



Soluble polystyrene-based sulfoxide reagents for Swern oxidation reactions

Matthew Kwok Wai Choi and Patrick H. Toy*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, People's Republic of China

Received 2 April 2003; revised 24 June 2003; accepted 4 July 2003

Abstract—Two new soluble polystyrene-based sulfoxide reagents are introduced. These polymeric reagents are used in Swern oxidation reactions where the resulting sulfide polymers are easily separated from the product by simple precipitation and filtration. The recovered reduced polymer reagents can be recycled by oxidation with *tert*-butyl hydroperoxide in the presence of acid. Attempts to use these reagents in a multi-polymer Swern oxidation reaction system were unsuccessful.

© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

The oxidation of alcohols to carbonyl compounds is one of the fundamental classes of reactions in organic chemistry. Methyl sulfoxide-based oxidation is one such reaction and it is among the most widely used methods for oxidizing primary and secondary alcohols to aldehydes and ketones, respectively.¹ The broad range of oxidation applications in which this reaction has been applied has meant that it is continuously being refined and improved.² In these reactions, methyl sulfoxide is activated and reacts with an alcohol to form a dimethylalkoxysulfonium salt. Upon treatment with a base, the salt is deprotonated and affords the desired carbonyl compound and methyl sulfide. A variety of electrophilic reagents have been used to activate methyl sulfoxide including acetic anhydride,³ *p*-toluenesulfonyl chloride,⁴ phosgene,⁵ and cyanuric chloride.⁶ Among the various activators, oxalyl chloride has established itself as the most broadly used reagent for methyl sulfoxide-based alcohol oxidation in what is known as the Swern oxidation reaction.⁷ However, one drawback of all of these reactions is that they produce the pungent smelling and highly volatile byproduct methyl sulfide and, thus, the modification of the Swern oxidation reaction to eliminate the formation of this toxic substance has been a popular research topic.

The use of insoluble polymer supports to deliver reagents and remove their byproducts is now commonplace.^{8,9} Vederas et al. have applied this methodology to the Swern oxidation reaction by attaching 6-(methylsulfinyl)hexanoic

acid to commercial chloromethyl polystyrene beads (Merrifield resin) to prepare an insoluble methyl sulfoxide equivalent.^{10,11} They observed that this reagent afforded high yields of oxidation products but that when the recovered polymer was oxidized by sodium periodate, the effectiveness of the recycled reagent was reduced. Therefore, they then attached 6-(methylsulfinyl)hexanoic acid to the soluble polymer poly(ethylene glycol).¹² This polymer supported reagent showed no loss of activity upon recycling. Recently, Crich et al. have reported a fluororous Swern oxidation reaction that uses tridecafluorooctylmethyl sulfoxide, which can be recovered and reused via a simple continuous fluororous extraction procedure followed by reoxidation with hydrogen peroxide.¹³ Finally, Node et al. have also introduced a new odorless protocol for the Swern oxidation that uses dodecyl methyl sulfoxide in place of methyl sulfoxide.¹⁴

Soluble polymers are alternative supports to insoluble resins for synthesis and reagent delivery and are becoming widely used.¹⁵ One such polymer, non-crosslinked polystyrene (NCPS) has been used in a range of application that include as a support for the synthesis of peptides¹⁶ and prostaglandins¹⁷ and for the delivery of tin¹⁸ and phosphorous¹⁹ reagents. It is easily prepared with a wide variety of functional groups by the radical co-polymerization of styrene with a functionalized styrene.²⁰ NCPS has even been used as a support for the Dess–Martin periodinane oxidation reagent.^{21,22}

We have previously reported the use of NCPS to deliver triethylamine equivalents in the REM resin-based solid-phase synthesis of tertiary amines.²³ This report is noteworthy in that it is one of the few published examples of a multi-polymer reaction system where a soluble polymer

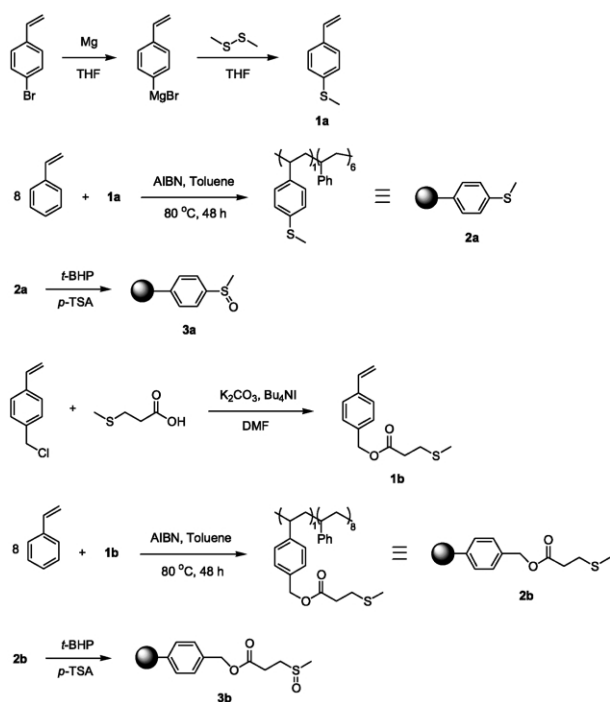
Keywords: Swern oxidation; polymer; *tert*-butyl hydroperoxide.

* Corresponding author. Tel.: +852-2859-2167; fax: +852-2857-1586; e-mail: phtoy@hkucc.hku.hk

is used to deliver a reagent or substrate to an insoluble polymer.^{24,25} Therefore, we sought to extend this methodology by using NCPS to deliver the base to methyl sulfoxide derivatized NCPS in a multi-polymer Swern oxidation reaction system.

2. Results and discussion

In order to develop a multi-polymer Swern oxidation reaction system, we prepared a soluble analogue of Crosby's thioanisole reagent¹¹ as outlined in Scheme 1. Monomer **1a** was prepared according to the literature procedure²⁶ and was co-polymerized with styrene to afford polymer **2a**.



Scheme 1. Synthesis of sulfoxide polymers **3a** and **3b**.

The sulfide moieties of **2a** were oxidized using *t*-butyl hydroperoxide (*t*-BHP)²⁷ to afford sulfoxide polymer **3a**. The loading level of **3a** was determined by elemental analysis (S content) to be 1.25 mmol/g. This was in agreement with the loading of **2a** determined by ¹H NMR analysis. The fact that the ratio of monomer incorporation (styrene:**1a**) differs from the ratio of monomer input indicates that **1a** more readily participates in the polymerization process (Section 4). The use of **3a** in the Swern oxidation of secondary alcohols was examined and these results are listed in Table 1. The reactions were carried out using oxalyl chloride activation and with triethylamine as the base. After addition of the base, the mixture was partially concentrated in vacuo and poured into methanol to precipitate the mixture of **2a** and **3a**. These polymers were filtered off and the resulting methanol solution was again concentrated in vacuo. The resulting product was then filtered through a plug of silica gel to afford the product ketone that was essentially pure as determined by ¹H NMR analysis. Having developed a protocol for the facile isolation of pure oxidation products using **3a**, we next examined replacing triethylamine with the polymer **4**²³

Table 1. Swern oxidation reactions using polymers **3a** and **3b**

Entry	Alcohol	Product	Yields (%)	
			Polymer 3a	Polymer 3b
1			92	82
2			65	75
3			55	79
4			61	63
5			60	80
6			61	71

(Fig. 1). Unfortunately, attempts to use **4** for the deprotonation step in a multi-polymer oxidation system failed.

The failure of **3a** to work in a multi-polymer system led us to prepare polymer **3b** (Scheme 1), in which the sulfoxide moieties are further removed from the polymer backbone than they are in **3a**, to examine if steric effects between the two polymer backbones caused the failure of **4**. Monomer **1b** was prepared from 4-(vinylbenzyl) chloride and 3-(methylthio)propionic acid using potassium carbonate and tetrabutylammonium iodide and then co-polymerized with styrene to afford polymer **2b**. This polymer was then oxidized with *t*-BHP to afford **3b**. The loading level of **3b** was determined by elemental analysis (S content) to be 0.94 mmol/g. Again, this was in agreement to the loading of **2b** determined by ¹H NMR analysis (Section 4). Polymer **3b** was used to oxidize the same set of alcohols that were oxidized with **3a**. As can be seen in Table 1, the two polymers afforded comparable yields of ketones. However, removing the sulfoxide moieties from the polymer backbone had no effect and **3b** also failed to work with **4** in a multi-polymer reaction system.

To study the failure of **4** we prepared small molecule analog **5** (Fig. 1). The successful application of **5** with polymers **3a** and **3b** in the oxidation 1-(4-bromophenyl)ethanol (53 and 40% yield, respectively) indicates that the polymeric nature of **4** is responsible for failure of the multi-polymer system. Further substantiation of this was found when **4** failed to afford the desired product when methyl

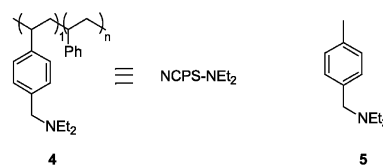


Figure 1.

sulfoxide was activated with oxalyl chloride. All attempts to use **4** resulted in intractable polymer residues that were difficult to separate from the reaction mixtures and analysis of the reaction mixtures by thin layer chromatography indicated that no desired product was present. To determine if it is the soluble nature of **4** that is the problem, we then examined commercially available insoluble diethylamino-methyl-polystyrene resin²⁸ and Amberlite® IRA-67 ion-exchange resin (basic form) as the base in the multi-polymer system, but they too failed to produce the desired products.

We next examined the recycling of the polymers recovered from the oxidation reactions. The mixtures of sulfide and sulfoxide polymers (**2a** with **3a**, and **2b** with **3b**) recovered from the oxidation reactions were reoxidized using *t*-BHP and the resulting polymers were reused. This cycle was repeated three times for both **3a** and **3b** and the results are listed in Tables 2 and 3, respectively. As can be seen from these tables, the recycled polymers were essentially as effective as were the original polymer with only a modest decrease in yields between cycles. It should be noted that even though reduced yields were observed, the products were all essentially pure after isolation. Although we cannot explain the decreased yields, we can say that based on ¹H NMR, **3a** and **3b** were essentially pure, with all of the sulfur moieties in the sulfoxide oxidation state.²⁹ Therefore, incomplete oxidation or over oxidation is not the cause of the observed results. Since the goal of modern combinatorial/parallel synthesis in the context of medicinal chemistry and drug discovery is the direct rapid production of pure compound samples for biological screening, the diminishing performance of **3a** and **3b** upon recycling may not limit their utility.

Table 2. Yield of 4'-bromoacetophenone from 1-(4-bromophenyl)ethanol oxidation using recycled polymer **3a**

Cycle Number	Yield (%)
1	92
2	86
3	79
4	75

Table 3. Yield of benzil from benzoin oxidation using recycled polymer **3b**

Cycle Number	Yield (%)
1	80
2	70
3	63
4	59

Interestingly, the fact that these polymers remain soluble and can be recycled at all indicates that previous speculation that the use of oxalyl chloride with polystyrene results in polymer cross-linking is not valid.¹⁰ If this were to happen, cross-linking of polymers **3a** and **3b** would have made them become insoluble and forced them to precipitate from the reaction mixtures. Therefore, our findings confirm that poor polymer compatibility with water was probably the cause for the previously reported diminished yields upon recycling of related insoluble polymer based sulfoxide reagents and that the use of oxidizing reagents that require organic

solvents, such as *t*-BHP, are preferred for polymer reoxidation.²⁷

3. Conclusions

In summary, two easily prepared and recyclable NCPS-based sulfoxide polymers have been developed that can be used in place of DMSO in Swern oxidation reactions. In the oxidation of secondary alcohols, the polymers afforded comparable yields of ketones that were isolated in essentially pure form via two simple filtration operations. The polymers were removed from the reaction product and recovered for reuse by precipitation and filtration. Oxidation of both the initially prepared and recovered polymers was accomplished using *t*-BHP in the presence of acid. Unfortunately, these polymers could not be successfully applied in a multi-polymer oxidation system. Considering the ease of preparation, cost of the starting materials, and chemical stability, polymer **3a** is preferred to **3b**. Since reagent recycling is not a major issue in modern drug discovery, the observed diminishing yields upon reuse of the polymers is not detrimental and **3a** should be useful in medicinal chemistry for the rapid synthesis of pure compounds for biological screening. The use of polymer **3a** in the high-throughput parallel synthesis of compounds that can be isolated essentially pure is currently being investigated.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich Chemical Company or TCI Tokyo Kasei Organic Chemicals and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a nitrogen atmosphere. Tetrahydrofuran was distilled under a nitrogen atmosphere over sodium and benzophenone. Dichloromethane and dimethyl formamide were distilled from calcium hydride. Merck silica gel 60 (230–400 mesh) was used for chromatography and filtration. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F₂₅₄. The NMR spectra were recorded using a Bruker DRX 400 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. Elemental analyses were conducted at the Analytical and Testing Center of the Shanghai Institute of Organic Chemistry.

4.1.1. 4-Vinylphenyl methyl sulfide (1a).²⁶ Methyl disulfide (21.6 g, 229 mmol) was added slowly at 0°C to a solution of the Grignard reagent prepared from 4-bromostyrene (28.0 g, 153 mmol) and Mg (7.4 g, 305 mmol) in dry THF (200 mL). The mixture was stirred at room temperature for 3 h. At this time, the reaction mixture was diluted with diethyl ether (500 mL), and then washed sequentially with water (250 mL), 10% aqueous HCl (250 mL), saturated aqueous NaHCO₃ (250 mL) and brine (250 mL). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford

1a as a clear, colorless liquid (16.0 g, 70%). ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H), 5.21 (dd, 1H, *J*=10.9, 0.9 Hz), 5.70 (dd, 1H, *J*=17.6, 0.9 Hz), 6.68 (dd, 1H, *J*=17.6, 10.9 Hz), 7.17–7.40 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 15.7, 113.1, 126.6 (4C), 134.5, 136.2, 138.0. HR FAB-MS: calcd for C₉H₁₀S, 150.0503; found, 150.0500.

4.1.2. 4-Vinylbenzyl 3-(methylthio)propanoate (1b). To an anhydrous DMF (200 mL) solution of 4-vinylbenzylchloride (21.7 g, 140 mmol) was added 3-(methylthio)propionic acid (19.0 mL, 170 mmol), potassium carbonate (38.7 g, 280 mmol) and tetrabutylammonium iodide (5.2 g, 14 mmol). The reaction mixture was stirred for 24 h at 50°C. After cooling to room temperature, it was then filtered through Celite and concentrated in vacuo. The crude product was dissolved in CH₂Cl₂ (300 mL) and washed sequentially with 10% aqueous HCl (250 mL), saturated, aqueous NaHCO₃ (250 mL) and brine (250 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **1b** as a pale yellow liquid (20.6 g, 62%). ¹H NMR (400 MHz, CDCl₃) δ 2.11 (s, 3H), 2.67 (t, 2H, *J*=7 Hz), 2.76 (t, 2H, *J*=7 Hz), 5.13 (s, 2H), 5.26 (dd, 1H, *J*=10.9, 0.8 Hz), 5.76 (dd, 1H, *J*=17.6, 0.8 Hz), 6.72 (dd, 1H, *J*=17.6, 10.9 Hz), 7.25–7.47 (m, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 15.5, 29.1, 34.5, 66.3, 114.4, 126.4, 128.5, 135.2 (2C), 136.3, 137.7 (2C), 171.8. HR FAB-MS: calcd for C₁₃H₁₆O₂S, 236.0871; found, 236.0817.

4.2. NCPS-sulfide polymers

4.2.1. Poly(styrene-co-4-vinylphenyl methyl sulfide) (2a). To a solution of styrene (55.5 g, 533 mmol) and **1a** (10.0 g, 67 mmol) in toluene (400 mL) was added AIBN (0.4 g, 3 mmol). The mixture was purged with N₂ for 30 min and the solution was stirred at 90°C for 24 h. The solution was concentrated in vacuo and then the residue was taken up in 40 mL of THF. This solution was added dropwise to a vigorously stirred cold methanol (1 L). The white precipitate was filtered and dried to afford **2a** as a white powder (25.7 g, 36%). ¹H NMR (400 MHz, CDCl₃) δ 1.26–2.05 (bm, 21H), 2.42 (bs, 3H) and 6.23–7.19 (bm, 33H). The ratio of monomer incorporation into **2a** was determined by ¹H NMR to be 6:1 (styrene/**1a**).

4.2.2. Poly(styrene-co-4-vinylbenzyl 3-[methylthio]propanoate) (2b). To a solution of styrene (35.3 g, 339 mmol) and **1b** (10.0 g, 42 mmol) in toluene (400 mL) was added AIBN (0.3 g, 2 mmol). The mixture was purged with N₂ for 30 min and the solution was stirred at 90°C for 24 h. The solution was concentrated in vacuo and then the residue was taken up in 40 mL of THF. This solution was added dropwise to vigorously stirred cold methanol (1 L). The white precipitate was filtered and dried to afford **2b** as a white powder (24.0 g, 52%). ¹H NMR (400 MHz, CDCl₃) δ 1.21–2.09 (bm, 24H), 2.11 (bs, 3H), 2.67 (bs, 2H), 2.78 (bs, 2H), 5.05 (bs, 2H) and 6.20–7.21 (bm, 36H). The ratio of monomer incorporation into **2b** was determined by ¹H NMR to be 8:1 (styrene/**1b**).

4.3. NCPS-sulfoxide polymers

4.3.1. Poly(styrene-co-4-vinylphenyl methyl sulfoxide) (3a). A solution of **2a** (25.7 g, 33 mmol) in CH₂Cl₂

(200 mL) was treated with 70% *t*-BHP (21.7 mL, 157 mmol) and *para*-toluenesulfonic acid (6.3 g, 33 mmol). The mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was taken up in 50 mL of THF and this solution was added dropwise to a vigorously stirred cold methanol (1 L). The white precipitate was filtered and dried to afford **3a** as a white powder (24.9 g, 94%). A sulfur loading level of 1.25 mmol/g was determined by elemental analysis. ¹H NMR (400 MHz, CDCl₃) δ 1.26–2.05 (bm, 21H), 2.62 (bs, 3H) and 6.23–7.19 (bm, 33H). The ratio of monomer incorporation into **3a** was determined by elemental analysis (4.03% S) to be 6.1:1 (styrene/**1a**). This corresponds to a loading level of 1.25 mmol/g of polymer.

4.3.2. Poly(styrene-co-4-vinylbenzyl 3-[methylsulfinyl]propanoate) (3b). A solution of **2b** (24.0 g, 22 mmol) in CH₂Cl₂ (200 mL) was treated with 70% *t*-BHP (13.8 mL, 100 mmol) and *para*-toluenesulfonic acid (4.2 g, 22 mmol). The mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was taken up in 50 mL of THF and this solution was added dropwise to vigorously stirred cold methanol (1 L). The white precipitate was filtered and dried to afford **3b** as a white powder (23.7 g, 95%). A sulfur loading level of 0.94 mmol/g was determined by elemental analysis. ¹H NMR (400 MHz, CDCl₃) δ 1.27–2.00 (bm, 24H), 2.55 (bs, 3H), 2.87 (bs, 2H), 3.00 (bs, 2H), 5.05 (bs, 2H) and 6.20–7.21 (bm, 36H). The ratio of monomer incorporation into **3b** was determined by elemental analysis (3.06% S) to be 7.8:1 (styrene/**1b**). This corresponds to a loading level of 0.94 mmol/g of polymer.

4.4. General procedure for alcohol oxidation

A solution of **3a** or **3b** (4 equiv.) in anhydrous CH₂Cl₂ (30 mL) was cooled to –70°C and oxalyl chloride (3.7 equiv.) was added dropwise. After 30 min a solution of the alcohol (1 equiv.) in anhydrous CH₂Cl₂ was added. The mixture is stirred for at low temperature for 1 h and then triethylamine (6 equiv.) was added. The solution is kept at –40°C for 1 h and then allowed to warm to room temperature. The reaction mixture was then concentrated in vacuo and then THF (10–15 mL) was added. The solution was then poured into cold methanol (100 mL) to precipitate the polymer.³⁰ After filtration the filtrate is concentrated in vacuo and the crude residue was filtered through a plug of silica gel to provide essentially pure oxidized product. (Table 1). These reactions were typically performed on a 1 mmol scale.

4.5. General procedure for recycling of the sulfoxide polymers 3a and 3b

The polymer mixtures (**2a** and **3a** or **2b** and **3b**) recovered from the oxidation reactions were treated with 70% *t*-BHP (5 equiv.) and *para*-toluenesulfonic acid (1 equiv.) in CH₂Cl₂ (50 mL). The mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was taken up in 20 mL of THF and this solution was added dropwise to vigorously stirred cold methanol (100 mL). The white precipitate was filtered and dried. The polymers were determined to be completely and cleanly oxidized to either **3a** or **3b** by ¹H NMR analysis.³¹

4.6. *N,N*-Diethyl-4-methylbenzylamine (**5**)³²

To a THF (100 mL) solution of 4-methylbenzyl chloride (21.2 g, 151 mmol) was added diethylamine (13.5 g, 186 mmol) and 30 mL of 5*N* aqueous NaOH. The reaction mixture was stirred for 24 h at room temperature. At this time, the reaction mixture was poured into water was extracted with diethyl ether (4×100 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated in vacuo. The light-yellow crude product was purified by distillation (90°C, 0.4 mm Hg) to afford **5** as a clear, colorless liquid (20.9 g, 78%). ¹H NMR (400 MHz, CDCl₃) δ 1.03 (t, 6H, *J*=7.1 Hz), 2.33 (s, 3H), 2.51 (q, 4H, *J*=7.1 Hz), 3.52 (s, 2H), 7.11 (d, 2H, *J*=8 Hz), 7.21 (d, 2H, *J*=8 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 11.7, 21.0, 46.5, 57.1, 128.7 (2C), 128.8 (2C), 135.9, 136.7. HR FAB-MS: calcd for C₁₂H₁₉N, 177.1517; found, 177.1516.

Acknowledgements

This research was supported financially by the University of Hong Kong and the Research Grants Council of the Hong Kong Special Administrative Region, P. R. of China (Project No. HKU 7112/02P). We would also like to thank Mr Michael McNello and the Aldrich Chemical Company for their gift of many of the reagents used in this project.

References

- (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660. (c) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148–4150. (d) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. (e) Marx, M.; Tidwell, T. T. *Org. React.* **1984**, *48*, 788–793. (f) Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572. (g) Tidwell, T. T. *Synthesis* **1990**, 857–870.
- (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276. (b) Bisai, A.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 8355–8357.
- Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416–2423.
- Albright, J. D. *J. Org. Chem.* **1974**, *39*, 1977–1979.
- Takano, S.; Inomata, K.; Tomita, S.; Yanase, M.; Samizu, K.; Ogasawara, K. *Tetrahedron Lett.* **1988**, *29*, 6619–6620.
- De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907–7909.
- (a) Chrisman, W.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 2053–2056. (b) Estieu, K.; Paugam, R.; Ollivier, J.; Salaun, J.; Cordero, F. M.; Goti, A.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 8276–8277. (c) Schmitz, W. D.; Messerschmidt, N. B.; Romo, D. *J. Org. Chem.* **1998**, *63*, 2058–2059.
- Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815–4195.
- For selected applications of various insoluble polymer supported oxidizing reagents that do not involve the activation of a methyl sulfoxide see: (a) Wade, L. G.; Stell, L. M. *J. Chem. Ed.* **1980**, *57*, 438. (b) Frechet, J. M. J.; Darling, P.; Farrall, M. J. *J. Org. Chem.* **1981**, *46*, 1728–1730. (c) Bergbreiter, D. E.; Chandran, R. *J. Am. Chem. Soc.* **1985**, *107*, 4792–4793. (d) Hinzen, B.; Ley, S. V. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1907–1908. (e) Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701–5704. (f) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A. G.; Hall, B. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2239–2241. (g) Bhalay, G.; Dunstan, A.; Glen, A. *Synlett* **2000**, *12*, 1846–1859.
- Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856–7859.
- In related work, an earlier report described the use of an insoluble methyl phenyl sulfoxide reagent that was activated with chlorine Crosby, G. A.; Weinshenker, N. M.; Uh, H.-S. *J. Am. Chem. Soc.* **1975**, *97*, 2232–2235.
- Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407–2409.
- (a) Crich, D.; Neelamkavil, S. *J. Am. Chem. Soc.* **2001**, *123*, 7449–7450. (b) Crich, D.; Neelamkavil, S. *Tetrahedron* **2002**, *58*, 3865–3870.
- Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177–5179.
- (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554. (c) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325–3344. (d) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345–3384.
- Shemyakin, M. M.; Ovchinnikov, Y. A.; Kinyushkin, A. A.; Kozhevnikova, I. V. *Tetrahedron Lett.* **1965**, *6*, 2323–2327.
- (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8742–8745. (b) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943–3946. (c) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859–1862. (d) Manzotti, R.; Tang, S. Y.; Janda, K. D. *Tetrahedron* **2000**, *56*, 7885–7892. (e) Lopez-Pelegrin, J. A.; Janda, K. D. *Chem. Eur. J.* **2000**, *6*, 1917–1922.
- (a) Enholm, E. J.; Gallagher, M. E.; Moran, K. M.; Lombardi, J. S.; Schulte, J. P., II. *Org. Lett.* **1999**, *1*, 689–691. (b) Enholm, E. J.; Schulte, J. P., II. *Org. Lett.* **1999**, *1*, 1275–1277.
- (a) Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. *J. Org. Chem.* **1983**, *48*, 3721–3728. (b) Charette, A. B.; Boezio, A. A.; James, M. K. *Org. Lett.* **2000**, *2*, 3777–3779. (c) Charette, A. B.; James, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178–2180.
- Malagu, K.; Guérin, P.; Guillemain, J. C. *Synlett* **2002**, *2*, 316–318.
- Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2047–2049.
- For insoluble polymer bound IBX reagents see: (a) Mülbauer, M.; Giannis, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4393–4394. (b) Sorg, G.; Mengei, A.; Jung, G.; Rademann, J. *Angew. Chem.* **2001**, *40*, 4395–4397.
- Toy, P. H.; Reger, T. S.; Janda, K. D. *Org. Lett.* **2000**, *2*, 2205–2207.
- For multipolymer solid-phase peptide synthesis see: (a) Frank, H.; Hagenmaier, H. *Experientia* **1975**, *31*, 131–133. (b) Heusel, G.; Bovermann, G.; Gohring, W.; Jung, G. *Angew. Chem. Int. Ed.* **1977**, *16*, 642–643.
- For a multipolymer solid-phase sharpless asymmetric dihydroxylation reaction see: Han, H.; Janda, K. D. *Angew. Chem. Int. Ed.* **1997**, *36*, 1731–1733.
- Hirao, A.; Shione, H.; Ishizone, T.; Nakahama, S. *Macromolecules* **1997**, *30*, 3728–3731.

27. Cole, D. C.; Stock, J. R.; Kappel, J. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1791–1793.
28. Aldrich catalog item, 53,733-0.
29. The completeness of the oxidation was monitored by ¹H NMR analysis using the S–Me group as the signal of reference.
30. A reviewer raised the issue that methanol may potentially be oxidized to undesirable formaldehyde during this step. There are several simple means to avoid this issue. One is to use hexanes as the precipitation solvent. When it was used to remove both **3a** and **3b** from the oxidation of 1-(4-bromophenyl)ethanol, 85 and 70% yields of 4-bromoacetophenone were observed, respectively.
31. A reviewer questioned if the use of excess *t*-BHP would lead to sulfone formation. As a test, thioanisole was allowed to react with 20 equiv. of *t*-BHP in the presence of AcOH at rt for 2 days. The only product observed was the sulfoxide. Our findings are in agreement with those reported in Ref. 27.
32. Oae, S.; Yamada, N.; Fujimori, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn* **1983**, *56*, 248–256.