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Pyrazinium Salts as Efficient Organocatalysts of Mild Oxidations with Hydrogen Peroxide

Petra Ménová,[a,b] František Kafka,[a,b] Hana Dvořáková,[c] Smita Gunnoo,[a,d] Miloslav Šanda,[b] and Radek Cibulka[a,*]

[a] Department of Organic Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic
Fax: (+420)-220-444-288; phone: (+420)-220-444-279; e-mail: cibulkar@vscht.cz
[b] Institute of Organic Chemistry and Biochemistry, Academy of Science of the Czech Republic, v.v.i., Flemingovo nám. 2, 166 10, Prague 6, Czech Republic
[c] Central Laboratories, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic
[d] Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, U.K.

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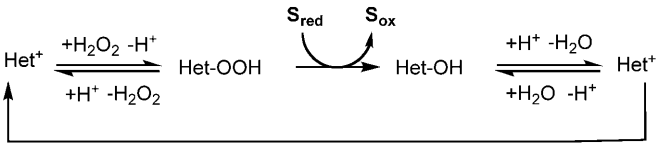
Abstract: A series of 3-substituted pyrazinium tetrafluoroborates was prepared as simple analogues of flavinium salts which are efficient organocatalysts for oxidations with hydrogen peroxide. It was shown that pyrazinium derivatives with an electron-withdrawing substituent catalyze mild oxidations of sulfides to sulfoxides and Baeyer–Villiger oxidations in a similar way to flavinium catalysts. The most reactive catalyst, 3-cyanopyrazinium tetrafluoroborate, was efficiently employed in preparative sulfoxidations of aromatic and aliphatic sulfides as well as in Baeyer–Villiger oxidations of cyclobutanones. A proposed mechanism for the catalysis is based on the formation of pyrazine hydroperoxide which is the agent oxidizing the substrate.

Keywords: Baeyer–Villiger oxidation; organocatalysis; peroxides; pyrazinium salts; sulfoxidation

Over the last two decades, organocatalytic oxidations using hydrogen peroxide as a terminal oxidant have been intensively investigated due to their potential applications in green chemistry.[1] One promising type of organocatalytic system is based on heteroarenium salts. They activate hydrogen peroxide *via* the formation of heterocyclic hydroperoxides which oxidize a substrate. After the oxygen transfer, heteroarenium salts are regenerated by the elimination of the hydroxy function (Scheme 1).[2] The use of heterocyclic hydroperoxides for oxidations is inspired by nature; flavin-4a-hydroperoxide and pterin-4a-hydroperoxide

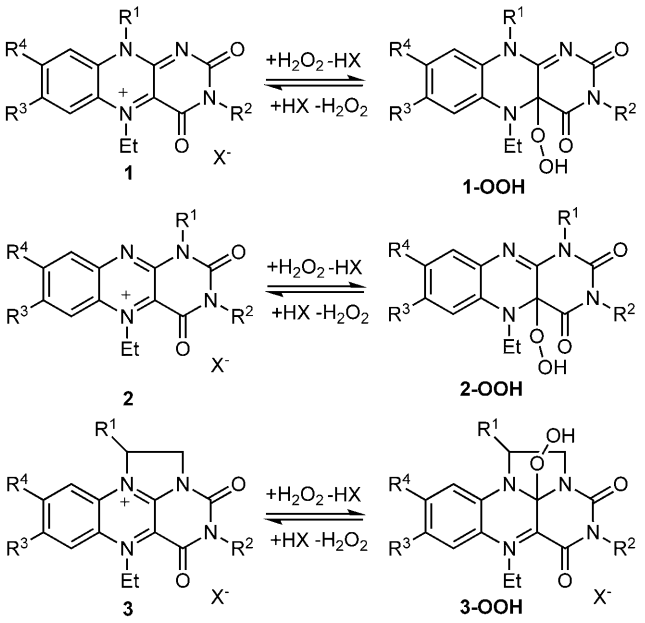


Scheme 1. Catalytic function of heteroarenium salts in the oxidation of a substrate **S** with hydrogen peroxide.

are the oxidizing agents in flavin- and pterin-dependent monooxygenases, respectively.[3]

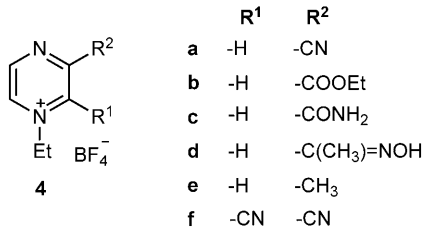
Although the formation and reactivity of various heterocyclic peroxides have already been described,[4] only flavinium salts[5] **1–3** (Scheme 2) have been systematically studied as catalysts for H_2O_2 oxidations.[2,6] It was found that flavinium salts catalyze H_2O_2 oxidations of sulfides to sulfoxides,[7] cyclobutanones to the corresponding lactones (Baeyer–Villiger oxidations),[8] secondary amines to nitrones[7a] and tertiary amines to *N*-oxides.[9] These reactions proceed under mild conditions with low catalyst loading (1–2 mol%). Several chiral flavinium salts were efficiently employed in enantioselective oxidations of prochiral sulfides and ketones.[10]

Flavinium salts **1–3** participate in catalysis by the reversible addition of hydrogen peroxide to either the azadiene group in isoalloxazine derivatives **1** or the central pyrazinium ring in alloxazines **2** and **3** (Scheme 2). Thus, these substructures seem to be essential for the catalytic function of flavinium salts. This idea led us to explore the catalytic ability of pyrazinium derivatives **4** as simpler structurally related analogues of the alloxazinium skeletons **2** and **3**. The advantage of pyrazinium salts is that they can be ob-



Scheme 2. Structures of flavinium salts and the corresponding flavin hydroperoxides.

tained from commercially available starting materials in only one step – quaternization.



	R^1	R^2
a	-H	-CN
b	-H	-COOEt
c	-H	$-CONH_2$
d	-H	$-C(CH_3)=NOH$
e	-H	$-CH_3$
f	-CN	-CN

4

In the first series of experiments, the ability of pyrazinium salts to catalyze oxidations with hydrogen peroxide was examined using the sulfoxidation of thioanisole as a model reaction. We have also explored the effect of substituents on the catalytic activity. Experiments were performed with 5 mol% of the catalyst under identical conditions to those used for oxidations catalyzed by flavinium salts, that is, in deuterated methanol at room temperature using 1.5 equivalents of aqueous hydrogen peroxide.[7] Conversion was monitored by ^{1}H NMR spectroscopy. In Figure 1, the kinetic profiles of sulfoxidations catalyzed by **4a–f** are compared with that of the non-catalyzed process.

The results show that pyrazinium salts bearing an electron-withdrawing group accelerate the sulfoxidation of thioanisole. Whilst the rate enhancement by **4c** and **4d** is relatively low, derivatives **4a** and **4b** with cyano and ethoxycarbonyl substituents accelerate the oxidation significantly. Interestingly, salt **4e** bearing an electron-donating methyl group has a negligible

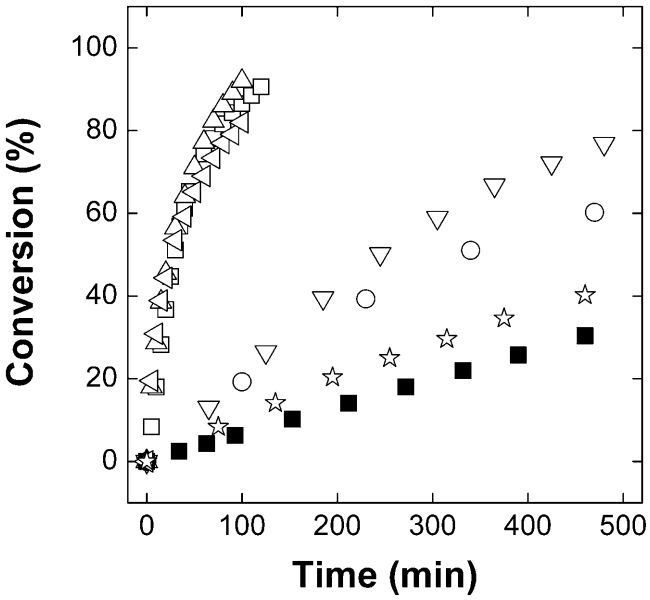
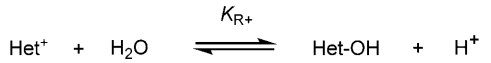


Figure 1. Course of the oxidation of thioanisole with H_2O_2 catalyzed by pyrazinium salts **4a** (△), **4b** (□), **4c** (▽), **4d** (○), **4e** (☆), and **4f** (◁). The non-catalyzed reaction (■) is shown for comparison. *Conditions:* n(thioanisole) = 0.255 mmol, $n(H_2O_2)$ = 0.392 mmol, n(**4**) = 12.8 μmol, T = 25 °C, solvent = CD_3OD/H_2O (see Experimental Section for full details).

effect on the rate of oxidation. We also tested the catalytic activity of the 2,3-dicyano derivative **4f** but the effect of the second cyano group on the observed efficiency was rather negative. At the beginning, the rate of reaction catalyzed by **4f** slightly exceeds the rate of reaction catalyzed by **4a** (Figure 1), but at conversions higher than 50% it decelerates due to the decomposition of **4f** in the catalytic system.

As a test to investigate whether both nitrogen atoms in the ring are necessary for catalytic activity of heteroarenium salts, sulfoxidations were performed with analogous pyridinium derivatives **5**. It was found that the rate of thioanisole oxidation was not enhanced with these salts even if they are substituted with an electron-withdrawing cyano group (for details see the Supporting Information). The inability of pyridinium salts **5** (in comparison with pyrazinium derivatives **4**) to catalyze sulfoxidations with hydrogen peroxide is probably caused by the substantially lower electrophilicity of the pyridinium *vs.* the pyrazinium nucleus which precludes the formation of the oxidative species, pyridine hydroperoxide, under the reaction conditions. The lower ability of pyridinium salts to react with nucleophiles can be easily demonstrated by their higher pK_{R+} values[11] representing the heteroarenium salt/pseudobase equilibrium (Table 1), that is, the ability of a heteroarenium salt to add a hydroxide ion. While the pK_{R+} value of the efficient pyrazinium salt **4a** (for the determination see the Supporting Information) fits well to those known for flavini-

Table 1. The pK_{R+} values for heteroarenium salt/pseudobase equilibrium.



Heteroarenium salt	pK_{R+}
1a	4.1[a]
2a	7.9[b]
4a	4.5
5b	12.2[c]

[a] Ref.[12a].
[b] Ref.[7h].
[c] Ref.[12b].

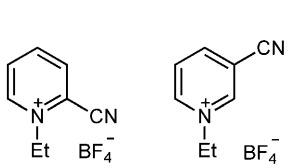
Table 2. Comparison of the catalytic activity of the pyrazinium salt **4a** with that of the alloxazine derivative **2a-H$_2$** in H_2O_2 sulfoxidations.[a]

Entry	Catalyst	Substrate	Rate enhancement[b]
1	**4a**	Ph–S–CH_3	30:1
2	**2a-H$_2$**	Ph–S–CH_3	64:1
3	**4a**	4-MeC_6H_4–S–CH_3	38:1
4	**2a-H$_2$**	4-MeC_6H_4–S–CH_3	74:1[c,d]
5	**4a**	4-MeOC_6H_4–S–CH_3	18:1
6	**2a-H$_2$**	4-MeOC_6H_4–S–CH_3	36:1[c,e]
7	**4a**	Bu–S–Bu	10.5:1
8	**2a-H$_2$**	Bu–S–Bu	12.5:1[c,e]

[a] *Reaction conditions:* n(substrate) = 0.255 mmol, $n(H_2O_2)$ = 0.392 mmol, 2 mol% catalyst, T = 25 °C.
[b] Rate enhancement for catalyzed *vs.* non-catalyzed reactions calculated by dividing the rate of the catalyzed reaction by that of the non-catalyzed reaction at low conversion (up to 10%).[7]
[c] Ref.[7b].
[d] 1.83 mol% catalyst.
[e] 1.60 mol% catalyst.

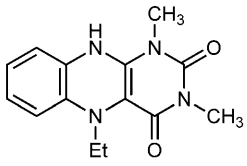
um catalysts **1a** ($R^1 = R^2 = R^3 = R^4 = CH_3$) and **2a** ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$), the value for analogous the 3-cyanopyridinium derivative **5b** is substantially higher. The lower electrophilicity of pyridinium salts in comparison with pyrazinium salts is also evident from thereduction potentials which are less negative for pyrazinium compounds (by about 550 mV).[13]

The catalytic activity of the pyrazinium salt **4a** was compared with that of an already known[7b–d] alloxazinium salt **2a** with the same pyrazinium core. Since alloxazinium salts **2** are not used directly as catalysts of H_2O_2 oxidations but are generated *in situ* from the corresponding dihydro forms **2-H$_2$**,[7b–d] the data for **2a-H$_2$** were taken into account for comparison. Table 2 shows that for aromatic substrates (entries 1–6), the catalytic efficiency of **4a** is approximately one half of that of **2a** generated from its dihydro derivative. The rate enhancement for dibutyl sulfide oxidation by **4a** is almost identical to that by **2a**.



5a

5b



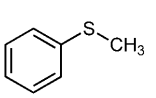
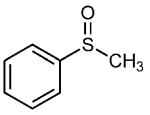
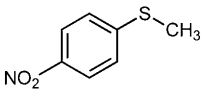
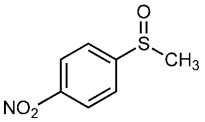
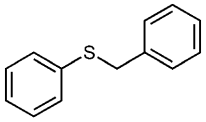
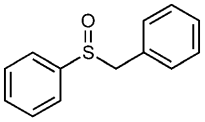
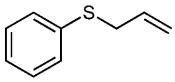
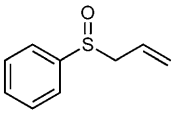
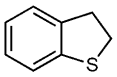
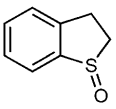
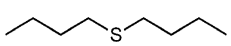
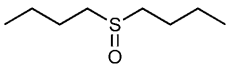
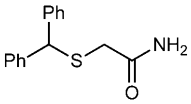
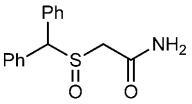
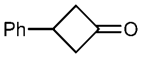
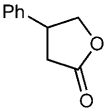
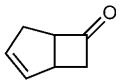
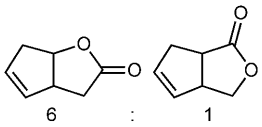
2a-H$_2$

The scope of application of the most active pyrazinium catalyst **4a** for H_2O_2 sulfoxidations was tested on a variety of sulfides on a 100-mg scale (Table 3). Using 5 mol% of **4a**, complete conversion of all the tested substrates was achieved within a relatively short time (20 min–24 h). Work-up of the reaction mixture was simple; the pure product without any traces of the catalyst was obtained by simple extraction in high yields. Similarly, as in the sulfoxidations catalyzed by flavinium salts[7], the reactions catalyzed by **4a** proceeded chemoselectively. Neither over-oxidation to sulfones, nor oxidation of the double bond (in allyl phenyl sulfide; Table 3, entry 4) was observed. The significant effect of the catalyst **4a** on the oxidations is evident by comparing conversions of the catalyzed and the non-catalyzed process after the same reaction time. For instance, the catalyzed oxidation of thioanisole (entry 1) and dihydrobenzothiophene (entry 5) was completed within 1 hour, the aliphatic dibutyl sulfide (entry 6) was oxidized within 20 min. After the same time, conversion of non-catalyzed processes did not exceed 4% and 1%, respectively. Conversely, the effect of the catalyst **4a** on the oxidation of the relatively electron-poor substrate *p*-nitrothioanisole (Table 3, entry 2) is much smaller. From the point of view of potential practical applications, an interesting result was obtained with the oxidation of (diphenylmethylthio)acetamide (a precursor of the psychostimulant Modafinil[14]; entry 7). After 24 h, the desired product Modafinil was obtained in a quantitative yield with the catalyzed process, whilst the yield of the non-catalyzed oxidation was only 4%.

Having observed promising catalytic activity of **4a** in sulfoxidations, we decided to test the catalyst also in Baeyer–Villiger oxidations of cyclobutanones in *t*-BuOH.[8a] The catalyst has a significant effect at loadings of 2 mol% (Table 3, entries 8 and 9). For the oxidation of bicyclo[3.2.0]heptenone (entry 9), a good regioselectivity with an excess of the "normal" lactone[15] was achieved.

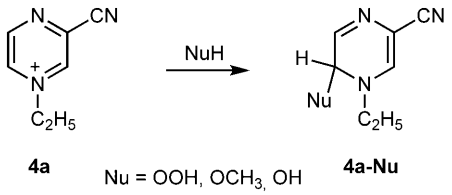
In order to prove the existence and structure of pyrazine hydroperoxide **4a-OOH** as the active oxidizing agent, a series of pyrazine adducts **4a-Nu** was prepared with hydrogen peroxide, methanol and water (Scheme 3). Due to their instability, the adducts were prepared *in situ* following a previously reported pro-

Table 3. Preparative H_2O_2 oxidations catalyzed by 5 mol% of pyrazinium salt **4a**.[a]

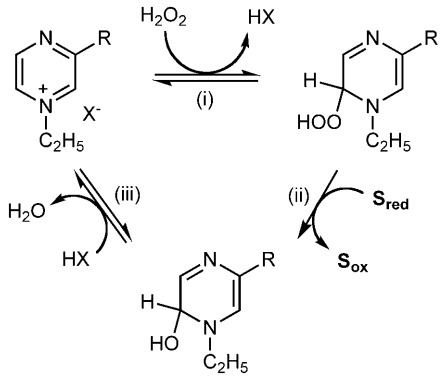
Entry	Substrate	Product	Time [h][b]	Conv. [%][c]	Yield [%][d]	Blank conv. [%][e]
1			1	100	90	4
2			24	96	88	37
3			8	99	96	10
4			6	100	84	6
5			1	100	95	4
6			0.3	100	94	1
7			24	100	92	4
8[f]			1	100	75	17
9[f]			0.4	100	91	20
		6 : 1				

[a] *Conditions for the preparative oxidations: m*(substrate) = 100 mg, 1.5 equiv. H_2O_2, 5 mol% catalyst, T = 25 °C.
[b] Reactions were performed until quantitative conversion was achieved (TLC monitoring).
[c] Conversions are based on ^{1}H NMR spectra.
[d] Isolated yields.
[e] Conversions of the non-catalyzed reactions after the same reaction time.
[f] 2 mol% of the catalyst.

cedure for adducts of flavinium salts,[7i,16] that is, by the addition of a nucleophile into the solution of the pyrazinium salt **4a** in pyridine (see the Supporting Information for details). The existence of **4a-Nu** adducts was confirmed by MS and NMR. After the addition of the nucleophile to the solution of the pyrazinium salt **4a** in pyridine-d_5, one signal of a hydrogen atom on the heterocyclic ring shifted from the aromatic region to 5.5 ppm, and the signals of the two remaining, originally heteroarenium, hydrogen atoms shifted upfield by about 2 ppm. Furthermore, the N–CH_2 signal (originally a quartet) split into two multiplets, which indicates the presence of a chiral centre close to the CH_2 group. A large upfield shift (from 143 to 57–80 ppm) of a carbon atom signal in ^{13}C NMR was also observed confirming the change of the carbon hybridization from sp^2 to sp^3. The attack of the nucleophile at position 6 of the pyrazinium ring (attack at position 2 could also be expected) was confirmed by



Scheme 3. Formation of pyrazine adducts with nucleophiles.



Scheme 4. Proposed mechanism of H_2O_2 oxidations catalyzed by pyrazinium salts **4**.

NOE experiments with the methoxy adduct **4a-OCH$_3$** (see the Supporting Information).

The proposed mechanism of sulfoxidations catalyzed by pyrazinium salts **4** is analogous to that in the presence of flavinium catalysts: (i) formation of pyrazine hydroperoxide **4-OOH**, (ii) oxidation of the substrate accompanied by the formation of the pseudobase **4-OH**, and (iii) regeneration of the catalyst by the elimination of a hydroxy function (see Scheme 4). Murahashi found[7a] that the rate-limiting step in N- and S-oxidations catalyzed by isoalloxazinium salt **1a** is the elimination of hydroxy group (step iii). This step is proposed to be much faster in oxidations catalyzed by alloxazinium derivatives **2** (with a pyrazinium core) due to the formation of a fused aromatic system.[7b] According to the values of pK_{R+} (see Table 1) representing the third (equilibrium) step of the catalytic cycle, the formation of a salt from its pseudobase seems to be disfavoured for pyrazinium salt **4a** (and most likely for all other pyrazine derivatives with an electron-withdrawing substituent) similarly as for isoalloxazinium salts **1**. Therefore, a slow elimination step (iii) is expected in sulfoxidations catalyzed by **4a**.

In conclusion, it has been shown that pyrazinium salts substituted with an electron-withdrawing group catalyze the oxidation of sulfides to sulfoxides and the Baeyer–Villiger oxidation of cyclobutanones with hydrogen peroxide under mild conditions. The catalytic activity of the most efficient 3-cyanopyrazinium derivative **4a** is almost comparable with that of the alloxazinium salts **2**, which are ranked amongst the most efficient organocatalysts of H_2O_2 sulfoxidations.[1a,4,7b] To the best of our knowledge, this is the first example of the application of structurally simple heteroarenium salts to the activation of hydrogen peroxide and for the catalysis of oxidations. Being easily available and environmentally benign, pyrazinium salts seem to be promising also from the point of view of practical applications. Studies on the use of other heteroarenium salts as well as the improvement of their activity are now under investigation.

Experimental Section

General Conditions

Mass spectra were recorded on a Thermo Scientific LXQ linear trap mass spectrometer in tandem with a Janeiro LC system consisting of two Rheos 2200 pumps and a CTC PAL autosampler. High-resolution mass spectra were obtained on a hybrid FT/MS mass spectrometer LTQ Orbitrap XL by direct infusion of the sample solution into the mobile phase (100% acetonitrile or methanol). The mass spectrometer operated in ESI+ mode with a resolution of 100000 and mass range 100–1500. NMR spectra were recorded on a Varian Mercury Plus 300 (299.97 MHz for ^{1}H and 75.44 MHz for ^{13}C), Bruker Avance DRX 500 (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C) and Bruker 600 Avance III (600.13 MHz for ^{1}H and 150.90 MHz for ^{13}C). Chemical shifts δ are given in ppm, using residual solvent or tetramethylsilane as an internal standard. Coupling constants are reported in Hz. Experimental procedures and spectroscopic data can be found in the Supporting Information.

Synthesis of Pyrazinium and Pyridinium Salts

The pyrazine (or pyridine) compound (2.3 mmol) was dissolved in dry chloroform (8 mL). Triethyloxonium tetrafluoroborate (0.475 g, 2.5 mmol) was added and the mixture was stirred for 4–24 h under a nitrogen atmosphere. The solid product was collected by filtration, washed with dichloromethane and dried under vacuum. The crude product was dissolved in a minimum volume of acetonitrile and precipitated with diethyl ether. For details about the synthesis and for the characterization, see Supporting Information.

Kinetic Experiments

The catalyst (5.1 μmol) and the substrate (0.255 mmol) were dissolved in MeOH-d_4 (600 μL). The solution was transferred to an NMR tube and thermostatted for 15 min at 25.0±0.5 °C. Hydrogen peroxide (30% aqueous solution, 40 μL, 0.392 mmol) was added, and the reaction was monitored by ^{1}H NMR. The resulting spectra of the products corresponded to the spectra of the authentic samples of sulfoxides.

Preparative Sulfoxidations

The substrate (100 mg) and **4a** (5 mol%) were dissolved in methanol (2 mL). The solution was thermostatted for 20 min at 25.0±0.5 °C. 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 toluene as a mobile phase. After complete conversion had been achieved, sodium sulfite (100 mg) was added to quench the excess of hydrogen peroxide. The solid was filtered off and the solution was evaporated under reduced pressure. The residue was partitioned between water (4 mL) and dichloromethane (4 mL). The phases were separated and the aque-

ous phase was extracted with dichloromethane (6×3 mL). The combined organic phases were washed with brine (5 mL) and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the product was analyzed by ^{1}H NMR.

Preparative Baeyer–Villiger Oxidations

The substrate (0.599 mmol) and **4a** (2 mol%, 6.6 mg, 0.030 mmol) were dissolved in *t*-BuOH (1 mL). Hydrogen peroxide (30% aqueous solution, 0.1 mL, 0.980 mmol) was added and the mixture was stirred at room temperature until complete conversion was achieved. The course of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate 4:1).

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