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A New Polymer-Attached Reagent for the Oxidation of Primary and Secondary Alcohols

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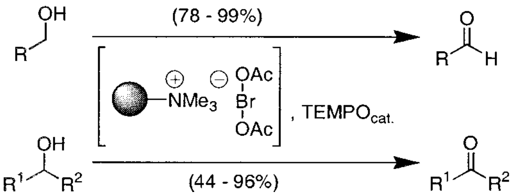
ABSTRACT

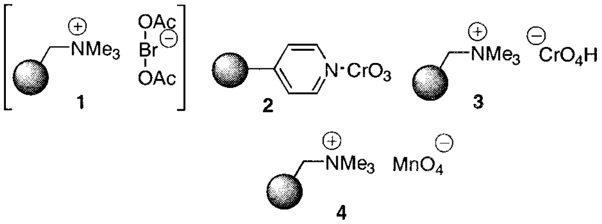


A new, polymer-bound reagent system for the efficient oxidation of primary alcohols to aldehydes and secondary alcohols to ketones in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) is described. In most cases, workup of this heavy metal-free oxidation is achieved by simple filtration followed by removal of the solvent. In selected examples this reagent was compared with the known polymer-bound permanganate and chromium(VI) reagents.

After an incubation time of more than 25 years, polymer-supported reagents have seen renewed interest lately.[1] Indeed, the dramatic developments in the need for compound libraries in pharmaceutical and agrochemical research has moved functionalized polymers from an academic curiosity to a widely recognized synthetic technique. The intrinsic advantage of this hybrid solid/solution phase technique lies in the simple purification and the possibility of using these reagents in excess to drive reactions in solution to completion. Furthermore, they may be adapted to continuous flow processes and hence used in automated synthesis.[2]

Oxidation of alcohols is a process which has been achieved with various polymer-bound reagents.[2] The most prominent and widely used examples are polymers that are functionalized with heavy metals such as CrO_3 (**2**),[3] $Cr_2O_7^{2-}$,[4] $ClCrO_3^-$,[5] $HCrO_4^-$ (**3**),[5a,6] MnO_4^- (**4**),[7] and RuO_4^- [8] ions (Scheme 1).[9]

Scheme 1



Typically, these oxidants are attached via different *N*-heterocycles or simple quarternary ammonium cations to the polymeric backbone.

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(1) Reviews: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* In press. (b) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97−148. (c) Pittman Jr.; C. U. *Polym. News* **1998**, *23*, 416−418. (d) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1998**, 1217−1239. (e) Kaldor, S. W.; Siegel, M.; G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101−106.

(2) Taylor, R. T. In *Polymer reagents and catalysts*; Ford, W. T., Ed.; ACS Symposium Series 308; American Chemical Society: Washington, DC, 1986; pp 132−154.

(3) Brunelet, T.; Gelbard, G. *Nouv. J. Chim.* **1983**, *7*, 483−490.

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Recently, Rychnovsky and co-workers[10] showed that on the basis of the work of Cella[11] and Anelli[12] the TEMPO-catalyzed oxidation of alcohols is achieved in the presence of *m*-CPBA and halide ions, where hypobromite was postulated to be the effective oxidant which oxidizes the nitroxyl radical to the *N*-oxo ammonium ion. Similarly, Espenson et al. found that hydrogen peroxide and the cocatalyst methyltrioxorhenium are only an efficient system for the oxidation of alcohols if a catalytic amount of bromide ions is added to the reaction mixture.[13] Recently, Kita and co-workers reported on polymer-bound (diacetoxy)iodo benzene which in the presence of a catalytic amount of bromide is an efficient oxidant for the transformation of secondary alcohols into ketones. Furthermore, it was shown that this reagent system oxidizes primary alcohols to the corresponding carboxylic acids.[14a] Related to this oxidation protocol is the use of (diacetoxy)iodo benzene and TEMPO.[14b]

These finding prompt us to disclose our results on the use of polymer-bound bromite(I) complex **1**[15] which is an effective oxidant for primary and secondary alcohols in particular when a catalytic amount of TEMPO is added.

However, from our earlier work on electrophilic bromite(I) complex **1**, we knew that it promotes the 1,2-haloacetoxylation of various alkenes under very mild conditions with high efficiency.[15,16] Therefore, the reagent seemed to be less well suited for the oxidation of alcohols.

Nevertheless, in initial experiments, we treated 1-phenylethanol **5** with polymer-attached reagent **1** which furnished acetophenone **6** in very good yield (Scheme 2). When the solvent was changed to toluene and the temperature was raised to 90 °C, α-acetoxy-α-bromo ketone **7** became the major product. Presumably, **7** was generated from **6** by double electrophilic bromination followed by nucleophilic displacement of one bromine atom by the acetate ion. This hypothesis was proven when acetophenone was subjected to the same reaction conditions that gave ketone **7** with a similar yield. Under these uncatalyzed conditions, benzyl alcohols **8** and **9** were also converted into the corresponding aldehydes **15** and **16** (Table 1).

Scheme 2

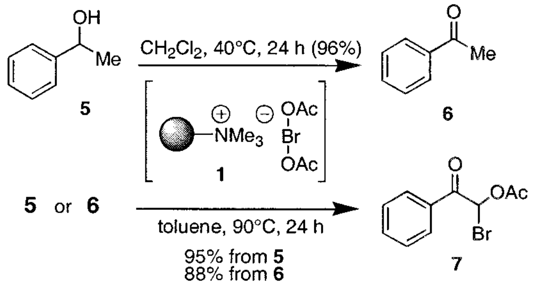
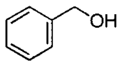
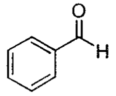
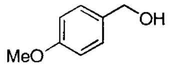
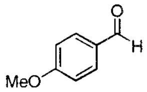
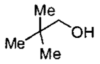
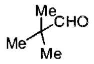
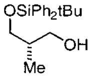
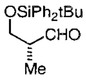
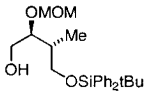
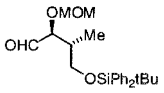
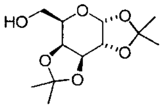
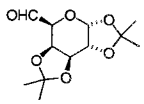


Table 1. Oxidation of Primary Alcohols

Alcohol	Conditions[a]	Product	Yield %[b]
 **8**	**1**, toluene, 40°C or **1**, CH_2Cl_2, rt, 1h TEMPO (*cat.*)	 **15**	(94)[c]
 **9**	**1**,CH_2Cl_2, 40°C, 24h	 **16**	78 (>90)
$CH_3(CH_2)_{10}CH_2OH$ **10**	**1**, CH_2Cl_2, ,rt, 3.5h, TEMPO (*cat.*)	$CH_3(CH_2)_{10}CHO$ **17**	93[c]
 **11**	**1**, $CDCl_3$, rt, 3.5h, TEMPO (*cat.*)	 **18**	(>95)[c,d]
 **12**	**1**, CH_2Cl_2, rt, 1.5h, TEMPO (*cat.*)	 **19**	99 (>95)
 **13**	**1**, CH_2Cl_2, rt, 2h TEMPO (cat.)	 **20**	99 (>95)
 **14**	**1**, CH_2Cl_2, 40°C, 24h, TEMPO (*cat.*)	 **21**	97 (>95)

[a] For details refer to the Supporting Information. [b] Transformations were quantitative and yields refer to isolated pure products. Values in parentheses refer to purity of the crude product determined by ^1H NMR spectroscopy or [c]Determined by GC. [d] The use of $CDCl_3$ allowed for the determination of the yield of the volatile product **18** by NMR spectroscopy.

Although these results were promising, we were unable to employ this procedure on less reactive secondary alcohols

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(4) Yang, H.; Li, B. *Synth. Commun.* **1991**, *21*, 1521−1526.

(5) (a) Abraham, S.; Rajan, P. K.; Sreekumar, K. *Polym. Int.* **1998**, *45*, 271−277. (b) Fréchet, J. M. J.; Warnock, J.; Farrall, M. J. *J. Org. Chem.* **1978**, *43*, 2618−2621. (c) Fréchet, J. M. J.; Darling, P.; Farrall, M. J. *J. Org. Chem.* **1981**, *46*, 1728−1730.

(6) Cainelli, G.; Cardillo, G.; Orena, M.; Sandri, S. *J. Am. Chem. Soc.* **1976**, 6737−6738.

(7) Caldarelli, M.; Habermann, J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 107−110.

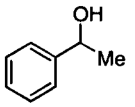
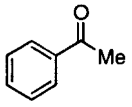
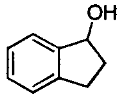
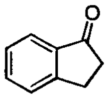
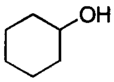
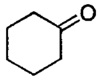
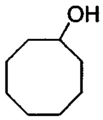
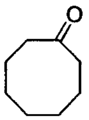
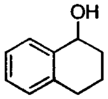
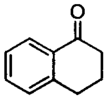
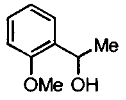
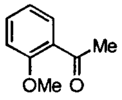
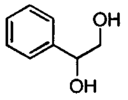
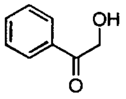
(8) (a) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907−1908. (b) Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977−979.

(9) Also the polymer-supported versions of the Swern oxidation: (a) Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407−2409. (b) Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856−7859. In addition, the Corey oxidation: (c) Crosby, G. A.; Weinshenker, N. M.; Uh, H.-S. *J. Am. Chem. Soc.* **1975**, *97*, 2232−2235.

(10) Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310−312.

(11) (a) Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860−1862. (b) Cella, J. A.; McGrath, J. P.; Kelley, J. A.; El Soukkary, O.; Hilpert, L. *J. Org. Chem.* **1977**, *42*, 2077−2080.

Table 2. Oxidation of Secondary Alcohols

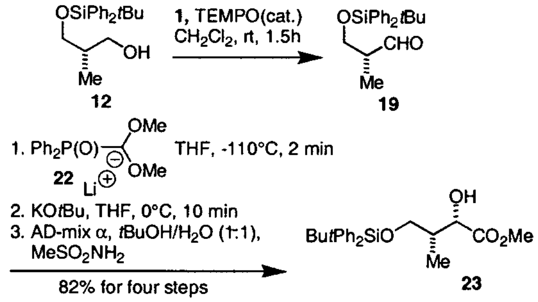
Ketone	Conditions^a	Product	Yield %^{b}
 **5**	**1**, CH_2Cl_2, rt, TEMPO (*cat.*)	 **6**	92 $(96)^c$
 **24**	**1**, CH_2Cl_2, 40°C, 24h **2**, cyclohexane, 4.5h, rt **3**, cyclohexane, 2h, rt **4**, cyclohexane, 14h, rt	 **30**	81 (95^c) $(99)^c$ $(99)^c$ $(97)^c$
 **25**	**1**, CH_2Cl_2, rt, 24h, TEMPO (*cat.*) **2**, cyclohexane, rt, 5d **4**, cyclohexane, rt, 40°C, 2d	 **31**	$(96)^c$ $(57)^c$ $--^d$
 **26**	**1**, CH_2Cl_2, rt, 24h, TEMPO (*cat.*)	 **32**	$(80)^c$
 **27**	**1**, CH_2Cl_2, rt, 24h, TEMPO (*cat.*)	 **33**	94 (>95)
 **28**	**1**, CH_2Cl_2, rt, 24h, TEMPO (*cat.*)	 **34**	96 (>95)
 **29**	**1**, CH_2Cl_2, rt, 24h, TEMPO (*cat.*)	 **35**	44^e (85)

^{a} For details refer to the Supporting Information. ^{b} Yields refer to isolated pure products. Values in parentheses refer to purity of the crude product determined by ^1H NMR spectroscopy. ^{c} Values in parentheses refer to purity of the crude product determined by GC. ^{d} 5% transformation as judged by GC. ^{e} Decomposition during chromatographic purification on silica gel.

such as cyclohexanol **25** (Table 2). However, addition of a catalytic amount of TEMPO (1−5 mol %) accelerated the oxidation process dramatically (Tables 1 and 2). Here, primary as well as secondary alcohols are converted into the corresponding aldehydes and ketones, respectively. Oxidation proceeds by treatment of alcohols **8**−**14** with a 3- to 6-fold excess of reagent **1**[17] (based on the amount of bromide[18] attached to the commercial resin) in the presence of TEMPO. Quantitative transformation of alcohols is achieved in dichloromethane. Toluene is also a suitable solvent. Except for partially protected D-galactose **14**, primary aldehydes are oxidized to aldehydes at room temperature. Considering that a polymer-bound reagent is employed, the reactions proceed rather rapidly (e.g., refer to alcohols **12** and **13**, Table 1). Importantly, we did not observe over-oxidation to the corresponding carboxylic acids.

Decisive for applications in natural product syntheses, we considered studies on the configurational integrity of a chiral center in the α-position during the reaction process and workup. On the basis of our earlier work on the asymmetric acylation of aldehydes,[19] we converted alcohol **12** into aldehyde **19** and reacted the crude product (>95% purity) with lithiated phosphine oxide **22** (Scheme 3). Elimination followed by asymmetric Sharpless dihydroxylation of the intermediate *O*,*O*-ketene acetal afforded α-hydroxy ester **23** in excellent yield as the only diastereomer, a clear indication of the high efficiency of the oxidation process. Furthermore, upscaling to 10 mmol was possible without causing reduced

Scheme 3



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(12) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem*. **1989**, *54*, 2970−2972.

(13) Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem*. **1999**, *64*, 1191−1196.

(14) (a) Tohma, H.; Takizawa, S.; Maegawa, T.; Kita Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 1306−138. (b) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piacantelli, G. *J. Org. Chem*. **1997**, *62*, 6974−6977.

(15) Preparation of reagent **1** was achieved by oxidative, iodine(III)-promoted ligand transfer onto polystyrene-bound bromide: Monenschein, H.; Sourkouni-Argirusi, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett*. **1999**, *1*, 2101−2104.

(16) (a) Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem.* **1999**, *111*, 2720−2722; *Angew. Chem., Int. Ed.* **1999**, *38*, 2594−2596. (b) Kirschning, A.; Jesberger, M.; Moneneschein, H. *Tetrahedron Lett*. **1999**, *40*, 8999−9002.

(17) Polymer-bound bromide was purchased from Fluka (3.5 mmol/g bromide). Polymer-bound reagent **1** is also available from Novabiochem (Switzerland).

(18) The need for an excess of **1** may be rationalized by assuming that only a proportional amount of immobilized halide was transformed into the hypervalent species or that only the most accessible haloate(I) anions are involved in the cohalogenation process. A 3-fold excess was sufficient in most cases but led to considerably longer reaction times as was shown by a series of oxidations of alcohol **8** to benzaldehyde **15** under varying conditions (equiv of **1**, reaction time; % transformation to **15**): 1, 24 h, 34%; 2, 24 h, 69%; 3, 24 h, >95%; 4, 2 h, >95%; 5, 1 h, >95%; 6, 30 min, >95%.

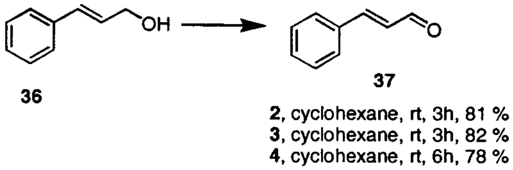
(19) (a) Kirschning, A.; Dräger, G.; Jung. A. *Angew. Chem.* **1997**, *109*, 253−255; *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 253−255. (b) Monenschein, H.; Dräger, G.; Jung, A.; Kirschning, A. *Chem. Eur. J.* **1999**, 5, 2270−2280.

selectivity or efficiency. In contrast to this result, the conventional Swern oxidation[20] in solution led to partial racemization of the intermediate aldehyde.

It is important to note that this reagent system allows oxidation of secondary aryl-substituted as well as aliphatic alcohols **5** and **24**−**29** with efficiency similar to that of primary alcohols. In general, the reaction times are prolonged because of the reduced reactivity of secondary alcohols toward polymer-bound oxidants. Still, only a few polymer-attached oxidants have been developed so far which are able to oxidize secondary alcohols. For example, solid-phase-attached perruthenate is very efficient for oxidizing primary and secondary benzylic alcohols, but it often fails to quantitatively oxidize primary aliphatic alcohols and cannot be employed for oxidizing secondary aliphatic alcohols. Therefore, we turned our attention to the more “classical” immobilized oxidants **2**−**4** and compared their properties with those of reagent **1**. Chromium(VI)-based reagents **2** and **3** are strong oxidants with reactivity comparable to that of polymer-bound bromate(I) reagent **1** as exemplified for the secondary alcohols indanol **24** and cyclohexanol **25** (Table 1).[21]

However, in our hands both reagents rapidly age within days; therefore they cannot be stored and have to be freshly prepared. This observation can be ascribed to possible self-oxidation of the polymeric backbone by the chromium(VI) species. Unlike reagent **1**, chromium(VI) reagents **2** and **3** are not well suited for recycling. Additionally, we found that polymer-bound permanganate **4** is a rather weak oxidant and can basically only be used for the oxidation of benzylic (Table 1; refer to indanol **24**)[7] and allylic alcohols such as **36** (Scheme 4). Secondary alcohols such as cyclohexanol **25** are not converted by this reagent. Therefore, it is obvious that future applications of functionalized polymer **4** will only be associated with these two groups of alcohols. This oxidant as well as polymer-bound chromium(VI) reagents **2** and **3** may complement reagent **1** (Scheme 4) in the field of unsaturated alcohols because the bromate(I) complex yields complex product mixtures when reacted with unsaturated alcohols such as **36**. Obviously, the ability of reagent **1** to add to alkenic double bonds[15,22] is not suppressed when TEMPO is used to initiate a radical-promoted oxidation.

Scheme 4



In summary, we developed a new polymer-bound non-heavy-metal-based oxidant.[23] In the presence of a catalytic amount of TEMPO, it is a powerful and generally applicable reagent for the high-yielding oxidation of primary and, importantly, secondary alcohols. The products isolated after filtration and evaporation of the solvent are very pure and can be used directly in the next step. These arguments along with the fact that all transformations proceed in the same solvent, dichloromethane, make this reagent potentially useful for automated synthesis. As long as no additional alkene functionality is present in the substrate, it is superior to polymer-bound chromium(VI) and manganese(VII) reagents in most respects.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie. We are grateful to M. Ries, M. Siemers, and H. Monenschein for expert preparative assistance.

Supporting Information Available: Spectra and descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Polymer-bound DMSO useful for the Swern oxidation may only be prepared via multistep solid-phase synthesis. Furthermore, compared to reagent **1** it is less easily recycled (refer to refs 9a and 9b).

(21) In our hands the chromium-based reagents **3** and **4** show the tendency of over-oxidation of primary alcohols.

(22) Hashem, Md. A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* **1998**, 195−197.

(23) The polymer-bound iodine-containing analogue of reagent **1** is also able to promote these kinds of oxidations. However, in part iodine is released into solution during the process, which can lead to byproducts.