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Electron-Deficient Heteroarenium Salts: An Organocatalytic Tool for Activation of Hydrogen Peroxide in Oxidations

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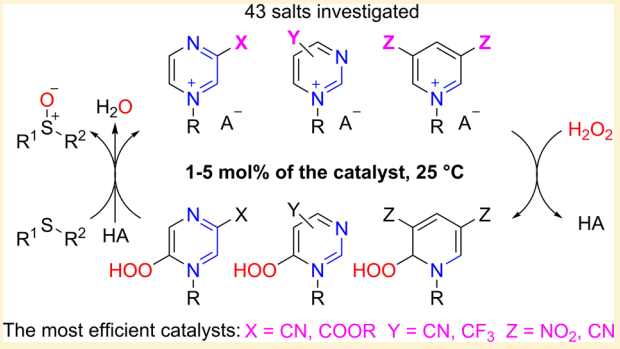
Supporting Information

ABSTRACT: A series of monosubstituted pyrimidinium and pyrazinium triflates and 3,5-disubstituted pyridinium triflates were prepared and tested as simple catalysts of oxidations with hydrogen peroxide, using sulfoxidation as a model reaction. Their catalytic efficiency strongly depends on the type of substituent and is remarkable for derivatives with an electron-withdrawing group, showing reactivity comparable to that of flavinium salts which are the prominent organocatalysts for oxygenations. Because of their high stability and good accessibility, 4-(trifluoromethyl)pyrimidinium and 3,5-dinitropyridinium triflates are the catalysts of choice and were shown to catalyze oxidation of aliphatic and aromatic sulfides to sulfoxides, giving quantitative conversions, high preparative yields and excellent chemoselectivity. The high efficiency of electron-poor heteroarenium salts is rationalized by their ability to readily form adducts with nucleophiles, as documented by low pK_{R+} values (pK_{R+} < 5) and less negative reduction potentials (E_{red} > −0.5 V). Hydrogen peroxide adducts formed in situ during catalytic oxidation act as substrate oxidizing agents. The Gibbs free energies of oxygen transfer from these heterocyclic hydroperoxides to thioanisole, obtained by calculations at the B3LYP/6-311++g(d,p) level, showed that they are much stronger oxidizing agents than alkyl hydroperoxides and in some cases are almost comparable to derivatives of flavin hydroperoxide acting as oxidizing agents in monooxygenases.

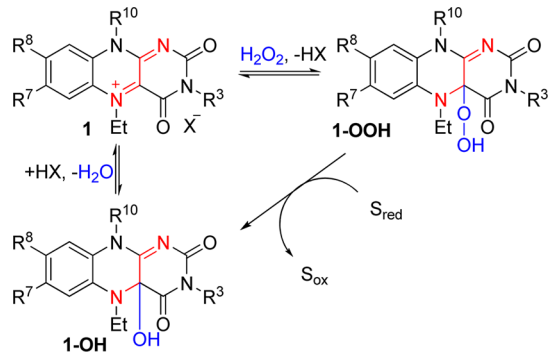


INTRODUCTION

The chemoselective and stereoselective introduction of oxygen into an organic substrate is among the key transformations in organic synthesis; thus, searching for new effective systems for selective oxygenations continues to represent an important goal. Currently, oxidation systems have been studied, especially with respect to sustainability and their environmental impact, which increases the interest in hydrogen peroxide as an inexpensive and environmentally benign oxidizing agent, producing water as the only byproduct.[1] Despite its high oxidation potential, hydrogen peroxide requires activation for most reactions with organic substrates due to relatively high activation barriers,[2] which has initiated the development of various catalytic systems for oxidations with hydrogen peroxide; the majority of these are based on transition metal complexes forming peroxo metal species with significantly higher reactivity.[3] Organocatalytic oxidations with hydrogen peroxide remain relatively underdeveloped.[4]

The reactivity of the hydroperoxy function is significantly enhanced by its connection to an electron-deficient heterocyclic ring, which was demonstrated in metal-free oxidations with several heterocyclic hydroperoxides of various structures; however, most of these compounds are used as stoichiometric oxidants prepared in advance.[5,6] The use of reactive hydroperoxides generated in a catalytic cycle remains the domain of organocatalytic oxidations mediated by flavinium salts **1** or **2** (Scheme 1 and 2).[5,7] As shown in Scheme 1 in the example of isoalloxazinium derivative **1**, flavinium catalysts react with hydrogen peroxide to form flavin-4a-hydroperoxide **1-OOH**. After oxygen is transferred to a substrate, the catalyst is regenerated by water elimination from a pseudobase **1-OH**.

Scheme 1. Catalytic Cycle of H_2O_2 Oxidations Catalyzed by Flavinium Salts 1



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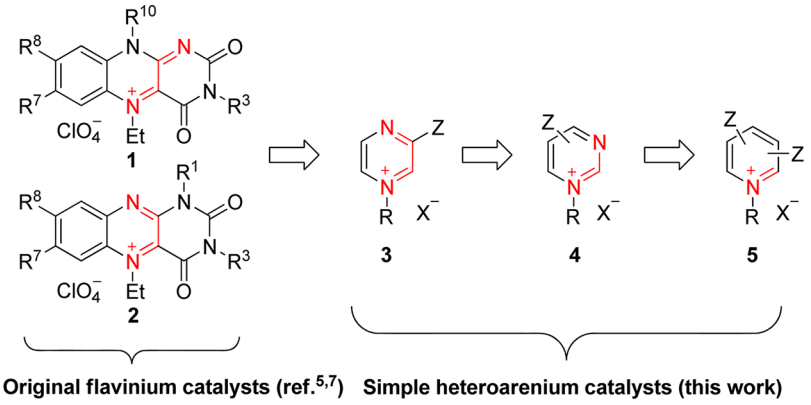
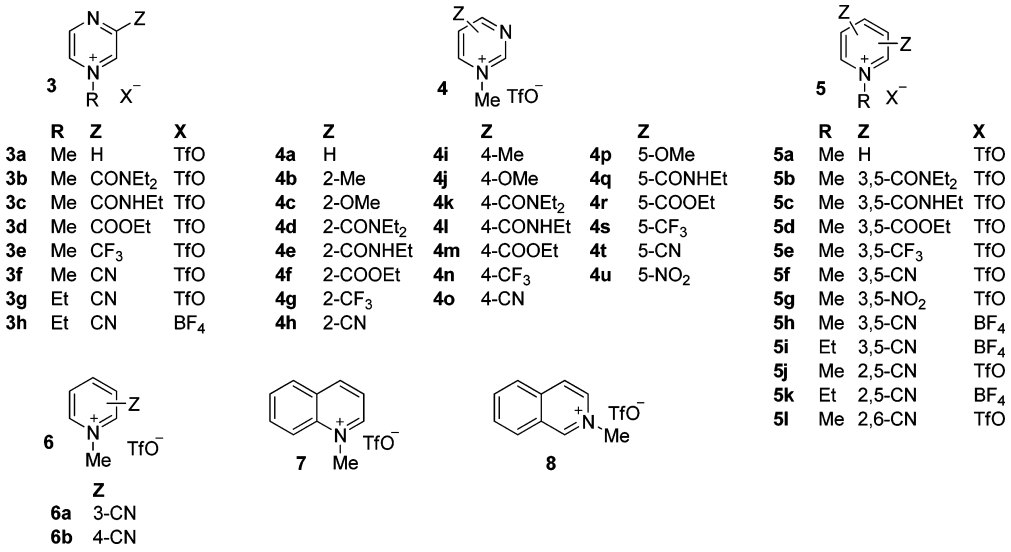
Scheme 2. Simplification of Heteroarenium Catalysts for H_2O_2 Oxidations





	R	Z	X
3a	Me	H	TfO
3b	Me	$CONEt_2$	TfO
3c	Me	CONHEt	TfO
3d	Me	COOEt	TfO
3e	Me	CF_3	TfO
3f	Me	CN	TfO
3g	Et	CN	TfO
3h	Et	CN	BF_4

	Z
4a	H
4b	2-Me
4c	2-OMe
4d	2-$CONEt_2$
4e	2-CONHEt
4f	2-COOEt
4g	2-CF_3
4h	2-CN

	Z		Z
4i	4-Me	4p	5-OMe
4j	4-OMe	4q	5-CONHEt
4k	4-$CONEt_2$	4r	5-COOEt
4l	4-CONHEt	4s	5-CF_3
4m	4-COOEt	4t	5-CN
4n	4-CF_3	4u	5-NO_2
4o	4-CN		

	R	Z	X
5a	Me	H	TfO
5b	Me	3,5-$CONEt_2$	TfO
5c	Me	3,5-CONHEt	TfO
5d	Me	3,5-COOEt	TfO
5e	Me	3,5-CF_3	TfO
5f	Me	3,5-CN	TfO
5g	Me	3,5-NO_2	TfO
5h	Me	3,5-CN	BF_4
5i	Et	3,5-CN	BF_4
5j	Me	2,5-CN	TfO
5k	Et	2,5-CN	BF_4
5l	Me	2,6-CN	TfO

	Z
6a	3-CN
6b	4-CN

Figure 1. Heteroarenium catalysts studied in this work.

The ability to reversibly add hydrogen peroxide and water, together with the high reactivity of flavin hydroperoxide (in sulfoxidations, hydroperoxide **1-OOH** is more reactive than hydrogen peroxide by 4 orders of magnitude[8]), makes flavinium salts very effective catalysts of oxidations.

The investigation of oxidations catalyzed by flavinium salts was initiated by discovery of the mode of action of hydroperoxides derived from flavin cofactors (FAD, FMN), which were recognized as oxidizing agents in flavoenzymes.[9] Later, this mild oxidation method became a real alternative to other oxidation protocols, mainly in sulfoxidations[10,11] and Baeyer–Villiger oxidations.[12] Even some chiral flavinium salts were shown to catalyze stereoselective oxidation of prochiral sulfides[13] and cyclobutanones.[14] Recently, new applications of flavinium-catalyzed oxygenations,[7a] i.e., in the Dakin oxidation,[15] hydroxylation of boronic acids,[16] oxidation of aldehydes to carboxylic acids,[17] and insertion of oxygen into methyl–rhenium bonds,[18] have also been described. To the best of our knowledge, except for derivatives of flavinium salts **1** and **2** (both derivatives **1**, with an isoalloxazinium core, and **2**, with an alloxazinium core, are classified as flavin derivatives in the literature), no example has been given in the literature of the in situ generation of a heterocyclic hydroperoxide by the addition of hydrogen peroxide to a simple heteroarenium salt simultaneously with using this adduct in catalytic oxidations. This fact is surprising because heteroarenium salts are known to form adducts with various nucleophiles; the formation of pseudobases by the addition of hydroxide anion to heteroarenium salts is one such example.[19]

In our preliminary investigation,[20] pyrazinium tetrafluoroborates **3** (X = BF_4 in Scheme 2) with an electron-withdrawing substituent were shown to catalyze sulfoxidations with hydrogen peroxide in a similar way as flavinium salts; i.e., hydrogen peroxide adds to salt **3** to form heterocyclic hydroperoxide **3-OOH**, which oxidizes a substrate. This important finding led us to consider if the ability to catalyze H_2O_2 oxygenations is limited to pyrazinium salts, representing simple models of alloxazinium catalysts **2** with the same diazadiene N=C–C=N grouping (Scheme 2) or if this useful property is general among nitrogen-containing heteroarenium compounds. Therefore, we extended our study to 2-, 4-, and 5-substituted pyrimidinium compounds **4** and disubstituted pyridinium compounds **5** as suitable representatives of simple heteroarenium compounds. Salts **3**–**5** are readily available by only a one-step synthesis from commercial material, making them attractive for potential practical applications. To gain insight into the mechanism of action of heteroarenium catalysts in sulfoxidations, structure vs catalytic activity relationship was studied using experimental and theoretical approaches.

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RESULTS AND DISCUSSION

Design and Synthesis of Heteroarenium Catalysts. The pyrimidine ring offers several structural modifications from the point of view of the relative position of a substituent and the quaternary nitrogen that is to be introduced. Additionally, the relative position of heteroaromatic nitrogen atoms in the pyrimidine ring (1,3-) differs from that in pyrazines and flavins (both isoalloxazines and alloxazines), which belong among 1,4-heterocycles. Therefore, pyrimidinium salts **4** (see Figure 1) were chosen as suitable probes to determine whether other heteroarenium salts are able to catalyze H_2O_2 sulfoxidations and, eventually, to find the characteristics that are required for a heteroarenium salt to be an active catalyst. To evaluate the effect of substitution, we prepared 2-, 4-, and 5-substituted derivatives with various types of substituents involving both electron-withdrawing and electron-donating groups. To design suitable derivatives in the pyridine series, we considered the fact that one substituent is not enough to make the pyridinium function effective in the catalysis of H_2O_2 sulfoxidations and the aspect of synthetic availability, which favors symmetrical 3,5-disubstituted pyridinium salts **5b–i**, derivatives of Hantzsch-type pyridines. Nevertheless, to study the effect of the relative position of substituents on the pyridinium ring, we also prepared 2,5- and 2,6-disubstituted analogues **5j–l** with the strongly electron-withdrawing cyano group. Monosubstituted pyridinium triflates **6**, unsubstituted derivatives **3a**, **4a**, and **5a**, as well as quinolinium and isoquinolinium analogues **7** and **8** were prepared for comparison. To eliminate the effect of the counteranion, all salts were prepared in the form of triflates, since preliminary experiments on quaternization showed methyl triflate to be superior to corresponding tetrafluoroborate as alkylating agent. Methyl triflate allowed all quaternary salts to be prepared in relatively high yield and high purity. Accordingly, a series of pyrazinium triflates **3a–g** were prepared as analogues of tetrafluoroborates studied in our preliminary communication.[20] In selected cases, tetrafluoroborates were also prepared to study the effect of the counteranion on the catalytic activity.

Most heteroarenium triflates were prepared from the corresponding heteroaromatic compounds by quaternization with an excess of alkyl triflate (alkyl = methyl or ethyl) at 0 °C in dichloromethane or chloroform. It is important to avoid any nucleophilic solvents or impurities, including water, during the entire synthetic procedure, as the majority of salts are prone to formation of the corresponding adducts; this is especially the case for electron-poor derivatives with cyano and nitro substituents, which add nucleophiles readily. Relatively pure products were obtained by simple evaporation of the reaction mixture. Nevertheless, the salts were additionally purified by precipitation from dry acetonitrile solution by the addition of dry diethyl ether to obtain final products of high purity. In some cases, the salts did not crystallize, and they were isolated as oils. To remove traces of solvents from the products, they were washed several times with dry diethyl ether. Quaternization of 4-methylpyrimidine under standard conditions led to a mixture of two regioisomeric quaternary salts, 1,4-dimethyl- (**4i**) and 1,6-dimethylpyrimidinium triflates, accompanied by decomposition products. To ensure highest selectivity and to avoid product decomposition, it was necessary to dilute and cool the reaction mixture by dry ice/ethanol mixture, which led preferably to **4i**, the product of alkylation on the less hindered nitrogen, still containing 18% of 1,6-isomer. 1-Methyl and 1-ethyl tetrafluoroborates were prepared using trialkyloxonium tetrafluoroborates according to the described procedure.[20]

Catalytic Activity. The catalytic activity of the prepared heteroarenium salts was measured by oxidation of thioanisole **9a** as a model substrate under conditions usually used for testing flavinium salts,[10d,f,11c,d,20,21] i.e., with 2 mol % of the catalyst, aqueous hydrogen peroxide (1.5 equiv) in deuterated methanol at 25 °C (Scheme 3). The efficiency of the heteroarenium salts was evaluated using the pseudo-first-order rate constant k_{obs} calculated from conversion vs time dependences or estimated from the rates in the early phase of the reactions. To evaluate the effect of substitution in each group of the catalysts, the values of the rate constants of the oxidations catalyzed by substituted heteroarenium salts related to those catalyzed by unsubstituted derivatives ($k_{rel} = k_{obs}^{Z}/k_{obs}^{H}$) are given. To assess overall efficiency, the values of the rate constants related to those of the uncatalyzed reaction (k_{obs}/k_0) are also shown (see Tables 1–5).

Scheme 3. Model Sulfoxidation for Testing the Catalytic Efficiency of Heteroarenium Salts 3–8 (Het^+X^-)

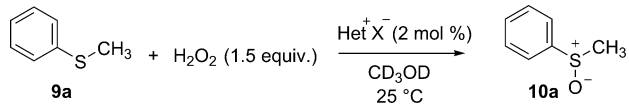

Table 1. Observed Catalytic Activity of Nonsubstituted Heteroarenium Salts and Monosubstituted Pyridinium Salts in Oxidation of Thioanisole 9a to 10a

catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{obs}/k_0[a]
3a	1.8	3.0
4a	5.2	8.7
5a	1.2	2.1
6a	1.3	2.2
6b	0.7	1.2
7	0.9	1.5
8	0.9	1.5

[a]Rate enhancement relative to noncatalyzed reaction; $k_0 = 0.6 \times 10^{-3}$ min^{-1}.

A remarkable effect of the heterocyclic nitrogen in the 3-position relative to the quaternary center on the catalytic activity of heteroarenium salts was observed when comparing the relative rate of thioanisole oxidation in the presence of unsubstituted salts (Table 1). While a small acceleration was observed with salts possessing only one heterocyclic nitrogen or with pyrazinium salt **3a**, pyrimidinium triflate **4a** accelerated the oxidation remarkably. In contrast, only a negligible effect on the oxidation was observed by substitution with an electron-withdrawing cyano group (cf. data for **6a** and **6b** with those for **5a**).

The effect of substituents on the catalytic efficiency was found to be more significant among pyrazinium, and mainly among disubstituted pyridinium, salts achieving maximal k_{obs}^{Z}/k_{obs}^{H} values of 15 and 35, respectively (cf. Tables 2–4). In the case of pyrimidinium salts, the activating effect of the second heterocyclic nitrogen acting as an electron-withdrawing group is dominant and further increase of the catalytic activity caused by substitution reaches the maximum value of only 6.9 (Table 2). The substitution in the 2-position even almost does not affect the efficiency of the pyrimidinium core, with the exception of

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Table 2. Observed Catalytic Activity of 2-, 4-, and 5-Substituted Pyrimidinium Salts 4 in Oxidation of Thioanisole 9a to 10a

	2-			4-			5-		
substituent	catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{rel}[a]	catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{rel}[a]	catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{rel}[a]
H	**4a**	5.2	1.0						
Me	**4b**	4.8	0.9	**4i**	4.1	0.8			
MeO	**4c**	1.4	0.3	**4j**	6.2	1.2	**4p**	6.2	1.2
$CONEt_2$	**4d**	6.7	1.3	**4k**	9.4	1.8			
CONHEt	**4e**	4.9	0.9	**4l**	13.8	2.7	**4q**	13.7	2.6
COOEt	**4f**	5.0	1.0	**4m**	11.3	2.2	**4r**	12.8	2.5
CF_3	**4g**	6.6	1.3	**4n**	29.0	5.6	**4s**	8.2	1.6
CN	**4h**	1.5[b]	0.3	**4o**	29.9	5.8	**4t**	35.9[c]	6.9
NO_2							**4u**	5.5[c]	1.1

[a] $k_{rel} = k_{obs}^{Z}/k_{obs}^{H}$; rate constant relative to reaction catalyzed by nonsubstituted derivative. [b] The reaction mixture was allowed to stand at 25 °C for 3 h before starting the oxidation to ensure the equilibrium between **4h** and corresponding adducts with nucleophiles is established. [c] Decomposition of the catalyst was observed.

the electron-donating methoxy group and, surprisingly, the cyano function, which both decrease the catalytic activity. Low efficiency of the cyano derivative **4h** is associated with slow and almost irreversible formation of the adduct with both solvent and hydrogen peroxide (the oxidant), which is unprecedented among quaternary salts studied (see chapter Reaction Mechanism: Adducts with Nucleophiles). Interestingly, the effects of substituents appear to be additive, as shown by the rate constant of oxidation in the presence of 1-methylpyrimidinium salt **4v** with a 2-methoxy and a 4-trifluoromethyl group (k_{obs}^{Z}/k_{obs}^{H} = 1.1). There, a deactivating effect of the 2-methoxy group (see catalyst **4c**) is compensated by a positive effect of the 4-trifluoromethyl substituent (see catalyst **4n**). Because decomposition of the 5-cyano derivative **4t** during oxidation precludes its application in catalysis, 4-trifluoromethyl and 4-cyano derivatives **4n** and **4o** appear to be the most promising catalysts among pyrimidinium salts.

The order of the efficiency of substituted 1-methylpyrazinium triflates **3a**–**f** corresponds to that found for analogous 1-ethylpyrazinium tetrafluoroborates (Table 3);[20] nevertheless,

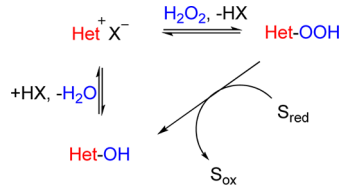
Table 3. Observed Catalytic Activity of Pyrazinium Salts 3 in Oxidation of Thioanisole 9a to 10a

catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{rel}[a]
3a	1.4	1.0
3b	1.9	1.4
3c	3.0	2.2
3d	19.7	14
3e	8.0	5.9
3f	20.6	15
3g	19.7	14
3h	14.3	10

[a] $k_{rel} = k_{obs}^{Z}/k_{obs}^{H}$; rate constant relative to reaction catalyzed by nonsubstituted derivative.

an effect of the counterion and 1-alkyl group was still observed. The change of a methyl for an ethyl group slightly increases the reactivity of the pyrazinium catalyst due to a steric effect (cf. catalysts **3f** and **3g**). Triflate **3g** showed higher catalytic activity than tetrafluoroborate **3h**, most likely because trifluoromethanesulfonic acid released during the first step of the catalytic cycle is fully dissociated due to its high acidity (in contrast to tetrafluoroboric acid), thus maximally supporting the specific acid catalyzed elimination (cf. Scheme 4).[22]

Scheme 4. Proposed Mechanism of H_2O_2 Oxidations Catalyzed by Heteroarenium Salt (Het^+X^-)



As already mentioned, monosubstituted pyridinium salts **6** do not accelerate sulfoxidation despite the presence of a strongly electron-withdrawing cyano group (Table 1). However, if two cyano functionalities are present, the pyridinium salt exhibits remarkable activity, especially if the substituents are located in the 3- and 5-positions (catalyst **5f**; see Table 4). An

Table 4. Observed Catalytic Activity of Pyridinium Salts 5 in Oxidation of Thioanisole 9a to 10a

catalyst	$k_{obs} \times 10^3$ (min^{-1})	k_{rel}[a]
5a	1.3	1.0
5b	0.7	0.6
5c	0.9	0.7
5d	1.0	0.8
5e	1.0	0.8
5f	34.2	26.7
5g	45.2	35.3
5h	21.2	16.6
5i	20.0	15.6
5j	6.1	6.8
5k	4.6	3.6
5l	2.6	2.0

[a] $k_{rel} = k_{obs}^{Z}/k_{obs}^{H}$; rate constant relative to reaction catalyzed by nonsubstituted derivative.

even better result was observed for the dinitro derivative **5g**, which is the best catalyst for H_2O_2 sulfoxidations among the heteroarenium salts investigated. In contrast, the use of substituents other than cyano or nitro has no effect, or even a negative effect, on the reactivity of the pyridinium ring (see the results for **5b**–**e**). Similarly as among pyrazinium salts, a remarkable counterion effect was shown, with triflates superior to tetrafluoroborates (cf. **5f** vs **5h** and **5j** vs **5k**).

The results clearly show that the cyano group has a positive effect on the reactivity of all types of heterocycles, regardless of

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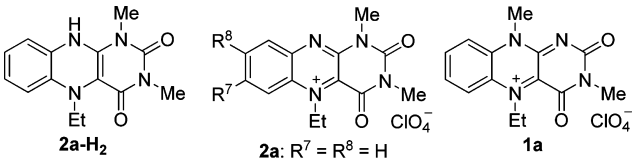
the substitution position, with the exception of 2-cyanopyrimidinium salt **4h**. The positive effect of a trifluoromethyl group was observed mainly for 4-substituted pyrimidinium salt **4n**, showing high reactivity and, moreover, very high stability. This is also the case for dinitropyridinium salt **5g**, which is the best simple heteroarenium sulfoxidation catalyst described today, with efficiency being (i) comparable to dihydroalloxazine **2a-H$_2$**,[10d,11c] the precursor of alloxazinium catalyst **2a** used, e.g., as a redox-active unit in alloxazine−cyclodextrin conjugates,[13c,d] efficient catalysts of enantioselective sulfoxidations, (ii) almost halved compared to 8-trifluoromethylalloxazinium perchlorate **2c**, one of the best known alloxazinium catalysts from the point of view of reactivity and stability,[10d] and (iii) one-third compared to the most efficient isoalloxazinium catalyst **1a** (Table 5).[10d,11d]

Table 5. Catalytic Activity of Selected Heteroarenium Salts in Oxidation of Thioanisole 9a to 10a



catalyst	k_{obs}/k_0[a]
3f	34
4n	48
4o	50
5f	57
5g	75
2a-H$_2$	79[b]
2b	18[b]
2c	192[b]
1a	220[b]

[a]Rate enhancement relative to noncatalyzed reaction; $k_0 = 0.6 \times 10^{-3}$ min^{-1}. [b]Calculated from the data from ref 10d.

Preparative Oxidations. Efficient catalysts **4n** and **5g** were tested in oxidations of various sulfides on a preparative scale (Table 6). With the exception of *p*-nitrothioanisole **9e** (entry 5) with catalyst **4n**, all sulfides **9** were quantitatively oxidized to the corresponding sulfoxides **10** within the maximum period of 24 h using 5 mol % of the catalyst. Similarly as for flavinium-catalyzed sulfoxidations, no overoxidation to the sulfone was observed in any case. Oxidation of thioanisole **9a** and thioanisoles **9b−d** (entries 1−4) with an electron-donating group were finished within 2−3 h; interestingly, derivative **9f** with a carboxy group was effectively converted to **10f** over 14 h using catalyst **4n** and even over only 4 h using catalyst **5g** (entries 7 and 8). Substrates **9d**, **9g**, and **9h** were oxidized chemoselectively without side oxidation of the phenol ring, the double bond, or the benzylic position, respectively (entries 4 and 9−11). Analogously, 2-[(diphenylmethyl)sulfanyl]-acetamide (**9l**), precursor of the psychostimulant modafinil (**10l**),[23] was chemoselectively oxidized to the active substance in quantitative conversion, while the uncatalyzed oxidation with hydrogen peroxide is very slow under the same conditions (entries 18 and 19). In the case of allylic substrate **9h**, which is relatively difficult to oxidize, catalyst loading down to 1 mol % was shown to be adequate for effective oxidation (entries 12 and 13).

Reaction Mechanism: Adducts with Nucleophiles. The general mechanism of sulfoxidations with hydrogen peroxide catalyzed by heteroarenium salts was proposed taking into account the mechanism of flavinium-based oxidations[10d,11d,21,24] (cf. Scheme 1) and previous findings on oxidations catalyzed by pyrazinium tetrafluoroborates[20] and consists of (i) reversible formation of a hydroperoxide adduct, (ii) oxygen transfer from the hydroperoxide to a substrate, and (iii) regeneration of the catalyst from a pseudobase (Scheme 4).

Adducts with *O*-nucleophiles play an important role in the catalytic cycle. To gain knowledge about their structure, the regioselectivity of nucleophilic addition was investigated using a model reaction of selected heteroarenium salts with methanol in the presence of sodium carbonate, which provides quantitative formation of the adduct. Due to their low stability in the form of pure substance, adducts were generated in situ in deuterated solvent and characterized by ^{1}H and ^{13}C NMR spectra and HR−MS analysis. In the previous communication,[20] 3-cyanopyrazinium tetrafluoroborate was found to add hydrogen peroxide, water, and methanol into the position 6 (Scheme 5A). Now, we observed formation of analogous adducts also for 3-(trifluoromethyl)pyrazinium triflate (**3e**) and for pyrimidinium triflates **4h**, **4k**, **4n**, and **4o**, regardless of substituent position, showing the nucleophile to prefer addition into the less hindered side next to the quaternary nitrogen (Scheme 5B). In the case of 3,5-disubstituted pyridinium salts, two electrophilic positions (2- and 4-) compete in the reaction with nucleophiles, as expected, on the basis of UV−vis spectroscopic studies.[19a] Nevertheless, under our conditions, ^{1}H NMR spectra showed formation of only one set of signals belonging to 2-methoxy-3,5-dinitro-1,2-dihydropyridine **13a**. Similarly, in deuterated methanol without the presence of a base[25] (Scheme 5C), the formation of the [2-^{2}H]methoxy adduct **13b**, the adduct with 3,5-dicyanopyridinium salt (**5f**), was observed. It should be noted that without the presence of a base, the signals of the adduct in the ^{1}H NMR spectra are accompanied by signals of the starting quaternary salt because an equilibrium is established. Accordingly, one should keep in mind that the electron-poor heteroarenium salt appears partly in the form of an adduct after dissolving it in any nucleophilic solvent; this is also the case in a methanolic solution of the catalyst before starting the catalytic oxidations. As we found, with the exception of the 2-cyanopyrimidinium salt **4h** forming quantitatively the adduct **11d** in the range of several hours, for all heteroarenium salts in the investigation, the equilibrium between free salt and its methoxy adduct was established within 3 min maximum (for examples of the courses of the methanol adduct formation, see Figure 2). Analogously, in almost cases methoxy adduct and free salt should be in fast equilibrium with hydroperoxy adduct (the oxidant) under conditions of sulfoxidation (in methanol) thus allowing oxidation to proceed without substantial delay.

Evaluation of Substitution Effect. As evident from the catalytic cycle, the ability to add nucleophiles is one important factor influencing the catalytic activity of heteroarenium salts. It can be quantified by pK_{R+} values representing the heteroarenium salt/pseudobase equilibrium[19a] (see Table 7). Although the pK_{R+} value is associated with the addition of water, it reflects also the ability to add other O-nucleophiles, such as hydrogen peroxide.[26] The ability of heteroarenium salts

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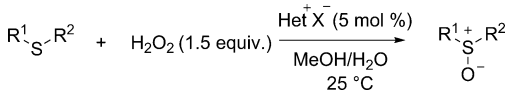
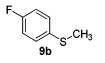
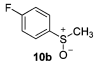
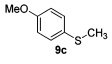
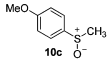
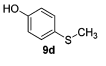
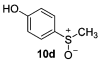
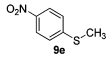
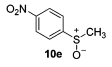
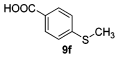
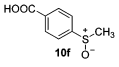
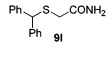
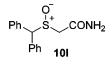
Table 6. Preparative Oxidations of Sulfides by Hydrogen Peroxide Catalyzed by Heteroarenium Salts 4n and 5g.[a]



Entry	Substrate	Product	Catalyst	Time [h]	Conversion [%]	Yield[b] [%]	Blank conv.[c] [%]
1	**9a**	**10a**	**4n**	2	quant.	100	8
2	 **9b**	 **10b**	**4n**	2	quant.	97	16
3	 **9c**	 **10c**	**4n**	2.5	quant.	100	35
4	 **9d**	 **10d**	**4n**	3	quant.	75	13
5	 **9e**	 **10e**	**4n**	24	86	84	37
6	**9e**	**10e**	**5g**	23	quant.	89	35
7[d]	 **9f**	 **10f**	**4n**	14	quant.	68	8
8	**9f**	**10f**	**5g**	4	96	73	2
9	 **9g**	 **10g**	**4n**	6.5	quant.	98	8
10	 **9h**	 **10h**	**4n**	6	quant.	98	6
11	**9h**	**10h**	**5g**	4	quant.	90	4
12	**9h**	**10h**	**5g**[e]	9	86	81	9
13	**9h**	**10h**	**5g**[e]	21	quant	90	22
14	 **9i**	 **10i**	**4n**	4	quant.	96	25
15	**9i**	**10i**	**5g**	2.25	quant.	91	14
16	 **9j**	 **10j**	**4n**	0.75	quant.	99	35
17	 **9k**	 **10k**	**4n**	0.33	quant.	98	49
18	 **9l**	 **10l**	**4n**	21.5	quant.	98	4
19	**9l**	**10l**	**5g**	16.5	quant.	99	3

[a]Conditions for the oxidations: *m* (substrate) = 100 mg, 1.5 equiv of H_2O_2, 5 mol % of the catalyst, methanol (2 mL), T = 25 ± 0.5 °C, monitored by TLC (dichloromethane−ethyl acetate 10:1). [b]Isolated yield. [c]Conversion of the noncatalyzed reaction after the same reaction time. [d]Performed in 3 mL of methanol. [e]1 mol % of the catalyst.

to react with nucleophiles—the electrophilicity—can be characterized also by their reduction potentials (Table 7).

pK_{R+} values and values of the first (the most positive) reduction potential clearly show (Table 7) that, in all series studied, electron-withdrawing groups increase the electrophilicity (less negative reduction potentials) of the heteroarenium core and its ability to add nucleophiles (lower pK_{R+} values). The effect of electron-donating groups is reversed. As expected, the effect is especially pronounced among pyridinium salts, being a result of double substitution. Nevertheless, the effect of the second group on the pyridinium ring is essential, as evident when comparing the values for 3-cyanopyridinium triflate **6a** and 3,5-dicyanopyridinium triflate **5f**. An alkyl chain in the 1-position influences only the value of pK_{R+} and not the reduction potential (cf. **5h** vs **5i**), which corresponds to the assumption about its dominating steric effect. Similar to the catalytic activity, the pK_{R+} value is also significantly influenced by nitrogen in the 3-position, providing evidence about the relatively easy formation of adducts of the unsubstituted pyrimidinium salt **4a** with nucleophiles.

As we already reported, catalytic activity of substituted alloxazinium salts **2** expressed as the logarithm of the rate constant nicely correlates with their pK_{R+} values and reduction potentials.[10d] The lower the values of pK_{R+} and the less negative values of reduction potential, the higher catalytic efficiency was observed. This smooth dependence showed heteroarenium salt/pseudobase or heteroarenium salt/hydroperoxide equilibria to be the most important steps in the catalytic cycle with alloxazinium catalysts. It corresponds with the findings of Bäckvall[11c,21] and Murahashi[11d] that formation

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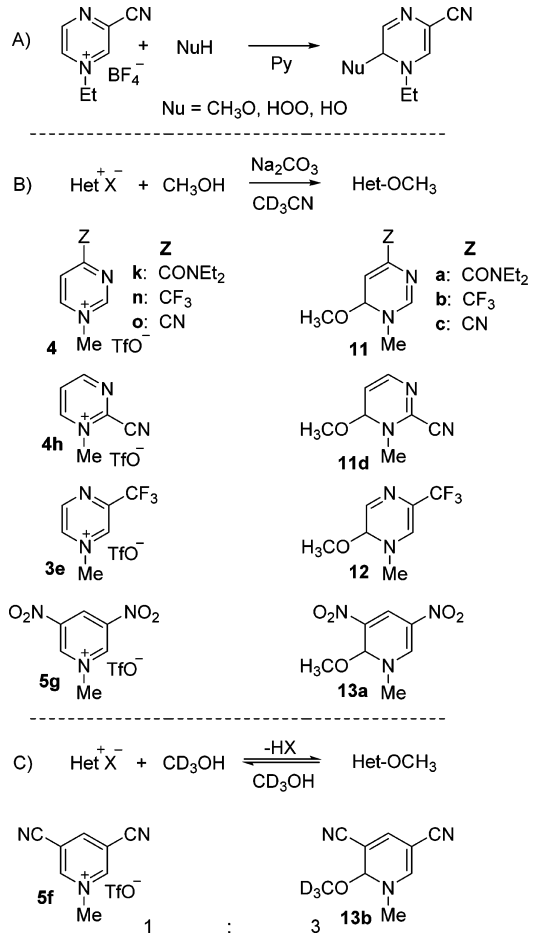
Scheme 5. Regioselectivity of Adduct Formation



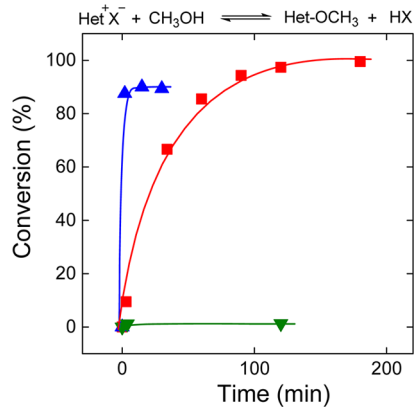
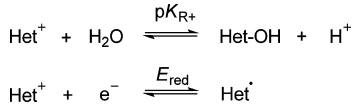


Figure 2. Course of the formation of methanol adduct **Het-OCH$_3$** with **4h** (red), **4o** (blue), and **4c** (green). Salts **4o** and **4c** were taken as examples of electron-poor and relatively electron-rich salts occurring in methanol preferably in the form of adduct and free salt, respectively.

of hydroperoxide or water elimination are rate-determining steps in oxidations catalyzed by alloxazinium or isoalloxazinium salts, respectively. We did not similarly find a close correlation in any of the series of simple heteroarenium salts **3**−**5**. Nevertheless, a visualized dependence of the relative rate constants k_{obs}/k_0 of sulfoxidation of thioanisole on the pK_{R+} and E_{red} values of the catalysts (Figure 3) shows a clear trend indicating that higher catalytic efficiency was observed for heteroarenium salts with lower values of pK_{R+} and with less

Table 7. Comparison of pK_{R+} Values and Reduction Potentials E_{red} for Heteroarenium Salts Used in Catalysis



series	catalyst	E_{red}[a] (V)	pK_{R+}[b]
pyrazinium	**3a**	−0.67	*f*
	3b	−0.60	*f*
	3c	−0.52	8.5
	3d	−0.45	6.6
	3e	−0.37	7.5
	3f	−0.24	4.0
	3g		4.3
	3h		4.5
2-pyrimidinium	**4a**	−0.95	6.7
	4b	−1.04	8.1
	4c	−0.94	8.5
	4d	−0.82	7.2
	4e	−0.74	5.1
	4f	−0.61	5.7
	4g	−0.54	3.1
	4h	−0.40	*f*
4-pyrimidinium	**4i**	−1.11	*f*
	4j	−1.39	9.6
	4k	−0.61	6.6
	4l	−0.52	7.3
	4m	−0.42	6.8
	4n	−0.44	5.1
	4o	−0.24	4.5
	4v	−0.56	6.6
5-pyrimidinium	**4p**	−0.84	10.2
	4q	−0.74	6.5
	4r	−0.69	4.8
	4s	−0.62	6.4
	4t	−0.44	4.5
pyridinium	**5b**	−0.99	*f*
	5c	−0.88	11.9
	5d	−0.78	9.3
	5e	−0.58	9.5
	5f	−0.41	3.7
	5g	−0.14	<1[c]
	5h	−0.40	3.7
	5i	−0.43	4.0
	5j	−0.18	*f*
	5l	−0.18	5.9
	6a	−0.85	12.2[d]
flavinium[e]	**1a**	0.35	2.0
	2a	0.10	7.9
	2b	0.18	6.9
	2c	0.28	4.8

[a]The first formal reduction potentials vs SCE in acetonitrile determined by cyclic voltammetry on platinum electrode. The measured reduction potentials were corrected using ferrocene/ferrocenium as a standard. [b]pK_{R+} = −log K_{R+}; K_{R+} = [HetOH]-[H$^+$]/[Het$^+$]; determined by UV−vis spectroscopy. [c]Estimated value from the half of titration curve measured by ^{1}H NMR (see the Supporting Information). [d]Reference 19a. [e]All data for flavinium salts taken from ref 10d were obtained under the same conditions. [f]Not determined because of instability of the compound or value is out of measurable range.

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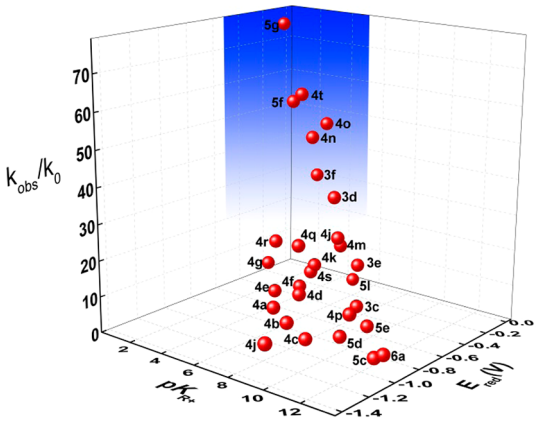
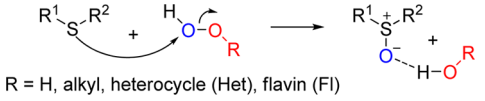


Figure 3. Visualization of the dependence of the catalytic activity of heteroarenium salts expressed by relative rate of thioanisole oxidation (k_{obs}/k_0) on pK_{R+} and E_{red} values. The blue color refers to the space with the most effective catalysts. Only catalysts with all data available are included.

negative values of reduction potential. The most effective catalysts (i.e., those with a k_{obs}/k_0 value higher than 30) are characterized by both (i) a pK_{R+} value lower than 5 and (ii) a reduction potential (E_{red}) less negative than −0.5 V. The exception is the efficient pyrazinium salt **3d**, with a slightly higher pK_{R+} value. On the other hand, the 2,6-dicyanopyridinium salt **5l** nearly meets the criteria noted above, but its efficiency is low, most likely due to steric hindrance.

It is interesting to compare the pK_{R+} and E_{red} values of the most efficient heteroarenium salts (**4o**, **4n**, **4t**, **5f**, and **5g**) with those for the efficient flavinium derivatives **2** and **1a** (see Table 7 for pK_{R+} and E_{red} values and Table 5 for catalytic activity). While the pK_{R+} values are comparable for both groups of catalysts (cf. **5f** and **2c** or **5g** and **1a**, for example), the reduction potentials of the simple heteroarenium salts are more negative by 0.3−0.6 V, even for the most efficient dinitropyridinium salt **5g**. This result means that although some simple heteroarenium salts are able to easily form adducts, they are not as electron poor as alloxazines and isoalloxazines. This property may be reflected in the rate of the S_N2-like oxygen-transfer step (Scheme 6), which was previously found to correlate with the ability of the RO group to escape the intermediate.[8] In oxidations with flavin hydroperoxide (FlOOH), electron-poor flavin skeleton causes FlO subunit to be very good leaving group which allows oxygen transfer to proceed readily; it means that it does not affect the overall rate of oxidation. On the other hand, the oxygen-transfer step from HetOOH appears to influence the overall rate of catalytic oxidation since the HetO group derived from less electron poor, simple heteroarenium salts is not as a good leaving group as FlO.

Scheme 6. Simplified S_N2-like Oxygen-Transfer Step in Sulfoxidations with Peroxide Compounds



Theoretical Calculations on the Oxygen-Transfer Step. To gain more insight into the oxidation step, we decided to estimate the barriers of the oxygen transfer from hydroperoxides to thioanisol based on quantum calculations. We assumed that the position of the hydroperoxy group in the heterocyclic hydroperoxide corresponds to that determined by NMR experiments for model methoxy adducts. From a mechanistic point of view, we considered a generally accepted S_N2-like mechanism, where the sulfur lone pair attacks the terminal oxygen atom[2,27] (Scheme 7A) or a model with one molecule of methanol participating in the process (Scheme 8A).[28]

For comparison, we calculated the values of the energy barriers and the Gibbs free energies for oxidation of thioanisole with isoalloxazine−hydroperoxide **1a-OOH** and with isomeric alloxazine−hydroperoxides **2-OOH** (Table 8) using a simplified model without participation of a solvent molecule in the oxygen transfer (Scheme 7A, Het = Fl). The energy barrier (54.6 kJ/mol) obtained for the isoalloxazine derivative **1a-OOH** is in good agreement with the previously reported value calculated by Bach at the B3LYP/6-31++g(d,p) level of theory for oxidation of dimethyl sulfide with the biomimetic flavin hydroperoxide **1c-OOH** (47.7 kJ/mol),[2,27a] taking into account that aromatic thioanisole requires more energetic conditions than aliphatic dimethyl sulfide and also possible error by using different basis set. Interestingly, while substitution of the benzene ring in alloxazine had a significant effect on the catalytic efficiency of the corresponding alloxazinium salt **2** (see Table 5), as well as their pK_{R+} and E_{red} values[10d] (see Table 7), the calculated oxidation barriers are minimally affected by the substitution (Table 8). This initially surprising result supports previous findings showing addition of hydrogen peroxide and elimination of water to be the most important steps for oxidations catalyzed by alloxazinium and isoalloxazinium salts, which are substantially influenced by substitution.

Energy barriers and Gibbs free energies for hypothetical hydroperoxides derived from substituted heteroarenium salts show that electron-withdrawing substituents facilitate oxygen transfer (Table 9). In the pyrimidine and pyrazine series, the effect is less significant, while the second atom of nitrogen also serves as an electron-withdrawing group. A very strong influence of substitution in the pyridine and 5-substituted pyrimidine series is most likely caused by the substituent in the *ortho* position relative to the hydroperoxy group. The most reactive hydroperoxide, derived from a 1-methyl-3,5-dinitropyridinium salt, has a Gibbs free energy of oxygen transfer almost identical (60.9 kJ/mol) to that for isoalloxazine hydroperoxides **1-OOH** (cf. with values in Table 8). The value, calculated taking into consideration hydrogen transfer mediated by one methanol molecule (63.5 kJ/mol), shows this hydroperoxide being somewhat weaker oxidant in comparison with isoalloxazine hydroperoxides, which corresponds better with its slightly lower catalytic activity.[29]

The calculated values for the energies of oxygen transfer from heterocyclic hydroperoxides are important to understand their intrinsic reactivity, as the experimental data are hard to achieve due to their low stability. It is necessary to realize that the data, which are certainly useful for the comparison of hydroperoxides with similar cores, may serve to compare the hydroperoxides of different structure only on a qualitative level. Nevertheless, taking into account the good correlation between the experimental and calculated data observed by Bach for sulfoxidations with various peroxide species,[27a] we used our data to estimate the relative oxidizing power of simple heterocyclic hydroperoxides. The $\Delta G^{\ddagger}$ and $\Delta E^{\ddagger}$ values for the oxidation of thioanisole with simple heterocyclic hydro-

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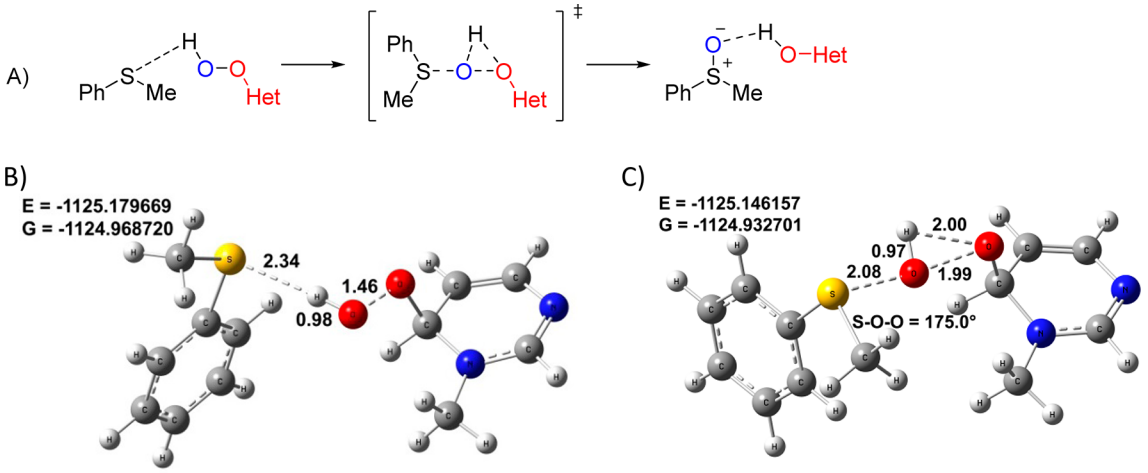
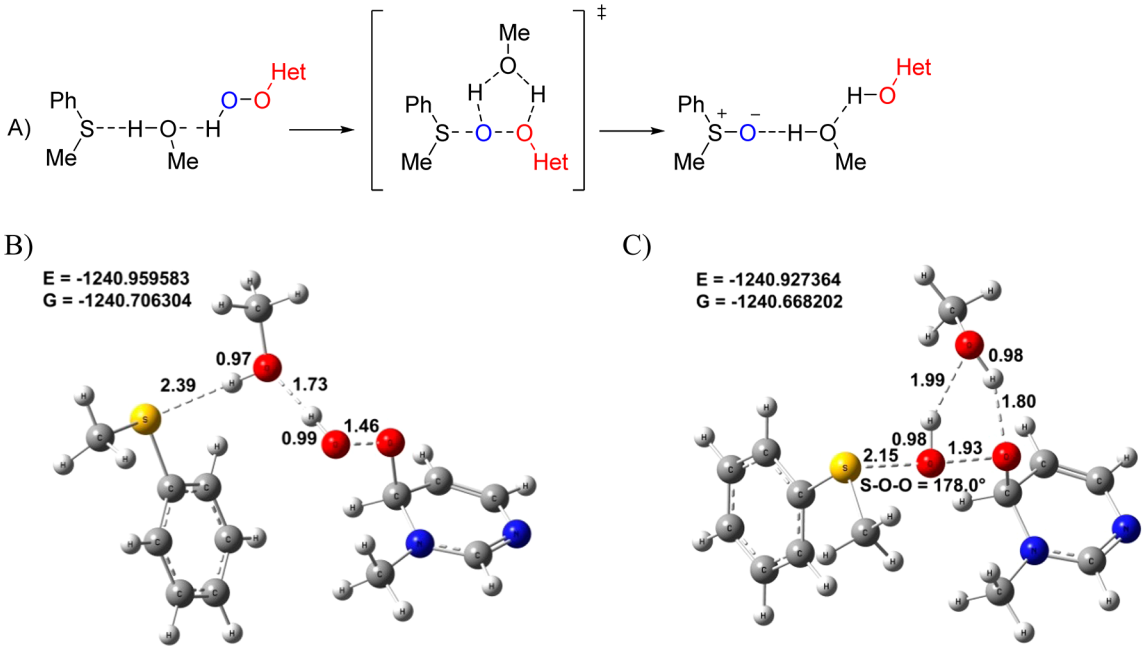
Scheme 7. Representation of Oxygen-Transfer Step in Sulfoxidations with Heterocyclic Peroxide Compounds (A) and Geometry of Prereaction Complex (B) of 2-Hydroperoxy-1-methyl-1,2-dihydropyrimidine with Thioanisole (9a) and Corresponding Transition States for Oxygen Transfer (C) Optimized at the B3LYP/6-311++g(d,p) Level[a]



[a]Energies are in hartrees; distances are in angstroms.

Scheme 8. Representation of Oxygen-Transfer Step in Sulfoxidations with Heterocyclic Peroxide Compounds with Participation of Solvent (A) and Geometry of Prereaction Complexes (B) of 2-Hydroperoxy-1-methyl-1,2-dihydropyrimidine with Thioanisole (9a) and Corresponding Transition States for Oxygen Transfer (C) Optimized at the B3LYP/6-311++g(d,p) Level[a]



[a]Energies are in hartrees; distances are in angstroms.

peroxides are within the 61−105 and 59−103 kJ mol^{-1} interval, respectively, which means that (i) the best hydroperoxides from our series achieve the reactivity of flavin hydroperoxides **1-OOH** and **2-OOH** ($\Delta G^{\ddagger}$ = 60−65 kJ mol^{-1}) and (ii) all of our hydroperoxides appear to be stronger agents than *tert*-butyl hydroperoxide[2,27a] ($\Delta E^{\ddagger}$ = 114 kJ mol^{-1} for oxidation of dimethyl sulfide). Noteworthy, all hydroperoxides derived from flavines and simple heterocycles still remain less reactive in comparison with peroxy acids[2] ($\Delta E^{\ddagger}$ = 15.5 kJ mol^{-1} for oxidation of dimethyl sulfide). Nevertheless, this "tuned" reactivity (between alkyl hydroperoxide and peroxy acids) can, for example, explain the extremely high chemoselectivity of sulfides oxidations mediated by heterocyclic hydroperoxides, which usually lead to sulfoxides without overoxidation to sulfones.

■ CONCLUSION

We showed that the ability to activate hydrogen peroxide for oxidations is not only the domain of flavinium salts, already established organocatalysts of H_2O_2 oxygenations and models of flavin cofactors in monooxygenases,[5,7b,c] but also most likely a general property of all electron-poor heteroarenium salts.

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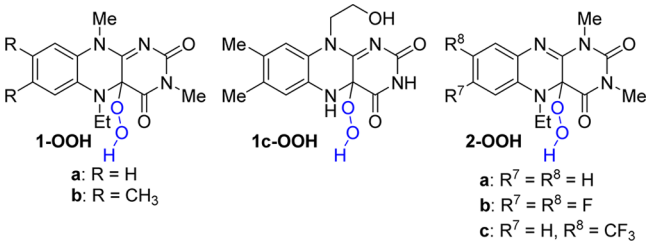
Table 8. Reaction Energy Barriers ($\Delta E^{\ddagger}$) and Gibbs Free Energies ($\Delta G^{\ddagger}$) for the Oxygen Atom Transfer from Flavin Hydroperoxides (FlOOH) to Thioanisole Calculated on B3LYP/6-311++g(d,p) Level



FlOOH	$\Delta E^{\ddagger}$ (kJ/mol)	$\Delta G^{\ddagger}$ (kJ/mol)
1a-OOH	54.6	60.2
1b-OOH	56.2	60.4
1c-OOH	47.7[a]	
2a-OOH	61.4	64.8
2b-OOH	59.3	61.3
2c-OOH	58.6	61.2

[a]The value for oxidation of dimethyl sulfide from refs 2 and 27a calculated on the B3LYP/6-31++g(d,p) level.

Structure vs reactivity studies of a series of pyrazinium, pyrimidinium, and pyridinium salts led us to the conclusion that, to be an effective catalyst of H_2O_2 oxidations, a heteroarenium salt should be electron poor enough to be able to readily add hydrogen peroxide, providing a high concentration of heterocyclic peroxide, which is the oxidizing agent in the catalytic cycle. The ability to form adducts can be simply quantified by the pK_{R+} values and reduction potentials, which were found to be lower than 5 and more positive than −0.5 V, respectively, for the outstandingly efficient heteroarenium catalysts. Moreover, the heterocyclic core of the efficient catalyst should be electrophilic enough to ensure that the corresponding hydroperoxide behaves as a strong oxidant because the S_N2-like oxygen transfer step to a substrate from a hydroperoxide derived from simple heteroarenium salts appears to be significant for the overall rate of catalytic oxidation beside addition and elimination step (unfortunately, elucidation of the rate-determining step is not possible on the basis of current knowledge). This is in contrast to oxidations catalyzed by flavinium (isoalloxazinium and alloxazinium) salts, where oxygen transfer takes place readily and formation of hydroperoxide or regeneration of the catalyst by water elimination from the pseudobase are the rate-determining steps.[11c,d,24] This difference was supported by the Gibbs free energy values ($\Delta G^{\ddagger}$) of the oxygen-transfer step from a hydroperoxide to a substrate being strongly dependent on the substituent in the case of simple heterocyclic hydroperoxides and almost independent of the substitution for alloxazine and isoalloxazine derivatives.

The idea to simplify the structure of flavinium salts led us to some very active pyrazinium, pyrimidinium, and pyridinium salts, which are accessible by one- or two-step syntheses from commercially available material. The catalytic efficiency of the heteroarenium core can be easily tuned by substitution. It should be noted that not only the type but also the position of the substituent is important for the activity of the catalyst, as the substitution effect is not fully transferred through the heterocyclic nitrogen. It is especially pronounced for the trifluoromethyl substituent. For pyridinium salts, two electron-withdrawing groups are necessary to ensure sufficient activity. The relative position of heterocyclic nitrogens influencing the reactivity of the heteroarenium core is the most advantageous in pyrimidinium derivatives. The effect of the counteranion was also observed, with slightly higher efficiency for triflates over tetrafluoroborates.

In summary, 3-(ethoxycarbonyl)pyrazinium (**3d**), 3-cyanopyrazinium (**3f**), 4-cyanopyrimidinium (**4o**), 4-(trifluoromethyl)pyrimidinium (**4n**), and 5-cyanopyrimidinium triflates (**4t**), as well as Hantzsch-type 3,5-dicyano- (**5f**) and 3,5-dinitropyridinium triflates (**5g**), showed significant catalytic activity; salt **5g**, today the most efficient among simple heteroarenium salts, even achieved the efficacy of the original flavinium salts **1** and **2**. Additionally, 3,5-dinitropyridinium (**5g**) and 4-(trifluoromethyl)pyrimidinium triflates (**4n**) showed very high stability. Therefore, the use of these derivatives, which were shown to mediate oxidations of various types of sulfides, is also recommended for other types of oxygenations or as redox-active units for the construction of catalysts for stereoselective oxidations. Our conclusions, in terms of structure vs activity studies, offer a tool in the search for further efficient heteroarenium catalysts for oxygenations.

EXPERIMENTAL SECTION

General Comments. All reagents were analytical grade, obtained from commercial suppliers, and used without further purification or prepared according to known procedures. Dry dichloromethane, chloroform, and acetonitrile were distilled from P_2O_5 and diethyl ether from sodium. Silica gel (0.040−0.063 mm) from Merck or a Redi*Sep* Rf Gold reversed-phase C18 column was used in preparative column chromatography. ^1H and ^{13}C NMR spectra are reported relative to the residual solvent signal, and ^{19}F NMR spectra are reported relative to CCl_3F. High-resolution mass spectra (HRMS) were acquired in electrospray (ESI) or atmospheric-pressure chemical ionization (APCI) mode using an orbitrap mass analyzer.

General Procedure 1 for Synthesis of Heteroarenium Salts. A solution of heterocycle (1 equiv) in dry dichloromethane or chloroform was cooled to 0 °C under argon atmosphere. Methyl trifluoromethanesulfonate (1.0−1.1 equiv) was added dropwise. The reaction mixture was allowed to stir for a specified reaction time. Precipitated solid was collected by filtration or the reaction mixture was evaporated. The crude product was purified by dissolving in small amount of dry acetonitrile and precipitation by the addition of dry diethyl ether (2 times). The final product was washed with small amount of dry diethyl ether and dried in vacuo.

General Procedure 2 for Synthesis of Heteroarenium Salts. Heterocycle (1 equiv) was dissolved in dry dichloromethane or chloroform, and trialkyloxonium tetrafluoroborate (1.0−1.5 equiv) was added under argon atmosphere. The mixture was allowed to stir at the specified temperature and time. Precipitated solid was collected by filtration. The solid was washed with a small amount of dry dichloromethane or chloroform and purified by dissolving in small amount of dry acetonitrile and precipitation by the addition of dry diethyl ether (2−3 times). The final product was washed with small amount of dry diethyl ether and dried in vacuo.

1-Methylpyrazinium Trifluoromethanesulfonate (3a). Prepared according to general procedure 1 from pyrazine (200 mg, 2.530 mmol) and methyl trifluoromethanesulfonate (436 mg, 2.650 mmol) in dry dichloromethane (4 mL), reaction time 6 h, to give the product as a white solid (391 mg, 64% yield): mp 58−60 °C; ^1H NMR (500 MHz, acetonitrile-d_3) δ 9.37 (dt, J = 4.9, 2.8 Hz, 2H), 8.75 (d, J = 3.1 Hz, 2H), 4.39 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 152.0, 138.9 (t, J = 9.4 Hz), 123.4 (q, J = 320.6 Hz), 50.2 (t, J = 5.1 Hz); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.17 (s, 3F). Anal. Calcd for $C_6H_7F_3N_2O_3S$: C, 29.51; H, 2.89; F, 23.34; N, 11.47; S, 13.13. Found: C, 29.29; H, 2.82; F, 23.19; N, 11.24; S, 12.85.

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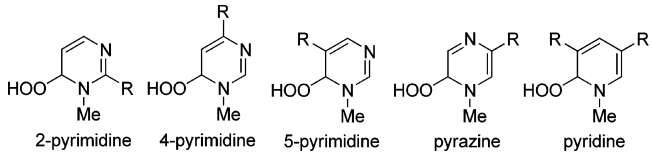
Table 9. Effect of Substituents on Reaction Energy Barriers ($\Delta E^{\ddagger}$) and Gibbs Free Energies ($\Delta G^{\ddagger}$) of Oxygen Atom Transfer to Thioanisole from Heterocyclic Hydroperoxides



heterocycle	position and substituent R	$\Delta E^{\ddagger a,c}$ (kJ/mol)	$\Delta G^{\ddagger a,c}$ (kJ/mol)	$\Delta G^{\ddagger}_{rel}{}^{b,c}$ (kJ/mol)
pyrimidine	2-COOEt	84.5 (82.1)	83.1 (90.8)	−11.5 (−9.3)
	2-CF_3	80.0 (78.9)	83.2 (86.7)	−11.3 (−13.4)
	2-CN	77.3 (77.0)	83.3 (78.8)	−11.2 (−21.2)
	2-$CONEt_2$	84.7 (83.1)	85.8 (95.0)	−8.8 (−5.0)
	2-CONHEt	85.3 (83.7)	87.8 (90.2)	−6.8 (−9.8)
	2-MeO	90.8 (86.2)	94.0 (94.5)	−0.6 (−5.6)
	H	88.0 (84.6)	94.6 (100.0)	0
	2-Me	91.4 (86.2)	95.6 (94.5)	1.1 (−5.5)
pyrimidine	4-CN	76.1 (76.1)	81.9 (82.7)	−12.7 (−17.3)
	4-CF_3	78.0 (78.5)	82.4 (78.0)	−12.2 (−22.0)
	4-CONHEt	82.7 (81.9)	84.1 (79.2)	−10.5 (−20.8)
	4-COOEt	80.8 (76.1)	84.3 (79.5)	−10.2 (20.5)
	4-$CONEt_2$	85.5 (81.4)	88.4 (85.4)	−6.2 (−14.6)
	4-MeO	91.1 (86.6)	94.0 (93.0)	−0.5 (−7.0)
	H	88.0 (84.6)	94.6 (100.0)	0
	4-Me	91.7 (86.1)	94.6 (91.9)	0 (−8.2)
	4-CF_3-2MeO	81.2 (80.1)	86.9 (88.6)	−7.7 (−11.4)
pyrimidine	5-NO_2	69.1 (71.7)	72.9 (71.9)	−21.7 (−28.1)
	5-CN	71.9 (73.5)	75.1 (75.1)	−19.5 (−24.9)
	5-CONHEt	71.5 (80.0)	75.3 (86.7)	−19.3 (−13.4)
	5-CF_3	76.8 (77.6)	80.5 (84.6)	−14.0 (−15.4)
	5-COOEt	81.3 (81.5)	85.4 (84.5)	−9.2 (−15.6)
	5-MeO	83.8 (80.3)	87.4 (88.4)	−7.2 (−11.6)
	H	88.0 (84.6)	94.6 (100.0)	0
pyrazine	3-CN	71.5 (73.3)	77.1 (74.9)	−12.5 (−13.1)
	3-COOEt	76.3 (75.7)	78.3 (79.4)	−11.3 (−8.7)
	3-CF_3	75.4 (76.8)	79.6 (80.6)	−10.0 (−7.4)
	3-CONHEt	78.1 (77.1)	79.9 (82.4)	−9.7 (−5.6)
	3-$CONEt_2$	80.2 (78.6)	82.3 (83.5)	−7.3 (−4.5)
	H	85.9 (82.9)	89.6 (88.0)	0
pyridine	3,5-NO_2	58.8 (67.6)	60.9 (63.5)	−43.7 (−34.2)
	3,5-CN	66.2 (71.1)	67.7 (76.5)	−36.9 (−21.2)
	2,6-CN	61.8 (67.4)	68.9 (72.2)	−35.7 (−25.5)
	3,5-CF3	74.7 (76.9)	75.7 (82.9)	−28.9 (−14.8)
	3,5-COOEt	79.6 (80.6)	83.4 (84.9)	−21.2 (−12.8)
	3,5-CONHEt	84.8 (83.5)	87.7 (86.7)	−16.9 (−11.0)
	3,5-$CONEt_2$	86.8 (86.5)	90.8 (92.3)	−13.8 (−5.4)
	H	102.6 (90.0)	104.6 (97.7)	0

[a]Calculated on B3LYP/6-311++g(d,p) level. [b]Values relative to nonsubstituted heterocyclic hydroperoxide ($\Delta G^{\ddagger R} - \Delta G^{\ddagger H}$). [c]Values calculated taking into account participation of methanol on hydrogen transfer are given in parentheses.

3-(Diethylcarbamoyl)-1-methylpyrazinium Trifluoromethanesulfonate (3b). Prepared according to general procedure 1 from *N*,*N*-diethylpyrazine-2-carboxamide (**14a**) (400 mg, 2.232 mmol) and methyl trifluoromethanesulfonate (385 mg, 2.343 mmol) in dry dichloromethane (10 mL), reaction time 6 h, to give the product as a beige solid (450 mg, 59% yield): mp 154−157 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.33−9.29 (m, 1H), 8.97 (s, 1H), 8.76 (d, J = 3.5 Hz, 1H), 4.42 (s, 3H), 3.55 (q, J = 7.1 Hz, 2H), 3.37 (q, J = 7.0 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 163.3, 156.6, 150.1, 139.3−139.0 (m), 138.7−138.4 (m), 123.2 (q, J = 320.7 Hz), 50.4−50.1 (m), 44.2, 41.5, 14.4, 12.8; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.05 (s, 3F). Anal. Calcd for $C_{11}H_{16}F_3N_3O_4S$: C, 38.48; H, 4.70; F, 16.60; N, 12.24; S, 9.34. Found: C, 38.37; H, 4.58; F, 16.37; N, 12.02; S, 9.28.

3-(Ethylcarbamoyl)-1-methylpyrazinium Trifluoromethanesulfonate (3c). Prepared according to general procedure 1 from *N*-ethylpyrazine-2-carboxamide (**14b**) (300 mg, 1.985 mmol) and methyl trifluoromethanesulfonate (342 mg, 2.084 mmol) in dry dichloromethane (10 mL), reaction time 12 h, to give the product as a white solid (620 mg, 99% yield): mp 147−149 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.37−9.34 (m, 1H), 9.33 (s, 1H), 8.90 (d, J = 3.6 Hz, 1H), 8.28 (s, 1H), 4.48 (s, 3H), 3.47 (qd, J = 7.2, 6.1 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 160.4, 152.3, 150.2, 140.7−140.5 (m), 138.6−138.3 (m), 122.0 (q, J = 320.5 Hz), 50.6−50.4 (m), 35.5, 14.8; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.04 (s, 3F). Anal. Calcd for $C_9H_{12}F_3N_3O_4S$: C, 34.29; H, 3.84; F, 18.08; N, 13.33; S, 10.17. Found: C, 34.10; H, 3.84; F, 17.75; N, 13.18; S, 10.05.

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3-(Ethoxycarbonyl)-1-methylpyrazinium Trifluoromethanesulfonate (3d). A solution of ethyl pyrazine-2-carboxylate (**14c**) (200 mg, 1.314 mmol) in dry dichloromethane (5 mL) was cooled in a dry ice/ethanol mixture under argon atmosphere. Methyl trifluoromethanesulfonate (237 mg, 1.446 mmol) was added dropwise. The reaction mixture was allowed to stir at the same temperature for 0.5 h and then at rt for 0.5 h. Precipitated crystals were collected by filtration. The crude product was purified by dissolving in small amount of dry acetonitrile and precipitation by the addition of dry diethyl ether (3 times) to give the product as a white solid (260 mg, 63% yield): mp 84−86 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.48 (s, 1H), 9.33 (s, 1H), 8.90 (s, 1H), 4.53 (q, J = 7.1 Hz, 2H), 4.46 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 161.6, 151.6, 150.4, 141.3−141.0 (m), 140.4−140.1 (m), 122.0 (q, J = 321.0 Hz), 64.6, 50.5, 14.3; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.06 (s, 3F). Anal. Calcd for $C_9H_{11}F_3N_2O_5S$: C, 34.18; H, 3.51; F, 18.02; N, 8.86; S, 10.14. Found: C, 34.17; H, 3.44; F, 17.88; N, 8.71; S, 10.08.

1-Methyl-3-(trifluoromethyl)pyrazinium Trifluoromethanesulfonate (3e). Prepared according to general procedure 1 from 2-(trifluoromethyl)pyrazine (200 mg, 1.351 mmol) and methyl trifluoromethanesulfonate (266 mg, 1.621 mmol) in dry dichloromethane (4 mL), reaction time 6 h, to give the product as white crystals (345 mg, 82% yield): mp 152−154 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.54 (s, 1H), 9.30 (s, 1H), 9.07 (d, J = 3.1 Hz, 1H), 4.51 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 152.3, 149.3 (q, J = 38.7 Hz), 143.0−142.7 (m), 137.6 (ddd, J = 13.2, 6.5, 3.4 Hz), 121.8 (q, J = 320.3 Hz), 120.4 (q, J = 274.2 Hz), 50.8−50.7 (m); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −67.76 (s, 3F), −78.09 (s, 3F). Anal. Calcd for $C_7H_6F6N_2O_3S$: C, 26.93; H, 1.94; F, 36.51; N, 8.97; S, 10.27. Found: C, 26.86; H, 1.88; F, 36.85; N, 8.82; S, 10.19.

3-Cyano-1-methylpyrazinium Trifluoromethanesulfonate (3f). Prepared according to general procedure 1 from pyrazine-2-carbonitrile (200 mg, 1.903 mmol) and methyl trifluoromethanesulfonate (319 mg, 1.941 mmol) in dry dichloromethane (5 mL), reaction time 4 h, to give the product as white crystals (300 mg, 59% yield): mp 115−118 °C (dec.). ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.49 (s, 1H), 9.26 (s, 1H), 9.01 (d, J = 3.4 Hz, 1H), 4.46 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 152.7, 143.2−143.0 (m), 142.6−142.3 (m), 135.8, 125.8−118.0 (m), 113.8, 50.9−50.8 (m); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.06 (s, 3F). Anal. Calcd for $C_7H_6F_3N_3O_3S$: C, 31.23; H, 2.25; F, 21.17; N, 15.61; S, 11.91. Found: C, 31.30; H, 2.30; F, 20.86; N, 15.28; S, 11.89.

3-Cyano-1-ethylpyrazinium Trifluoromethanesulfonate (3g). A solution of pyrazine-2-carbonitrile (200 mg, 1.903 mmol) in dry dichloromethane (3 mL) was cooled to 0 °C under argon atmosphere. Ethyl trifluoromethanesulfonate (356 mg, 1.998 mmol) was added dropwise. The reaction mixture was allowed to stir for 12 h. Precipitated crystals were collected by filtration. The crude product was purified by dissolving in small amount of dry acetonitrile and precipitation by the addition of dry diethyl ether (3 times). The final product was washed with small amount of dry diethyl ether and dried in vacuo to give the product as a white solid (238 mg, 44% yield): mp 110−112 °C (dec.); ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.50 (s, 1H), 9.32 (s, 1H), 9.08 (d, J = 3.5 Hz, 1H), 4.74 (q, J = 7.4 Hz, 2H), 1.66 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 153.0, 142.3−142.0 (m), 141.7−141.3 (m), 136.2, 121.9 (q, J = 320.6 Hz), 113.9, 60.6, 15.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.06 (s, 3F). Anal. Calcd for $C_8H_8F_3N_3O_3S$: C, 33.93; H, 2.85; F, 20.12; N, 14.84; S, 11.32. Found: C, 33.95; H, 2.81; F, 20.56; N, 14.55; S, 11.11.

3-Cyano-1-ethylpyrazinium Tetrafluoroborate (3h). Prepared according to general procedure 2 from pyrazine-2-carbonitrile (250 mg, 2.380 mmol) and triethyloxonium tetrafluoroborate (678 mg, 3.570 mmol) in dry dichloromethane (10 mL), reaction 24 h at rt, to give the product as a white solid (327 mg, 62% yield): mp 100−103 °C (lit.[20] mp 101−103 °C); ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.50 (d, J = 2.5 Hz, 1H), 9.26 (s, 1H), 9.02 (d, J = 2.8 Hz, 1H), 4.72 (q, J = 7.3 Hz, 2H), 1.65 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 153.1, 142.1 (t, J = 9.1 Hz), 141.5 (t, J = 8.5 Hz), 136.2, 114.0, 60.7, 15.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −150.35 (^{10}B−F, s), −150.40 (^{11}B−F, s).

1-Methylpyrimidinium Trifluoromethanesulfonate (4a). Prepared according to general procedure 1 from pyrimidine (500 mg, 6.24 mmol) and methyl trifluoromethanesulfonate (1025 mg, 6.24 mmol) in dry dichloromethane (4 mL), reaction time 12 h, to give the product as colorless oil (1105 mg, 73% yield), which solidified upon further standing at 4 °C: ^{1}H NMR (300 MHz, acetone-d_6) δ 9.85 (s, 1H), 9.53 (dd, J = 4.9, 1.6 Hz, 1H), 9.46 (dt, J = 6.5, 1.4 Hz, 1H), 8.35 (t, J = 5.5 Hz, 1H), 4.58 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.2, 155.3, 154.1 (t, J = 7.7 Hz), 124.5, 122.0 (q, J = 321.2 Hz), 46.2; ^{19}F NMR (282 MHz, acetone-d_6) δ −77.95 (s, 3F); HRMS-ESI (m/z) [M − CF_3SO_3]$^+$ calcd for $C_5H_7N_2$ 95.06037, found 95.06088.

1,2-Dimethylpyrimidinium Trifluoromethanesulfonate (4b). Prepared according to general procedure 1 from 2-methylpyrimidine (**15a**) (150 mg, 0.606 mmol) and methyl trifluoromethanesulfonate (109 mg, 0.666 mmol) in dry dichloromethane (5 mL), reaction time 3 h, to give the product as a white solid (140 mg, 34% yield): mp 105−106 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.43−9.33 (m, 2H), 8.19−8.12 (m, 1H), 4.49 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 165.8, 165.2, 155.0, 122.5, 122.1 (q, J = 321.6 Hz), 46.6, 23.3; ^{19}F NMR (282 MHz, acetone-d_6) δ −77.91 (s, 3F). Anal. Calcd for $C_7H_9F_3N_2O_3S$: C, 32.56; H, 3.51; F, 22.07; N, 10.85; S, 12.42. Found: C, 32.48; H, 3.39; F, 22.06; N, 10.74; S, 11.97.

2-Methoxy-1-methylpyrimidinium Trifluoromethanesulfonate (4c). Prepared according to general procedure 1 from 2-methoxypyrimidine (**15b**) (200 mg, 1.816 mmol) and methyl trifluoromethanesulfonate (298 mg, 1.816 mmol) in dry dichloromethane (3 mL), reaction time 2 h, to give the product as a white solid (361 mg, 73% yield): mp 118−120 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.27 (ddd, J = 4.8, 2.2, 0.5 Hz, 1H), 9.16 (ddd, J = 6.3, 2.2, 0.5 Hz, 1H), 7.79 (dd, J = 6.3, 4.7 Hz, 1H), 4.42 (s, 3H), 4.17 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.9, 159.4, 155.5, 122.0 (q, J = 321.6 Hz), 117.0, 59.3, 42.4; ^{19}F NMR (282 MHz, acetone-d_6) δ −77.87 (s, 3F). Anal. Calcd for $C_7H_9F_3N_2O_4S$: C, 30.66; H, 3.31; F, 20.78; N, 10.22; S, 11.69. Found: C, 30.27; H, 3.17; F, 20.32; N, 9.97; S, 11.74.

2-(Diethylcarbamoyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4d). Prepared according to general procedure 1 from *N*,*N*-diethylpyrimidine-2-carboxamide (**15d**) (200 mg, 1.116 mmol) and methyl trifluoromethanesulfonate (183 mg, 1.116 mmol) in dry dichloromethane (4 mL), reaction time 8 h, to give the product as an orange-yellow oil (245 mg, 64% yield): ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.36 (ddd, J = 5.0, 1.9, 0.5 Hz, 1H), 9.04 (ddd, J = 6.4, 1.9, 0.6 Hz, 1H), 8.13 (dd, J = 6.4, 5.0 Hz, 1H), 4.21 (s, 3H), 3.60 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 165.5, 159.2, 156.2, 155.9, 124.3, 121.5 (q, J = 320.6 Hz), 45.9, 43.6, 40.3, 13.5, 12.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.07 (s, 3F). Anal. Calcd for $C_{11}H_{16}F_3N_3O_4S$: C, 38.48; H, 4.70; F, 16.60; N, 12.24; S, 9.34. Found: C, 38.26; H, 4.79; F, 16.15; N, 11.94; S, 9.18.

2-(Ethylcarbamoyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4e). Prepared according to general procedure 1 from *N*-ethylpyrimidine-2-carboxamide (**15e**) (100 mg, 0.662 mmol) and methyl trifluoromethanesulfonate (109 mg, 0.662 mmol) in dry dichloromethane (2 mL), reaction time 8 h, to give the product as an orange-yellow oil (142 mg, 68% yield): ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.36 (dd, J = 4.9, 1.9 Hz, 1H), 9.07 (dd, J = 6.4, 1.9 Hz, 1H), 8.38 (s, 1H), 8.17 (dd, J = 6.3, 4.9 Hz, 1H), 4.46 (s, 3H), 3.45 (qd, J = 7.2, 5.9 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 165.2, 159.1, 156.9, 154.0, 125.7, 121.8 (q, J = 320.3 Hz), 48.2, 35.9, 14.4; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.03 (s, 3F). Anal. Calcd for $C_9H_{12}F_3N_3O_4S$: C, 34.29; H, 3.84; F, 18.08; N, 13.33; S, 10.17. Found: C, 34.22; H, 3.73; F, 17.83; N, 12.91; S, 10.01.

2-(Ethoxycarbonyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4f). Prepared according to general procedure 1 from ethyl pyrimidine-2-carboxylate (**15f**) (200 mg, 1.314 mmol) and methyl trifluoromethanesulfonate (216 mg, 1.314 mmol) in dry dichloromethane (4 mL), reaction time 8 h, to give the product as a yellowish oil (267 mg, 64% yield): ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.43 (ddd, J = 5.0, 1.9, 0.6 Hz, 1H), 9.14 (ddd, J = 6.3, 1.9, 0.6 Hz, 1H), 8.25 (dd, J = 6.3, 4.9 Hz, 1H), 4.58 (q, J = 7.1 Hz, 2H), 4.44

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(s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 165.7, 159.4, 157.1, 151.8, 126.5, 121.9 (q, J = 320.5 Hz), 66.1, 48.5, 14.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.04 (s, 3F). Anal. Calcd for $C_9H_{11}F_3N_2O_5S$: C, 34.18; H, 3.51; F, 18.02; N, 8.86; S, 10.14. Found: C, 34.07; H, 3.39; F, 18.14; N, 8.52; S, 10.02.

1-Methyl-2-(trifluoromethyl)pyrimidinium Trifluoromethanesulfonate (4g). Prepared according to general procedure 1 from 2-(trifluoromethyl)pyrimidine (**15h**) (150 mg, 0.922 mmol) and methyl trifluoromethanesulfonate (166 mg, 1.014 mmol) in dry dichloromethane (3 mL), reaction time 12 h, to give the product as a white solid (200 mg, 70% yield): mp 66−68 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.50 (d, J = 4.5 Hz, 1H), 9.29 (d, J = 6.2 Hz, 1H), 8.41 (t, J = 5.6 Hz, 1H), 4.47 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 165.7, 159.0, 149.5 (q, J = 40.7, 39.8 Hz), 128.1, 121.9 (q, J = 320.3 Hz), 118.4 (q, J = 277.2 Hz), 47.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −65.76 (s, 3F), −78.08 (s, 3F). Anal. Calcd for $C_7H_6F_6N_2O_3S$: C, 26.93; H, 1.94; F, 36.51; N, 8.97; S, 10.27. Found: C, 26.63; H, 2.00; F, 36.35; N, 8.77; S, 10.45.

2-Cyano-1-methylpyrimidinium Trifluoromethanesulfonate (4h). Prepared according to general procedure 1 from pyrimidine-2-carbonitrile (**15j**) (250 mg, 2.379 mmol) and methyl trifluoromethanesulfonate (410 mg, 2.498 mmol) in dry dichloromethane (5 mL), reaction time 12 h, to give the product as a colorless oil (430 mg, 67% yield): ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.45 (ddd, J = 5.0, 1.8, 0.5 Hz, 1H), 9.27 (ddd, J = 6.3, 1.9, 0.6 Hz, 1H), 8.38 (dd, J = 6.3, 5.0 Hz, 1H), 4.51 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 165.7, 156.9, 139.4, 127.6, 121.8 (q, J = 320.3 Hz), 110.8, 48.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.02 (s, 3F). Anal. Calcd for $C_7H_6F_3N_3O_3S$: C, 31.23; H, 2.25; F, 21.17; N, 15.61; S, 11.91. Found: C, 31.12; H, 2.31; F, 21.13; N, 15.19; S, 11.76.

1,4-Dimethylpyrimidinium Trifluoromethanesulfonate (4i). A solution of 4-methylpyrimidine (**16a**) (200 mg, 2.125 mmol) in dry dichloromethane (3 mL) was cooled to −75 °C under argon atmosphere. Methyl trifluoromethanesulfonate (349 mg, 2.125 mmol) in dry dichloromethane (1 mL) was added during 15 min. The resulting mixture was stirred for 1 h at the same temperature and then allowed to slowly reach −20 °C (1 h). The upper dichloromethane layer was removed, and the oily residue was dried in a stream of dry argon at −20 °C and then in vacuo to give a mixture of regioisomers (according to ^{1}H NMR the product contains 18% of 1,6-dimethylpyrimidinium trifluoromethanesulfonate) as a yellow oil (640 mg, 93% yield). Data for **4i**: ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.24 (s, 1H), 8.76 (dd, J = 6.3, 1.9 Hz, 1H), 7.92 (d, J = 6.6 Hz, 1H), 4.20 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 178.6, 154.1, 151.9, 124.1, 122.0 (q, J = 320.6 Hz), 45.5, 25.6. Data for 1,6-dimethylpyrimidinium trifluoromethanesulfonate: ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.32 (s, 1H), 9.11 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 5.1 Hz, 1H), 4.13 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 166.1, 163.9, 155.3, 125.9, 122.0 (q, J = 320.6 Hz), 43.2, 20.7. Both regioisomers: ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.08 (s); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for $C_6H_9N_2$ 109.07602, found 109.07650.

4-Methoxy-1-methylpyrimidinium Trifluoromethanesulfonate (4j). Prepared according to general procedure 1 from 4-methoxypyrimidine (**16b**) (500 mg, 3.09 mmol, 68% solution in dichloromethane) and methyl trifluoromethanesulfonate (557 mg, 3.400 mmol) in dry dichloromethane (6 mL), reaction time 3 h, to give the product as a colorless oil (810 mg, 96% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 9.45 (s, 1H), 8.97 (dd, J = 7.1, 2.1 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 4.35 (s, 3H), 4.26 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 172.7, 157.0, 152.6, 128.6−115.5 (m), 111.2, 57.5, 44.2; ^{19}F NMR (282 MHz, acetone-d_6) δ −77.91 (s, 3F); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for $C_6H_9N_2O$ 125.07094, found 125.07131.

4-(Diethylcarbamoyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4k). Prepared according to general procedure 1 from *N*,*N*-diethylpyrimidine-4-carboxamide (**16d**) (250 mg, 1.395 mmol) and methyl trifluoromethanesulfonate (240 mg, 1.465 mmol) in dry dichloromethane (4 mL), reaction time 12 h, to give the product as a yellowish solid (390 mg, 81% yield): mp 54−55 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.41 (s, 1H), 9.05 (ddd, J = 6.6, 1.7, 0.6 Hz, 1H), 8.13 (dd, J = 6.5, 1.2 Hz, 1H), 4.30 (s, 3H), 3.52 (q, J = 7.1 Hz, 2H), 3.21 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 168.9, 164.5, 155.1, 122.7, 121.9 (q, J = 320.3 Hz), 46.3, 43.8, 40.8, 14.3, 12.8; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.07 (s, 3F). Anal. Calcd for $C_{11}H_{16}F_3N_3O_4S$: C, 38.48; H, 4.70; F, 16.60; N, 12.24; S, 9.34. Found: C, 38.26; H, 4.41; F, 16.20; N, 11.98; S, 9.29.

4-(Ethylcarbamoyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4l). Prepared according to general procedure 1 from *N*-ethylpyrimidine-4-carboxamide (**16e**) (100 mg, 0.662 mmol) and methyl trifluoromethanesulfonate (119 mg, 0.728 mmol) in dry dichloromethane (2 mL), reaction time 24 h, to give the product as a yellowish solid (185 mg, 89% yield): mp 130−132 °C; ^{1}H NMR (600 MHz, acetonitrile-d_3) δ 9.46 (s, 1H), 9.13 (d, J = 6.2 Hz, 1H), 8.58 (d, J = 6.3 Hz, 1H), 8.35 (s, 1H), 4.34 (s, 3H), 3.46 (qd, J = 7.2, 5.9 Hz, 2H), 1.22 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, acetonitrile-d_3) δ 163.1, 160.2, 156.0, 154.7, 122.1 (q, J = 320.7 Hz), 121.9, 46.5, 35.7, 14.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.07 (s, 3F). Anal. Calcd for $C_9H_{12}F_3N_3O_4S$: C, 34.29; H, 3.84; F, 18.08; N, 13.33; S, 10.17. Found: C, 34.14; H, 3.68; F, 18.06; N, 13.19; S, 10.06.

4-(Ethoxycarbonyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4m). Prepared according to general procedure 1 from ethyl pyrimidine-4-carboxylate (**16f**) (230 mg, 1.512 mmol) and methyl trifluoromethanesulfonate (273 mg, 1.663 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a white solid (310 mg, 65% yield): mp 66−68 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.55 (s, 1H), 9.23 (dd, J = 6.5, 1.2 Hz, 1H), 8.57 (d, J = 5.8 Hz, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.36 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 161.9, 161.2, 156.4 (t, J = 8.2 Hz), 155.6, 124.3, 128.5−115.5 (m), 64.8, 46.7, 14.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.08 (s, 3F). Anal. Calcd for $C_9H_{11}F_3N_2O_5S$: C, 34.18; H, 3.51; F, 18.02; N, 8.86; S, 10.14. Found: C, 33.92; H, 3.32; F, 18.00; N, 8.64; S, 9.99.

1-Methyl-4-(trifluoromethyl)pyrimidinium Trifluoromethanesulfonate (4n). Prepared according to general procedure 1 from 4-(trifluoromethyl)pyrimidine (**16h**) (1000 mg, 6.080 mmol) and methyl trifluoromethanesulfonate (1995 mg, 12.150 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a white solid (1275 mg, 67% yield): mp 81−83 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.65 (s, 1H), 9.38 (d, J = 6.7 Hz, 1H), 8.52 (d, J = 6.3 Hz, 1H), 4.42 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 160.5 (d, J = 39.1 Hz), 158.3−157.7 (m), 156.4−156.0 (m), 122.0, 121.9 (q, J = 320.3 Hz), 120.2 (q, J = 206.7 Hz), 47.2 (t, J = 4.4 Hz); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −69.50 (s, 3F), −78.12 (s, 3F). Anal. Calcd for $C_7H_6F_6N_2O_3S$: C, 26.93; H, 1.94; F, 36.51; N, 8.97; S, 10.27. Found: C, 26.51; H, 1.79; F, 36.35; N, 8.78; S, 10.08.

4-Cyano-1-methylpyrimidinium Trifluoromethanesulfonate (4o). Prepared according to general procedure 1 from pyrimidine-4-carbonitrile (**16j**) (100 mg, 0.951 mmol) and methyl trifluoromethanesulfonate (172 mg, 1.047 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a beige solid (225 mg, 88% yield): mp 95−98 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.55 (s, 1H), 9.28 (d, J = 6.6 Hz, 1H), 8.53 (d, J = 6.4 Hz, 2H), 4.37 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 156.9 (t, J = 9.0 Hz), 155.8 (t, J = 6.4 Hz), 147.0 (t, J = 5.1 Hz), 128.6, 121.9 (q, J = 320.5 Hz), 114.7, 47.4 (t, J = 3.9 Hz); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.07 (s, 3F). Anal. Calcd for $C_7H_6F_3N_3O_3S$: C, 31.23; H, 2.25; F, 21.17; N, 15.61; S, 11.91. Found: C, 30.98; H, 2.24; F, 21.49; N, 15.27; S, 11.60.

5-Methoxy-1-methylpyrimidinium Trifluoromethanesulfonate (4p). Prepared according to general procedure 1 from 5-methoxypyrimidine (**17a**) (200 mg, 1.816 mmol) and methyl trifluoromethanesulfonate (328 mg, 1.998 mmol) in dry dichloromethane (3 mL), reaction time 1 h, to give the product as a yellowish oil (450 mg, 85% yield): ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.05 (s, 1H), 9.03 (d, J = 2.9 Hz, 1H), 8.76−8.69 (m, 1H), 4.27 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 155.6, 153.0, 147.1, 139.3 (t, J = 8.5 Hz), 121.9 (q, J = 320.4 Hz), 58.9, 46.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.10 (s, 3F); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for $C_6H_9N_2O$ 125.07094, found 125.07130.

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Anal. Calcd for $C_7H_9F_3N_2O_4S$: C, 30.66; H, 3.31; F, 20.78; N, 10.22; S, 11.69. Found: C, 30.38; H, 3.41; F, 20.46; N, 10.11; S, 11.32.

5-(Ethylcarbamoyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4q). Prepared according to general procedure 1 from *N*-ethylpyrimidine-5-carboxamide (**17b**) (150 mg, 0.992 mmol) and methyl trifluoromethanesulfonate (171 mg, 1.042 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a white solid (186 mg, 60% yield): mp 126−129 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.61 (d, J = 2.0 Hz, 1H), 9.48 (d, J = 1.7 Hz, 1H), 9.41−9.33 (m, 1H), 7.92 (s, 1H), 4.34 (s, 3H), 3.43 (qd, J = 7.3, 5.5 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 163.4, 160.1, 155.7, 153.2, 131.0, 121.8 (q, J = 320.1 Hz), 46.5, 36.1, 14.5; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.07 (s, 3F). Anal. Calcd for $C_9H_{12}F_3N_3O_4S$: C, 34.29; H, 3.84; F, 18.08; N, 13.33; S, 10.17. Found: C, 34.36; H, 3.84; F, 18.05; N, 13.14; S, 10.12.

5-(Ethoxycarbonyl)-1-methylpyrimidinium Trifluoromethanesulfonate (4r). Prepared according to general procedure 1 from ethyl pyrimidine-5-carboxylate (250 mg, 1.643 mmol) and methyl trifluoromethanesulfonate (283 mg, 1.725 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a white solid (440 mg, 82% yield): mp 101−103 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.75 (d, J = 1.8 Hz, 1H), 9.54 (s, 1H), 9.50−9.42 (m, 1H), 4.50 (q, J = 7.1 Hz, 2H), 4.35 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz,) δ 165.2, 161.1, 157.2, 154.6, 127.5, 121.9 (q, J = 320.4 Hz), 64.5, 46.6, 14.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.08 (s, 3F). Anal. Calcd for $C_9H_{11}F_3N_2O_5S$: C, 34.18; H, 3.51; F, 18.02; N, 8.86; S, 10.14. Found: C, 33.85; H, 3.41; F, 17.87; N, 8.66; S, 9.95.

1-Methyl-5-(trifluoromethyl)pyrimidinium Trifluoromethanesulfonate (4s). Prepared according to general procedure 1 from 5-(trifluoromethyl)pyrimidine (150 mg, 1.013 mmol) and methyl trifluoromethanesulfonate (183 mg, 1.114 mmol) in dry dichloromethane (1 mL), reaction time 1 h, to give the product as a white solid (255 mg, 81% yield): mp 170−172 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.69 (d, J = 1.0 Hz, 1H), 9.65 (s, 1H), 9.48 (s, 1H), 4.39 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 163.1, 157.8, 152.8, 127.2 (q, J = 37.5 Hz), 122.0 (q, J = 320.4 Hz), 121.7 (q, J = 273.1 Hz), 47.0; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −62.26 (s, 3F), −78.34 (s, 3F). Anal. Calcd for $C_7H_6F_6N_2O_3S$: C, 26.93; H, 1.94; F, 36.51; N, 8.97; S, 10.27. Found: C, 26.63; H, 2.04; F, 37.11; N, 8.62; S, 9.88.

5-Cyano-1-methylpyrimidinium trifluoromethanesulfonate (4t). A solution of pyrimidine-5-carbonitrile (**17d**) (70 mg, 0.666 mmol) in dry dichloromethane (1.5 mL) was cooled to 0 °C under argon. Methyl trifluoromethanesulfonate (111 mg, 0.679 mmol) was added dropwise. The mixture was stirred for 1 h at the same temperature and then allowed to slowly reach rt. Solvent was removed by a stream of dry argon and dried in vacuo to give crude product as a colorless oil which was not further purified. The product immediately reacted with moisture from solvents; therefore, two species are seen in the spectrum: salt **4t** (55%) and hydroxy adduct **4t-OH** (45%). Data for **4t**: ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.63 (d, J = 1.9 Hz, 1H), 9.60 (s, 1H), 9.49−9.44 (m, 1H), 4.35 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 167.9, 157.5, 157.1, 121.8 (q, J = 320.0 Hz), 112.3, 111.9, 47.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.06 (s, 3F); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for $C_6H_6N_3$ 120.05562, found 120.05611. Data for 6-hydroxy-1-methyl-5-cyano-1,6-dihydropyrimidine (**4t-OH**): ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.20−8.15 (m, 1H), 7.39 (dd, J = 5.1, 1.0 Hz, 1H), 6.22 (s, 1H), 5.71 (s, 1H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 150.7, 135.4, 121.8 (q, J = 320.4 Hz), 115.5, 94.6, 76.9, 40.6; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.06 (s, 3F); HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_6H_8N_3O$ 138.06619, found 138.06633.

1-Methyl-5-nitropyrimidinium Trifluoromethanesulfonate (4u) Characterized in the Form of 6-Hydroxy-1-methyl-5-nitro-1,6-dihydropyrimidine (4u-OH). A solution of 5-nitropyrimidine (**17h**) (60 mg, 0.480 mmol) in dry dichloromethane (1.5 mL) was cooled to 0 °C under argon. Methyl trifluoromethanesulfonate (80 mg, 0.489 mmol) was added dropwise. The mixture was stirred for 1 h at the same temperature and then allowed to slowly reach rt. Solvent was removed by a stream of dry argon and dried in vacuo to give crude product as a yellow oil which was not further purified. The product reacted with moisture to form a hydroxy adduct, which was characterized; traces of salt were present in the spectrum: ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 8.34 (s, 1H), 8.12 (s, 1H), 6.26 (s, 1H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 151.2, 131.5, 130.3, 121.7 (q, J = 321.1 Hz), 76.3, 41.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.32 (s, 3F); HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_5H_8N_3O_3$ 158.05602, found 158.05591.

2-Methoxy-1-methyl-4-(trifluoromethyl)pyrimidinium Trifluoromethanesulfonate (4v). Prepared according to general procedure 1 from 2-methoxy-4-(trifluoromethyl)pyrimidine (**16m**) (300 mg, 1.684 mmol) and methyl trifluoromethanesulfonate (290 mg, 1.769 mmol) in dry dichloromethane (5 mL), reaction time 24 h, to give the product as a white solid (302 mg, 52% yield): mp 86−89 °C; ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 9.09 (d, J = 6.5 Hz, 1H), 7.95 (d, J = 6.4 Hz, 1H), 4.38 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 162.6 (q, J = 39.0 Hz), 160.0, 159.7, 122.0 (q, J = 320.6 Hz), 119.9 (q, J = 275.9 Hz), 113.4 (q, J = 2.6 Hz), 60.8, 43.4; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −70.00 (s, 3F), −78.10 (s, 3F). Anal. Calcd for $C_8H_8F_6N_2O_4S$: C, 28.08; H, 2.36; F, 33.31; N, 8.19; S, 9.37. Found: C, 27.90; H, 2.25; F, 33.17; N, 8.03; S, 9.20.

1-Methylpyridinium Trifluoromethanesulfonate (5a). Prepared according to general procedure 1 from pyridine (100 mg, 1.264 mmol) and methyl trifluoromethanesulfonate (228 mg, 1.391 mmol) in dry dichloromethane (5 mL), reaction time 24 h (rt instead of 0 °C), to give a white semicrystalline solid (290 mg, 94% yield): ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.66 (d, J = 5.2 Hz, 2H), 8.49 (t, J = 7.9 Hz, 1H), 8.04−7.96 (m, 2H), 4.31 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 146.4, 146.5−146.2 (m), 129.0, 122.1 (q, J = 320.6 Hz), 49.3 (t, J = 5.4 Hz); ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.16 (s, 3F); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for C_6H_8N 94.06513, found 94.06541.

1-Methyl-3,5-bis(diethylcarbamoyl)pyridinium Trifluoromethanesulfonate (5b). Prepared according to general procedure 1 from *N,N,N′,N′*-tetraethylpyridinedicarboxamide (**18a**) (140 mg, 0.600 mmol) and methyl trifluoromethanesulfonate (99 mg, 0.600 mmol) in dry chloroform (2.5 mL), reaction time 24 h. The solid was collected by filtration and purified by chromatography on reversed phase (water−methanol gradient) to give the product as a colorless oil (70 mg, 47% yield): ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 8.70 (s, 2H), 8.39 (s, 1H), 4.32 (s, 3H), 3.51 (q, J = 6.6 Hz, 4 H), 3.25 (q, J = 6.9 Hz, 4H), 1.21 (t, J = 6.9, 6H) 1.10 (t, J = 6.9, 6H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 164.0, 144.3, 141.0, 138.8, 122.1 (q, J = 320.7 Hz), 49.7, 44.4, 40.7, 14.3, 12.9; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.17 (s, 3F). Anal. Calcd for $C_{17}H_{26}F_3N_3O_5S$: C, 46.25; H, 5.94; N, 9.52. Found: C, 46.22; H, 5.90; N, 9.42.

1-Methyl-3,5-bis(ethylcarbamoyl)pyridinium Trifluoromethanesulfonate (5c). Prepared according to general procedure 1 from *N,N′*-diethylpyridine-3,5-dicarboxamide (**18b**) (140 mg, 0.700 mmol) and methyl trifluoromethanesulfonate (115 mg, 0.700 mmol) in dry chloroform (2.5 mL), reaction time 24 h, to give the product as a white solid (205 mg, 84% yield): mp 182−184 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.14 (d, J = 0.7 Hz, 2H), 9.07 (t, J = 1.6 Hz, 1H), 7.75 (s, 2H), 4.40 (s, 3H), 3.44 (qd, J = 7.3, 5.5 Hz, 4H), 1.23 (t, J = 7.3 Hz, 6H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 161.4, 147.5, 141.6, 135.6, 121.9 (q, J = 320.3 Hz), 49.9, 36.1, 14.6; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.19 (s, 3F). Anal. Calcd for $C_{13}H_{18}F_3N_3O_5S$: C, 40.52; H, 4.71; N, 10.90. Found: C, 40.27; H, 4.60; N, 10.69.

1-Methyl-3,5-bis(ethoxycarbonyl)pyridinium Trifluoromethanesulfonate (5d). Prepared according to general procedure 1 from diethylpyridine-3,5-dicarboxylate (**18c**) (13 mg, 0.058 mmol) and methyl trifluoromethanesulfonate (10 mg, 0.061 mmol) in dry chloroform (1 mL), reaction time 24 h, to give the product as a white solid (23 mg, 98% yield): mp 227−232 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.36−9.34 (m, 2H), 9.26−9.25 (m, 1H), 4.50 (q, J = 7.1 Hz, 4H), 4.43 (s, 3H), 1.43 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 161.8, 150.3, 145.7, 132.2, 64.5, 50.1, 14.3; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.29 (s, 3F). Anal. Calcd for

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$C_{13}H_{16}F_3NO_7S$: C, 40.31; H, 4.16; N, 3.62. Found: C, 40.44; H, 4.13; N, 3.54.

1-Methyl-3,5-bis(trifluoromethyl)pyridinium Trifluoromethanesulfonate (5e). Prepared according to general procedure 1 from 3,5-bis(trifluoromethyl)pyridine (100 mg, 0.500 mmol) and methyl trifluoromethanesulfonate (99 mg, 0.600 mmol) in dry chloroform (2 mL), reaction time 12 h, to give the product as a white solid (120 mg, 68% yield): mp 227−232 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.38 (s, 2H), 9.16 (s, 1H), 4.48 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 148.6, 141.7, 122.1 (q, J = 320.7 Hz), 121.8 (q, J = 273.6 Hz), 50.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −62.42 (s, 6F), −78.31 (s, 3F). Anal. Calcd for $C_9H_6F_9NO_3S$: C, 28.51; H, 1.59; N, 3.69. Found: C, 28.44; H, 1.52; N, 3.69.

3,5-Dicyano-1-methylpyridinium Trifluoromethanesulfonate (5f). Prepared according to general procedure 1 from pyridine-3,5-dicarbonitrile (**18e**) (140 mg, 1.090 mmol) and methyl trifluoromethanesulfonate (197 mg, 1.200 mmol) in dry chloroform (2 mL), reaction time 72 h, to give the product as a white solid (207 mg, 65% yield): mp 206−208 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.34 (d, J = 1.8 Hz, 2H), 9.15 (t, J = 1.4 Hz, 1H), 4.41 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 153.3, 152.8, 122.0, 115.2, 112.6, 50.9; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.29 (s, 3F). Anal. Calcd for $C_9H_6F_3N_3O_3S$: C, 36.87; H, 2.06; N, 14.33. Found: C, 36.68; H, 2.00; N, 13.93.

1-Methyl-3,5-dinitropyridinium Trifluoromethanesulfonate (5g). Prepared according to general procedure 1 from 3,5-dinitropyridine (**18f**) (200 mg, 1.183 mmol) and methyl trifluoromethanesulfonate (204 mg, 1.242 mmol) in dry dichloromethane (2 mL), reaction time 8 h, to give the product as a slightly yellowish solid (298 mg, 76%): mp 185−187 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.94−9.92 (m, 2H), 9.75 (t, J = 1.8 Hz, 2H), 4.60 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 148.4, 147.3, 135.9, 121.8 (q, J = 320.3 Hz), 51.4; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.19 (s, 3F). Anal. Calcd for $C_7H_6F_3N_3O_7S$: C, 25.23; H, 1.82; F, 17.11; N, 12.61; S, 9.62. Found: C, 25.34; H, 1.79; F, 16.72; N, 12.17; S, 9.67.

3,5-Dicyano-1-methylpyridinium Tetrafluoroborate (5h). Prepared according to general procedure 2 from pyridine-3,5-dicarbonitrile (**18e**) (100 mg, 0.780 mmol) and triethyloxonium tetrafluoroborate (138 mg, 0.930 mmol) in dry chloroform (2 mL), reaction time 48 h, to give the product as a white solid (112 mg, 63% yield): mp 257−259 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.30 (s, 2H), 9.15 (s, 1H), 4.40 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 153.3 (t, J = 8.7 Hz), 152.8, 115.3, 112.6, 51.0; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −150.49 (^{10}B−F, s), −150.54 (^{11}B−F, s). Anal. Calcd for $C_8H_6BF_4N_3$: C, 41.60; H, 2.62; N, 18.19. Found: C, 41.32; H, 2.59; N, 17.86.

3,5-Dicyano-1-ethylpyridinium Tetrafluoroborate (5i). Prepared according to general procedure 2 from 3,5-dicyanopyridine (**18e**) (72 mg, 0.56 mmol) and triethyloxonium tetrafluoroborate (144 mg, 0.760 mmol) in dry chloroform (1 mL), reaction time 24 h, to give the product as a white solid (76 mg, 55% yield): mp 239−242 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.36 (s, 2H), 9.14 (s, 1H), 4.70 (q, J = 7.3 Hz, 2H), 1.65 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 152.8, 152.6−152.0 (m), 115.7, 112.7, 60.9, 15.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −150.42 (^{10}B−F, s), −150.47 (^{11}B−F, s). Anal. Calcd for $C_9H_8BF_4N_3$: C, 44.12; H, 3.29; N, 17.15. Found: C, 43.88; H, 3.11; N, 16.84.

1-Methyl-2,5-dicyanopyridinium Trifluoromethanesulfonate (5j). Prepared according to general procedure 1 from 2,5-dicyanopyridine (**18h**) (140 mg, 1.090 mmol) and methyl trifluoromethanesulfonate (197 mg, 1.200 mmol) in dry chloroform (2 mL), reaction time 0.5 h at rt, 72 h in cold, to give the product as a white solid (91 mg, 29% yield): mp 160−161 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.41 (s, 1H), 9.02 (dd, J = 8.3, 1.7 Hz, 1H), 8.66 (d, J = 8.3 Hz, 1H), 4.54 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 153.3, 151.3, 135.2, 131.4, 122.0 (q, J = 320.5 Hz), 117.6, 113.0, 110.6, 50.7; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.14 (s, 3F). Anal. Calcd for $C_9H_6F_3N_3O_3S$: C, 36.87; H, 2.06; N, 14.33. Found: C, 36.45; H, 2.02; N, 13.89.

1-Ethyl-2,5-dicyanopyridinium Tetrafluoroborate (5k). Prepared according to general procedure 2 from 2,5-dicyanopyridine (**18h**) (100 mg, 0.780 mmol) and triethyloxonium tetrafluoroborate (163 mg, 0.850 mmol) in dry chloroform (2 mL), reaction time 0.5 h at rt, 24 h in cold, to give the product as a white solid (80 mg, 42% yield): mp 174−180 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.41 (d, J = 1.4 Hz, 1H), 9.01 (dd, J = 8.3, 1.7 Hz, 1H), 8.67 (d, J = 8.3 Hz, 1H), 4.89 (q, J = 7.3 Hz, 2H), 1.71 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 152.2, 151.2, 135.9, 130.5, 118.1, 113.2, 110.6, 60.5, 15.2; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −150.68 (s), −150.74 (s). Anal. Calcd for $C_9H_8BF_4N_3$: C, 44.12; H, 3.29; N, 17.15. Found: C, 43.67; H, 3.27; N, 16.82.

2,6-Dicyano-1-methylpyridinium Trifluoromethanesulfonate (5l). Prepared according to general procedure 1 from 2,6-dicyanopyridine (**18j**) (140 mg, 1.090 mmol) and methyl trifluoromethanesulfonate (197 mg, 1.200 mmol) in dry chloroform (2 mL), reaction time 72 h at rt, 12 h in cold, to give the product as a white solid (42 mg, 13% yield): mp 174−176 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 8.95 (t, J = 8.1 Hz, 1 H), 8.80 (d, J = 8.1 Hz, 2 H), 4.73 (s, 3 H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 149.5, 138.0, 131.8, 122.0 (q, J = 320.5 Hz), 110.6, 50.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.13 (s, 3F). Anal. Calcd for $C_9H_6F_3N_3O_3S$: C, 36.87; H, 2.06; N, 14.33. Found: C, 36.50; H, 1.94; N, 14.16.

3-Cyano-1-methylpyridinium Trifluoromethanesulfonate (6a). Prepared according to general procedure 1 from pyridine-3-carbonitrile (150 mg, 1.441 mmol) and methyl trifluoromethanesulfonate (260 mg, 1.585 mmol) in dry dichloromethane (5 mL), reaction time 24 h at rt, to give the product as a white solid (310 mg, 78% yield): mp 131−133 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.15 (s, 1H), 8.89 (d, J = 6.3 Hz, 1H), 8.84−8.75 (m, 1H), 8.18 (dd, J = 8.4, 6.0 Hz, 1H), 4.37 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 150.3−149.8 (m), 149.5, 129.7, 122.0 (q, J = 320.5 Hz), 114.7, 113.9, 50.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.17 (s, 3F); HRMS-ESI (m/z) $[M - CF_3SO_3]^+$ calcd for $C_7H_7N_2$ 119.06037, found 119.06036.

4-Cyano-1-methylpyridinium Trifluoromethanesulfonate (6b). Prepared according to general procedure 1 from pyridine-4-carbonitrile (154 mg, 1.500 mmol) and methyl trifluoromethanesulfonate (263 mg, 1.600 mmol) in dry chloroform (2 mL), reaction time 0.5 h at rt, 12 h in cold, to give the product as a white solid (310 mg, 78% yield): mp 131−133 °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 8.85 (d, J = 6.50 Hz, 2H), 8.31−8.33 (m, 2H), 4.37 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 147.9, 131.9. 129.1, 122.0 (m), 115.0, 50.4; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.18 (s, 3F). Anal. Calcd for $C_8H_7F_3N_2O_3S$: C, 35.82; H, 2.63; N, 10.44. Found: C, 35.86; H, 2.56; N, 10.24.

1-Methylquinolinium Trifluoromethanesulfonate[30] (7). Prepared according to general procedure 1 from quinoline (200 mg, 1.548 mmol) and methyl trifluoromethanesulfonate (267 mg, 1.626 mmol) in dry dichloromethane (3 mL), reaction time 8 h, to give the product as a white solid (380 mg, 84%): mp 123−124 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 9.12 (d, J = 5.1 Hz, 1H), 9.10 (d, J = 8.5 Hz, 1H), 8.40−8.37 (m, 1H), 8.37−8.35 (m, 1H), 8.25 (ddd, J = 8.7, 7.0, 1.5 Hz, 1H), 8.05−8.02 (m, 1H), 8.02−7.99 (m, 1H), 4.58 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 150.7, 148.6, 139.9, 136.9, 131.5, 131.3, 130.8, 122.8, 122.1 (q, J = 320.7 Hz), 119.7, 46.6; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.05 (s, 3F). Anal. Calcd for $C_{11}H_{10}F_3NO_3S$: C, 45.05; H, 3.44; F, 19.44; N, 4.78; S, 10.93. Found: C, 44.85; H, 3.37; F, 19.78; N, 4.59; S, 10.82.

2-Methylisoquinolinium Trifluoromethanesulfonate (8). Prepared according to general procedure 1 from isoquinoline (200 mg, 1.548 mmol) and methyl trifluoromethanesulfonate (267 mg, 1.626 mmol) in dry dichloromethane (3 mL), reaction time 8 h, to give the product as a white solid (358 mg, 79%): 104−105 mp °C; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 9.59 (s, 1H), 8.42−8.34 (m, 3H), 8.23 (d, J = 8.2 Hz, 1H), 8.18 (t, J = 7.7 Hz, 1H), 8.00 (t, J = 7.7 Hz, 1H), 4.45 (s, 3H); ^{13}C NMR (126 MHz, acetonitrile-d_3) δ 151.3, 138.2, 138.0, 136.4, 132.4, 131.0, 128.6, 128.3, 127.0, 122.1 (q, J = 320.8 Hz), 49.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −78.05 (s, 3F). Anal.

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Calcd for $C_{11}H_{10}F_3NO_3S$: C, 45.05; H, 3.44; F, 19.44; N, 4.78; S, 10.93. Found: C, 44.84; H, 3.41; F, 19.73; N, 4.60; S, 10.81.

General Procedure 3 for Preparation of Adducts. To a solution of heteroarenium salt (1 equiv, usually about 40−50 mg) in acetonitrile-d_3 (0.6 mL) was added dry methanol (5−10 equiv), and the mixture was allowed to stand for 5 min. Sodium carbonate (5 equiv) was added, the mixture was sonicated for 10 min and centrifuged to remove solids, and the solution was transferred to a NMR tube.

General Procedure 4 for Preparation of Adducts. Heteroarenium salt (about 15 mg) was dissolved in methanol-d_4. The solution was transferred to a NMR tube, and spectra were acquired after 6 h.

***N,N*-Diethyl-6-methoxy-1-methyl-1,6-dihydropyrimidine-4-carboxamide (11a).** Prepared according to general procedure 3 from salt **4k**, dry methanol, and sodium carbonate: ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 7.35 (d, J = 1.2 Hz, 1H), 5.53 (dd, J = 4.5, 1.0 Hz, 1H), 5.23 (dd, J = 4.5, 1.3 Hz, 1H), 3.47−3.27 (m, 4H), 3.07 (s, 3H), 3.02 (s, 3H), 1.18−1.03 (m, 6H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 169.9, 151.9, 146.1, 102.4, 83.1, 49.5, 44.0, 40.2, 38.0, 14.7, 13.0; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{20}N_3O_2$ 226.15500, found 226.15486.

6-Methoxy-1-methyl-4-(trifluoromethyl)-1,6-dihydropyrimidine (11b). Prepared according to general procedure 3 from **4n**, dry methanol, and sodium carbonate: ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 7.40 (s, 1H), 5.69−5.65 (m, 1H), 5.58−5.54 (m, 1H), 3.09 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 152.5, 140.3 (q, J = 33.1 Hz), 122.9 (q, J = 271.9 Hz), 103.4 (q, J = 4.2 Hz), 82.7, 49.9, 37.9; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −71.22 (s, 3F), −78.39 (s, 3F); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_7H_{10}F_3N_2O$ 195.07397, found 195.07397.

6-Methoxy-1-methyl-1,6-dihydropyrimidine-4-carbonitrile (11c). Prepared according to general procedure 3 from **4o**, dry methanol, and sodium carbonate: ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 7.35 (s, 1H), 5.86 (dd, J = 4.6, 1.2 Hz, 1H), 5.50 (dd, J = 4.6, 0.9 Hz, 1H), 3.08 (t, J = 0.4 Hz, 3H), 3.04 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 152.7, 126.4, 118.2, 114.6, 82.3, 50.3, 38.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_7H_{10}N_3O$ 152.08184, found 152.08185.

6-Methoxy-1-methyl-1,6-dihydropyrimidine-2-carbonitrile (11d). Prepared according to general procedure 3 from **4h**, dry methanol, and sodium carbonate: ^{1}H NMR (600 MHz, acetonitrile-d_3) δ 6.85 (d, J = 6.9 Hz, 1H), 5.49 (d, J = 4.6 Hz, 1H), 5.37 (dd, J = 7.0, 4.5 Hz, 1H), 3.27 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (151 MHz, acetonitrile-d_3) δ 138.5, 136.0, 113.2, 108.5, 83.9, 50.2, 38.3; HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_7H_{10}N_3O$ 152.08184, found 152.08159.

2-Methoxy-1-methyl-5-(trifluoromethyl)-1,2-dihydropyrazine (12). Prepared according to general procedure 3 from **3e**, dry methanol, and sodium carbonate. Residual pyrazinium salt was present in the spectrum: ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 7.08 (q, J = 1.1 Hz, 1H), 7.05−7.01 (m, 1H), 5.27−5.22 (m, 1H), 3.17 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, acetonitrile-d_3) δ 139.0, 132.1 (d, J = 4.4 Hz), 125.1 (q, J = 265.9 Hz), 114.3 (q, J = 35.4 Hz), 81.9, 53.0, 41.1; ^{19}F NMR (282 MHz, acetonitrile-d_3) δ −65.19 (s, 3F); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_7H_{10}F_3N_2O$ 195.07397, found 195.07375.

2-Methoxy-1-methyl-3,5-dinitro-1,2-dihydropyridine (13a). Prepared according to general procedure 3 from **5g**, dry methanol, and sodium carbonate: ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.65 (dd, J = 1.3, 0.7 Hz, 1H), 8.51 (dd, J = 2.0, 0.9 Hz, 1H), 6.30 (s, 1H), 3.52 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 149.7, 128.3, 126.7, 122.4, 85.4, 54.7, 43.6. HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_9N_3NaO_5$ 238.04344, found 238.04315.

2-[$^2H_3$]Methoxy-1-methyl-1,2-dihydropyridine-3,5-dicarbonitrile (13b). Prepared according to general procedure 4 from **5f**. The product **13b** was accompanied by starting salt **5f** (25%) in equilibrium: ^{1}H NMR (500 MHz, methanol-d_4) δ 7.83 (s, 1H), 7.34 (s, 1H), 5.86 (s, 1H), 3.38 (s, 3H); ^{13}C NMR (126 MHz, methanol-d_4) δ 152.6, 139.9, 120.5, 119.6, 119.1, 118.8, 85.4, 41.9; HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_9H_7D_3N_3O$ 179.10067, found 179.10008.

***N,N*-Diethylpyrazine-2-carboxamide[31] (14a).** Pyrazine-2-carboxylic acid (10 g, 81 mmol) was suspended in dry benzene (80 mL), and thionyl chloride (18 mL, 243 mmol) was added. Two drops of *N,N*-dimethylformamide were added, and the mixture was heated to reflux for 2 h. The excess of thionyl chloride and benzene were removed under reduced pressure. Crude pyrazine-2-carbonyl chloride was not further purified and used immediately. Pyrazine-2-carbonyl chloride was suspended in dry dichloromethane (50 mL) and cooled to 0 °C. Diethylamine (15.39 g, 210 mmol) in dry dichloromethane (50 mL) was added, and the mixture was allowed to stir at rt overnight and evaporated. The crude product was dissolved in dichloromethane (250 mL), washed with saturated sodium bicarbonate solution (1 × 100 mL), water (2 × 100 mL), and brine (1 × 50 mL), and dried with sodium sulfate. After evaporation of solvent, crude product was purified by CC (dichloromethane/ethyl acetate = 10:1) to give **14a** (7.25 g, 52%) as an orange oil: ^{1}H NMR (300 MHz, chloroform-d) δ 8.89 (d, J = 1.5 Hz, 1H), 8.61 (d, J = 2.5 Hz, 1H), 8.53 (dd, J = 2.5, 1.5 Hz, 1H), 3.57 (q, J = 7.1 Hz, 2H), 3.39 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 166.3, 150.5, 145.1, 142.7, 43.4, 40.6, 14.5, 12.9; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_9H_{14}N_3O$ 180.11314; found 180.11301.

***N*-Ethylpyrazine-2-carboxamide (14b).** Pyrazine-2-carboxylic acid (10.0 g, 81 mmol) was suspended in dry benzene (80 mL), and thionyl chloride (18 mL, 243 mmol) was added. Two drops of *N,N*-dimethylformamide were added, and the mixture was heated to reflux for 2 h. The excess thionyl chloride and benzene were removed at reduced pressure and the mixture dried in vacuo. Crude pyrazine-2-carbonyl chloride was not further purified and immediately used. Pyrazine-2-carbonyl chloride was suspended in dry dichloromethane (50 mL) and cooled to 0 °C. Ethaneamine solution (70%, 13.56 g, 16.8 mL) in dry diethyl ether was added, and the mixture was allowed to stir at rt overnight and evaporated. The crude product was dissolved in dichloromethane (250 mL), washed with saturated sodium bicarbonate solution (1 × 100 mL), water (2 × 100 mL), and brine (1 × 50 mL), and dried with sodium sulfate. After evaporation of solvent, crude product was purified by column chromatography (dichloromethane/ethyl acetate = 10:1) to give **14b** (7.6 g, 63%) as a white solid: mp 64−65 °C (lit.[32] mp 67 °C); ^{1}H NMR (300 MHz, chloroform-d) δ 9.35 (d, J = 1.4 Hz, 1H), 8.68 (d, J = 2.5 Hz, 1H), 8.47 (dd, J = 2.5, 1.5 Hz, 1H), 7.81 (s, 1H), 3.53−3.42 (m, 2H), 1.22 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 162.8, 147.2, 144.6, 144.4, 142.5, 34.4, 14.8; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_9N_3ONa$ 174.06378, found 174.06355.

Ethyl Pyrazine-2-carboxylate (14c). Pyrazine-2-carboxylic acid (20.0 g, 161 mmol) was suspended in ethanol (140 mL), and thionyl chloride (29 mL, 403 mmol) was added dropwise. The mixture was heated to reflux for 5 h, cooled to rt, diluted with water (100 mL), and neutralized with sodium carbonate. The mixture was partially evaporated, and extracted with ethyl acetate (3 × 150 mL). Organic layers were combined, washed with water (1 × 100 mL) and brine (1 × 100 mL), dried with magnesium sulfate, and concentrated in vacuo. The crude solid was dissolved in ethanol (100 mL), refluxed with active carbon, filtrated, and evaporated. The crude solid was recrystallized from hexane to give **14c** (19.0 g, 78%) as colorless crystals: mp 46−48 °C (lit.[33] mp 50−51 °C); ^{1}H NMR (300 MHz, chloroform-d) δ 9.26 (d, J = 1.5 Hz, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.68 (dd, J = 2.4, 1.5 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-d) δ 163.9, 147.7, 146.3, 144.4, 143.5, 62.4, 14.3; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_8N_2O_2Na$ 175.04780, found 175.04750.

2-Methylpyrimidine[34] (15a). Acetamidine hydrochloride (9.98 g, 106 mmol) was dissolved in dry methanol (53 mL), and dry hydrogen chloride was bubbled through during 45 min. Temperature was maintained between 5−10 °C. 1,1,3,3-Tetramethoxypropane (11.55 g, 70.3 mmol) in dry methanol (18 mL) was added, maintaining temperature at the same level. The mixture was stirred for 5 h at the same temperature and then at rt for 2 days. The mixture was

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evaporated under reduced pressure, and 50% sodium hydroxide (30 mL) was added. Then the mixture was stirred for 3 h and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo. Crude product was purified by column chromatography (dichloromethane/ethyl acetate = 15:1) to give **15a** (1.00 g, 15%) as a colorless liquid: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.63 (d, J = 4.9 Hz, 2H), 7.10 (t, J = 4.9 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 168.5, 157.1, 118.4, 26.2; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_7N_2$ 95.06037, found 95.06055.

2-Methoxypyrimidine[35] (15b). Sodium (1.10 g, 48.0 mmol) was dissolved in dry methanol (30 mL), and 2-chloropyrimidine (5.00 g, 43.7 mmol) in dry methanol (20 mL) was slowly added. The mixture was stirred for another 1 h at 50 °C. Precipitated solid was filtered off, and the mixture was diluted with dichloromethane (100 mL) and washed with water (2 × 50 mL). Combined aqueous layers were washed with dichloromethane (2 × 50 mL). Combined organic layers were washed with brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo to give **15b** (4.332 g, 90%) as a colorless liquid: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.51 (d, J = 4.8 Hz, 2H), 6.92 (t, J = 4.8 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 165.7, 159.4, 115.0, 54.9; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_7N_2O$ 111.05529, found 111.05547.

Pyrimidine-2-carboxylic Acid[36] (15c). Pyrimidine-2-carbonitrile (5 g, 47.6 mmol) was added to a solution of sodium hydroxide (4.00 g, 100 mmol), and the suspension was heated at 55 °C for 2 h. The mixture was cooled to rt and stirred overnight. pH was adjusted with dilute hydrochloric acid to 4, and the mixture was evaporated. Evaporation residue was extracted with methanol (3 × 100 mL), and diethyl ether (300 mL) was added. White precipitate was filtered off, washed with diethyl ether, and dried in vacuo to give **15c** (3.535 g, 60%) as a white powder: mp 239−243 °C dec (lit.[37] mp 200 °C dec; ^{1}H NMR (300 MHz, methanol-d_4) δ 8.87 (d, J = 4.9 Hz, 2H), 7.54 (t, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, methanol-d_4) δ 170.4, 162.7, 158.8, 123.2; HRMS-ESI (m/z) [M − H]$^-$ calcd for $C_5H_3N_2O_2$ 123.02000, found 123.01935.

***N,N*-Diethylpyrimidine-2-carboxamide (15d).** Pyrimidine-2-carboxylic acid (**15c**) (2.00 g, 16.12 mmol) was suspended in dry dichloromethane (15 mL), and thionyl chloride (3.51 mL, 48.3 mmol) was added followed by two drops of dry *N,N*-dimethylformamide. The mixture was heated to reflux for 2 h. Solvents and excess of thionyl chloride were removed in vacuo, and the resulting solid was dried. The obtained acyl chloride was used without further purification. Dry dichloromethane (100 mL) was added to acyl chloride, diethylamine (11.79 g, 161 mmol) in dry dichloromethane (50 mL) was added dropwise, and the reaction mixture was stirred overnight. The mixture was extracted with water (2 × 100 mL). Combined aqueous layers were washed with chloroform (2 × 75 mL). Combined organic layers were washed with hydrochloric acid 2% (2 × 50 mL) and brine (1 × 100 mL), dried with sodium sulfate, and concentrated in vacuo to give **15d** (975 mg, 34%) as an orange oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.81 (d, J = 5.0 Hz, 2H), 7.33 (t, J = 4.9 Hz, 1H), 3.59 (q, J = 7.2 Hz, 2H), 3.21 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 166.5, 163.3, 157.5, 121.2, 43.2, 39.8, 14.3, 13.0; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_9H_{14}N_3O$ 180.11314, found 180.11308.

***N*-Ethylpyrimidine-2-carboxamide (15e).** Pyrimidine-2-carboxylic acid (**15c**) (2.00 g, 16.12 mmol) was suspended in dry dichloromethane (15 mL), and thionyl chloride (3.51 mL, 48.3 mmol) was added followed by two drops of dry *N,N*-dimethylformamide. The mixture was stirred for 2 h at reflux. Solvents and excess of thionyl chloride were removed in vacuo, and the resulting solid was dried. The obtained acyl chloride was used without further purification. Dry dichloromethane (150 mL) was added to acyl chloride, and a solution of ethanamine in diethyl ether (59.1 g, 12% in diethyl ether (7.24 g, 161 mmol of pure ethanamine)) was added dropwise, maintaining the temperature at rt for 2 h. The mixture was washed with water (2 × 100 mL) and brine (1 × 50 mL). The water layers were combined, extracted with dichloromethane (3 × 100 mL), and washed with brine (1 × 50 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was dissolved in benzene (30 mL) and refluxed with charcoal for 3 h. After filtration and evaporation of solvent, **15e** (1.03 g, 42%) was obtained as an orange oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.87 (d, J = 4.9 Hz, 2H), 8.00 (s, 1H), 7.43 (t, J = 4.9 Hz, 1H), 3.56 (qd, J = 7.3, 5.9 Hz, 2H), 1.28 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 162.2, 157.9, 157.5, 122.5, 34.8, 14.9; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_9N_3ONa$ 174.06378, found 174.06348.

Ethyl Pyrimidine-2-carboxylate (15f). Pyrimidine-2-carboxylic acid (**15c**) (2.00 g, 16.12 mmol) was suspended in dry dichloromethane (15 mL), and thionyl chloride (3.51 mL, 48.3 mmol) was added followed by one drop of dry *N,N*-dimethylformamide, and the mixture was heated to reflux for 1 h. Solvents and excess of thionyl chloride were removed in vacuo, and the resulting solid was dried. The obtained acyl chloride was used without further purification. Dry dichloromethane (150 mL) was added to acyl chloride, and ethanol (4.58 mL, 81 mmol) with dry triethylamine (6.74 mL, 48.3 mmol) in dry dichloromethane (30 mL) was added dropwise maintaining temperature at rt. After being stirred overnight, the mixture was extracted with water (2 × 100 mL). The combined aqueous layers were washed with dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo to give a brownish oil, which was further purified by column chromatography (dichloromethane/ethyl acetate = 5:1) to give **15f** (810 mg, 33%) as a yellowish solid: mp 60−62 °C (lit.[38] mp 64−65 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.92 (d, J = 4.9 Hz, 2H), 7.46 (t, J = 4.9 Hz, 1H), 4.51 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 163.4, 157.9, 156.8, 123.2, 62.9, 14.3. HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_8N_2O_2Na$ 175.04780, found 175.04750.

2-Bromopyrimidine[39] (15g). 2-Aminopyrimidine (20.00 g, 210 mmol), sodium nitrite (30.0 g, 435 mmol), and sodium bromide (90 g, 875 mmol) in water (80 mL) were cooled to −10 °C, and hydrobromic acid (48%, 48 mL) was added dropwise, maintaining the temperature between −10 and −8 °C during 2.5 h. The reaction mixture was stirred at −5 °C for 30 min, and then was air bubbled through reaction mixture to remove nitrogen oxides and bromine. The resulting solution was made strongly alkaline with 40% sodium hydroxide solution and extracted with dichloromethane (4 × 150 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to obtain a crude product which was recrystallized from hexane to give **15g** (9.16 g, 27%) as a white solid: mp 52−53 °C (lit.[39] mp 55.5−57.0 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.56 (d, J = 4.9 Hz, 2H), 7.31 (t, J = 4.8 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 159.5, 153.4, 120.3; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_4H_4{}^{79}BrN_2$ 158.95524, found 158.95505.

2-(Trifluoromethyl)pyrimidine[40] (15h). 2-Bromopyrimidine (**15g**) (2.20 g, 13.84 mmol), dry sodium 2,2,2-trifluoroacetate (18.82 g, 138 mmol), and copper(I) iodide (13.18 g, 69.2 mmol) were mixed, and dry *N,N*-dimethylformamide (150 mL) was added under argon atmosphere. The resulting suspension was heated to reflux for 6 h. The reaction mixture was filtered through Celite, and the solution was diluted with water (800 mL). The solids were decanted, and the solution was extracted with ethyl acetate (3 × 200 mL). Combined organic layers were washed with water (2 × 100 mL) and brine (1 × 100 mL), dried with sodium sulfate, and concentrated in vacuo (35 °C, 130 Torr). The crude tarry product was purified by vacuum distillation (65−68 °C, 42 Torr) to give **15h** (640 mg, 31.2%) as a yellowish liquid: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.90 (d, J = 4.9 Hz, 2H), 7.52 (t, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 158.08, 156.9 (q, J = 36.7 Hz), 123.4, 119.6 (q, J = 275.4 Hz); ^{19}F NMR (282 MHz, chloroform-*d*) δ −71.10 (s, 3F); HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_5H_4F_3N_2$ 149.03211, found 149.03159.

2-Chloropyrimidine[41] (15i). 2-Aminopyrimidine (57.0 g, 600 mmol) was dissolved in hydrochloric acid 36% (250 mL) and cooled to −15 to −7 °C. A solution of sodium nitrite (75 g, 1.087 mol) in water (120 mL) was added dropwise during 2 h, maintaining the temperature at the same level. The reaction mixture was stirred for further 15 min at the same temperature and then allowed to reach 0

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°C and basified with ammonia solution. The reaction mixture was extracted with dichloromethane (4 × 200 mL). The combined organic layers were washed with water (1 × 100 mL) and brine (1 × 100 mL), dried with sodium sulfate, and concentrated in vacuo. The solid was dissolved in benzene and stirred with charcoal overnight at rt. After evaporation of solvent, the residue was recrystallized from hexane and dried in vacuo to give **15i** (23.4 g, 34%) as a white solid: mp 62−63 °C (lit.[41] mp 65−66 °C); ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.64 (d, J = 4.8 Hz, 2H), 7.29 (t, J = 4.8 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 161.8, 159.7, 119.9; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_4H_4ClN_2$ 115.00575, found 115.00577.

Pyrimidine-2-carbonitrile[42] (15j). To a solution of sodium cyanide (2.70 g, 55.0 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.59 g, 5.24 mmol) in DMSO (30 mL) with water (15 mL), 2-chloropyrimidine (**15i**) (6 g, 52.4 mmol) in DMSO (20 mL) was added dropwise during 15 min, and the reaction mixture was stirred overnight. The mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo to give **15j** (4.50 g, 82%) as a beige solid in sufficient purity. The analytical sample was obtained by dissolving product in benzene and refluxing the mixture with active charcoal: mp 39−40 °C (lit.[43] mp 40.0−41.5 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.86 (d, J = 5.0 Hz, 2H), 7.56 (t, J = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 158.2, 145.4, 123.8, 115.7; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_4N_3$ 106.03997, found 106.04015.

4-Methylpyrimidine[44] (16a). The apparatus consisted of a 3-necked flask (250 mL), Liebig condenser (for better removal of salt which may precipitate in condenser during the reaction), distillation head, and thermometer. Formamide (108 mL, 2.726 mol), ammonium chloride (14.67 g, 0.274 mol), and water (7.21 mL, 0.400 mol) were mixed together and the resulting mixture warmed to 175 °C. 4,4-Dimethoxybutan-2-one (128.3 g, 0.874 mol) was added dropwise during 7 h, and the reaction mixture was stirred at the same temperature for another 2 h. The temperature at the top was maintained in a range from 40 to 60 °C to remove methanol and methyl formate. The reaction temperature fell to 135 °C when the addition was complete. The reaction mixture was allowed to reach rt, poured to 1 M sodium hydroxide (130 mL), and continuously extracted by chloroform. The chloroform layers were dried with sodium sulfate, and chloroform was distilled off at normal pressure. The crude product was purified by vacuum distillation (bp 55−65 °C, 72 Torr) collecting product to ice-cooled flask to give **16a** (43.33 g, 53%) as a colorless liquid: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.11−9.04 (m, 1H), 8.56 (d, J = 5.2 Hz, 1H), 7.21−7.12 (m, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 167.1, 158.6, 156.6, 121.2, 24.3; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_7N_2$ 95.06037, found 95.06059.

4-Methoxypyrimidine (16b). Phosphoryl trichloride (41 mL, 435 mmol) was added to pyrimidine-4.6-diol (6.00 g, 53.5 mmol), and the mixture was stirred at 70 °C for 24 h. The reaction mixture was poured on ice (400 g) and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. The solid was dried in vacuo to give 4,6-dichloropyrimidine (840 mg, 11%) as a yellow solid, which was used without further purification: mp 63−64 °C (lit.[45] mp 63.5−64 °C); ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.85−8.79 (m, 1H), 7.45 (d, J = 1.0 Hz, 1H). A freshly prepared solution of sodium methoxide prepared from sodium (61.7 mg, 2.68 mmol) and dry methanol (1 mL) was added dropwise at rt during 5 min to a solution of 4,6-dichloropyrimidine (400 mg, 2.68 mmol) in dry methanol (3 mL), maintaining the temperature at the same level. The resulting solution was stirred at rt for 30 min. The solution was diluted with dichloromethane (10 mL) and washed with water (2 × 5 mL). The organic layer was dried with sodium sulfate and concentrated in vacuo to give 4-chloro-6-methoxypyrimidine[46] (270 mg, 70%) as a yellowish oil. ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.58 (s, 1H), 6.77 (s, 1H), 4.00 (s, 3H). 4-Chloro-6-methoxypyrimidine (270 mg, 1.868 mmol) was dissolved in ethanol (5 mL), and ammonium hydroxide (1 mL) and palladium on charcoal (10%) (20 mg) were added. The mixture was stirred for 12 h under hydrogen atmosphere (1 atm.). Reaction progress was monitored by TLC (hexane/ethyl acetate = 2:1). The mixture was filtered through Celite and carefully evaporated. The residue was suspended in chloroform (20 mL) and extracted with water (2 × 15 mL). The organic layer was dried with sodium sulfate and concentrated in vacuo to give **16b** (73 mg, 36%) as a yellowish oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.79 (s, 1H), 8.41 (d, J = 5.8 Hz, 1H), 6.74 (dd, J = 5.9, 1.2 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 169.4, 158.6, 157.0, 108.8, 53.9; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_7N_2O$ 111.05529, found 111.05503.

Pyrimidine-4-carboxylic Acid[47] (16c). Selenium dioxide (76.0 g, 0.685 mol) was added to a solution of 4-methylpyrimidine (**16a**) (43.0 g, 0.457 mol) in pyridine (300 mL). The mixture was stirred for 2 h at 55−60 °C and then 3 h at 85−90 °C. After being cooled and stirred overnight at rt, the mixture was filtered, and the residue was washed with pyridine (50 mL) and evaporated. The solid was washed with water (20 mL) and diethyl ether (50 mL) and dried in vacuo to give crude **16c** (31.2 g, 55%) as a brown solid which was used without further purification: mp 218−221 °C (lit.[48] mp 226−230 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.37 (d, J = 1.4 Hz, 1H), 9.07 (d, J = 5.1 Hz, 1H), 8.01 (dd, J = 5.1, 1.4 Hz, 1H); HRMS-ESI (m/z) [M − H]$^-$ calcd for $C_5H_3N_2O_2$ 123.02000, found 123.01934.

***N,N*-Diethylpyrimidine-4-carboxamide (16d).** Pyrimidine-4-carboxylic acid (**16c**) (1.783 g, 14.37 mmol) was suspended in dry dichloromethane (35 mL), and oxalyl chloride (1.727 mL, 20.11 mmol) was added followed by one drop of *N*,*N*-dimethylformamide. The mixture was allowed to stir overnight. The mixture was evaporated and dissolved in dry dichloromethane (15 mL), and diethylamine (7.43 mL, 71.8 mmol) in dry dichloromethane (10 mL) was added dropwise, maintaining temperature at rt for 3 h. The mixture was diluted with chloroform (200 mL) and water (200 mL) and separated, and the aqueous layer was extracted with chloroform (3 × 200 mL). The combined organic layers were washed with water (2 × 150 mL) and brine (1 × 100 mL), dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate = 1:2) to give **16d** (1.860 g, 72%) as a brownish oil which partially solidified upon further standing: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.20 (d, J = 1.4 Hz, 1H), 8.84 (d, J = 5.1 Hz, 1H), 7.54 (dd, J = 5.1, 1.4 Hz, 1H), 3.53 (q, J = 7.1 Hz, 2H), 3.33 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 166.3, 162.0, 158.3, 158.0, 120.0, 43.2, 40.3, 14.4, 12.8; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_9H_{14}N_3O$ 180.11314, found 180.11295.

***N*-Ethylpyrimidine-4-carboxamide (16e).** Pyrimidine-4-carboxylic acid (**16c**) (1.50 g, 12.09 mmol) was suspended in dry dichloromethane (30 mL), and oxalyl chloride (1.45 mL, 16.92 mmol) was added followed by one drop of *N*,*N*-dimethylformamide. The mixture was allowed to stir overnight, evaporated, and dried in vacuo. The crude acyl chloride was used without further purification. The solid was suspended in dry dichloromethane (25 mL), and ethanamine (12% ether solution) (22.15 g, 60.4 mmol) was added dropwise maintaining temperature at rt. The mixture was stirred overnight, diluted with water (50 mL), and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with water (1 × 50 mL) (pH was adjusted by 10% hydrochloric acid to 7) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate = 1:2) to give **16e** (0.81 g, 44%) as an orange oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.17 (d, J = 1.4 Hz, 1H), 8.92 (d, J = 5.0 Hz, 1H), 8.08 (dd, J = 5.0, 1.4 Hz, 1H), 7.97 (s, 1H), 3.48 (qd, J = 7.3, 6.0 Hz, 2H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 162.4, 159.2, 157.7, 156.4, 118.5, 34.5, 14.7; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_9N_3ONa$ 174.06378, found 174.06350.

Ethyl Pyrimidine-4-carboxylate (16f). Pyrimidine-4-carboxylic acid (**16c**) (3.00 g, 24.17 mmol) was suspended in ethanol (23 mL), and thionyl chloride (5.3 mL, 72.5 mmol) was added dropwise. The mixture was heated to reflux for 11 h. The mixture was cooled to rt and basified with sodium bicarbonate to pH 8, ethanol was evaporated

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at reduced pressure, and water (100 mL) was added. The mixture was extracted with ethyl acetate (4 × 75 mL). The combined organic layers were washed with brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. Crude product was purified by column chromatography (dichloromethane/ethyl acetate = 1:2) to give **16f** (2.87 g, 78%) as yellowish oil which solidify upon further standing: mp 35−36 °C (lit.[37] mp 38−40 °C); ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.34 (d, J = 1.3 Hz, 1H), 8.93 (d, J = 5.0 Hz, 1H), 7.96 (dd, J = 5.0, 1.4 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 164.0, 159.2, 159.1, 154.9, 120.9, 62.8, 14.2; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_8N_2O_2Na$ 175.04780, found 175.04754.

(*E*)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one[49] (16g). 2,2,2-Trifluoroacetic anhydride (26.9 mL, 190 mmol) was cooled to −10 °C under argon atmosphere, and a mixture of ethoxyethene (20.03 mL, 209 mmol) with pyridine (15.34 mL, 190 mmol) was added dropwise, maintaining the temperature between −10 and 0 °C. After addition of about half of the solvents, the reaction mixture was diluted with dry diethyl ether (30 mL). When the addition was completed, the mixture was put into an ice bath, allowed to slowly reach rt, and stirred overnight. The solid was filtered off and washed with diethyl ether (200 mL). The mixture was evaporated at reduced pressure (30 °C, 40 Torr), and the residue was diluted with dichloromethane (200 mL), washed with 0.1 M hydrochloric acid (4 × 60 mL) and water (2 × 60 mL), dried with magnesium sulfate, and evaporated (max 35 °C, 75 Torr) for 1 h to give **16g** (30.32 g, 95%) as a yellow liquid which was used without further purification for synthesis: ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.90 (d, J = 12.3 Hz, 1H), 5.85 (d, J = 12.3 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 180.0 (q, J = 35.2 Hz), 168.0 (q, J = 1.3 Hz), 116.4 (q, J = 291.1 Hz), 97.9, 69.0, 14.32; ^{19}F NMR (282 MHz, chloroform-*d*) δ −78.54 (s, 3F); MS (GC−MS EI+, 70 eV) [M + H]$^+$ calcd for $C_6H_8F_3O_2$ 169, found 169; 141 (100, [M − Et + H]$^+$), 113, 93, 75, 43.

4-(Trifluoromethyl)pyrimidine (16h). Sodium (7.73 g, 336 mmol) was dissolved in dry methanol (250 mL). A suspension of formamidine acetate (35.00 g, 336 mmol) in dry methanol (50 mL) was added at once. After 10 min, (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**16g**) (51.40 g, 306 mmol) was added in one portion. During the addition, the solution turned to yellow. The mixture was stirred for 3 h, poured into water (700 mL), extracted with dichloromethane (3 × 150 mL), dried with magnesium sulfate, and concentrated in vacuo (380 Torr/30 °C). The crude product was distilled at atmospheric pressure (110−115 °C) to give **16h** (15.00 g, 33%) as a colorless liquid: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.38 (s, 1H), 9.00 (d, J = 5.0 Hz, 1H), 7.66 (dd, J = 5.1, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 159.4, 159.4, 155.6 (q, J = 36.7 Hz), 120.4 (q, J = 275.0 Hz), 117.3 (q, J = 2.7 Hz); ^{19}F NMR (282 MHz, chloroform-*d*) δ −70.61; HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_5H_4F_3N_2$ 149.03211, found 149.03171.

Pyrimidine-4-carboxamide (16i). Ammonium hydroxide (100 mL, 651 mmol) was added at once to solid ethyl pyrimidine-4-carboxylate (**16f**) (30 g, 197 mmol) and the mixture allowed to stir overnight at rt. The reaction mixture was filtered through a sintered glass funnel. The solid was washed with water (1 × 10 mL) and dried in vacuo to give **16i** (21.7 g, 89%) as a tan solid which was used without further purification: mp 192−193 °C (lit.[37] mp 193−194 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (d, J = 1.4 Hz, 1H), 9.05 (d, J = 5.0 Hz, 1H), 8.34 (s, 1H), 8.01 (dd, J = 5.0, 1.4 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.8, 159.6, 158.0, 156.9, 118.6; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_6N_3O$ 124.05054, found 124.05054.

Pyrimidine-4-carbonitrile (16j). Pyrimidine-4-carboxamide (**16i**) (1.655 g, 13.44 mmol) was suspended in phosphoryl trichloride (20.69 mL, 222 mmol) and the mixture stirred overnight. The mixture was heated to reflux for 30 min, the excess of phosphoryl trichloride was distilled off at reduced pressure, and ice-cold saturated potassium carbonate solution (30 mL) was added dropwise to the ice-cooled reaction mixture. The mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate = 10:1) to give **16j** (500 mg, 35%) as a yellowish oil which partially solidified: ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.36 (d, J = 1.5 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 7.68 (dd, J = 5.0, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 159.8, 158.9, 141.4, 124.5, 115.3; HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_5H_4N_3$ 106.03997, found 106.04021.

4-(Trifluoromethyl)pyrimidin-2-ol[50] (16k). (*E*)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (**16g**) (41.21 g, 245 mmol) in ethanol (245 mL) was mixed with urea (15.02 g, 250 mmol), and 35% hydrochloric acid (82 mL) was added at once. The mixture was sonicated for 5 min to dissolve the solids and stirred at rt overnight. The mixture was evaporated, and toluene was added and evaporated to remove moisture (2 × 100 mL). The solid was washed with ether (2 × 75 mL) and dried in vacuo to give **16k** (31.42 g, 78%) as a white solid: mp 217−218 °C (lit.[50] mp 222 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.38 (d, J = 6.2 Hz, 1H), 6.82 (d, J = 6.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.5 (q, J = 35.2, 34.8 Hz), 156.4, 153.3, 119.7 (q, J = 277.2 Hz), 99.8; ^{19}F NMR (282 MHz, DMSO-d_6) δ −69.97 (s, 3F); HRMS-APCI (m/z) [M + H]$^+$ calcd for $C_5H_3F_3N_2O$ 165.02702, found 165.02675.

2-Chloro-4-(trifluoromethyl)pyrimidine (16l). Phosphoryl trichloride (17 mL, 183 mmol) was added to 4-(trifluoromethyl)-pyrimidin-2-ol (**16k**) (10.00 g, 60.9 mmol) and heated at 65 °C for 4 h. The reaction mixture was poured on ice (150−200 g) and immediately extracted with hexane (3 × 75 mL). The organic layers were combined, washed with water (1 × 75 mL) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo to give **16l** (6.781 g, 61%) as a yellowish oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.91 (d, J = 4.9 Hz, 1H), 7.63 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 162.4, 162.2, 158.2 (q, J = 37.6 Hz), 119.7 (q, J = 275.5 Hz), 115.7 (q, J = 2.6 Hz); ^{19}F NMR (282 MHz, chloroform-*d*) δ −70.34 (s, 3F); HRMS-APCI (m/z) [M − H]$^-$ calcd for $C_5H_1ClF_3N_2$ 180.97858, found 180.97820.

2-Methoxy-4-(trifluoromethyl)pyrimidine (16m). 2-Chloro-4-(trifluoromethyl)pyrimidine (**16l**) (1.400 g, 7.67 mmol) was dissolved in dry methanol (10 mL) and sodium methoxide solution (from sodium (0.185 g, 8.05 mmol), and dry methanol (5 mL) was added dropwise. The mixture was stirred for 2 h at rt. The solids were removed by filtration, and the filtrate was diluted with dichloromethane (30 mL) and washed with water (3 × 20 mL). The aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo to give **16m** (1.149 g, 84%) as a yellowish oil: ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.77 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 4.8 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 166.0, 162.1, 157.8 (q, J = 36.6 Hz), 120.2 (q, J = 275.1 Hz), 110.5 (q, J = 2.6 Hz), 55.7; ^{19}F NMR (282 MHz, chloroform-*d*) δ −70.78 (s, 3F); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_6H_6F_3N_2O$ 179.04267, found 179.04250.

5-Methoxypyrimidine[51] (17a). Sodium methoxide solution prepared by the reaction of sodium (0.578 g, 25.2 mmol) with methanol (20.62 mL, 503 mmol) was added to 5-bromopyrimidine (2.000 g, 12.58 mmol), and the mixture was heated at 110 °C for 24 h in a sealed tube. After cooling, the mixture was poured to water (75 mL), and methanol was evaporated under reduced pressure. The mixture was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and washed with water (1 × 50 mL) and brine (1 × 25 mL), dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate = 5:1) to give **17a** (560 mg, 40%) as a yellow solid: mp 41−43 °C (lit.[51] mp 43 °C); ^{1}H NMR (300 MHz, chloroform-*d*) δ 8.80 (s, 1H), 8.36 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 153.5, 151.5, 143.2, 55.9; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_5H_7N_2O$ 111.05529, found 111.05517.

***N*-Ethylpyrimidine-5-carboxamide (17b).** Ethaneamine solution (70%, 2.6 mL, 2.117 g) in dry diethyl ether was added to ethyl pyrimidine-5-carboxylate (1.000 g, 6.57 mmol). The mixture was stirred at rt for 3 days, evaporated, and purified by column chromatography (dichloromethane/ethyl acetate = 5:1) to give **17b**

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(400 mg, 40%) as a beige solid: mp 74−75 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.24 (s, 1H), 9.08 (s, 2H), 7.00 (s, 1H), 3.46 (qd, *J* = 7.3, 5.6 Hz, 2H), 1.22 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 163.6, 160.4, 155.7, 128.2, 35.3, 14.8; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_7H_{10}N_3O$ 152.08184, found 152.08162.

Pyrimidine-5-carboxamide (17c). Ammonium hydroxide (25%, 7.59 mL, 49.3 mmol) was added to ethyl pyrimidine-5-carboxylate (1.5 g, 9.86 mmol), and the mixture was stirred at rt for 5 h. After approximately 0.5 h, the white solid was precipitated. The solid was collected by filtration and dried in vacuo, and the liquid portion was evaporated under reduced pressure and dried in vacuo to give 0.855 g (precipitate) and 0.35 g (evaporated liquid). The combined solids gave **17c** (1.205 g, 99%) as a white powder: mp 214−216 °C (lit.[38] mp 214 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (s, 1H), 9.18 (s, 2H), 8.34 (s, 1H), 7.82 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.7, 160.1, 156.1, 127.6; HRMS-ESI (*m*/*z*) calcd for $C_5H_6N_3O^+$ ($[M + H]^+$) 124.05054, found 124.05066.

Pyrimidine-5-carbonitrile (17d). Pyrimidine-5-carboxamide (**17c**) (1.16 g, 9.42 mmol) was dissolved in dry *N*,*N*-dimethylformamide (15 mL), and phosphoryl trichloride (2.6 mL, 28.3 mmol) was added dropwise during 0.5 h at 15 °C. The mixture was allowed to stir overnight at rt. Water (150 mL) was added, and the pH was adjusted to 6 by the addition of sodium bicarbonate. The mixture was extracted with diethyl ether (3 × 75 mL). The organic layers were combined and washed with water (2 × 50 mL) and brine (1 × 50 mL), dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography (dichloromethane/ethyl acetate = 10:1) to give **17d** (232 mg, 24%) as a white solid: mp 83−84 °C (lit.[38] mp 85−86 °C); ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.40 (s, 1H), 9.02 (s, 2H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 160.6, 159.6, 114.2, 110.3; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_5H_4N_3$ 106.03997, found 106.04002.

5-Nitropyrimidine-2,4-diol[52] (17e). Pyrimidine-2.4-diol (15 g, 134 mmol) was dissolved in nitric acid (95%) (60 mL, 1.428 mol), and sulfuric acid (7.5 mL, 138 mmol) was added. The mixture was heated at 60 °C for 4 h and then poured on ice. The solid was collected by filtration, washed with ice-cold water (2 × 50 mL), and dried in vacuo at 50 °C to give **17e** (17.38 g, 83%) as a yellowish solid: mp 305−308 °C (lit.[52] mp 294−295 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 11.77 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.5, 149.8, 147.9, 125.1; HRMS-ESI (*m*/*z*) $[M - H]^-$ calcd for $C_4H_2N_3O_4$ 156.00508, found 156.00444.

2,4-Dichloro-5-nitropyrimidine[53] (17f). *N*,*N*-Dimethylaniline (18 mL, 142 mmol) was added at rt to phosphoryl trichloride (75 mL, 802 mmol), and 5-nitropyrimidine-2,4-diol (**17e**) (15 g, 95 mmol) was added during 5 min. The mixture was heated at 110 °C for 4 h. The excess phosphoryl trichloride was removed by vacuum distillation, and the dark residue was poured on ice. The mixture was quickly extracted with diethyl ether (4 × 150 mL). The organic layers were combined, dried with sodium sulfate overnight, and concentrated in vacuo to give crude oily product. The crude material was distilled by vacuum distillation (84−85 °C/1 Torr; lit.[53] 138−139 °C/14 Torr) to give **17f** (12.79 g, 69%) as a yellow oil: ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.17 (s, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 162.8, 156.6, 155.7.

2,4-Dihydrazinyl-5-nitropyrimidine[54] (17g). Hydrazine hydrate (65%, 17.5 mL, 563 mmol) was added to diethyl ether (750 mL). A solution of 2,4-dichloro-5-nitropyrimidine (**17f**) (9.7 g, 50.0 mmol) in diethyl ether (150 mL) was added. The mixture was stirred for 15 min, and the brown solid was filtered, washed with water (2 × 25 mL), ethanol (2 × 15 mL), and diethyl ether (2 × 25 mL), and dried in vacuo to give **17g** (7.59 g, 82%) as a brown solid: mp 258−263 °C (lit.[54] mp 270 °C dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (brs, 1H), 8.75 (s, 1H), 5.06 (brs, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 157.0, 152.7, 117.4; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_4H_8N_7O_2$ 186.07340, found 186.07309.

5-Nitropyrimidine[55] (17h). Silver carbonate (3.30 g, 11.97 mmol) was suspended in water (10 mL), acetic acid (1.427 g, 23.76 mmol) was added, and the mixture was stirred for 1 h. 2,4-Dihydrazinyl-5-nitropyrimidine (**17g**) (1.00 g, 5.40 mmol) was added to the resulting suspension and stirred for 5 min. Chloroform (50 mL) was added, and the mixture was stirred for 1.5 h. The solution was neutralized with sodium bicarbonate, and the chloroform layer was separated. The aqueous layer was extracted with chloroform (2 × 50 mL). The organic layers were combined, dried with magnesium sulfate, and evaporated. The crude solid was purified by column chromatography (dichloromethane/ethyl acetate = 10:1) to give **17h** (141 mg, 21%) as a yellowish solid: mp 54−56 °C (lit.[55] mp 57−58 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.52 (s, 2H), 9.50 (s, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 162.5, 152.5, 142.6; HRMS-ESI (*m*/*z*) $[M]^-$ calcd for $C_4H_3N_3O_2$ 125.02307, found 125.02233.

***N*,*N*,*N*′,*N*′-Tetraethylpyridine-3,5-dicarboxamide[56] (18a).** Pyridine-3,5-dicarboxylic acid (1.0 g, 6.0 mmol) was suspended in thionyl chloride (17 mL), and *N*,*N*-dimethylformamide (3 drops) was added. The mixture was heated to reflux until the acid was dissolved and then for an additional 1 h. The excess of thionyl chloride was removed in vacuo. The resulting acyl chloride was dissolved in benzene (27 mL), and the solvent was evaporated under reduced pressure. A mixture of diethylamine (1.75 g, 24.0 mmol) in dichloromethane (20 mL) was cooled to 0 °C. The solution of pyridine-3,5-dicarbonyl dichloride in dichloromethane (15 mL) was slowly added. After the addition was complete, the solution was stirred at room temperature for 30 min. After addition of 1 M sodium hydroxide solution (10 mL), the layers were separated. The aqueous layer was saturated with sodium chloride and extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (1 × 10 mL), dried with sodium sulfate, and concentrated in vacuo The crude product was purified by recrystallization (diethyl ether) to give **18a** (715 mg, 48%) as white crystals: mp 76−77 °C (lit.[56] mp 81−81.5 °C); ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.64 (d, *J* = 2.1 Hz, 2H), 7.71 (td, *J* = 2.1, 0.5 Hz, 1H), 3.53 (brs, 4H), 3.24 (brs, 4H), 1.23 (brs, 6H), 1.12 (brs, 6H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 167.9, 147.7, 132.9, 132.7, 43.6 (brs), 39.7 (brs), 14.4 (brs), 12.9 (brs); HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{23}N_3O_2$ 278.18630, found 278.18608.

***N*,*N*′-Diethylpyridine-3,5-dicarboxamide[56] (18b).** Pyridine-3,5-dicarboxylic acid (1.0 g, 6.0 mmol) was suspended in thionyl chloride (17 mL), and *N*,*N*-dimethylformamide (3 drops) was added. The mixture was heated to reflux until the acid was dissolved and then for an additional 1 h. The excess of thionyl chloride was removed in vacuo. The resulting acyl chloride was dissolved in benzene (27 mL) and evaporated under reduced pressure. The mixture of ethylamine (1.6 mL, 24.0 mmol) in dichloromethane (20 mL) was cooled to 0 °C, and the solution of pyridine-3,5-dicarbonyl dichloride in dichloromethane (15 mL) was slowly added. After the addition was complete, the solution was stirred at rt for 40 min. After addition of 1 M sodium hydroxide solution (10 mL), the layers were separated. The aqueous layer was saturated with sodium chloride and extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (1 × 10 mL), dried with sodium sulfate, and concentrated in vacuo.The crude product was purified by crystallization (chloroform−diethyl ether) to give **18b** (660 mg, 50%) as white crystals: mp 158−162 °C (lit.[56] mp 160−164 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.08 (s, 2 H), 8.49 (d, *J* = 1.5 Hz, 1 H), 6.95 (s, 2 H), 3.52 (m, 4 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 165.0, 150.4, 133.6, 130.1, 35.2, 14.7; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{11}H_{16}N_3O_2$ 222.12370, found 222.12370.

Diethyl Pyridine-3,5-dicarboxylate[56] (18c). A stirred suspension of pyridine-3,5-dicarboxylic acid (0.6 g, 3.6 mmol) in dry ethanol (6 mL) was cooled to −5 °C. Thionyl chloride (1.2 mL, 16.2 mmol) was added slowly to the suspension, maintaining the temperature below 5 °C. After the addition was completed, the mixture was heated to reflux for 2 h. The solvent was removed at reduced pressure, dichloromethane (1 mL) with tetrachloromethane (1.6 mL) were added, and the mixture was heated to reflux for 2 h. Dichloromethane (30 mL) was added, and the organic layer was washed with a 10% sodium bicarbonate solution (1 × 20 mL) and water (1 × 20 mL). The organic layer was dried with magnesium sulfate and concentrated in vacuo. Crude product was purified by crystallization (hexane) to

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give **18c** (278 mg, 36%) as white crystals: mp 48.5−49 °C (lit.[56] mp 48−50 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 (d, J = 2.0 Hz, 2 H), 8.63 (t, J = 2.0 Hz, 1 H), 4.39 (q, J = 7.1 Hz, 2 H), 1.36 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.8, 153.5, 136.8, 125.9, 61.6, 14.0; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{14}NO_4$ 224.09173, found 224.09156.

Pyridine-3,5-dicarboxamide[57] (18d). Pyridine-3,5-dicarboxylic acid (2 g, 12 mmol) was suspended in dichloromethane (25 mL). Thionyl chloride (5.3 mL) and *N*,*N*-dimethylformamide (3 drops) were added, and the resulting mixture was heated to reflux until the acid dissolved and then for additional 1 h. The solvent and the excess of thionyl chloride were removed in vacuo. The resulting acyl chloride was dissolved in benzene (27 mL) and evaporated under reduced pressure. The solid was dissolved in dioxane (30 mL), and aqueous ammonia (75 mL) was added. After 30 min, the white precipitate was collected by filtration, washed with water (1 × 10 mL), and dried in vacuo to give **18d** (1.8 g, 88%) as a white solid: mp 311−315 °C (lit.[58] mp 318−319 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.12 (d, J = 1.95 Hz, 2 H), 8.64 (s, 1 H), 8.25 (s, 2 H), 7.68 (s, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.0, 150.7, 134.4, 129.5; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_7H_8N_3O_2$ 166.06110, found 166.06096.

Pyridine-3,5-dicarbonitrile[59] (18e). Pyridine-3,5-dicarboxamide (1.73 g, 10.48 mmol) was dissolved in *N*,*N*-dimethylformamide. Phosphoryl trichloride (5.4 mL) was added, and the mixture was stirred for 2 h at room temperature and allowed to stand overnight. The excess of phosphoryl trichloride was quenched with water (190 mL). The mixture was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by recrystallization (isopropyl alcohol) to give **18e** (980 mg, 73%) as a white crystalline solid: mp 109−111 °C (lit.[59] mp 111−113 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.10 (d, J = 1.9 Hz, 2 H), 8.29 (t, J = 2.0 Hz, 1 H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 155.3, 142.6, 114.8, 111.1; HRMS-ESI (m/z) [M-H]$^-$ calcd for $C_7H_2N_3$ 128.02542, found 128.02502.

3,5-Dinitropyridine[60] (18f). 2-Chloro-3,5-dinitropyridine (2.00 g, 9.83 mmol) was suspended in methanol (20 mL) and cooled to 0 °C. Hydrazine hydrate (0.77 mL, 14.74 mmol) was added during 10 min, and the mixture was allowed to reach rt and stirred overnight. The dark red solid was collected by filtration, washed with methanol (2 × 10 mL), and dried in vacuo. 2-Hydrazinyl-3,5-dinitropyridine was isolated in almost quantitative yield and used without any purification: HRMS (ESI) calcd for $C_5H_5N_5O_4^-$ ([M]$^-$) 199.03470, found 199.03437. 2-Hydrazinyl-3,5-dinitropyridine (1.94 g, 9.73 mmol) was suspended in water (100 mL), and silver nitrate (5.01 g, 29.5 mmol) was added. The mixture was heated to reflux for 5 h, cooled, and extracted with dichloromethane (4 × 50 mL). The organic layers were combined, washed with ammonia solution (25%) (2 × 25 mL), water (1 × 50 mL), and brine (1 × 25 mL), and dried with sodium sulfate. Crude product was purified by column chromatography (dichloromethane/ethyl acetate = 10:1) to give **18f** (0.53 g, 32%) as a yellowish solid: mp 98−101 °C (lit.[60] mp 106 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (d, J = 2.3 Hz, 2H), 9.13 (t, J = 2.3 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.5, 144.1, 127.0; HRMS-ESI (m/z) [M]$^-$ calcd for $C_5H_3N_3O_4$ 169.01290, found 169.01245.

Pyridine-2,5-dicarboxamide[57] (18g). Pyridine-2,5-dicarboxylic acid (2.0 g, 12 mmol) was suspended in dichloromethane (25 mL). Thionyl chloride (5.3 mL) and *N*,*N*-dimethylformamide (3 drops) were added, and the resulting mixture was heated to reflux until the acid dissolved and then for an additional 1 h. The solvent and the excess of thionyl chloride were removed in vacuo. The resulting pyridine-2,5-dicarbonyl dichloride was dissolved in benzene (27 mL), and the solvent was evaporated under reduced pressure. The solid was dissolved in dioxane (30 mL), and aqueous ammonia (75 mL) was added. After 30 min, the white precipitate was collected by filtration, washed with water, and dried in vacuo to give **18g** (1.72 g, 87%) as a white solid: mp 314−316 °C (lit.[61] mp 300 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.37 (dd, J = 8.1, 2.2 Hz, 1H), 8.29 (s, 1H), 8.22 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.75 (s, 1H), 7.73 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 165.4, 152.1, 147.7, 136.7, 131.7, 121.6; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_7H_8N_3O_2$ 166.06110, found 166.06094.

Pyridine-2,5-dicarbonitrile[62] (18h). Pyridine-2,5-dicarboxamide (**18g**) (1.1 g, 6.7 mmol) was dissolved in *N*,*N*-dimethylformamide (70 mL), and phosphoryl trichloride (3.7 mL, 40 mmol) was added. The mixture was stirred for 4 h at room temperature and then allowed to stand overnight. The excess of the phosphoryl trichloride was quenched with water (160 mL). The mixture was neutralized with sodium bicarbonate and extracted with diethyl ether (3 × 100 mL). The organic layers were combined, dried with sodium sulfate, and concentrated in vacuo. The crude product was purified by recrystallization (water) to give **18h** (550 mg, 64%) as a white crystalline solid: mp 108−110 °C (lit.[61] mp 112−113 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 9.00−8.97 (m, 1H), 8.15 (dd, J = 8.1, 2.1 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 152.2, 140.6, 136.6, 128.2, 115.8, 115.0, 113.1; HRMS-ESI (m/z) [M]$^-$ calcd for $C_7H_3N_3$ 129.03215, found 129.03262.

Pyridine-2,6-dicarboxamide[56] (18i). Pyridine-2,6-dicarboxylic acid (2.0 g, 12 mmol) was suspended in dichloromethane (25 mL). Thionyl chloride (5.3 mL) and *N*,*N*-dimethylformamide (3 drops) were added, and the resulting mixture was heated to reflux until the acid dissolved and then for an additional 1 h. The solvent and the excess of thionyl chloride were removed in vacuo. The resulting pyridine-2,6-dicarbonyl dichloride was dissolved in benzene (27 mL) and evaporated under reduced pressure. The solid was dissolved in dioxane (30 mL), and aqueous ammonia (75 mL) was added. After 30 min, the white precipitate was collected by filtration, washed with water (1 × 10 mL), and dried in vacuo to give **18i** (1.46 g, 74%) as a white solid: mp 311−313 °C (lit.[63] mp 305−306 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 2 H), 8.13−8.20 (m, 3 H), 7.71 (s, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.8, 149.5, 139.6, 124.6; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_7H_7N_3O_2Na$ 188.04305, found 188.04291.

Pyridine-2,6-dicarbonitrile[62] (18j). Pyridine-2,6-dicarboxamide (**18i**) (1.45 g, 8.8 mmol) was dissolved in dry *N*,*N*-dimethylformamide (92 mL). Phosphoryl trichloride (4.9 mL, 52.5 mmol) was added, and the mixture was stirred for 4 h at rt and then allowed to stand overnight. The excess of phosphoryl trichloride was quenched with water (200 mL). The mixture was neutralized with sodium bicarbonate and extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified by crystallization (propan-2-ol) to give **18j** (768 mg, 68%) as a white crystalline solid: mp 124−125 °C (lit.[62] mp 123−124 °C); ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.10 (t, J = 7.9 Hz, 1 H), 7.95 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (126 MHz, chloroform-*d*) δ 138.9, 135.4, 131.1, 115.4; HRMS-APCI (m/z) [M]$^-$ calcd for $C_7H_3N_3$ 129.03215, found 129.03253.

Kinetic Measurements. The catalyst (0.004 mmol) and thioanisole **9a** (0.200 mmol) were dissolved in methanol-d_4 (600 μL). The solution was transferred into an NMR tube and thermostated for 15 min (or 3 h in the case of **4h**) at 25.0 ± 0.5 °C. The reaction was started by the addition of hydrogen peroxide (30%, 31 μL, 0.300 mmol). In the blank experiments, no catalyst was present, and the hydrogen peroxide was added to a solution of the substrate in methanol-d_4. The reaction was monitored by ^{1}H NMR (signals of methyl group) until at least 90% conversion was achieved.

Preparative Sulfoxidations. The substrate (100 mg) and the catalyst (1 or 5 mol %) were dissolved in methanol (2 mL). The solution was thermostated for 20 min at 25.0 ± 0.5 °C, and the reaction was initiated by the addition of hydrogen peroxide (30% aqueous solution; 1.5 equiv). The reaction mixture was stirred at 25.0 ± 0.5 °C, and the course of the reaction was monitored by TLC using dichlormethane/ethyl acetate (10:1) as a mobile phase. After complete conversion was achieved (or after 24 h in the case of substrates more difficult to oxidize), sodium sulfite (100 mg) was added to quench the excess of hydrogen peroxide. Most of the solvents were evaporated under reduced pressure, and the residue was dissolved in water (6 mL) and dichloromethane (6 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (4 × 6 mL). The combined organic phases were washed with brine (10 mL) and dried

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over magnesium sulfate. The solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography (dichloromethane/ethyl acetate 10:1). The products were characterized by ^{1}H NMR spectra which corresponded to those published in the literature (see the Supporting Information).[10a,64]

pK_{R+} Values. The pK_{R+} values representing heteroarenium salt/pseudobase equilibrium in water were calculated by nonlinear regression analysis of absorbance versus pH data at the maximum absorption wavelengths of salt **Het$^+$** and its pseudobase **Het-OH**. The pH of the systems was adjusted by perchloric acid (for pH < 1.6), phosphate buffers (for pH 1.6−7.2 and 9.4−12.0), and borate buffers (for pH 7.3−8.9).

Electrochemical Measurements. The electrochemical measurements were performed using a standard three-electrode system in a methrom-type electrochemical cell with a stationary platinum disk working electrode (diameter 1 mm). The saturated calomel reference electrode was separated from the investigated aprotic solution by a glass frit and a salt bridge filled with the same electrolyte. A platinum wire served as an auxiliary electrode. The cyclic voltammetry measurements were carried out in acetonitrile containing a heteroarenium salt ($c = 1 \times 10^{-3}$ mol L^{-1}) and tetrabutylammonium hexafluorophosphate ($c = 1 \times 10^{-1}$ mol L^{-1}) as supporting electrolyte under argon atmosphere The scan rate was 100 mV s^{-1} The measured reduction potentials were corrected using ferrocene/ferrocenium as a standard.

Computational Details. Quantum chemistry calculations were carried out using the Gaussian 09 program, revision D.01.[65] All geometries were fully optimized without geometry constraints at the DFT level of theory using the B3LYP functional[66a] and 6-311++g(d,p) basis set and ultrafine grid for integral evaluation. It should be noted that the computed energies with geometries from B3LYP calculations using other functionals (BMK,[66b] MN12SX,[66c] PBE0,[66d] M062X[66e]) with the same basis set follow a similar trend (see the Supporting Information), but absolute values are higher than those for B3LYP by about 20 kJ/mol for MN12SX and PBE0, 40 kJ/mol for BMK, and 50 kJ/mol for M062X functional. Methanol as a solvent was approximated by the CPCM model of solvation.[67] Vibrational frequency calculations at the same level of theory were performed to characterize stationary points as minima or transition structures (first-order saddle point), where the only imaginary frequency corresponds to oxygen transfer from heteroarenium hydroperoxide to sulfide **9a**, forming methyl phenyl sulfoxide (**10a**) bound to heteroarenium hydroxide. The prereaction complexes of thioanisole (**9a**) and heteroarenium hydroperoxide were optimized to minima that were chosen by analysis of different orientations of thioanisole and hydroperoxide, and then the corresponding transition state was calculated. It should be noted that the energy difference between at least three geometries is below 1 kJ/mol. All Gibbs free energies are calculated at 298 K, include ZPE correction and gas phase thermochemistry, and are not scaled.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra of all new compounds including assignment of the signals, copies of NMR spectra of precursors and the prepared sulfoxides, UV−vis spectra, pK_{R+} evaluation, electrochemical data for heteroarenium salts and sulfoxidations in the presence of TEMPO and computational data. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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