

Article

Innovative Application of Polyether Amine as a Recyclable Catalyst in Aerobic Thiophenol Oxidation

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Abstract: Polyether amines are versatile compounds characterized by a flexible structure, consisting of polyoxypropylene and polyoxyethylene as the backbone, with amine groups at each end. They have widespread applications in various industrial processes and daily life. Despite their versatility, the utilization of polyether amines as base catalysts is rare. In this study, one kind of three-arm polyether amine **1** was employed as an environmentally friendly, cost-effective catalyst for the aerobic oxidation of thiophenols, leading to the synthesis of disulfides. The oxidative coupling of thiols serves as a fundamental pathway for the production of disulfides, which are vital in both chemical and biological processes. In contrast to known methods for thiol oxidation, this polyether amine-based catalytic process eliminates the need for expensive stoichiometric oxidants and minimizes the formation of over-oxidized by-products. Using a mere 0.5 mol % of the polyether amine **1** as the catalyst, a remarkable > 96% yield was achieved for all 16 tested substrates, encompassing a diverse range of functional groups, under the catalytic aerobic oxidation conditions. Furthermore, it is noteworthy that over 90% of the polyether amine catalyst can be efficiently recovered for reuse without loss of activity, making this a sustainable and cost-effective catalytic approach.

Keywords: polyether amine; polymer catalyst; aerobic oxidation; disulfides; thiophenol



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1. Introduction

Polymer catalysts, which feature catalytically active functional groups integrated into their polymer structure, are widely used in the field of organic synthesis. Among their various applications, their role in facilitating asymmetric synthesis is particularly noteworthy [1]. Due to the high stability and non-volatile nature of polymers, the advantages of using recyclable polymer catalysts over traditional small molecule catalysts are their being non-corrosive and eco-friendly, with fewer disposal problems and easy recovery; hence, they are vital for various processes in the chemical industry. Some selected examples of polymer catalysts used in organic synthesis are shown in Figure 1 [1,2], such as polyaniline [2]. Polyether amine, also known as terminal amine polyether, is a type of polymer wherein the main chain structure of polyether and hydroxyl groups at the ends is replaced by that of amino groups. This unique structure imparts excellent performance to polyether amine. It is widely utilized in various applications, including polyurethane reaction injection molding materials [3], polyurea coatings [4], epoxy resin curing agents [5], and gasoline detergent formulations [6]. Polyether amine has been previously employed as a phase-transfer catalyst [7,8], but its broader catalytic applications have not been thoroughly investigated. Herein, we systematically explored the efficacy of one specific kind of three-arm polyether amine **1** as a base catalyst for the aerobic oxidative coupling of thiophenols to synthesize disulfides.

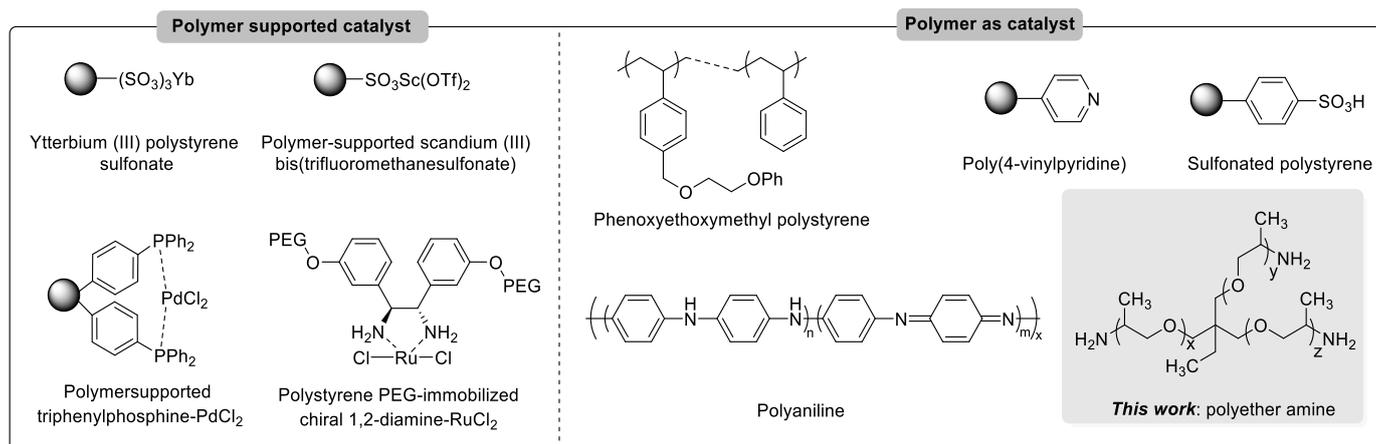


Figure 1. Selected examples of polymer catalysts in organic synthesis.

Disulfide bonds (S-S) are a ubiquitous structural element frequently encountered in peptides and proteins within biological organisms. Organic compounds featuring functionalized disulfide bonds have received significant attention due to their diverse applicability in various sectors, including industry [9,10], pharmaceuticals [11–14], pesticides [15], protein chemistry [16–18], and more (Figure 2). For instance, electron-rich aromatic symmetrical disulfides such as 1,2-Bis(4-methoxyphenyl)disulfane can be employed to catalyze the aerobic oxidative cleavage of C=C bonds [19]. Consequently, the rapid and efficient synthesis of disulfides is of utmost importance in the field of organic synthetic methodology. One of the most important methods to prepare disulfides is the appropriate oxidation of thiols [20,21]. Traditionally, during the chemical synthesis of disulfides, stoichiometric strong oxidizing agents such as iodine/bromine [22], hydrogen peroxide [23], ammonium peroxydisulfate [24], and $\text{Cu}(\text{NO}_3)_2 \cdot \text{H}_2\text{O}$ [25] are employed. Nevertheless, the employment of stoichiometric oxidizing agents always results in environmental concerns, along with the formation of over-oxidized by-products of thiol, including thiosulfinate, thiosulfonate, and sulfonic acids [26]. Given these issues, the catalytic oxidation of thiols using environmentally benign terminal oxidants like molecular oxygen or air has attracted increasing interest. Various catalysts have been explored for the catalyzed oxidative coupling of thiols to synthesize the corresponding disulfides, including but not limited to 1-butyl-3-methylimidazolium methylseleninic acid salt (Scheme 1a) [27] and heterocyclic bismuth (III) compounds (Scheme 1b) [28], as well as some base catalysts such as Cs_2CO_3 (Scheme 1c) [29]. However, challenges related to toxicity and limited recyclability remain to be addressed. Therefore, the development of environmentally friendly and recyclable catalysts for the catalyzed aerobic oxidation of thiols continues to be a critical objective. To our knowledge, there is no report available for the synthesis of disulfides using polyether amine as a green catalyst.

In the present study, we unveiled a novel application of polyether amine **1** as a base catalyst for the aerobic oxidation of thiophenols to synthesize corresponding disulfides under room temperature conditions (Scheme 1d). The main benefits, such as environmental friendliness, reusability, ease of handling, and no peroxide by-product, make the reaction process economically viable.

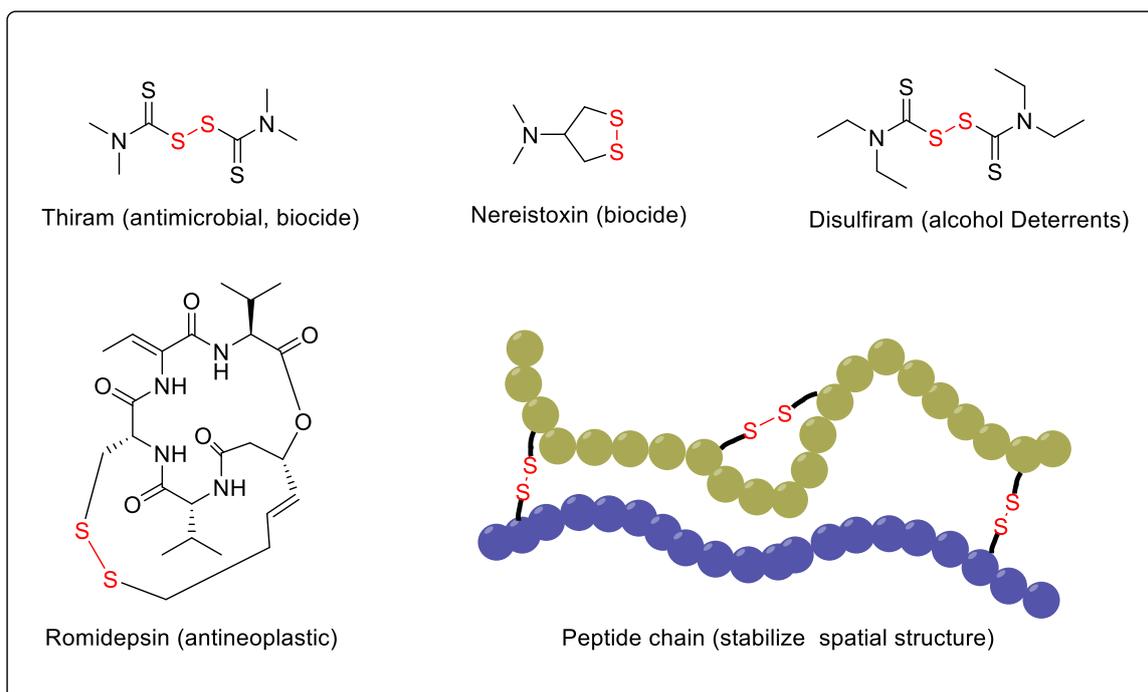
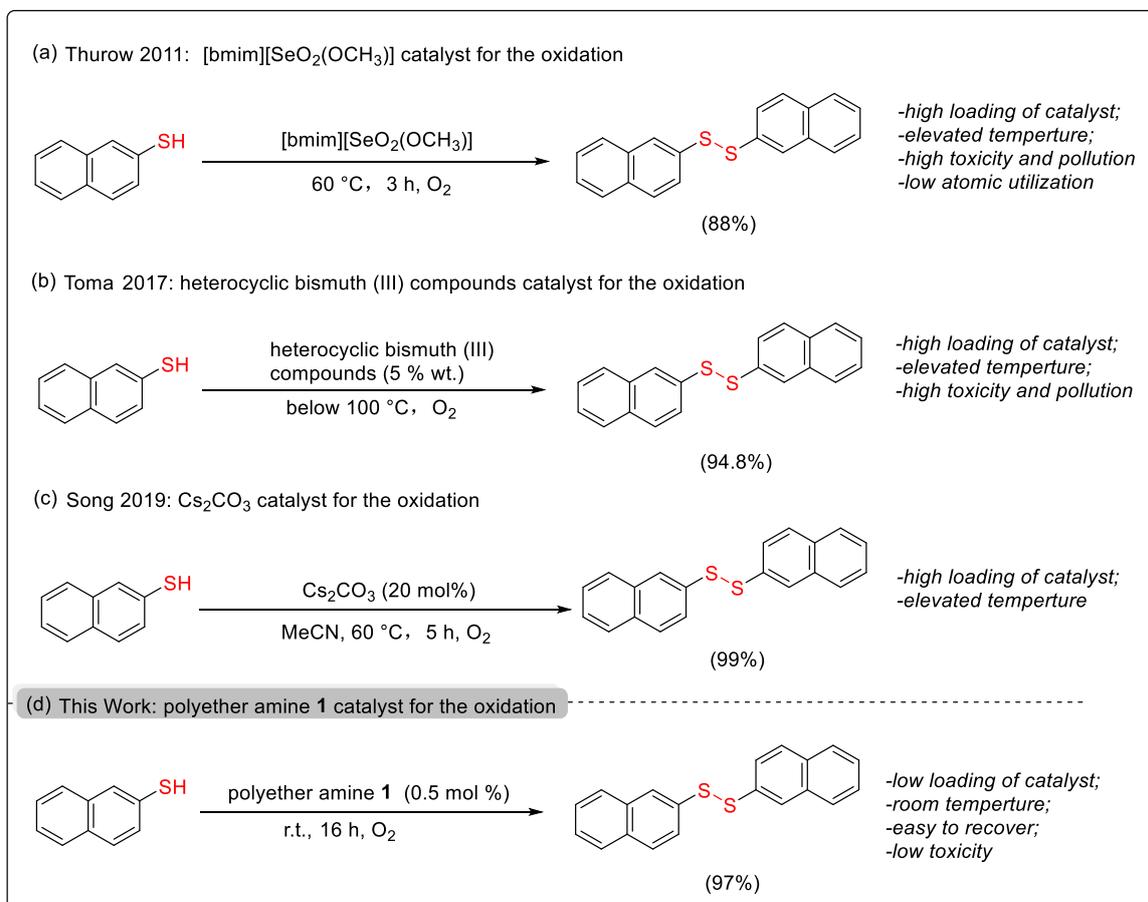


Figure 2. Selected applications of disulfides.



Scheme 1. The catalyzed aerobic oxidation of thiophenols.

2. Materials and Methods

2.1. General Information

The three-arm polyether amine (polyether amine **1**, CAS number: 39423-51-3) adapted in this study is a kind of polypropylene oxide mainly terminated by the primary amino group, and it is characterized by low viscosity, low coloration, and low vapor pressure. The polyether amine **1** was sourced from Zibo Zhengda Polyurethane Co., Ltd. (Zibo, China). The structure, along with the specific properties of polyether amine **1**, are detailed in Table 1.

Table 1. The structure and properties of polyether amine **1**.

Structure	Properties	Specifications
	Molecular weight	About 440
	Appearance	Colorless-to-pale-yellow liquid
	Degree of functionality	~3
	Total amine meq/g	6.1–6.6
	Primary amine %	≥90
	Color, Pt-Co (APAH)	≤50
	Water, wt%	≤0.25
	Density g/mL (lb/gal), 25 °C	0.978 (8.12)
	Viscosity cSt, 25 °C	72
	Flash point PMCC, °C (°F)	218.5 (425.3)
	pH	11.6
	CAS number	39423-51-3

The glassware underwent overnight drying in an oven prior to being put to use. All chemicals and acetonitrile (CH₃CN) were purchased from commercial suppliers and applied directly without additional purification unless specified otherwise. All the thiophenols were supplied by Energy Chemical and InnoChem. Oxygen and argon were obtained from Jinghui Gas. Deionized water was utilized in all experimental procedures. The term “Room temperature (r.t.)” refers to temperatures within the range of 20 to 25 °C.

NMR spectra were acquired with a Bruker Avance NOE 500 operating for ¹H NMR at 500 MHz and ¹³C NMR at 126 MHz, employing TMS as internal standard. And the ¹H NMR and ¹³C{¹H} NMR data were manipulated either directly from the spectrometer or via a networked PC with appropriate software. Unless otherwise stated, all samples were analyzed in CDCl₃. Reference values for the residual solvent were set as δ = 7.27 (CDCl₃) and δ = 2.50 (DMSO-*d*₆) for ¹H NMR, and as δ = 77.1 (CDCl₃) for ¹³C{¹H} NMR. The multiplicity of coupled signals was denoted by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; br = broad signal. They were expressed in Hz.

Thin-layer chromatography was conducted on SIL G/UV254 silica glass plates, and plates were visualized using ultra-violet light (254 nm) and KMnO₄ solution. Silica gel flash column chromatography employed silica gel 60, 35–70 μm.

2.2. Calculation of the Yield by Internal Standard Using ¹H NMR

The NMR internal standard method excels in quantifying yields with precision and versatility in organic synthesis. Its real-time monitoring, non-destructive nature, and robustness against external factors ensure reliable results. Additionally, the method's simplicity in data interpretation makes it highly user-friendly for researchers in the field.

In the process of the optimization studies, 1,1,2,2-tetrachloroethane was chosen as the internal standard for calculating yields utilizing the ¹H NMR internal standard approach. The procedure involves the integration of ¹H NMR signals corresponding to the target product and an internal standard, which is a known quantity introduced into the reaction mixture. The ratio of the integrated areas of these signals provides a quantitative measure

of the product formation. By comparing this ratio to the known quantity of the internal standard, the yield of the desired product can be accurately determined.

Yields were determined via ^1H NMR using the following equation:

$$\text{Yield} = \left(\frac{\text{Area}_{\text{product}}}{\text{Area}_{\text{internal standard}}} \right) \left(\frac{n_{\text{internal standard}}}{n_{\text{theoretical product}}} \right) \times 100\%. \quad (1)$$

$\text{Area}_{\text{product}}$ represents the integration of the product peak, $\text{Area}_{\text{internal standard}}$ represents the integration of the internal standard peak, $n_{\text{internal standard}}$ represents the quantity of moles of the internal standard, and $n_{\text{theoretical product}}$ represents the theoretical quantity of moles of the product.

2.3. Optimization Studies for the Catalyzed Aerobic Oxidation of Thiophenols

4-methylbenzenethiol (62.1 mg, 0.500 mmol) and polyether amine **1** (0.5–100 mol %) in CH_3CN (0.500 mL) were introduced into a 10 mL dried round-bottom flask. The flask was subsequently purged with air or oxygen and stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with EtOAc (10.0 mL) and washed with saturated salt solution three times (3×5.00 mL) to get rid of polyether amine **1**, which possibly influenced the calculation of the yield via the internal standard using ^1H NMR. The organic layers were combined, dried over anhydrous Na_2SO_4 , filtered, and then concentrated via rotary evaporation. The crude product was characterized by ^1H NMR (CDCl_3 , 500 MHz), and the yield was determined through the use of the internal standard (1,1,2,2-tetrachloroethane) and comparison with corresponding samples.

2.4. General Procedure for the Catalyzed Aerobic Oxidation of Thiophenols

A solution of polyether amine **1** (22.0 mg, 0.0500 mmol) in 10 mL CH_3CN was prepared in a 10 mL dried volumetric flask. Subsequently, a 10 mL dried round-bottom flask was supplemented with thiophenol (0.500 mmol) and 0.500 mL of the polyether amine **1** solution in CH_3CN . The flask was then filled with oxygen via a needle from a balloon filled with the gas, and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc (10.0 mL) and washed with saturated salt solution three times (3×5.00 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 , filtered, and then concentrated via rotary evaporation. The crude product was purified via silica gel flash column chromatography (silica, 0–65% EtOAc/hexane) to obtain the desired product, and the structure of the target product was characterized through ^1H NMR and ^{13}C NMR.

1,2-Di-p-tolyldisulfane (**2a**) [30]. According to the general procedure, the oxidation of 4-methylbenzenethiol (62.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O_2 atmosphere. After silica gel flash column chromatography (100% hexane), 61.0 mg of **2a** was afforded in 99% yield as a white solid. ^1H NMR (500 MHz, CDCl_3 , ppm) δ 7.40–7.35 (m, 4H), 7.09 (m, 4H), 2.31 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3 , ppm) δ 137.5, 11.1 mg, 0.0025 mmol 34.0, 129.9, 128.6, 21.1.

1,2-Di-m-tolyldisulfane (**2b**) [31]. According to the general procedure, the oxidation of 3-methylbenzenethiol (62.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O_2 atmosphere. After silica gel flash column chromatography (100% hexane), 60.4 mg of **2b** was afforded in 98% yield as a white solid. ^1H NMR (500 MHz, CDCl_3 , ppm) δ 7.22 (d, $J = 7.3$ Hz, 4H), 7.13–7.08 (m, 2H), 6.95 (m, 2H), 2.24 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3 , ppm) δ 138.9, 137.0, 129.0, 128.1 ($\times 2$), 124.6, 21.4.

1,2-Bis(4-methoxyphenyl)disulfane (**2c**) [30]. According to the general procedure, the oxidation of 4-methoxybenzenethiol (70.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O_2 atmosphere. After silica gel flash column chromatography (0–12.5% EtOAc/hexane), 67.5 mg of **2c** was afforded in 97% yield as a colorless oil. ^1H NMR (500 MHz, CDCl_3 , ppm) δ 7.35–7.29 (m, 4H), 6.75 (m, 4H), 3.72 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3 , ppm) δ 160.0, 132.7, 128.5, 114.7, 55.4.

1,2-Bis(2-methoxyphenyl)disulfane (**2d**) [30]. According to the general procedure, the oxidation of 4-methoxybenzenethiol (70.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (0–12.5% EtOAc/hexane), 68.2 mg of **2d** was afforded in 98% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.53 (m, 2H), 7.18 (m, 2H), 6.91 (m, 2H), 6.85 (m, 2H), 3.90 (s, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 156.7, 127.8, 127.7, 124.7, 121.4, 110.6, 56.0.

1,2-Bis(3,4-dimethoxyphenyl)disulfane (**2e**) [30]. According to the general procedure, the oxidation of 3,4-dimethoxybenzenethiol (85.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (0–12.5% EtOAc/hexane), 82.9 mg of **2e** was afforded in 98% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.06 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 7.01 (m, 2H), 6.79 (s, 1H), 6.78 (s, 1H), 3.87 (s, 6H), 3.83 (s, 6H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 149.6, 149.2, 128.7, 123.9, 114.1, 111.3, 56.0, 55.9.

1,2-Bis(3,5-dimethoxyphenyl)disulfane (**2f**) [32]. According to the general procedure, the oxidation of 3,5-dimethoxybenzenethiol (85.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (0–12.5% EtOAc/hexane), 82.1 mg of **2f** was afforded in 97% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.09 (dd, *J* = 8.1, 6.9 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 4H), 2.25 (s, 12H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 143.5, 134.8, 129.3, 128.1, 21.5.

4,4'-Disulfanediyldianiline (**2g**) [33]. According to the general procedure, the oxidation of 4-aminobenzenethiol (62.6 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (50–65% EtOAc/hexane), 61.5 mg of **2g** was afforded in 99% yield as a yellow solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.25 (m, 4H), 6.57 (m, 4H), 3.76 (br, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 147.2, 134.0, 125.8, 115.5.

3,3'-Disulfanediyldianiline (**2h**) [33]. According to the general procedure, the oxidation of 3-aminobenzenethiol (62.6 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (50–65% EtOAc/hexane), 60.8 mg of **2h** was afforded in 98% yield as a yellow solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.06 (t, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 7.0 Hz, 2H), 6.80 (d, *J* = 2.1 Hz, 2H), 6.50 (m, 2H), 3.68 (s, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 147.2, 138.1, 129.9, 117.1, 113.9, 113.0.

2,2'-Disulfanediyldianiline (**2i**) [33]. According to the general procedure, the oxidation of 2-aminobenzenethiol (62.6 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (50–65% EtOAc/hexane), 60.8 mg of **2i** was afforded in 98% yield as a yellow solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.17–7.12 (m, 4H), 6.69 (dd, *J* = 8.4, 1.3 Hz, 2H), 6.58 (td, *J* = 7.5, 1.3 Hz, 2H), 4.19 (s, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 148.7, 136.9, 131.6, 118.8, 118.3, 115.3.

1,2-Di(naphthalen-2-yl)disulfane (**2j**) [30]. According to the general procedure, the oxidation of naphthalene-2-thiol (80.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 77.2 mg of **2j** was afforded in 97% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.97 (m, 2H), 7.79–7.74 (m, 4H), 7.71 (m, 2H), 7.61 (m, 2H), 7.48–7.40 (m, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 134.4, 133.6, 132.6, 129.1, 127.8, 127.6, 126.8, 126.7, 126.3, 125.8.

1,2-Bis(4-fluorophenyl)disulfane (**2k**) [30]. According to the general procedure, the oxidation of 4-fluorobenzenethiol (64.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 61.7 mg of **2k** was afforded in 97% yield as a colorless oil. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.47–7.41 (m, 4H), 7.00 (m, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 162.7 (d, *J*_{C-F} = 248.0 Hz), 132.3 (d, *J*_{C-F} = 3.4 Hz), 131.4 (d, *J*_{C-F} = 8.0 Hz), 116.4 (d, *J*_{C-F} = 22.5 Hz).

1,2-Bis(3,5-difluorophenyl)disulfane (**2l**) [34]. According to the general procedure, the oxidation of 3,5-difluorobenzenethiol (73.1 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 71.8 mg of **2l** was afforded in 99% yield as a colorless oil. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.03 (tt, *J* = 7.1, 3.8 Hz, 2H), 6.70 (tt, *J* = 8.7, 2.2 Hz, 1H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 163.2 (dd, *J*_{C-F} = 252.5, 13.0 Hz), 139.8 (t, *J*_{C-F} = 9.1 Hz), 111.2–106.3, 103.1 (t, *J*_{C-F} = 25.5 Hz).

1,2-Bis(4-chlorophenyl)disulfane (**2m**) [30]. According to the general procedure, the oxidation of 4-chlorobenzenethiol (72.3 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 70.4 mg of **2m** was afforded in 98% yield as a light yellow solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.42–7.38 (m, 4H), 7.29–7.26 (m, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 135.2, 133.7, 129.4 (×2).

1,2-Bis(4-bromophenyl)disulfane (**2n**) [30]. According to the general procedure, the oxidation of 4-bromobenzenethiol (94.5 mg, 0.500 mmol) was catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 92.1 mg of **2n** was afforded in 98% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.42 (m, 4H), 7.33 (m, 4H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 135.8, 132.3, 129.5, 121.6.

1,2-Bis(2-bromophenyl)disulfane (**2o**) [33]. According to the general procedure, the oxidation of 2-bromobenzenethiol (94.5 mg, 0.500 mmol) catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (100% hexane), 93.1 mg of **2o** was afforded in 99% yield as a white solid. ¹H NMR (500 MHz, CDCl₃, ppm) δ 7.53 (m, 4H), 7.28–7.25 (m, 2H), 7.08 (m, 2H); ¹³C{¹H} NMR (126 MHz, CDCl₃, ppm) δ 136.2, 133.0, 128.3, 128.0, 127.0, 121.1.

1,2-Bis(4-nitrophenyl)disulfane (**2p**) [35]. According to the general procedure, the oxidation of 4-nitrobenzenethiol (77.6 mg, 0.500 mmol) catalyzed by **1** (1.1 mg, 0.0025 mmol) under a pure O₂ atmosphere. After silica gel flash column chromatography (12.5–25% EtOAc/hexane), 74.0 mg of **2p** was afforded in 96% yield as a yellow solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.25 (m, 4H), 7.81 (m, 4H); ¹³C{¹H} NMR (126 MHz, DMSO-*d*₆) δ 146.6, 143.6, 126.7, 124.6.

2.5. A 50 mmol Scale Reaction and the Recycle of Polyether Amine **1** Catalyst

Solutions of 4-methylbenzenethiol **1a** (6210.0 mg, 50.000 mmol) and polyether amine **1** (110.0 mg, 0.2500 mmol) in 50.0 mL CH₃CN were introduced into a 250 mL dried round-bottom flask. The flask was filled with oxygen via a needle from a balloon filled with the gas, and the reaction mixture was stirred at room temperature. After 16 h, the reaction mixture was concentrated by rotary evaporator. Then it was diluted with EtOAc (100 mL) and washed with water (3 × 50.0 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and then concentrated via rotary evaporation. The crude product was purified via silica gel flash column chromatography (100% hexane), and it afforded 6022.1 mg of **2a** in 98% yield as a white solid. And the water layers were freeze-dried to give 99.5 mg of recovered **1** with 90% recovery rate. Moreover, the recovered **1** was employed for the oxidation of **1a** according to the general procedure, and 60.4 mg of **2a** was afforded in 98% yield.

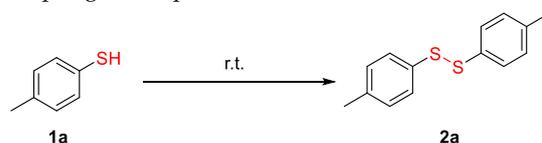
2.6. Mechanistic Investigation

A mixture of 4-methylbenzenethiol **1a** (62.1 mg, 0.500 mmol), polyether amine **1** (73.5 mg, 0.167 mmol), and 1.0 mL DMSO-*d*₆ was introduced into a 10 mL dried round-bottom flask filled with argon. The reaction mixture was stirred at room temperature for 0.5 h. Under argon atmosphere, 0.5 mL of the reaction mixture was carefully transferred into an NMR tube, which was occupied by argon ahead of time. The reaction mixture was characterized by ¹H NMR (DMSO-*d*₆, 500 MHz) to reveal the interaction between the polyether amine and the thiophenol.

3. Results and Discussion

This study commenced with the optimization of reaction conditions, wherein 4-methylbenzenethiol **1a** was selected as the model compound for reaction condition optimization. In order to assess the catalytic activity of polyether amine **1**, an initial comparative study under air was undertaken to evaluate the efficacy of various bases as catalysts, including polyether amine **1**, pyridine, BTMG, DBU, triethanolamine, and Et₃N (entries 1–6, Table 2). Our results confirmed that polyether amine **1** and Et₃N exhibited the highest catalytic activity for the aerobic oxidation of thiols (entries 5–6, Table 2), presenting a high catalytic efficiency of polyether amine **1** for the aerobic oxidation of thiophenol. Thereafter, the loading of polyether amine **1** was determined. Further study revealed that reducing the concentration of polyether amine **1** from 100 mol % to 5 mol % did not adversely impact the yield of **2a**, consistently achieving >98% yield across varying concentrations (entries 7–10, Table 2). However, a further reduction in the concentration of polyether amine **1** from 5 mol % to 0.5 mol % led to diminished yield from >98% to 62% (entries 11–13, Table 2). To enhance the yield at this lower catalyst loading, a pure O₂ atmosphere was employed in lieu of ambient atmospheric air. The results demonstrated that a pure O₂ atmosphere can significantly improve the yield of **2a** to >98% at the catalyst loading of 0.5 mol % (entry 14, Table 2). Owing to this, a pure O₂ atmosphere was chosen to conduct the subsequent reactions. Finally, a control experiment was conducted in the absence of catalyst yielded a mere 3% of **2a** (entry 15, Table 2), thereby affirming the catalytic role of polyether amine **1** in this oxidation process. In consequence, the catalyst loading of 0.5 mol % and a pure O₂ atmosphere were identified as the optimal reaction parameters for the aerobic oxidative coupling of thiophenols.

Table 2. Reaction condition optimization of the polyether-amine-1-catalyzed aerobic oxidative coupling of thiophenols.



Entry	Base (Equiv.)	Solvent	Time	Atmosphere	Yield ^a (%)
1	pyridine/100 mol %	CH ₃ CN	1 h	Air	16
2	BTMG/100 mol %	CH ₃ CN	1 h	Air	11
3	DBU/100 mol %	CH ₃ CN	1 h	Air	11
4	triethanolamine/100 mol %	CH ₃ CN	1 h	Air	5
5	Et ₃ N/100 mol %	CH ₃ CN	1 h	Air	>98
6	polyether amine 1 /100 mol %	CH ₃ CN	1 h	Air	>98
7	polyether amine 1 /30 mol %	CH ₃ CN	1 h	Air	>98
8	polyether amine 1 /20 mol %	CH ₃ CN	1 h	Air	>98
9	polyether amine 1 /10 mol %	CH ₃ CN	1 h	Air	>98
10	polyether amine 1 /5 mol %	CH ₃ CN	1 h	Air	>98
11	polyether amine 1 /3 mol %	CH ₃ CN	1 h	Air	95
12	polyether amine 1 /1 mol %	CH ₃ CN	1 h	Air	80
13	polyether amine 1 /0.5 mol %	CH ₃ CN	1 h	Air	62
14	polyether amine 1 /0.5 mol %	CH ₃ CN	1 h	O ₂	>98
15	-	CH ₃ CN	1 h	Air	3

^a Determined by ¹H NMR.

With the optimal reaction conditions in hand (entry 14, Table 2), we conducted the substrate scope exploration. Various substituted thiophenols were subjected to polyether-amine-catalyzed aerobic oxidation (Figure 3). Substrates containing electron-donating groups, such as methyl (**1a**, **1b**), methoxy (**1c**–**1f**), and amino (**1g**–**1i**), and those with electron-withdrawing groups, like fluorine (**1k**, **1l**), chlorine (**1m**), bromine (**1n**, **1o**), and nitro (**1p**), as well as polycyclic aromatic hydrocarbon (**1j**), were efficiently converted to their respective disulfides with high yields of >96%. It is worth noting that both electron-donating groups

led to high reaction yields, electron-withdrawing groups resulted in decreased reaction yields achieved with remarkable efficiency, and no peroxide by-products were detected, underscoring the robust group tolerance and high selectivity of this new protocol.

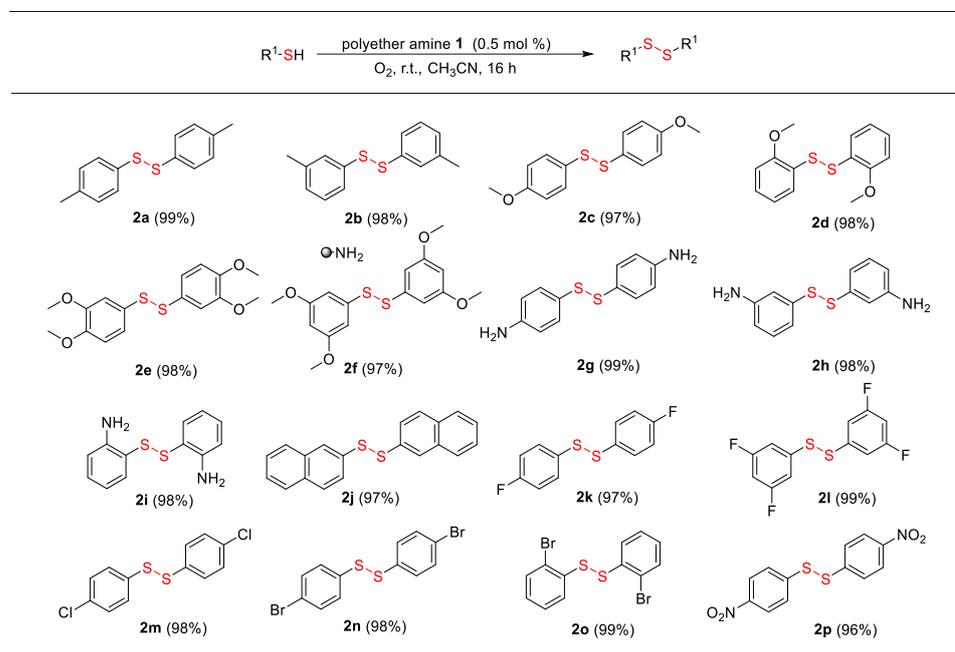
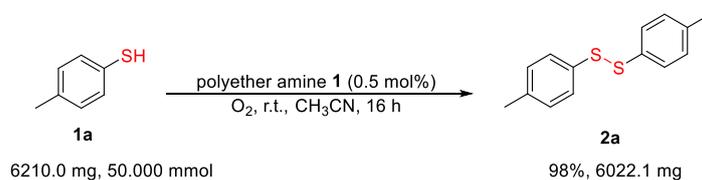


Figure 3. Polyether-amine-1-catalyzed aerobic oxidation of thiophenols to disulfides. Reaction conditions: thiols (0.5 mmol), polyether amine 1 (0.5 mol %), CH_3CN , under O_2 , r.t., 16 h.

Moreover, the scalability of the reaction was effectively demonstrated through an upscaling to 50 mmol, while still preserving compound **2a** with a remarkable separation yield of 98% (Scheme 2). The catalyst employed in this reaction was recovered through water extraction followed by freeze-drying, achieving an impressive recovery rate of 90%. And the employment of recovered polyether amine **1** in the oxidation of **1a** proved that polyether amine **1** can be recovered without loss of activity. In essence, our research not only showcased the feasibility of this reaction in small-scale experiments but also validated its scalability for larger-scale synthesis and the high recovery of the catalyst polyether amine, offering robust evidence for the widespread application of this reaction in practical scenarios.



Scheme 2. 50 mmol-scale reaction.

In our investigation into the reaction mechanism of this process, we delved into the interaction between 4-methylbenzenethiol and polyether amine **1**. As demonstrated by the control experiment (entry 15, Table 2), polyether amine **1** was necessary to trigger this reaction. Under an argon atmosphere, 4-methylbenzenethiol and polyether amine **1** was mixed in deuterated solvent. Analysis of this reaction mixture using ^1H NMR spectrum (Figure 4) provided strong evidence for the deprotonation of thiophenol. In the NMR spectrum, the $-\text{SH}$ peak at 5.22 ppm for 4-methylbenzenethiol disappeared, concomitant with the $-\text{NH}_2$ peak of polyether amine **1** at 2.41 ppm, while a broad peak emerged at 5.91 ppm, which suggested the formation of $-\text{NH}_3^+$.

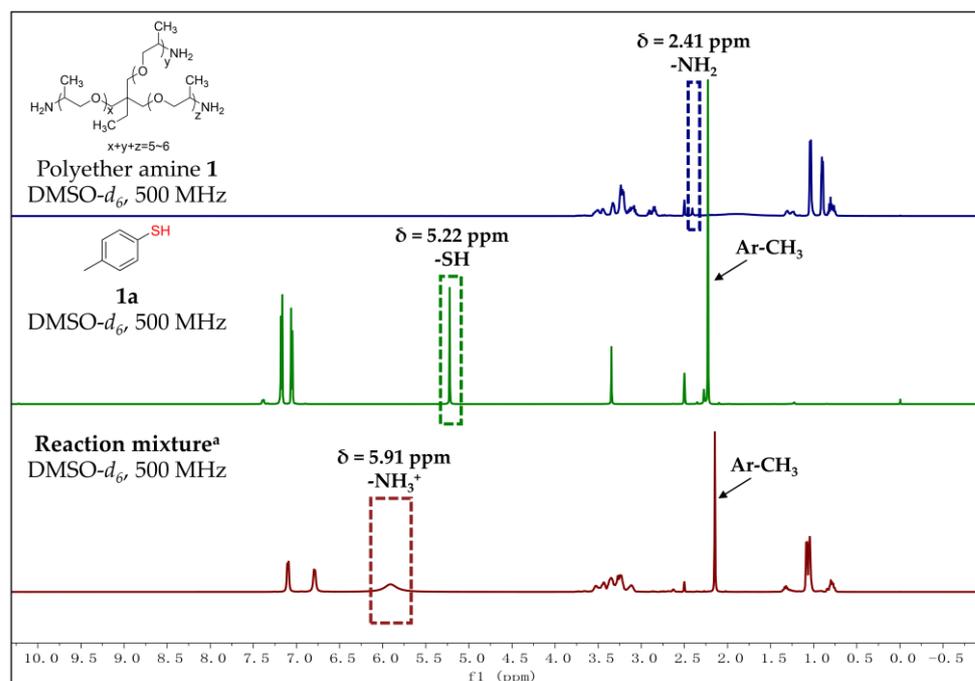
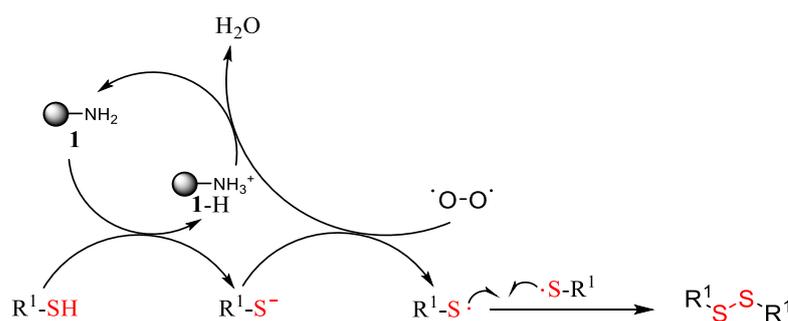


Figure 4. The study of the interaction between the thiol and the polyether amine **1**. ^a “Reaction mixture” refers to the reaction mixture for mechanistic investigation.

The observed behavior of this reaction aligns with the base-catalyzed mechanism for thiol oxidation [36]. Thiophenols initially undergo a base-mediated reaction, reacting with polyether amine **1** to form $R-S^-$. In comparison to $R-SH$, $R-S^-$ displays higher reactivity with oxygen. The oxidation of $R-S^-$ by triplet oxygen yields $R-S\cdot$, and the subsequent dimerization of two thiol radicals results in the formation of disulfide as the final product (Scheme 3). The reduced oxygen is transformed into water, which is a benign by-product. The proton in the water formed is from the protonated polyether amine **1**. Once the protonated polyether amine **1** transfers its proton to the reduced oxygen, the active polyether amine catalyst is regenerated.



Scheme 3. Mechanism of polyether-amine-1-catalyzed aerobic oxidation of thiophenols.

4. Conclusions

In summary, this study revealed a new application of polyether amine as a recoverable catalyst for the aerobic oxidation of thiophenols to synthesize disulfides. This new protocol exhibited high efficiency and broad substrate scope. Both thiophenols with electron-donating and electron-withdrawing groups were tolerated, and >96% yields were obtained in all the substrates, employing only 0.5 mol % polyether amine **1** as the catalyst and O_2 as the terminal oxidant. In addition, over-oxidation by-products was not observed in any tested substrate. Importantly, it should be noted that this reaction can be scaled up to 50 mmol and the catalyst can be recovered with an impressive 90% efficiency and without

loss of activity. This work marks the pioneering use of polyether amine in the realm of organic synthesis. The untapped potential of polyether amine in organic synthesis will be the subject of our future study.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/org5020005/s1>, including all the ^1H NMR and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of **2a–2p**.

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