Resin-F, the reaction was found to be sluggish and, even worse, gave only 24% of **3a** together with 76% of **4a** and 22% of the phosphorus by product **5a** (entry 4). On the other hand, using a catalytic amount of Resin-F, **3a** was obtained in 85% yield and the amount of undesired side products **4a** and **5a** was reduced to 15 and 16%, respectively (entry 5). Among the proton sources, methanol, isopropyl alcohol, tertiary butanol, and water, the former was found to be superior (entries 5−8). It should be noted that all reactions mentioned above were performed using neat reagents and were therefore found to be somewhat violent. Thus, the addition of dichloromethane (DCM) as a solvent led to milder conditions in which much less fluorophosphate **5a** was observed (entries 9 and 10). Complete eradication of side products **4a** and **5a** along with the best yields of **3a** was obtained after turning to CsF (1 equiv) as an inorganic fluoride source (entries 11 and 12). This may have resulted from the relatively higher basicity of CsF in the reaction medium, compared to that of TMAF and TBAF (for Et_3N, MeOH, F; pH 13 vs 12, respectively), precluding the formation of side products **4a** and **5a**.

Interestingly and unexpectedly, control reactions without a fluoride source led to mixtures of **3a**, **4a**, **5b**, and **3a**−**5a** and **5b**, with and without DCM, respectively (entries 15 and 14). The fact that fluorophosphate **5a** was observed in the reaction without a fluoride source (without DCM) implies that phosphonate **1** may also act as a fluoride "source" by the possible degradation of the difluorocarbene. This could occur,

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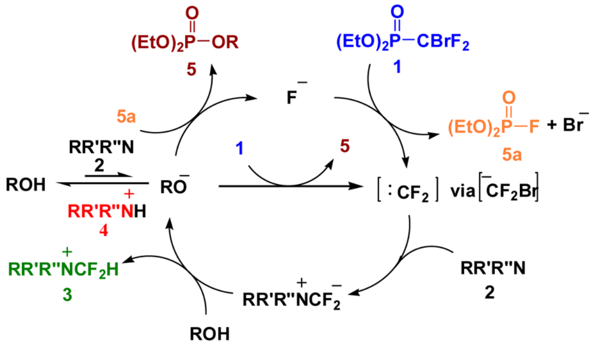
for example, by its hydrolysis to fluoride and formate ions.[5c] Hence, this may be the reason why in the presence of only 0.05 equiv of fluoride, the reaction without DCM led to relatively large amounts of fluorophosphate **5a**, much more than the maximum expected 5% (entries 5−8 and 14). The absence of **5a** when DCM was added suggests that the undesired side reaction of the difluorocarbene intermediate leading to the formation of the fluoride ion is much less dominant when this solvent is used as a reaction medium. Therefore, we propose the mechanism depicted in Scheme 1 for the reaction in DCM.

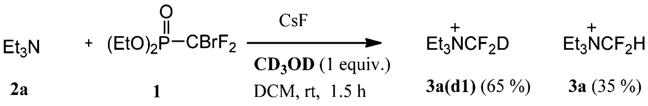
Scheme 1. Proposed Reaction Mechanism for the Reaction of Tertiary Amine with Phosphonate 1 with and without Fluoride Ion in the Presence of Alcohol



The catalytic cycle, starting with P−C bond cleavage, can be initiated by either fluoride from a source such as CsF or R_3N/MeOH, which directly attacks the phosphonate to obtain difluorocarbene intermediate. The efficiency of the latter initiator obviously strongly depends on the amine structure (steric effect) and on its basicity (electronic effect). For example, contrary to trimethylamine, the reaction with the more sterically hindered trioctylamine, in the absence of cesium fluoride, was sluggish and led to a mixture of the corresponding difluoromethylammonium product **3d** and the undesired trioctylamine hydrobromide **4d** in a 3.5:1 ratio (Scheme 2). However, the same reaction with cesium fluoride led rapidly and exclusively to the desired product **3d**. The basicity of the amine compound dramatically determines the reaction course; for example, as we will show later, the reactions of pyridine derivatives (weak bases) without CsF do not occur at all, emphasizing the importance of this catalyst.

Evidence for the next step in the cyclic mechanism, involving a nucleophilic attack of the amine free base on difluorocarbene followed by protonation at the CF_2 carbanion, was obtained by performing the reaction of triethylamine with **1** in the presence of 1 equiv of deuterated methanol (Scheme 3). The deuterated product **3a(d1)**, observed as a singlet by ^{19}F NMR at −33.3 ppm, was the major product of this reaction (the minor product **3a** was obtained due to residual water).

Scheme 3. Reaction of Triethylamine with Phosphonate 1 in the Presence of Deuterated Methanol (CD_3OD)



The substrate scope of this fluoride-promoted difluoromethylation was explored under the optimized conditions described in Table 1, entry 12, using DCM as a solvent. Over the course of our study, we realized that for successful workup of product isolation one should leave the reaction for 24 h (rt), a period of time in which the side product **5a**, if nevertheless formed, is converted to the favored product **5b**. However, in a few cases in which an extended reaction time was required to gain full conversion of the amine itself or when *sec*-BuOH was used as a proton source (**3o**, **3r**), side product **5a** was obtained in relatively large amounts (see Experimental Section). Inspection of the structures and data presented in Table 2 reveals that the reaction tolerates functionalities such as hydroxyl, alkene, alkyne, ester, carbonyl, oxirane, and thiophene. Therefore, this reaction may be considered as a mild and highly chemoselective difluoromethylation approach. Simple difluoromethylated quaternary ammonium bromide compounds were easily synthesized in excellent isolated yields (**3a−f**). Bicyclic ammonium compounds bearing an azabicyclo skeleton such as **3g** and **3h** were obtained in fair isolated yields. With starting materials containing an alkene group or both alkyne and hydroxyl groups, the difluoromethylation occurred only on the amine moiety, yielding **3i** and **3j**, respectively. Contrary to the stability of the propargylic ammonium product **3j**, the unsubstituted allylic ammonium product **3i** was found to be unstable under the isolation procedure, and therefore, its isolated yield was not determined. Aromatic amines such as DMAP or imidazoles react exclusively via the nitrogen located at the $C(sp^2)−N(sp^2)$ bond to give the corresponding products **3k−3m** in good to excellent yields. A notable expression for both the chemoselectivity and the mildness of our difluoromethylation procedure was shown with the reactions of the multifunctional compound cinchonidine. With this compound, the difluoromethylation occurred solely on the nitrogen at the $N(sp^3)$ moiety (**3n**, 98% conversion) but not on the hydroxyl, $N(sp^2)$, or ethenyl groups. With challenging sensitive esters, products **3o** and **3p** were obtained in excellent isolated yields. As mentioned above, without CsF, the pyridinium product **3p** was not obtained at all even after prolonged reaction time (2 weeks). The poorly reactive pyridine precursor emphasizes the necessity of the fluoride ion source for this reaction. Exploring the unique system pyridoxime, in which the oxime group is known as a reactive functionality toward active phosphorus compounds,[15] revealed that its difluoromethylation (**3q**) was slower and led to the formation of undesired and unknown side products. Therefore, the product **3q** was isolated after partial conversion (ca. 10%). The product **3r** revealed again that the

Scheme 2. Reaction of Trioctylamine with Phosphonate 1 with and without Cesium Fluoride

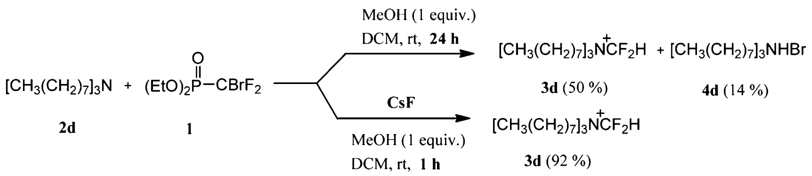
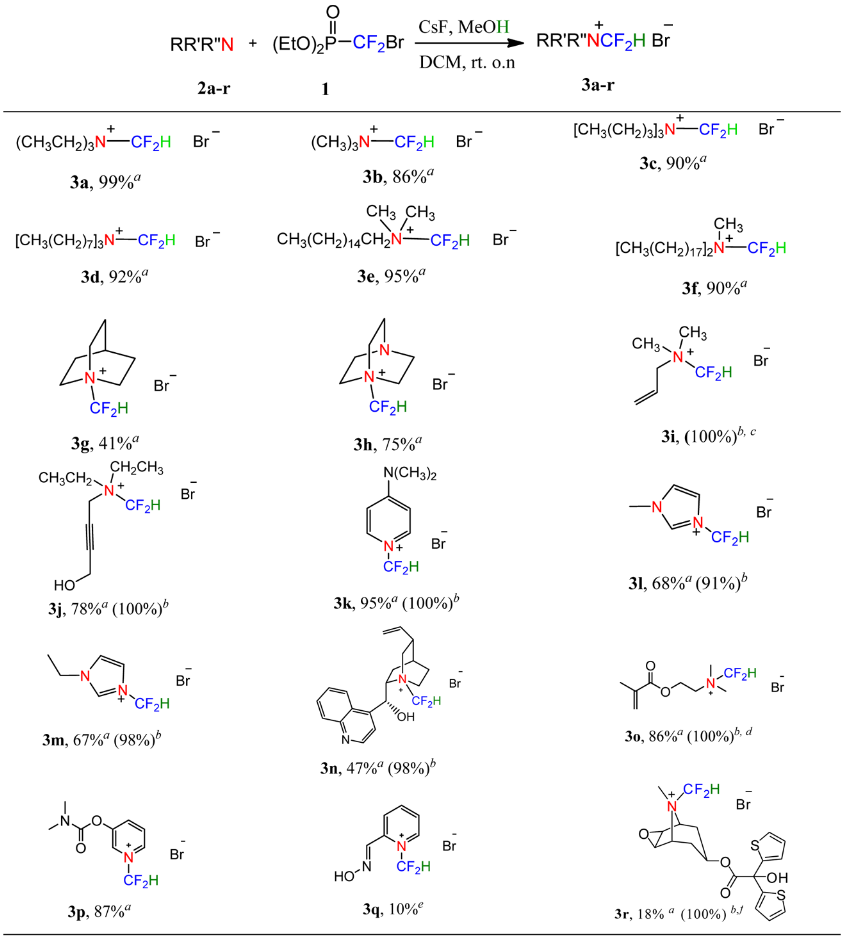


Table 2. Substrate Scope

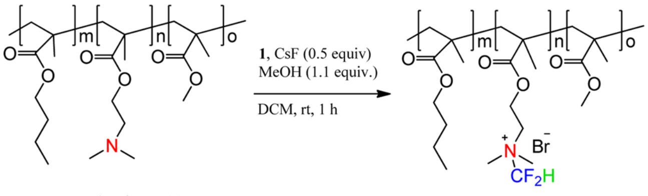


3a, 99%[a]; **3b**, 86%[a]; **3c**, 90%[a]; **3d**, 92%[a]; **3e**, 95%[a]; **3f**, 90%[a]; **3g**, 41%[a]; **3h**, 75%[a]; **3i**, (100%)[b, c]; **3j**, 78%[a] (100%)[b]; **3k**, 95%[a] (100%)[b]; **3l**, 68%[a] (91%)[b]; **3m**, 67%[a] (98%)[b]; **3n**, 47%[a] (98%)[b]; **3o**, 86%[a] (100%)[b, d]; **3p**, 87%[a]; **3q**, 10%[e]; **3r**, 18%[a] (100%)[b,f]

[a]Isolated yield. [b]Amine conversion. [c]The product was not isolated after full conversion due to its degradation during the workup procedure. [d]2-Methyl-2-butanol was used instead of methanol. [e]The product was not isolated from the sodium bromide salt used during the purification process, and therefore, the yield was calculated according to an internal standard. [f]This product is unstable at room temperature, and therefore, the isolated yield is considerably low.

difluoromethylation took place exclusively on the nitrogen atom even with a multifunctional amine containing thiophene, hydroxyl, ester, and epoxide groups (100% conversion). However, the product was found to be unstable at room temperature, and unfortunately, it decomposed during and after workup. Finally, polymers bearing tertiary amines such as Eudragit E-100 could also be difluoromethylated on the nitrogen moiety to produce the appropriate quaternized polymer **3s**, as observed by its solution ^{19}F and ^{1}H NMR (Scheme 4). This reaction was analyzed only by ^{1}H and ^{19}F NMR (see Supporting Information Figure S32) of an incompletely separated product **3s**, which still awaits further optimization and analysis.

Scheme 4. Difluoromethylation of Eudragit E-100 Using Phosphonate 1



Eudragit E-100 **3s**

The substrate scope described above represents high chemoselectivity and tolerability of the reaction conditions to diverse functional groups and was designed to include representative compounds from a wide range of practical disciplines. For example, compounds **3e** and **3f** (CTAB-F2 and DODAB-F2) are representatives of the surfactant family and antibacterial compounds;[16] **3l** and **3m** represent the ionic liquids family; **3n** acts as a phase transfer catalyst;[17] **3o** may serve as a methacrylate monomer;[18] **3p**−**3r** can act as difluoromethylated analogues of pyridostigmine, 2-PAM, and tiotropium (scopine di(2-thienyl)glycolate) drugs,[19] respectively. Eudragit analogue polymer **3s** is an example for a possible post-polymerization approach for difluoromethylation of polymers containing tertiary amines.

A preliminary assessment of the effect of a α-difluoromethyl group on quaternary ammonium compounds has been performed using two of the above-mentioned compounds. Located at the carbon positioned α to the nitrogen in quaternary ammonium salt, the fluorine atoms may cause some interesting effects on their physical, chemical, and, where relevant, biological properties. It has been shown that the positive charge of ammonium salts is delocalized on the hydrogen atoms of the α-carbons, which interact with the counteranion through hydrogen bonding.[20] An interesting

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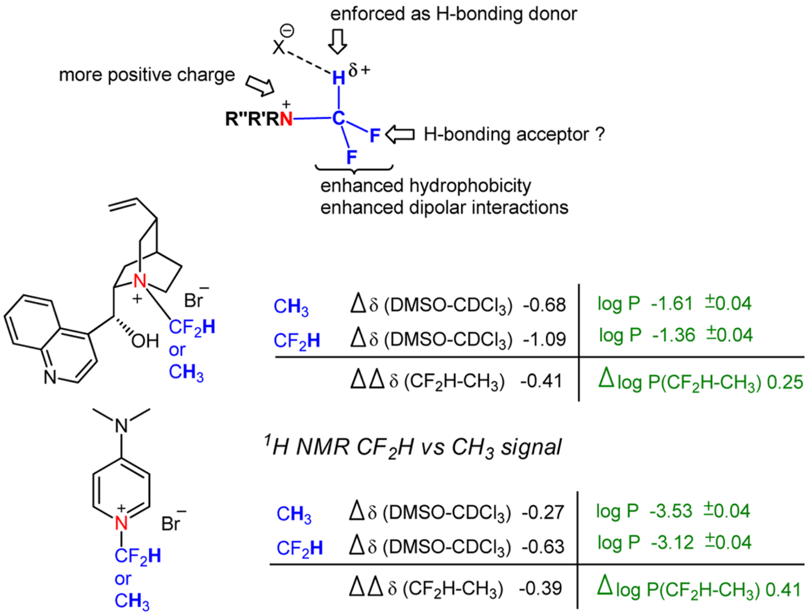

Figure 2. Preliminary assessment of the effect of a *α*-difluoromethyl group on quaternary ammonium compounds.

hydrogen-bonding catalysis with a scholarly designed quaternary ammonium salt that contains electron-withdrawing groups at the *α* positions was reported, most recently, by Shirakawa et al.[21] The dual property of the fluorine group as a hydrophobic moiety together with its high electronegativity (enforcing hydrogen-bonding strength of the adjacent hydrogen) and relatively small size may result in different types of interactions (Figure 2). We examined the effect that solvents have on the chemical shifts of the representatives pairs (NCH_3 vs NCF_2H) using Abraham's method where calculating $\Delta\delta$(DMSO−$CDCl_3$) may lead to interesting insights into the solute−solvent interaction, inter alia, hydrogen bonds.[22] In this case, the counterion itself significantly affects the chemical shift of the *α*-hydrogens.[23] Using bromide as a counterion, we compared only the adjacent CF_2H versus CH_3 group and found a significant shielding effect from DMSO, which strongly implies that the proton at the CF_2H group is more prone to participate in H-bonding (Figure 2). For each pair, there are further interesting data, such as shifting the other hydrogens at the *α*-carbons, shifting and changes in the fluorine atoms, counterion effects, and so forth. This important interaction may significantly affect various chemical, physical, and drug-like properties. For example, attenuation of the hydrophilicity of the quaternary ammonium compounds may be achieved through the addition of fluorine atoms. This may facilitate absorption of such compounds, which are generally highly water-soluble and poorly absorbed through biological membranes. The measurement of log*P* (hydrophobicity) for both couples of compounds, that is, Δlog*P*(CF_2H−CH_3), showed an increase of 0.25 and 0.41 log*P* units for **3n** and **3k**, respectively. These results show that, as in many other cases, the addition of fluorine atoms leads to an increase in lipophilicity. These issues are currently under investigation.

CONCLUSIONS

To conclude, the described method for difluoromethylation of tertiary amines, using phosphonate **1**, CsF, and methanol was found to be very practical for the synthesis of various *α*-difluoromethylated quaternary ammonium compounds. Although the reaction mechanism involves a difluorocarbene intermediate, the use of fluoride as a trigger under mild conditions enables a remarkable tolerance of functional groups such as hydroxyl, alkenyl, alkynyl, esters, and so forth. Combining the two highly important issues of fluorinated organic compounds and quaternary ammonium salts may lead to interesting changes in chemical and physical properties and seems to be promising for applications in the research fields of surfactants, ionic liquids, phase transfer catalysts, drugs, and polymers.

EXPERIMENTAL SECTION

General. Commercially available high-grade reagents and solvents were used without further purification. NMR spectra were recorded on 300 MHz spectrometer (300.1 MHz for ^1H NMR, 75.5 MHz for ^{13}C NMR, 121.5 MHz for ^{31}P NMR, and 282.4 MHz for ^{19}F NMR) or 500 MHz spectrometer (500.2 MHz for ^1H NMR, 125.8 MHz for ^{13}C NMR, 202.5 MHz for ^{31}P NMR, and 470.7 MHz for ^{19}F NMR). Chemical shifts are reported in parts per million (δ, ppm). ^1H and ^{13}C NMR chemical shifts were referenced to the residual $CDCl_3$ solvent peaks ($\delta = 7.26$ ppm for ^1H and $\delta = 77.0$ ppm for ^{13}C). ^{31}P and ^{19}F chemical shifts are reported downfield from external trimethylphosphate and trifluoroacetic acid in D_2O, respectively. High-resolution mass spectra were obtained with LC-HRMS mass spectrometer operated in the positive ESI mode. Ion exchange chromatography was performed with commercial SCX columns (2 g). UV absorbance for log*P* calculations were recorded on a UV−vis spectrophotometer.

General Procedure for Difluoromethylation of Tertiary Amines. All reactions were conducted under inert atmosphere in a sealed tube or vial, equipped with a magnetic stirrer. To a mixture of tertiary amine (1 mmol), CsF (1.05 mmol), and anhydrous methanol (1.5 mmol) in anhydrous dichloromethane (1 mL) was added diethyl bromodifluoromethylphosphonate (1.1 mmol) in one portion. The reaction mixture was stirred at 25 °C until completion (specific times are reported in the following procedures). The crude product was extracted from the reaction mixture with dry $CHCl_3$ (3 × 2 mL) and then dry CH_3CN (3 × 2 mL), filtered, and evaporated under reduced pressure. The residue was purified by ion exchange chromatography (SCX column, 2 g): The SCX column was prewashed with water and methanol and then charged with the residue; impurities were washed out with methanol, and the desired product was eluted with 10% NaBr in methanol. Spot detection of the product was obtained by

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Dragendorff's reagent spray. Removal of NaBr from the purified product/NaBr mixture was accomplished by evaporation of the methanol and extraction of the product from the solid residue with dry CHCl$_3$ (3 × 2 mL) or with dry CHCl$_3$/CH$_3$CN, 1:1 (3 × 2 mL). The solvent was evaporated under reduced pressure to give the difluoromethylammonium bromide product.

Specific experimental data for the difluoromethylammonium compounds are reported below. Experimental data for products **3a**,[7,8,24] **3b**,[24] **3c**,[9] **3d**,[9] **3e**,[9] **3h**,[24] **3k**,[24] **3l**,[7] and **3m**[7] were reported previously. NMR characterization data for known compounds prepared by our new method were consistent with literature precedent. Full NMR and HRMS analyses for all new compounds are reported below.

*Difluoromethyltriethylammonium Bromide (**3a**).* Known product, according to the general procedure. The mixture was stirred for 3 h. The product was isolated as a white solid (229 mg, 99% yield): ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.28 (t, J_{HF} = 57.5 Hz, 1H), 3.89 (q, 6H), 1.51 (t, J = 10 Hz, 9H); ^{19}F NMR (470.7 MHz, CDCl$_3$) δ −35.17 (d, J_{HF} = 57.4 Hz); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 115.1 (t, J_{CF} = 277.9 Hz), 52.8, 8.9.

*Difluoromethyltrimethylammonium Bromide (**3b**).* Known product, according to the general procedure. For this reaction trimethyl amine in ethanol (4.2 M) was used, therefore no methanol was added to the reaction mixture. The mixture was stirred overnight. The product was isolated as a white solid (163 mg, 86% yield): ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.25 (t, J_{HF} = 60 Hz, 1H), 3.38 (s, 9H); ^{19}F NMR (470.7 MHz, CD$_3$OD) δ −40.63 (d, J_{HF} = 58.8 Hz); ^{13}C NMR (125.8 MHz, CD$_3$OD) δ 115.9 (t, J_{CF} = 276.3 Hz), 48.65.

*Difluoromethyltributylammonium Bromide (**3c**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as a white solid (285 mg, 90% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.45 (t, J_{HF} = 57.8 Hz, 1H), 3.75 (t, J = 8.6 Hz, 6H), 1.84 (m, 6H), 1.45 (m, 6H), 1.02 (t, J = 7.4, 9H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ −32.99 (d, J_{HF} = 57.5 Hz).

*Difluoromethyltrioctylammonium Bromide (**3d**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as a white solid (446 mg, 92% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.46 (t, J_{HF} = 57.9 Hz, 1H), 3.68−3.73 (m, 6H), 1.75−1.85 (m, 6H), 1.21−1.38 (m, 30H), 0.85 (t, J = 6.6 Hz, 9H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ −33.50 (d, J_{HF} = 58.4 Hz).

*Difluoromethylhexadecyldimethylammonium Bromide (**3e**).* Known product, according to the general procedure. The mixture was stirred overnight. The residue was purified by a SCX column (5 g), and the product was isolated as a white solid (380 mg, 95% yield): ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.26 (t, J_{HF} = 59.0 Hz, 1H), 3.82 (m, 2H), 3.58 (s, 6H), 1.38−1.25 (m, 28H) 0.87 (t, J = 6.6 Hz, 3H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ −38.62 (d, J_{HF} = 59.2 Hz).

*Difluoromethylmethyldioctadecylammonium Bromide (**3f**).* According to the general procedure, the mixture was stirred overnight. The residue was purified by a SCX column (5 g), and impurities were washed out with CHCl$_3$/MeOH (1:4). The product was isolated as a white solid (600 mg, 90% yield): mp 94−98 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.28 (t, J_{HF} = 58.5 Hz, 1H), 3.73 (m, 4H), 3.51 (s, 3H), 1.81−1.79 (m, 4H), 1.34−1.22 (m, 60H), 0.84 (t, J = 6.4 Hz, 6H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ −35.63 (d, J_{HF} = 57.8 Hz); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 114.6 (t, J_{CF} = 248.8 Hz), 59.1, 44.6, 31.9, 29.8, 29.8, 29.8, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 29.0, 26.5, 22.9, 22.7, 14.1; HRMS (ESI$^+$-QTOF) m/z calcd for C$_{38}$H$_{78}$F$_2$N [M + H]$^+$ 586.6097, found 586.6093.

*1-(Difluoromethyl)quinuclidin-1-ium Bromide (**3g**).* According to the general procedure, the mixture was stirred overnight. The product was isolated as a white solid (99 mg, 41% yield): mp 73−78 °C. ^{1}H NMR (500 MHz, CD$_3$OD) δ 6.98 (t, J_{HF} = 60 Hz, 1H), 3.69 (m, 6H), 2.29 (m, 1H), 2.10 (m, 6H); ^{19}F NMR (470.7 MHz, CD$_3$OD) δ −41.5 (d, J_{HF} = 58.8 Hz); ^{13}C NMR (125.8 MHz, CD$_3$OD) δ 115.5 (t, J_{CF} = 273.0 Hz), 79.4, 51.4, 23.8; HRMS (ESI$^+$-QTOF) m/z calcd for C$_8$H$_{14}$F$_2$N [M + H]$^+$ 162.1089, found 162.1089.

*1-Difluoromethyl-4-aza-1-azoniabicyclo[2.2.2]octane Bromide (**3h**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as a white solid (182 mg, 75% yield): ^{1}H NMR (500 MHz, MeOD) δ 7.17 (t, J_{HF} = 58.5 Hz, 1H), 3.71 (t, J = 7.2 Hz, 6H), 3.38 (t, J = 8.5 Hz, 6H); ^{19}F NMR (470.7 MHz, MeOD) δ −40.59 (d, J_{HF} = 58.2 Hz).

*Allyldifluoromethyldimethylammonium Bromide (**3i**).* According to the general procedure, the mixture was stirred overnight. Full conversion was determined by ^{19}F NMR and ^{1}H NMR spectroscopy. The product was not isolated due to its poor stability on the SCX column: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (t, J_{HF} = 57.5 Hz, 1H), 5.98−5.88, (m, 1H), 5.82 (d, J = 17.0 Hz, 1H), 5.67 (d, J = 10.5 Hz, 1H), 4.45 (d, J = 7.5 Hz, 2H), 3.36 (s, 6H); ^{19}F NMR (470.7 MHz, CDCl$_3$) δ −38.30 (d, J_{HF} = 58 Hz).

*Difluoromethyldiethyl-(4-hydroxybut-2-ynyl)ammonium Bromide (**3j**).* According to the general procedure, the mixture was stirred overnight. The product was isolated as a brown oil (212 mg, 78% yield): ^{1}H NMR (500 MHz, CD$_3$OD) δ 7.41 (t, J_{HF} = 60 Hz, 1H), 4.70 (s, 2H), 4.32 (s, 2H), 3.84 (q, J = 10 Hz, 4H), 1.50 (t, J = 10 Hz, 6H); ^{19}F NMR (470.7 MHz, CD$_3$OD) δ −37.82 (d, J_{HF} = 57.4 Hz); ^{13}C NMR (125.8 MHz, CD$_3$OD) δ 116.7 (t, J_{CF} = 276.0 Hz), 93.4, 71.3, 54.3, 49.5, 47.8, 8.6; HRMS (ESI$^+$-QTOF) m/z calcd for C$_9$H$_{16}$F$_2$NO [M + H]$^+$ 192.1194, found 192.1200.

*Difluoromethyl-4-dimethylaminopyridinium Bromide (**3k**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as a brown solid (240 mg, 95% yield): ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.85 (d, J = 10 Hz, 2H), 8.55 (t, J_{HF} = 58.5 Hz, 1H), 7.16 (d, J = 10 Hz, 2H), 3.41 (s, 6H); ^{19}F NMR (470.7 MHz, CDCl$_3$) δ −19.85 (d, J_{HF} = 58.3 Hz); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 158.3, 138.1, 111.7 (t, J_{CF} = 261.5 Hz), 109.5, 41.4.

*1-Difluoromethyl-3-methyl-3H-imidazol-1-ium Bromide (**3l**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as an orange solid (145 mg, 68% yield): ^{1}H NMR (300 MHz, CD$_3$CN) δ 9.97 (t, 1H), 8.18 (t, J_{HF} = 58.8 Hz, 1H), 7.63 (t, J = 1.95 Hz, 1H), 7.54 (t, J = 1.65 Hz, 1H), 3.98 (s, 3H); ^{19}F NMR (282.4 MHz, CD$_3$CN) δ −21.39 (d, J_{HF} = 59 Hz); ^{13}C NMR (75.5 MHz, CD$_3$CN) δ 137.6, 126.0, 119.4, 109.4 (t, J_{CF} = 248.8 Hz), 37.7.

*3-(Difluoromethyl)-1-ethyl-1H-imidazol-3-ium Bromide (**3m**).* Known product, according to the general procedure. The mixture was stirred overnight. The product was isolated as a brown oil (152 mg, 67% yield): ^{1}H NMR (300 MHz, D$_2$O) δ 10.3 (s, 1H), 8.30 (t, J = 58.5 Hz, 1H),7.85 (br d, 2H), 4.34 (q, J = 7.5 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ −21.20 (d, J_{HF} = 57.6 Hz).

*1-Difluoromethyl-2-(hydroxyquinolin-4-ylmethyl)-5-vinyl-1-azoniabicyclo[2.2.2]octane Bromide (**3n**).* According to the general procedure, to a mixture of cinchonidine (1 mmol), CsF (1.1 mmol), and anhydrous methanol (2.4 mmol) in anhydrous dichloromethane (4 mL) was added diethyl bromofluoromethyl phosphonate (1.1 mmol) in one portion. The mixture was stirred at 40 °C in a pressure tube for 1 h and then cooled to room temperature and stirred for an additional 1 h. The crude product was extracted from the reaction mixture with 9:1 CHCl$_3$/MeOH (3 × 2 mL), and the product was isolated on SCX as described in the general procedure. Removal of NaBr from the purified product/NaBr mixture was accomplished by evaporation of the methanol and extraction of the product with dry 9:1 DCM/MeOH (3 × 2 mL). The product was then subjected to further purification by silica gel chromatography with 92:8 DCM/MeOH as eluent to give the isolated product as a yellow liquid (199 mg, 47% yield): ^{1}H NMR (500 MHz, MeOD) δ 8.9 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 4.7 Hz, 1H), 7.83 (t, J = 8.2 Hz, 1H), 7.81 (t, J_{HF} = 57.6 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 6.41 (bs, 1H), 5.70−5.67 (m, 1H), 5.17 (d, J = 17.2 Hz, 1H), 5.00 (d, J = 10.5 Hz, 1H), 4.65−4.61 (m, 1H), 4.17 (t, J = 8.6 Hz, 1H), 4.11 (t, J = 10.8 Hz, 1H), 3.78−3.75 (m, 2H), 3.02 (bs, 1H), 2.37−2.16 (m, 4H), 1.42 (t, J = 12.6 Hz, 1H); ^{19}F NMR (470.7 MHz, MeOD) δ −36.32 (dd, J_{HF} = 57 Hz, 217 Hz, 1F), δ −41.35 (dd, J_{HF} = 57 Hz, 217 Hz, 1F); ^{13}C NMR (125.8 MHz, MeOD) δ 149.7, 147.21, 145.1, 136.5, 129.8, 129.0, 127.8, 124.5, 121,7, 119.8, 116.5, 114.3 (t, J_{CF} = 271.9 Hz), 65.9, 64.7, 56.1, 50.4, 36.7, 26.4, 23.6, 19.9. HRMS (ESI$^+$-QTOF) m/z calcd for C$_{20}$H$_{23}$F$_2$N$_2$O [M + H]$^+$ 345.1773, found 345.1772.

*Difluoromethyldimethyl[2-(2-methylacryloyloxy)ethyl]-ammonium Bromide (**3o**).* The reaction was conducted according to the general procedure with slight modification: 2-methyl-2-butanol was used as a proton source instead of MeOH. The mixture was stirred overnight. The product was isolated as a brown liquid (247 mg, 86% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (t, J_{HF} = 59 Hz, 1H), 6.10 (s, 1H), 5.62 (s, 1H), 4.70 (t, J = 4.5 Hz, 2H), 4.34 (t, J = 4.5 Hz, 2H), 3.60 (s, 6H), 1.89 (s, 3H); ^{19}F NMR (470.7 MHz, $CDCl_3$) δ −38.48 (d, J_{HF} = 59 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.2, 135.1, 127.5, 113.9 (t, J_{CF} = 278.0 Hz), 60.2, 57.6, 46.6, 18.2; HRMS (ESI$^+$-QTOF) m/z calcd for $C_9H_{16}F_2NO_2$ $[M + H]^+$ 208.1144, found 208.1140.

*1-Difluoromethyl-3-dimethylcarbamoyloxypyridinium Bromide (**3p**).* According to the general procedure, the mixture was stirred for 5 days. The product was isolated as a brown liquid (258 mg, 87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, J = 5.9 Hz, 1H), 9.61 (s, 1H), 9.25 (t, J_{HF} = 58.5 Hz, 1H), 8.71 (d, J = 8.6 Hz, 1H), 8.51 (dd, J = 8.4 Hz, 6.4 Hz, 1H), 3.17 (s, 3H), 3.04 (s, 3H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −20.86 (d, J_{HF} = 58.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.9, 143.5, 138.2, 134.0, 129.5, 111.8 (t, J = 273.2 Hz), 37.2, 36.9; HRMS (ESI$^+$-QTOF) m/z calcd for $C_9H_{11}F_2N_2O_2$ $[M + H]^+$ 217.0783, found 217.0785.

*1-Difluoromethyl-2-(hydroxyiminomethyl)pyridinium Bromide (**3q**).* According to the general procedure, the mixture was stirred overnight. At the last step of the workup, the product (purple solid) could not be separated from the NaBr. Therefore, the yield of the reaction was determined by ^{19}F NMR spectroscopy by comparing the ^{19}F NMR resonance of the product to that of an internal standard (trifluorotoluene): ^{19}F NMR yield = 10%; ^{1}H NMR (500 MHz, CD_3OD) δ 9.43 (d, J = 6.0 Hz, 1H), 8.90 (t, J = 8.0 Hz, 1H), 8.76 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H), 8.54 (t, J_{HF} = 57.0 Hz, 1H), 8.32 (t, J = 7.0 Hz, 1H); ^{19}F NMR (470.7 MHz, CD_3OD) δ −21.2 (d, J_{HF} = 57.0 Hz); ^{13}C NMR (125.8 MHz, CD_3OD) δ 149.8, 146.8, 140.4, 140.1, 127.4, 127.3, 112.2 (t, J_{CF} = 287.0 Hz); HRMS (ESI$^+$-QTOF) m/z calcd for $C_7H_7F_2N_2O$ $[M + H]^+$ 173.0521, found 173.0527.

*9-Difluoromethyl-7-(2-hydroxy-2,2-dithiophen-2-yl-acetoxy)-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide (9-Difluoromethyltiotropium Bromide) (**3r**).* The reaction was conducted according to the general procedure with slight modification: 2-methyl-2-butanol was used as a proton source instead of MeOH. The mixture was stirred overnight, and the crude product was extracted from the reaction mixture with 9:1 $CHCl_3$/MeOH (3 × 2 mL). The product was isolated on SCX as described in the general procedure. Removal of NaBr from the purified product/NaBr mixture was accomplished by evaporation of the methanol and extraction of the product with dry 9:1 $CHCl_3$/MeOH (3 × 2 mL). The product was isolated as an unstable purple solid (91 mg, 18% yield): ^{1}H NMR (300 MHz, CD_3OD + $CDCl_3$) δ 7.76 (t, J_{HF} = 57.0 Hz, 1H), 7.42 (d, J = 3.9 Hz, 2H), 7.18 (d, J = 3.3 Hz, 2H), 7.04−7.02 (m, 2H), 5.31 (t, J = 5.7 Hz, 1H), 4.49 (s, 2H), 3.51 (s, 2H), 3.40 (s, 3H), 2.92−2.79 (m, 2H), 2.24 (d, J = 18.0 Hz, 2H); ^{19}F NMR (282 MHz, CD_3OD) δ −41.15 (d, J_{HF} = 57.0 Hz); ^{13}C NMR (125.8 MHz, CD_3OD+$CDCl_3$) δ 170.8, 146.5, 127.6, 127.16, 126.9, 113.7 (t, J_{CF} = 272 Hz), 67.7, 64.2, 53.8, 28.8; HRMS (ESI$^+$-QTOF) m/z calcd for $C_{19}H_{20}F_2NO_4S_2$ $[M + H]^+$ 428.0796, found 428.0790.

*Eudragit-E-100-CF$_2$H (**3s**).* The reaction was conducted according to the general procedure with slight modifications: the amount of DCM was doubled and that of cesium fluoride was halved. Immediate precipitation of the polymeric mass was observed during the addition of phosphonate **1**. After 1 h at room temperature, the reaction solution was removed and the polymeric chunk was dissolved in methanol (2 mL). Impurities were precipitated by the addition of 6 mL of chloroform, and the solution was filtered. The solvent was removed under reduced pressure to give a semisolid colorless product: ^{1}H NMR (500 MHz, CD_3OD) δ 7.41 (m, CHF_2, 1H), 4.56 (m, 2H), 4.11−4.00 (m, 4H), 3.63 (bs, 3H), 3.50 (bs, 6H), 1.93 (m, 6H), 1.66 (m, 2H), 1.46 (m, 2H), 1.12−0.89 (m, 12H); ^{19}F NMR (282 MHz, CD_3OD) δ −39.5 (m, 2F).

Determination of Octanol−Water Partition Coefficients (log*P*). The partition coefficients were calculated as the logarithm of the ratio of the salt concentration in the octanol phase to its concentration in the aqueous phase. The “shake-flask” method was used for the determination of log*P* values.[25] Both octanol and water were presaturated with each other for at least 24 h before the experiment. The representative salts were dissolved in octanol saturated water to obtain a concentration of 10 mM. The maximum wavelength (λ_{max}) for each compound was determined and the absorbance recorded using UV spectroscopy. Measurements were performed on dilute solutions, giving absorbance in the range of 0.2−1. To 45 mL of water-saturated octanol was added 0.3 mL of the water solution, and the mixture was shaken for 5 min. The solutions were then centrifuged at 3000 rpm for 5 min. An aliquot of the aqueous phase was diluted, and absorbance was measured. The experiment was repeated three times for each sample. The extraction ratio was obtained by difference, and log*P* was calculated taking account of the volume ratio between the water and octanol.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01728.

NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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