Selenium-Catalyzed Oxidations with Aqueous Hydrogen Peroxide. 2. Baeyer−Villiger Reactions in Homogeneous Solution[1]

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Several diselenides were tested for catalytic activity in Baeyer−Villiger reactions with 60% aqueous hydrogen peroxide. Bis[3,5-bis(trifluoromethyl)phenyl] diselenide forms the corresponding 3,5-bis-(trifluoromethyl)benzene seleninic acid in situ, which is a highly reactive and selective catalyst for the oxidation of carbonyl compounds in 1,1,1,3,3,3-hexafluoro-2-propanol, 2,2,2-trifluoroethanol, or dichloromethane.

Introduction

In 1899 Adolf Baeyer and Victor Villiger reported the oxidation of menthone to its corresponding lactone using a mixture of persulfate and concentrated sulfuric acid (Caro's acid, see Figure 1).[2]

Since then, the Baeyer−Villiger reaction has become a valuable tool in organic synthesis.[3,4] The success is largely due to its versatility: (i) a variety of carbonyl compounds can be converted: ketones are converted into esters, cyclic ketones into lactones, benzaldehydes into phenols, or carboxylic acids and α-diketones into anhydrides, (ii) a large number of functional groups is tolerated, (iii) the regiochemistry is highly predictable with the migratory aptitude tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > CH$_3$, (iv) the reaction is generally stereoselective, i.e., the migrating group retains its configuration and, last, (v) a wide range of oxidants can be used with activity decreasing from CF$_3$CO$_3$H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > *p*-nitroperbenzoic acid > *m*-CPBA ∼ HCO$_3$H > C$_6$H$_5$CO$_3$H > CH$_3$CO$_3$H ≫ H$_2$O$_2$ > *t*-BuOOH.

Although more than a century has gone by since its discovery, Baeyer−Villiger reactions are still performed with peracids in more than stoichiometric amounts, in a buffered solution, thus generating copious amounts of waste. In addition, transport and storage of, for example, peracetic acid is subject to restrictions, and the reactions often require elevated temperatures.[5] Therefore, there has been increasing activity—especially in the past three years—to develop new catalysts that activate hydrogen peroxide as a clean oxidant for BV-reactions.[6]

The use of hydrogen peroxide has many advantages: it is safe, cheap, the active oxygen content is high, it does not require a buffer, and it is clean, since the byproduct
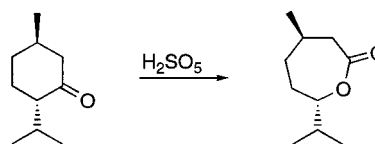

Figure 1. Oxidation of menthone with Caro's acid.

formed is water. Reports on this particular subject comprise homogeneous catalysts based on Se,[7] As,[8] Mo,[9] Re,[10] Pt,[11] Zr,[12] or (soluble) acid[13] and heterogeneous catalysts containing As,[14] or Se,[15] titanium silicalite,[16] or solid acids.[17] In most cases there are one or more drawbacks, for instance, low activity or selectivity of the catalyst, high cost of the catalyst, or the need for anhydrous hydrogen peroxide.

Among the first catalysts to be used for the epoxidation and Baeyer−Villiger reactions with H$_2$O$_2$ were the substituted benzeneseleninic acids reported by Syper.[7] He investigated the effect of nitro substituents at the ortho and para position of benzeneseleninic acid, obtaining optimum results when only one nitro substituent was

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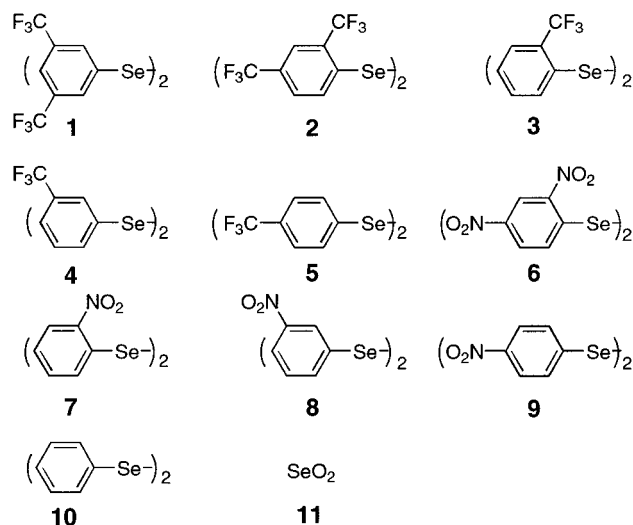(6) Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198.

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Figure 2. Selenium compounds tested for Baeyer−Villiger oxidation of cyclopentanone.

present in the ortho position. Recently,[1] we found that 3,5-bis(trifluoromethyl)benzeneseleninic acid was significantly more active than other previously described selenium catalysts in epoxidation reactions and could almost match the state-of-the-art epoxidation catalysts such as methyltrioxorhenium (MTO) or manganese-1,4,7-triazacyclononane (Mn-tacn). Herein we report the successful application of the same catalyst in the Baeyer−Villiger reactions.[18,19]

Results and Discussion

Substituent Effect. We initially investigated the effect of a wide range of electron-withdrawing substituents in benzeneseleninic acid (formed in situ from the corresponding diselenide) on its activity as a catalyst for the BV-reaction of cyclopentanone (see Figure 2 and Table 1).

Table 1 shows that electron-withdrawing substituents such as trifluoromethyl and nitro groups improve the reactivity of the selenium catalysts in BV-reactions, in the order meta > para > ortho. The decreased activity of both *o*-trifluoromethylbenzeneseleninic acid and *o*-nitrobenzeneseleninic acid is probably due to increased steric hindrance. Their activities are somewhat improved with a second trifluoromethyl substituent or nitro substituent at the para position. Furthermore, the *o,m,p*-trifluoromethylbenzeneseleninic acids are more active than their *o,m,p*-nitrobenzeneseleninic acid analogons. The most active catalyst is **1**, as was found for epoxidation reactions.[1] Overall, the somewhat lower activity of bis(2,4-dinitrophenyl) diselenide **6**, bis(2-nitrophenyl) diselenide **7**, bis(3-nitrophenyl) diselenide **8**, and bis(4-nitrophenyl) diselenide **9** is surprising. The reaction

(18) Selenium is not a cancer suspect agent and is not considered highly dangerous (source: US EPA, http://www.epa.gov.ngispgm3/iris/subst/0472.htm). It is a relatively cheap metal, retail price ca. $35 per 100 g of selenium. (Compare: Se = $ 0.03/mmol; 3,5-bis(trifluoromethyl)bromobenzene = $ 0.56/mmol; MTO = $ 35/mmol).

(19) The selenium catalysts **1−10** may be recycled. Sharpless described the recovery of the diphenyl diselenide catalyst in the oxidation of (*E*)-4-octene by reducing the benzeneseleninic acid (with NaHSO₃) back to the diselenide. Recovery: 21.9 g of pure diphenyl diselenide (93%) after several purification steps. Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689. We carried out BV-reactions with ca. 0.01 g of catalyst. On this scale the diselenide is nearly impossible to recover.

Table 1. Effect of Electron-Withdrawing Substituents on the Oxidation of Cyclopentanone[a]

catalyst	conversion (%)[b]	selectivity (%)[b,c]
1	62	95
2	26	95
3	21	91
4	45	87
5	40	81
6	27	94
7	19	95
8	31	93
9	30	90
10	37	75
11	15	35

[a] Conditions: 1 mol % diselenide (2 mol % SeO₂), 2 mmol cyclopentanone, 4 mmol 60% H₂O₂, 0.4 mmol Bu₂O as internal standard, 2 mL of 2,2,2-trifluoroethanol, 20 °C, 4 h. [b] Determined by GC. [c] Selectivity to δ-valerolactone, byproducts are a.o. cyclobutanecarboxylic acid, 5-hydroxypentanoic acid.

Scheme 1. Reaction Sequence for Catalytic Baeyer−Villiger Oxidation
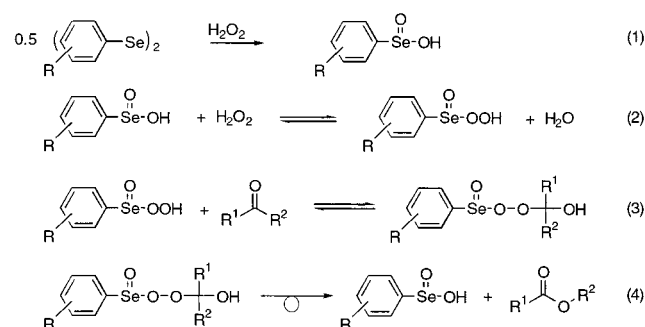
sequence in Scheme 1 below may explain the observed phenomena. On the basis of the strong electron-withdrawing properties of the nitro substituents, the seleninic acids derived from diselenides **6−9** should be the most acidic. It can be anticipated, therefore, that their corresponding peracids are the most active oxidants *in stoichiometric reactions* (reaction steps 3 and 4). In the case of a catalytic reaction with hydrogen peroxide, these substituents do not improve the reaction rates as in stoichiometric reactions. Apparently, the nitro substituents encumber oxidation of the diselenide to seleninic acid. This is seen qualitatively in the activation stage of the reaction 1, where the trifluoromethyl-substituted diselenides **1−5** lose their color within a minute to form (per)seleninic acids, whereas diselenides **6−9** need 2−5 h to decolorize. On the basis of the results of the *catalytic reactions* with preformed (per)seleninic acids, reoxidation of the seleninic acid to the perseleninic acid also seems to be disfavored by the strong electron-withdrawing nitro substituents (2).

Diaryl diselenides with electron-withdrawing substituents are more selective than diphenyl diselenide **10** itself. With both the trifluoromethyl- and nitro-substituted seleninic acids the selectivity decreases in the order ortho > meta > para. The selectivity of the nitro-substituted seleninic acids is generally higher than their trifluoromethyl-substituted counterparts throughout the reaction. One of the main side-reactions—ring contraction—is believed to follow a Wagner−Meerwein mechanism.[20]

(20) (a) Ferraz, H. M. C.; Silva, L. F. *J. Org. Chem.* **1998**, *63*, 1716. (b) Ferraz, H. M. C.; Silva, L. F. *Tetrahedron Lett.* **1997**, *38*, 1899. (c) Granger, R.; Boussinesq, J.; Girard, J. P.; Rossi, J. C.; Vidal, J. P. *Bull. Soc. Chim. Fr.* **1969**, 2806.

Table 2. Solvent Effect on the Oxidation of Cyclopentanone[a]

solvent	conversion (%)[b]	selectivity (%)[b,c]
$CF_3CHOHCF_3$	100	92
CF_3CH_2OH	62	95
CH_2Cl_2	53	93
$ClCH_2CH_2Cl$	49	95
C_6H_5Cl	26	86
$C_6H_5CF_3$	18	75
CH_3NO_2	46	82
$C_4H_8SO_2$[d]	42	72

[a] Conditions: 1 mol % **1**, 2 mmol cyclopentanone, 4 mmol 60% H_2O_2, 0.4 mmol Bu_2O as internal standard, 2 mL of solvent, 20 °C, 4 h. [b] Determined by GC. [c] Selectivity to δ-valerolactone, byproducts are a.o. cyclobutanecarboxylic acid, 5-hydroxypentanoic acid. [d] Sulfolane at 30 °C (mp = 27 °C).

This would involve addition of some selenium species to the double bond of the enol-tautomer. This reaction is indeed favored by more electron-rich seleninic acids.[19,21,22] Steric hindrance would probably also have a larger deleterious effect on a Wagner−Meerwein type reaction than on a Baeyer−Villiger type reaction. This might explain why the selectivity for lactones is higher with ortho-substituted diaryl diselenides. Increasing the electron-poor nature of the catalyst by having two trifluoromethyl groups at the meta positions leads to increased selectivity in combination with high reactivity. All tested diselenides are far superior in terms of activity and selectivity to selenium dioxide, which is used frequently in both lab-scale[22] and bulk-scale[23] reactions.

Solvent Effect. The choice of solvent is of great importance in oxidation chemistry. Therefore, **1** was put to the test in a range of solvents that are polar, aprotic, noncoordinating, and non-oxidizable (Table 2).

As Table 2 shows, in contrast with epoxidation reactions, the solvent plays a relatively minor role in activity and selectivity of the catalytic system. We note that 1,1,1,3,3,3-hexafluoro2-propanol is by far the best solvent,[24] but because it is very expensive it is not very practical to use. More suitable solvents are 2,2,2-trifluoroethanol, dichloromethane, and 1,2-dichloroethane, which differ only slightly in terms of reactivity and selectivity. When the toxicities of the various solvents are considered, nitromethane and the halogenated hydrocarbons 1,2-dichloroethane, chlorobenzene, and α,α,α-trifluorotoluene would not seem to be the solvent of choice.[25] Sulfolane, on the other hand, is far less toxic, but shows decreased selectivity. So, recommended solvents for further reactions would be 2,2,2-trifluoroethanol or dichloromethane.

Base Effect. Although the Baeyer−Villiger reaction is acid catalyzed, trace amount of acids in the hydrogen peroxide have no influence on the reaction, since we observed no blank reaction in 2,2,2-trifluoroethanol at room temperature. Addition of sodium acetate to buffer

the solution had virtually no effect on the activity or selectivity of **1**.[26] The absence of this base effect also indicates that for the oxidation of cyclopentanone catalyzed by **1**, the formation of side products is not predominantly caused by (unselective) acid-catalyzed Baeyer−Villiger reaction or acid-catalyzed hydrolysis of the lactone. It is more likely that this is caused by a competing pathway[21] catalyzed by **1**, as discussed above.

Substrate Scope. With an optimized system in hand we tested a range of ketones and aldehydes (Table 3).

Overall, the carbonyl compounds are converted faster and with higher selectivities than with most existing catalyst systems. The cycloalkanones give the corresponding lactones in good selectivities and show little tendency to give ring contraction to cycloalkanecarboxylic acids. The observed relative reactivities are in accordance with values from literature, where increased ring strain and electron density give higher reaction rates. Due to these effects, linear ketones react more slowly to their corresponding esters, and reaction times up to 24 h are required to obtain appreciable conversions. When products are formed that are sensitive toward hydrolysis, such as linear esters or strained lactones, the use of dichloromethane as a solvent is recommended instead of the very polar 2,2,2-trifluoroethanol. In dichloromethane this hydrolysis process is slower, partly due to decreased polarity and partly due to the biphasic nature of water−CH_2Cl_2 mixtures. Nevertheless, after longer reaction times the difference may become negligible. It should be noted that conversions may be significantly lower in CH_2Cl_2 compared with CF_3CH_2OH.

The highly electron-rich 3,4,5-trimethoxybenzaldehyde gives a fast migration of the phenyl ring to yield the ester of formic acid and free 3,4,5-trimethoxyphenol. With the less electron-rich p-tolualdehyde there is a competing phenyl and hydrogen migration leading to the formation of a mixture of almost equal amounts of p-cresol (~55%) and p-toluic acid (~45%). With the electron-poor p-nitrobenzaldehyde it is the hydrogen atom which exclusively migrates to yield p-nitrobenzoic acid. Similarly, octanal and 3-phenylpropionaldehyde are selectively oxidized to octanoic acid and 3-phenylpropionic acid, respectively. Last, a 1,2-dione such as phenanthrenequinone can be oxidized to form an anhydride which hydrolyzes under the reaction conditions to a dicarboxylic acid.

Conclusions

In conclusion, we have shown that Baeyer−Villiger reactions can be carried out successfully with (aqueous) hydrogen peroxide as the oxidant at room temperature. The optimum selenium catalyst for this reaction was found to be 3,5-bis(trifluoromethyl)benzeneseleninic acid. This catalyst is easy to prepare and is active and selective in combination with aqueous hydrogen peroxide. The best solvents for the Baeyer−Villiger reaction are 1,1,1,3,3,3-hexafluoro-2-propanol, 2,2,2-trifluoroethanol, and dichloromethane.
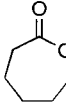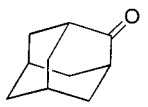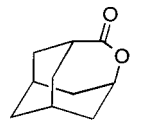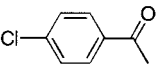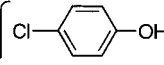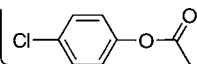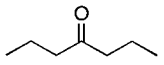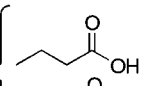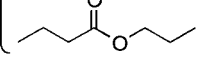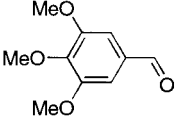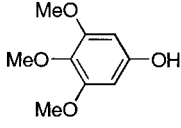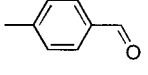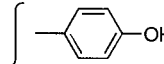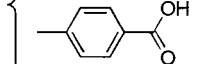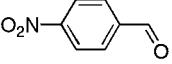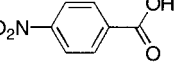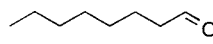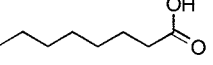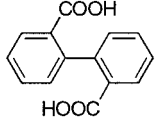
Experimental Section

Materials. The diselenides **1−5**, **8**, and **9** were prepared as outlined in ref 1. Diselenide **7** and SeO_2 were purchased from Acros. Diselenide **6** was prepared via reaction of 1-chloro-

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(22) (a) Krief, A.; Hevesi, L. In *Organoselenium Chemistry*; Springer-Verlag: Berlin, 1988; vol 1, pp 156−162. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

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(24) Neimann, K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861.

(25) (a) 2,2,2-Trifluoroethanol is a common industrial solvent and a known metabolite of the inhalation anaesthetics "fluroxene" (2,2,2-trifluoroethyl vinyl ether) and "halothane" (2-bromo-2-chloro-1,1,1-trifluoroethane). Selinsk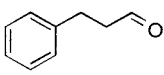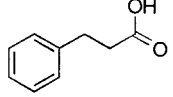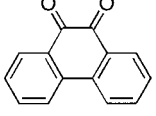y, B. S.; Rusyniak, D. E.; Warsheski, J.; Joseph, A. P. *Biochem. Pharmacol.* **1991**, *42*, 2229. (b) Many chlorinated solvents (CH_2Cl_2, $CHCl_3$, CCl_4, $ClCH_2CH_2Cl$, CCl_3CH_3, etc.) are cancer suspect agents, and their use is an issue of debate. Hileman, B.; Long, J. R.; Kirschner, E. M. *Chem. Eng. News* **1994**, *72*, 12.

(26) Mares and Jacobson observed a beneficial effect from mild bases in a similar system: Mares, F.; Jacobson, S. E. US Patent 4213906, 1978.

Table 3. Baeyer–Villiger Oxidation of Several Carbonyl Compounds[a]

Substrate	Product	Time (h)	Conversion (%)[b]	Selectivity (%)[b]
cyclobutanone	γ-butyrolactone	1	99	90
cyclopentanone	δ-valerolactone	8	95	94
cyclohexanone	ε-caprolactone	4	95	99
2-adamantanone	lactone	1	100	99
4'-chloroacetophenone	chlorophenol	24	25	50
	chlorophenyl acetate			50
4-heptanone	butyric acid	24	25	55
	propyl butyrate			45
3,4,5-trimethoxybenzaldehyde	2,3,4-trimethoxyphenol	0.25	99	~99[c]
p-tolualdehyde	p-cresol	2	99	55[c,d]
	p-toluic acid			45
4-nitrobenzaldehyde	4-nitrobenzoic acid	2	98	98[d]
octanal	octanoic acid	3	88	96[d]
3-phenylpropanal	3-phenylpropanoic acid	3	90+	99[d]
9,10-phenanthrenequinone	diphenic acid	16	98+	95

[a] Standard conditions: 1 mol % **1**, 2 mmol substrate, 4 mmol 60% H_2O_2, 0.4 mmol Bu_2O as internal standard, 2 mL of CF_3CH_2OH, 20 °C. [b] Determined by GC. [c] Selectivity to substituted phenol after base hydrolysis during workup. [d] 60 °C.

2,4-dinitrobenzene and KSeCN[27] and subsequent reduction of 2,4-dinitro-1-selenocyanatobenzene with sodium ethanolate in ethanol.[28] Diselenide **10** was prepared via reaction of phenyl-magnesium bromide with selenium and subsequent oxidation with air.[29] Substrates were purchased from Acros in their highest available purity. Hydrogen peroxide (60%) was a gift from Solvay Interox. Solvents: 1,1,1,3,3,3-Hexafluoro-2-propanol (99+%), 2,2,2-trifluoroethanol (99+%), α,α,α-trifluorotoluene (99+%), and nitromethane (98%) were purchased from Fluka. Dichloromethane (99.5+%), 1,2-dichloroethane (99+%), and chlorobenzene (99+%) were purchased from Baker. Sulfolane (99+%) was purchased from Acros. All substrates and solvents were used without further purification.

Catalytic Experiments. Hydrogen peroxide (60%, 4 mmol, 200 μL) was added to a stirred solution (1000 rpm) of catalyst (1 mol % of diselenide)[19] in 2 mL of solvent in a closed flask. After the solution had become colorless, dibutyl ether (0.4 mmol, 67 μL) as internal standard and substrate (2 mmol) were added. The reaction temperature was kept at 20 $\pm$ 1 °C with a water bath. Samples ($\sim$50 μl) were first treated with MnO_2 (10 mg) + $MgSO_4$ in Et_2O (2 mL) and subsequently filtered and analyzed with GC. Identities of the products were confirmed by GC/MS or ^{1}H NMR plus melting point (diphenic acid) and by comparing retention times with those of commercially available products.

Preparative Scale Reactions. Oxidation of Cyclohexanone. Warning: combinations of hydrogen peroxide with (cyclic) ketones may form dimeric and trimeric ketone peroxides.[30] Such compounds are potentially explosive. Therefore, isolation of the lactones should be carried out after taking proper safety measures. Hydrogen peroxide (60%, 20 mmol, 1 mL) was added to a solution of **1** (0.1 mmol, 0.0586 g) in CF_3-CH_2OH (10 mL). After 10 min cyclohexanone (10 mmol, 0.98 g, 1.03 mL) was added. The mixture was stirred for 4 h, and water was added to 100 mL. The aqueous mixture was extracted with ether (4 × 20 mL). The organic layer was washed with 10% $NaHSO_3$ (20 mL), 10% $NaHCO_3$ (20 mL), and water (20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified via bulb-to-bulb distillation (bp 65 °C, 0.02 mm). Yield 0.64 g (5.6 mmol, 56%) of ϵ-caprolactone.

Oxidation of 3,4,5-Trimethoxybenzaldehyde and Subsequent Base Hydrolysis. Hydrogen peroxide (60%, 20 mmol, 1 mL) was added to a solution of **1** (0.1 mmol, 0.0586 g) in CF_3CH_2OH (10 mL). After 10 min 3,4,5-trimethoxybenzaldehyde (10 mmol, 1.96 g) was added, and the mixture was stirred for 3 h. Then water was added to ca. 100 mL, and a yellow solid was filtered off. The residue was washed with 10% $NaHSO_3$ (20 mL), 10% $NaHCO_3$ (20 mL), and water (20 mL) and air-dried to yield 1.5 g (7.1 mmol, 71%) of nearly pure 3,4,5-trimethoxyphenyl formate. The filtrate was extracted with CH_2Cl_2 (2 × 25 mL), and the organic layer was treated as described for the workup of ϵ-caprolactone to yield a further 0.4 g of a mixture of the ester and 3,4,5-trimethoxyphenol. The combined yields were dissolved in MeOH (20 mL), KOH (25 mmol, 1.4 g) was added, and the mixture was stirred for 2 h. The mixture was concentrated to ca. 10 mL, extracted with ether, and acidified with 2 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (20 mL) and was dried over Na_2SO_4. The solvent was removed in vacuo to yield 1.4 g (8.5 mmol, 85%) of 3,4,5-trimethoxyphenol.

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