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Efficient and Selective Sulfoxidation by Hydrogen Peroxide, Using a Recyclable Flavin−[BMIm]PF_6 Catalytic System

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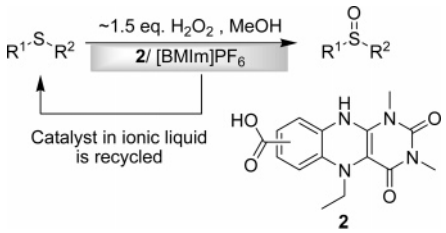

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A new flavin catalyst **2** immobilized in an ionic liquid ([BMIm]PF_6) was used for the highly selective oxidation of sulfides to sulfoxides by hydrogen peroxide. The sulfoxides were obtained in good to high yields and high selectivity without any detectable overoxidation to sulfone. The catalyst in the ionic liquid was recycled up to seven times without loss of activity or selectivity.

Introduction

Organosulfur compounds are important synthetic intermediates and they occur in a variety of pharmaceuticals. Furthermore, enantiomerically pure sulfoxides are often used as chiral ligands and auxiliaries in asymmetric synthesis.[1,2] Because of the interest in sulfoxides there is an increasing demand of selective and efficient methods for their preparation.[3]

There are a number of methods available for the preparation of sulfoxides; however, many of these are associated with low selectivity.[3] We have previously reported on a highly chemoselective oxidation of sulfides by H_2O_2 using flavin **1** as catalyst both for simple sulfides[4] and for allylic sulfides.[5,6] The same flavin was also utilized as an efficient catalyst for the oxidation of amines to amine oxides[7] and this made possible an in situ reoxidation of NMM (*N*-methylmorpholine) to NMO (*N*-methylmorpholine *N*-oxide) in a H_2O_2-based osmium-catalyzed dihydroxylation of olefins.[8] The effect of substituents on the oxidation potential of the flavin has been recently reported by us.[9]

There are a number of ways to reuse a catalyst and a common way is to immobilize it on a solid support.[10,11] Some recent approaches involve anchoring the catalyst via a tether to a solid surface.[11] This requires tedious synthetic work and it is often difficult to quantify the amount of catalyst on the surface. Ionic

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(7) (a) Bergstad, K.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6650−6655. (b) For a H_2O_2-based oxidation of secondary amines to nitrones catalyzed by a flavin see ref 4c.

(8) (a) Bergstad, K.; Jonsson, S. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 10424−10425. (b) Bergstad, K.; Piet, J. J. N.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 2545−2548. (c) Jonsson, S. Y.; Adolfsson, H.; Bäckvall, J.-E. *Chem. Eur. J.* **2003**, *9*, 2783−2788. (d) Jonsson, S. Y.; Adolfsson, H.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 3463−3466. (e) Jonsson, S. Y.; Färnegårdh, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2001**, *123*, 1365−1371.

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(10) (a) Bolm C.; Gerlach, A. *Eur. J. Org. Chem.* **1956**, *21*, 1−27. (b) Thomas, J. M.; Raja, R. *J. Organomet. Chem.* **2004**, *689*, 4110−4124.

(11) Kirschning, A. Immobilized Catalysts. In *Top. Curr. Chem.* **2004**, *242*.

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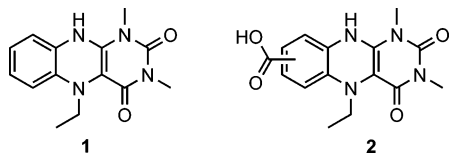
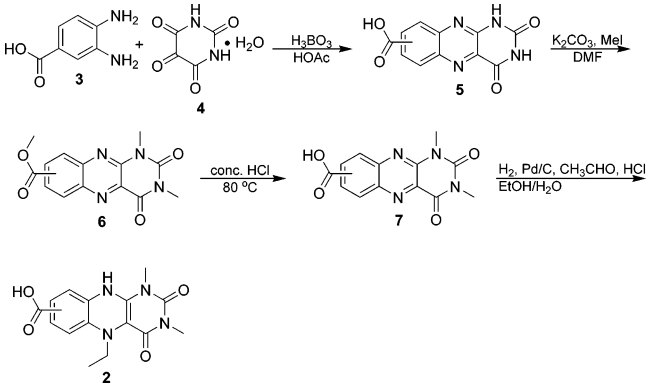


FIGURE 1. Flavins **1** and **2**.

SCHEME 1. Synthesis of the Catalyst



liquids have attracted considerable attention in recent years as good and reusable reaction media for organic reactions.[12] The reusability arises from the fact that ionic liquids have essentially no vapor pressure and that they are easily extractable. They are generally good solvents for organic compounds as well as for a wide range of inorganic complexes such as metal catalysts.[13] Many reactions have been reported utilizing ionic liquids as solvents, and among them one finds examples of metal catalysis,[12,14] as well as bio- and organocatalysis.[12] So far only two groups have reported on the oxidation of sulfides to sulfoxides in ionic liquid.[15,16]

Attempts to immobilize flavin **1** in an ionic liquid for sulfoxidation and recycling gave poor results.[17] In this work we have prepared the new flavin **2** and report on its use as an ionic liquid-immobilized catalyst for the highly selective H_2O_2 oxidation of sulfides to sulfoxides. An important feature of this system is that it can be recycled many times without any detectable loss of activity.

Results and Discussion

Flavin **2** was synthesized from 3,4-diaminobenzoic acid (**3**) and alloxane monohydrate (**4**) in good yield according to standard procedures (Scheme 1).[9] The first step afforded flavin **5** in quantitative yield, in 1:1 ratio of the 7- and 8-hydroxycarbonyl regioisomers, and was subsequently methylated by methyl iodide to form flavin **6** in 86% yield, in a 3:2 ratio of the 7- and 8-regioisomers. In this step also the acid moiety was methylated to give the ester. The ester was hydrolyzed by reaction with concentrated hydrochloric acid, which afforded flavin **7** in 85% yield in a 3:2 ratio of the 7- and 8-regioisomers. The precatalyst **2** was obtained in 67% yield by reductive alkylation of **7**.

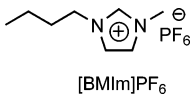


FIGURE 2. The ionic liquid.

Our previous studies on the substituent effects have shown that electron-withdrawing substituents on the flavin increase its oxidation potential and hence the rate of the corresponding flavin-catalyzed oxidation.[9] Thus, flavin **2** is expected to give a faster sulfoxidation with H_2O_2 compared to **1**. Furthermore, and more importantly, the carboxylate group makes an immobilization of **2** in an ionic liquid very efficient. Flavin **2** is most likely present in its zwitterionic form or as its carboxylate ion. The ^{1}H NMR spectrum of **2** is consitent with a zwitterionic form with the nitrogen in the 5-position protonated since in both isomers the two hydrogens of the CH_2 group in the ethyl group on N-5 are coupled with an additional proton. Furthermore, the ^{1}H NMR shows that the two protons in the CH_2 group are nonequivalent and appear at different shifts ($\Delta\delta = 0.48$ ppm; see the Experimental Section). In previous studies we have used flavin **1** in ionic liquid [BMIm]PF_6 for the recycling of NMM to NMO in the osmium-catalyzed dihydroxylation.[18] One problem with flavin **1** is that it leaches on recycling and attempts to immoblize **1** in [BMIm]PF_6 for sulfoxidation by H_2O_2 were unsuccessful due to severe leaching.[17] *p*-Tolyl methyl sulfide (**8a**) was used as a model substrate in the tuning of reaction conditions. We found that sulfide **8a** was efficiently oxidized to sulfoxide **8b** using 2 mol % of flavin **2** and 1.5 equiv of H_2O_2 in the ionic liquid [BMIm]PF_6/methanol mixture. The immobilized catalytic system showed high activity and no overoxidation was detected. The new system was applied to several other sulfides and the results are presented in Table 1.

The sulfides were oxidized to sulfoxides by H_2O_2 in high yields at room temperature with short reaction times (Scheme 2). In all cases a high selectivity for sulfoxide was obtained with no overoxidation to sulfone. The system tolerates both electron-rich and electron-deficient substrates, although electron-deficient sulfides required slightly longer reaction times. The electron-rich sulfides **8a**−**10a** gave the corresponding sulfoxides **8b**−**10b**, respectively, within 3 h in good to excellent yields (Table 1, entries 1−3). The electron-deficient *p*-bromophenyl methyl sulfide **11a** yielded 83% of the sulfoxide **11b** in 5 h (Table 1, entry 4). The electronic properties do not explain why naphthyl sulfide **12a** required about 3 times longer reaction time to be oxidized than the corresponding tolyl derivative **8a** (Table 1, entry 5 vs entry 1). We observed that the starting sulfide **12a** was poorly soluble in the reaction medium, and this may explain the slightly longer reaction time. The more sterically hindered sulfide **13a**−**15a** afforded the corresponding sulfoxides **13b**−**15b** in good yields within 4.5 h (Table 1, entries 6−8).

To investigate the chemoselectivity of the new catalytic system a few allylic sulfides were tested. The system is compatible with allylic sulfides **17a**−**21a** leaving the double

(12) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015−1060.

(13) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275−297.

(14) Special Issue on Organometallic Chemistry in Ionic Liquids; Bäckvall, J. E., Adams, R. D., Eds. *J. Organomet. Chem.* **2005**, *690* (15).

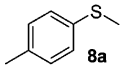
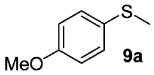
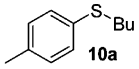
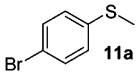
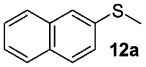
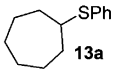
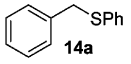
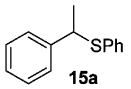
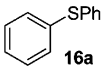
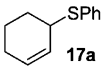
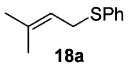
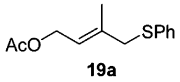
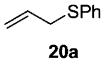
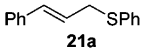
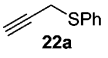
(15) (a) Cimpeanu, V.; Parvulescu, V. I.; Amorós, P.; Beltrán, D.; Thompson, J. M.; Hardacre, C. *Chem. Eur. J.* **2004**, *10*, 4640−4646. (b) Cimpeanu, V.; Parvulescu, A. N.; Parvulescu, V. I.; On, D. T.; Kaliaguine, S.; Thompson, J. M.; Hardacre, C. *J. Catal.* **2005**, *232*, 60−67.

(16) Okrasa, K.; Guibe-Jampel, E.; Therisod, M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2487−2490.

(17) Recycling experiments with catalyst **1** in [BMIm]PF_6 for sulfoxidation of **8a** and **12a** with H_2O_2 gave poor results (% yield of sulfoxide); run 1 91−99%, run 2 55−60%, run 3 40−50%.

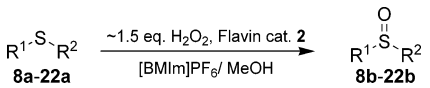
(18) Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* **2004**, 1494−1495.

TABLE 1. Oxidation of Sulfides by Hydrogen Peroxide in [BMIm]PF_6/MeOH with Use of 2 mol % of 2[a]

entry	substrate	product	time(h)	yield[b] (%)
1	 **8a**	**8b**	2	84
2	 **9a**	**9b**	1.5	87[d]
3	 **10a**	**10b**	3	95
4	 **11a**	**11b**	5	83
5	 **12a**	**12b**	7	87
6	 **13a**	**13b**	3.5	99
7	 **14a**	**14b**	3	75
8	 **15a**	**15b**	4.5	79[c]
9	 **16a**	**16b**	5	60[d]
10	 **17a**	**17b**	4.5	76
11	 **18a**	**18b**	2	91
12	 **19a**	**19b**	4.5	82
13	 **20a**	**20b**	2	78
14	 **21a**	**21b**	4	80
15	 **22a**	**22b**	6	66

[a] Unless otherwise noted the reactions were run with 1 mmol of sulfide in 0.5 mL of [BMIm]PF_6 and 3.2 mL of MeOH. Flavin **2** (6.3 mg, 2 mol %) and H_2O_2 (150−170 μL, ∼1.5 equiv) were added and the reaction mixture was stirred for the given time. [b] Isolated yields unless otherwise noted. [c] Diastereomeric ratio 4:1. [d] NMR yield.

SCHEME 2. General Reaction Procedure for the Sulfoxidation



bond untouched (Table 1, entries 10−14). The sulfoxides **17b**−**21b** were formed in good to excellent yield within 4.5 h. The diphenyl sulfide (**16a**) and propargyl phenyl sulfide (**22a**) (Table 1, entries 9 and 15) gave the lowest yields. The reaction of **22a** stopped at 86% conversion, which is higher than that with the previous method,[5] and the product **22b** was isolated in 66% yield.

Even though the conversions are above 95% in most of the cases the isolated yields are lower for the more polar substrates. This is due to the fact that the sulfoxides formed are not fully extracted out of the ionic liquid.

The background reactions (in the absence of flavin **2**) were negligible for all sulfides within the reaction time and for the oxidation of methyl *p*-tolyl sulfide the reaction was monitored with GC both with and without catalyst **2**. The results are presented in Figure 3. The recycling of catalyst **2** is highly efficient and was demonstrated with four different sulfoxidations (Scheme 3, Table 2). The reactions were run as above but now the cosolvent methanol was evaporated after completion of the reaction and the residual ionic liquid phase was extracted 3 times with 10 mL of diethyl ether. The remaining H_2O_2 in the ethereal phase was quenched with sodium dithionite and the ether phase

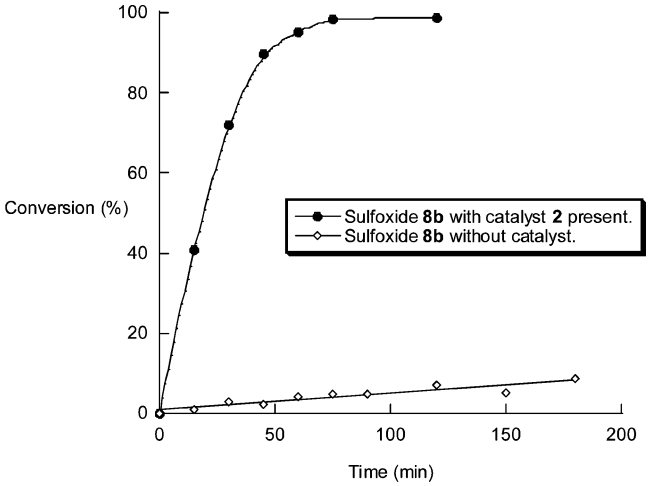


FIGURE 3. The amount of sulfoxide **8b** with and without precatalyst **2** present.

SCHEME 3. General Reaction Procedure for the Recycling Experiments

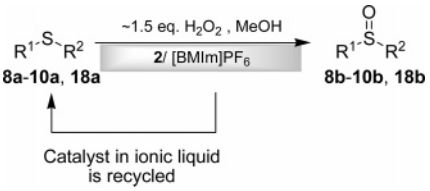


TABLE 2. Recycling of the Flavin Catalyst in Ionic Liquid[a,b]

		yield[c] (%)					
entry	substrate/ product	run 1	run 2	run 3	run 4	run 5	run 6/7
1	**8a/8b**	78	84	80	88	91	89/−
2[d]	**9a/9b**	87[e]	87[e]	87[e]	87[e]	87[e]	87[e]/88
3	**10a/10b**	95	98	89	86	92	94/−
4	**18a/18b**	91	94	88	−	−	−/−

[a] Unless otherwise noted the reactions were run with use of 1 mmol of sulfide in 0.5 mL of [BMIm]PF_6 and 3.2 mL of MeOH. Flavin **2** (6.3 mg, 2 mol %) and H_2O_2 (150−170 μL, ∼1.5 equiv) were added and the reaction was stirred for 1.5−2.5 h. [b] Conversion determined by ^{1}H NMR, 96−99%. [c] Isolated yield. [d] A seventh run gave 88% yield. [e] The crude products of runs 1−6 were combined to give 482% isolated yield converted on one run, which gives in average 87% yield per run.

was washed with 10 mL of water.[19] The water phase was subsequently extracted 3 times with 10 mL of diethyl ether. It was demonstrated that the ionic liquid−catalyst system can be recycled up to 7 times for the *p*-methoxyphenyl methyl sulfide (**9b**) without significant loss of either activity or selectivity. The results are given in Table 2.

As is clear from the recycling experiments, the catalyst stays in the ionic liquid and no detectable leaching of the catalyst takes place. The system is equally active in the seventh run as in the first run. It is important to note that the catalyst system could be stored in the freezer for days between the runs with neither decomposition nor loss of activity of the catalyst. This is noteworthy since the flavin catalysts are usually sensitive toward autooxidative degradation in solution.

In conclusion, we have developed a mild and robust catalytic system for sulfoxidation. The combination of an electron-deficient flavin catalyst with the use of an ionic liquid as medium leads to an efficient and stable system. We have shown that a variety of sulfides can be selectively oxidized to sulfoxides in good yields. It was demonstrated that the catalyst in the ionic liquid can be recycled up to seven times. The selectivity and yield did not decrease on recycling, and the only product obtained was the desired sulfoxide. The efficient immobilization of flavin **2** is most likely due to it being present as its zwitterion form and therefore it is not extracted by ether.

Experimental Section

Synthesis of 7/8-Hydroxycarbonylalloxazine (5). To a stirred solution of 3,4-diaminobenzoic acid (**3**, 3.04 g, 20 mmol) in 170 mL of acetic acid were added boric acid (1.36 g, 22 mmol) and alloxane (**4**) monohydrate (3.36 g, 21 mmol). The reaction was stirred for 3 h at room temperature after which the precipitated product was filtered off and washed, first with acetic acid then with diethyl ether, water, and last diethyl ether. The product **5** (green powder) was isolated in a 3:2 ratio of the 7- and 8-isomer in quantitative yield. **Major isomer:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 11.79 (s, 1H), 8.29 (d, J = 1.9 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 1.9, 8.8 Hz, 1H). **Minor isomer:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 11.80 (s, 1H), 8.55 (d, J = 2.0 Hz), 8.25 (dd, J = 2.0, 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) for the mixture δ 167.0, 167.0, 160.8, 160.8, 150.7, 150.7, 148.6, 148.1, 145.4, 142.5, 141.4, 138.8, 135.1, 134.0, 133.7, 132.8, 132.5, 131.1, 130.8, 129.1, 128.0, 127.9.

Synthesis of *N1,N3*-Dimethyl-7/8-methoxycarbonylalloxazine (6).[9] To a stirred solution of 7/8-hydroxycarbonylalloxazine (**5**) (2.58 g, 10 mmol) in 500 mL of dimethylformamide (DMF) were added potassium carbonate (K_2CO_3) (4.70 g, 34 mmol) and methyl iodide (2 mL, 32 mmol). The reaction mixture was stirred overnight (22 h) after which it was filtered through a glass filter funnel to remove inorganic salts. The liquids were collected and the solvents removed under reduced pressure. The solids were then suspended in 500 mL of chloroform ($CHCl_3$) and extracted with 200 mL of 2 M hydrochloric acid (HCl), 200 mL of diluted brine, and finally 200 mL of brine. The organic phase was dried over sodium sulfate (Na_2SO_4) and after filtration the solvents were removed and the product dried under vacuum. The product **6** was isolated in 86% yield as a yellow solid. The product was a mixture of the 7-methoxycarbonyl derivative and the 8-methoxycarbonyl derivative in a 3:2 ratio. **Major isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 1.7 Hz, 1H), 8.29 (d, J = 8.9 Hz, 1H), 8.23 (dd, J = 1.7, 8.9 Hz, 1H), 3.99 (s, 3H), 3.78 (s, 3H), 3.56 (s, 3H). **Minor isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 1.8 Hz, 1H), 8.38 (dd, J = 1.9, 8.9 Hz, 1H), 7.98 (d, J = 8.9 Hz), 3.97 (s, 3H), 3.78 (s, 3H), 3.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) for the mixture δ 165.7, 159.4, 159.3, 150.5, 146.4, 145.9, 145.3, 142.6, 141.5, 138.9, 134.5, 133.3, 133.2, 131.1, 131.0, 130.7, 130.5, 130.2, 128.4, 128.1, 53.0, 52.9, 29.8, 29.8, 29.4, 29.4.

Synthesis of *N1,N3*-dimethyl-7/8-hydroxycarbonyl alloxazine (7). The *N1,N3*-dimethyl-7/8-methoxycarbonyl alloxazine (**6**) (1 mmol, 300 mg) was suspended in concentrated hydrochloric acid (4 mL) and the mixture was heated at 80 °C for 22 h. The reaction mixture was allowed to cool to room temperature and poured into 12 mL of ice−water. The formed precipitate was filtered off and washed with water and small amounts of diethyl ether and dried under vacuum. The product was obtained as a yellow solid in 85% yield as a 3:2 mixture of the 7- and 8-regioisomer. **Major product 7-hydroxycarbonyl derivative:** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.49 (d, 1.7, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.21 (dd, J = 1.8, 8.7 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H). **Minor product 8-hydroxycarbonyl derivative:** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.67 (d, 1.7, 1H), 8.36 (dd, J = 1.8, 8.7 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H).

Synthesis of Dihydroflavin 2. *N1,N3*-Dimethyl-7/8-hydroxycarbonylalloxazine (**7**) (0.421 g, 1.5 mmol) was suspended in a mixture of degassed ethanol (25 mL) and water (20 mL). Palladium (10%) on charcoal (0.162 g, preactivated under vacuum) was added followed by hydrochloric acid (3.2 mL) and acetaldehyde (3.2 mL). The reaction was stirred overnight under 30 psi of H_2 (g). After 26 h the reaction mixture was filtered through a Celite plug, in a Schlenk equipped with a frit, which was connected to a Schlenk. The Celite was washed with degassed ethanol until all yellow substance was removed from the Celite plug. The Schlenk frit was then replaced with a tube connected to a cold trap and the solvents were removed under vacuum. The residual solids were suspended in water and filtered in another Schlenk frit after which they were left to dry over P_2O_5. Product **2** was obtained as an orange-red powder in 67% yield. MS (MALDI-TOF) *m/z* calcd for $C_{15}H_{16}N_4O_4$ $[M]^+$ 316.31, found 316.27. **Major product 7-hydroxycarbonyl derivative:** ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 2.1, 8.9 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 4.11 (m, J = 2.6, 7.2, 14.6 Hz, 1H), 3.63 (m, J = 6.6, 6.6, 14.6 Hz, 1H), 3.52 (s, 3H), 3.25 (s, 3H), 1.53 (t, J = 6.9 Hz, 3H). **Minor product 8-hydroxycarbonyl derivative:** ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, J = 1.0 Hz, 1H), 7.51 (dd, J = 1.3, 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 4.11 (m, J = 2.6, 7.2, 14.6 Hz, 1H), 3.63 (m, J = 6.6, 6.6, 14.6 Hz, 1H), 3.52 (s, 3H), 3.26 (s, 3H), 1.55 (t, J = 6.9 Hz, 3H).

General Procedure for the Sulfoxidation. The catalyst precursor **2** (6.3 mg, 0.02 mmol) was dissolved in [BMIm]PF_6 (0.5 mL) and methanol (3.2 mL) in a 20 mL vial. The sulfide (1 mmol) was then added followed by hydrogen peroxide (30% in water) (170 μL). The reactions were stirred for the given time (the reactions were followed by TLC) after which the methanol was removed and the residual ionic liquid was extracted with diethyl ether (3 × 15 mL). The combined ether layers were treated with sodium dithionite and washed with water (3 × 10 mL). The ether phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The products were purified by conventional or Biotage flash chromatography.

***p*-Tolyl Methyl Sulfoxide (8b).** Isolated yield after 1 h of reaction time, 78%. The NMR data were in accordance with those previously reported.[4] The conversions (Figure 3) were determined by GC analysis of the reaction mixture: t_R(*p*-tolyl methyl sulfide) = 12.7 min; t_R(*p*-tolyl methyl sulfoxide) = 17.2 min.

General Procedure for the Recycling of the Ionic Liquid−Catalyst System. The catalyst precursor **2** (6.3 mg, 0.02 mmol) was dissolved in [BMIm]PF_6 (0.5 mL) and methanol (3.2 mL) in a 20 mL vial. The sulfide (1 mmol) was then added followed by hydrogen peroxide (170 μL). The reaction was stirred for the given

(19) It is important that no hydrogen peroxide is left in the ether phase since it causes overoxidation after removal of the solvent.

time (the reaction was followed by TLC) after which the methanol was removed and the residual ionic liquid was extracted with diethyl ether (3 × 15 mL). The combined ether layers were treated with sodium dithionite and washed with water (10 mL). The water phase was back extracted with diethyl ether (3 × 10 mL). The combined ether phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The products were isolated by flash chromatography. The ionic liquid phase was reused after evaporation of the remaining diethyl ether. Sulfide (1 mmol) and H_2O_2 (1.5 equiv) were added after addition of methanol (3.2 mL).

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Supporting Information Available: General experimental and characterization of compounds **9b**−**22b**; copies of NMR spectra of compounds **2**, **5**−**7**, **10b**, **13b**, **14b**, **15b**, **16b**, and **21b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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