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- [10] Compare entry 1 or entry 6 with our previous best results with sulfide **1**, which was 55 % yield, 97 % *ee*, and 3:1 d.r.^[3] Note this result used stoichiometric amounts of **1** and cannot be easily scaled up (see citation [3] in ref. [5]). Antilla and Wulff's process (ref. [1d]) is complementary to ours as it uses preformed diazoesters and gives *cis* aziridines (ours uses diazoalkanes/diazoalkenes and gives *trans*-aziridines).
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- [16] 2-Propenoic acid 2-bis[(1,1-dimethylethoxy)carbonyl]amino-methyl ester was prepared from serine and Boc-ON by the method described by: P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Tetrahedron Lett.* **1998**, 39, 9575–9578. We have found that this acrylate can be prepared in one step from serine methyl ester and (Boc)₂O.
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- [19] We have found from crossover experiments relating to aziridination that betaine formation is irreversible. Thus, the diastereoselectivity is controlled by nonbonding interactions that lead to the betaine.

Oxoammonium Resins as Metal-Free, Highly Reactive, Versatile Polymeric Oxidation Reagents**

Steffen Weik, Graeme Nicholson, Günther Jung, and Jörg Rademann*

Complex organic molecules can be constructed either in solution or attached to an insoluble polymeric support. Polymer-assisted solution-phase (PASP) synthesis^[1–3] offers a highly attractive supplement to these concepts by exploiting the virtues of both traditional approaches. Polymeric reagents^[4, 5] can be used in high excess and are removed by filtration, the products can be easily analyzed and further transformed in solution. They are especially suitable for parallel combinatorial synthesis.^[6, 7] They allow preparation of complex libraries by multistep syntheses in solution, they can be utilized in automated and in flow-through systems, and finally they can be employed—as will be demonstrated herein—to transform single compounds as well as complex mixtures.^[8]

The oxidation of alcohols to carbonyl compounds is one of the most relevant transformations in organic synthesis, owing to the large diversity of products that can be obtained from aldehyde and ketone precursors.^[9] Common oxidative agents for this transformation include dimethyl sulfoxide (DMSO),^[10] periodinanes^[11] as well as various heavy-metal reagents, the latter usually based on either chromium^[12] or ruthenium oxides.^[13] There are several examples of polymer-supported oxidation reagents,^[14] including heavy-metal oxides bound to ion-exchange resins.^[15, 16] One resin of this type has been recently employed in a reaction sequence leading to heterocyclic compounds.^[17] However, low reactivity with non-benzylic alcohols, potential persistence of highly toxic heavy metals in the products as well as overoxidation of aldehydes limits the use of solid-supported metal oxides in parallel syntheses.

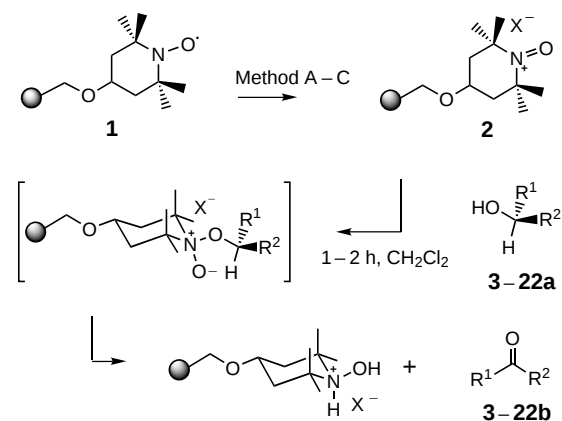
Herein we report on the generation of oxoammonium halides as oxidizing reactive species on a solid support and on the use of this reagent in the oxidation of single alcohols and of complex compound collections. Oxoammonium salts have been postulated as reactive intermediates in oxidations employing the 2,2,6,6-tetramethylpiperidine 1-oxyl radical (TEMPO), which is commonly employed under phase-transfer conditions with, for example, sodium hypochlorite as activating oxidant in the aqueous phase.^[18, 19] Recently TEMPO has been used in solution together with a polymer-attached oxidizing agent^[20] and as a catalyst on silica.^[21] No reports were found about using oxoammonium salts on insoluble, crosslinked polymers, which would allow the

[*] Dr. J. Rademann, Dipl.-Chem. S. Weik, G. Nicholson, Prof. Dr. G. Jung
Institut für Organische Chemie, Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-295560
E-mail: joerg.rademann@uni-tuebingen.de

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integration in common polymer-assisted solution-phase synthesis operations.^[22] We decided to synthesize and employ reactive oxoammonium salts in a water-free system with the intention of generating a highly reactive oxidation agent that avoids over-oxidation to the acid due to the absence of oxygen donors.^[23]

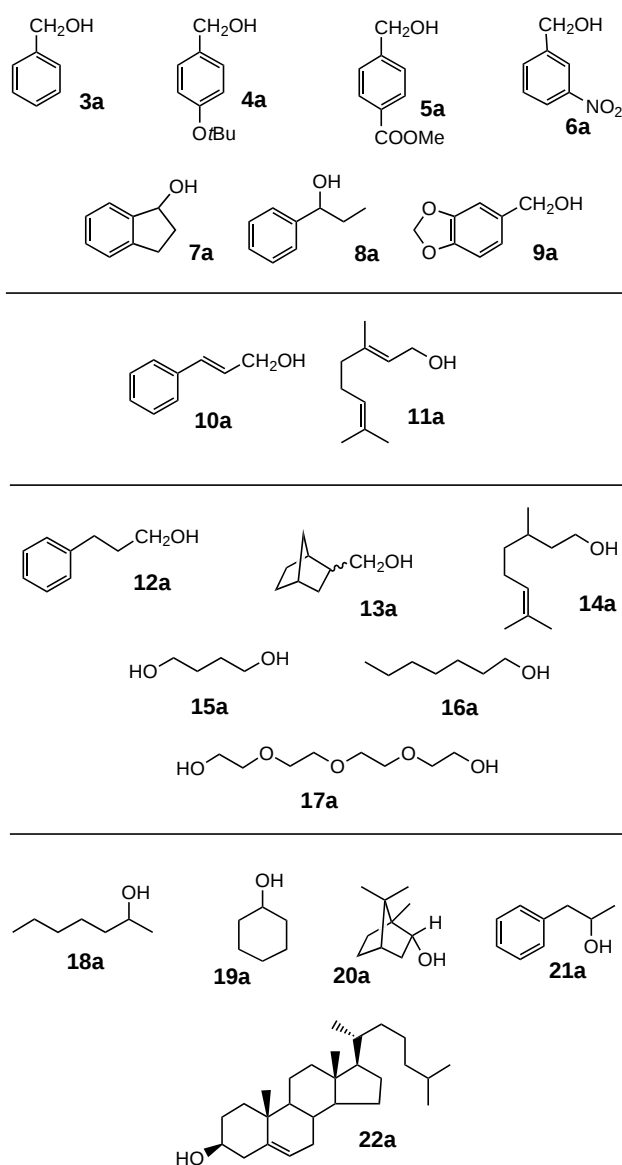
The 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl radical was coupled to 1% divinylbenzene polystyrene resin by employing sodium hydride as base (Scheme 1). Elemental analysis of



Scheme 1. Oxoammonium resin **2** was prepared in a three-step procedure from chloromethylated polystyrene resin and was employed in the oxidation of alcohols **3a–22a**. Oxidation of resin **1** was effected by Br_2 , Cl_2 , or NCS/HCl (Methods A–C).

the resulting resin **1** revealed a loading of 0.93 mmol g^{-1} of the radical; the presence of the free radical electron was proved by ESR spectroscopy, which displayed the characteristic triplet signal due to coupling with the ^{14}N nucleus. Likewise, the high-resolution magic angle spinning (HR-MAS) NMR spectrum displayed significant line broadening, which can be attributed to enhanced relaxation of the nuclear magnetization through interaction with the persistent electron spins. Oxidation of the radical was performed with elemental bromine, chlorine, and *N*-chlorosuccinimide/ HCl (Methods A–C; Scheme 1). Following oxidation, the resulting resin **2** displays a strong absorption at 1700 cm^{-1} in the attenuated total reflection IR spectrum (FT-ATR-IR), presumably characteristic for the $\text{N}=\text{O}$ double bond of the reactive intermediate. The oxidation is accompanied by a distinct color change from colorless to a bright orange-red in case of chloride as counterion and brown-red in case of bromide.

We investigated the reactivity of reagent **2** towards a selection of 20 different alcohols **3a–22a**, representing the categories of benzylic, allylic, primary as well as secondary aliphatic alcohols. Comparing the different counterions, chloride was more reactive than bromide and led to fewer side products, presumably due to the presence of the Br_3^- ion in the case of bromine oxidation. Various temperatures were tested; all comparative reactions were conducted at room temperature (Table 1). Analysis and quantification of all reactions were conducted by GC either with a flame-ionization detector (FID) or a mass-sensitive detector (EI-MS, 70 eV). Compounds were identified by comparison with pure samples, by software-based structure assignment using the



mass spectra and the NIST spectral library, or by NMR analysis.

First, alcohol **9a** was treated with various amounts of **2**. Complete conversion within 1 h was achieved with three equivalents of **2** (Figure 1). Results of the oxidation (Table 1) can be summarized as follows: Clean and fast quantitative conversion of the starting alcohols was observed in general, only in the case of alcohol **17a** was the starting material detected after the reaction. All benzylic or allylic alcohols yielded aldehyde or ketone products in very good purities. The same was found for open-chain primary and secondary alcohols. Representative yields for less volatile products such as aldehydes **9b**, **10b**, or **20b** were determined by weight and were around 90%; the identity of the products was confirmed by NMR analysis (250 MHz , CDCl_3).^[24]

Very easily enolizable primary ketones obtained from cyclohexanol (**19a**), 1-phenylpropan-2-ol (**21a**), and cholesterol (**22a**) could be further converted to the diones, **19c**, **21c**, and **22c**, respectively (Scheme 2). In this reaction the primary

Table 1. Results of the oxidation of the alcohols **3a–22a**.

Starting alcohol	Main product ^[a]	Product purity [%]	GC-EI-MS-analysis (characteristic signals ^[b] [<i>m/z</i>])
3a	3b	> 95	106 [<i>M</i> ⁺], 105, 77, 51
4a	4b	> 95	178 [<i>M</i> ⁺], 163, 121, 93, 77, 65, 57, 41
5a	5b	> 95	164 [<i>M</i> ⁺], 133, 119, 105, 77, 51
6a	6b	> 95	151 [<i>M</i> ⁺], 150, 105, 77, 51
7a	7b	85	132 [<i>M</i> ⁺], 104, 78, 63, 51
8a	8b	> 95	134 [<i>M</i> ⁺], 105, 77, 51
9a	9b	> 95	150 [<i>M</i> ⁺], 149, 121, 91, 63
10a	10b	> 95	132 [<i>M</i> ⁺], 131, 103, 77, 51
11a	11d	83	150 [<i>M</i> ⁺], 135, 122, 107, 95, 91, 82, 77, 54, 39
12a	12b	90	134 [<i>M</i> ⁺], 105, 91, 78, 65, 51, 39
13a	13b	72 ^[c]	124 [<i>M</i> ⁺], 106, 95, 91, 80, 67, 55
14a	14c	60 ^[d]	154 [<i>M</i> ⁺], 139, 136, 121, 111, 95, 84, 81, 71, 55, 41
15a	15c	65	86 [<i>M</i> ⁺], 56, 42, 41, 39
16a	16b	> 95	96, 86, 81, 70, 57, 55, 44, 41
17a	17c	30 ^[e]	146, 102, 86, 73, 58, 45, 43, 32
18a	18b	90	114 [<i>M</i> ⁺], 99, 85, 71, 58, 43, 39
19a	19c	85	112 [<i>M</i> ⁺], 97, 83, 70, 55, 51, 43, 39
20a	20b	> 95	152 [<i>M</i> ⁺], 137, 108, 95, 81, 69, 55, 41
21a	21c	76	148 [<i>M</i> ⁺], 105, 77, 51, 43
22a	22c	79	398 [<i>M</i> ⁺], 383, 370, 356, 285, 243, 137

[a] Ketones or aldehydes obtained in the primary oxidation are designated as compounds **3b–22b**. [b] In accordance with EI mass spectra from the NIST spectral library. Further products see Scheme 2. [c] Decarbonylated by-product. [d] 20% **14b**. [e] Mainly recovered diol.

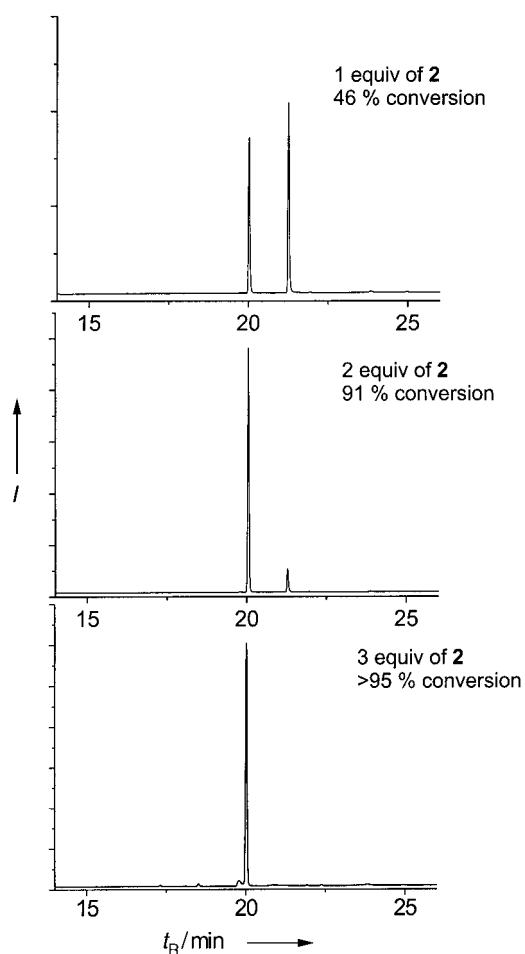
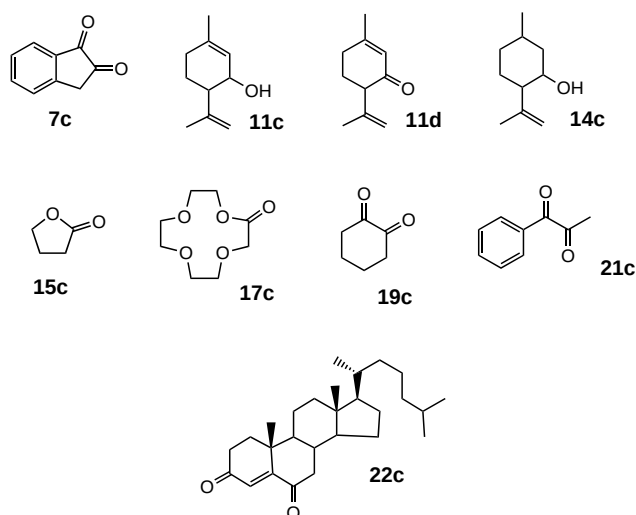


Figure 1. GC analysis (FID) of the reaction of **9a** in CH_2Cl_2 (1 mg mL^{-1}) for 1 h with one, two, and three equivalents of the polymeric oxoammonium salt **2**.



Scheme 2. Secondary oxidation products obtained from alcohols by treatment with resin **2**.

oxidation product, for example, cyclohexanone is transformed to the final diketone product via an enolized intermediate.^[25] In contrast, diols (**15a**, **17a**) are converted to lactones (**15c**, **17c**) in the secondary oxidation step. Interestingly, cascade-like reactions were observed with terpene alcohols such as geraniol (**11a**) and citronellol (**14a**). Monitoring by GC-MS revealed that with an excess of reagent **2**, the primary oxidation products, the open-chain terpene aldehydes (**11b**, **14b**) were cyclized in an ene-type reaction to furnish the secondary alcohols (**11c**, **14c**).^[26] For the geraniol system the secondary product could be further oxidized to yield the terpene ketone **11d** in good purity.

Finally, a compound collection consisting of 15 alcohols (**3a–10a**, **12a**, **13a**, **15a**, **16a**, **18a–20a**) was employed to investigate the feasibility of converting complex mixtures

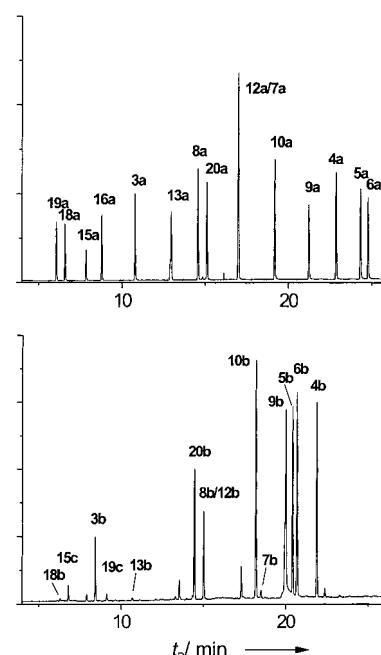


Figure 2. GC analysis (FID) of a mixture of 15 alcohols (top) and the product mixture obtained following oxidation with resin **2** (bottom).

of chemically diverse alcohols (Figure 2). The mixture (1 mg mL⁻¹ per alcohol) was analyzed by GC-FID as well as GC-MS. In the starting mixture all alcohols could be separated and identified by their mass spectra. Following treatment with resin **2** for 2 h, GC analysis revealed the complete disappearance of all of the alcohol precursors. All but one of the expected aldehyde, ketone, lactone, or dione products could be separated and identified; **8b** and **12b** co-eluted, whereas **16b** was not detected at all. The concentration of products with a low-boiling point eluting early in the GC was reduced, whereas the concentration of the high-boiling aldehydes and ketones remained stable in the complex mixture.

In summary, the reported polymer-bound oxoammonium reagent should be of great value in polymer-supported transformations in solution, in automated parallel synthesis operations, and in flow-through reactors in up-scaled production processes. Herein we have only considered the preformed oxoammonium salts as reactive species. The potential of the TEMPO–resin should, however, be exploitable as well as in situ generated oxoammonium salt, obtained by one of the available regeneration systems (e.g. Cu^{II}/O₂), in multiple phases, or by electrochemical means.

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- [24] Experimental details: a) Preparation of TEMPO resin **1**. Sodium hydride (1.28 g, stabilized with paraffin oil, 60%, 32.1 mmol) was

suspended in dry DMF (40 mL) in a 100 mL round-bottom flask. 2,2,6,6-Tetramethylpiperidine 1-oxyl (3.57 g, 20.7 mmol) was added slowly, the flask was sealed with a drying tube, and stirred for 3 h. Chloromethylated divinylbenzene (1%)/polystyrene (loading 1.07 mmol g⁻¹, 100–200 mesh, 2 g, 2.14 mmol) was added and the reaction was agitated for three days at room temperature. The resin was filtered and thoroughly washed with water, water/DMF (1/1), DMF, THF, CH₂Cl₂, and MeOH and dried in vacuo. Loading: 0.93 mmol g⁻¹. Chlorine content: 0.07%. b) Oxidation to oxoammonium resin **2** (Method C; Scheme 1). *N*-Chlorosuccinimide (6 equiv) was dissolved in CH₂Cl₂, 4 M HCl in dioxane was added (5 equiv). After 5 min the solution was added to resin **1** (1 equiv) swollen in dry CH₂Cl₂. Agitation for 15 min was followed by filtration of the resin and washing with dry CH₂Cl₂. Half-life time (*t*_{1/2}) of the activated form was about one week when stored in vacuo at 4°C. c) Oxidation of alcohols. Alcohols **3a–22a** (1 equiv) were dissolved in dry CH₂Cl₂. Freshly prepared oxoammonium resin **2** (5 equiv as calculated from the loading of resin **1**) was added and agitated at room temperature for 1 h for the primary alcohols and 2 h for the secondary alcohols. The resin was filtered and washed with CH₂Cl₂, the washings were employed for analysis by GC, using a 25 m × 0.32 mm Permaabond SE 54 (*d*_f = 1.0 μ) fused silica capillary. Temperature program: 50°C, 2 min isotherm, 5°C min⁻¹ to 200°C. H₂ was used as carrier gas (*p*_i = 50 kPa) for FI detection and He for GC-MS in the EI-mode (70 eV). Purities are reported in Table 1. Exemplified yields for 10 mg alcohol, after reaction for 1 h, washing with CH₂Cl₂ (4 × 3 mL), and evaporation of the solvent at room temperature: **9b**: 8.9 mg, 90%; **10b**: 8.7 mg, 88%; **20b**: 9.2 mg, 91%. The identity of the isolated products was confirmed by NMR analysis (250 MHz, CDCl₃).

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Thwarting β-Hydride Elimination: Capture of the Alkylpalladium Intermediate of an Asymmetric Intramolecular Heck Reaction**

Martin Oestreich, Philip R. Dennison, Jeremy J. Kodanko, and Larry E. Overman*

Dedicated to Professor Dieter Hoppe on the occasion of his 60th birthday

The asymmetric intramolecular Heck reaction^[1, 2] has proven to be one of the most efficient methods for enantioselective construction of quaternary carbon centers.^[3] We

[*] Prof. Dr. L. E. Overman, Dr. M. Oestreich, Dr. P. R. Dennison,^[†] J. J. Kodanko
Department of Chemistry
University of California
516 Rowland Hall, Irvine, CA 92697-2025 (USA)
Fax: (+1) 949-824-3866
E-mail: leoverma@uci.edu

[†] NMR analyses

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