Polymer-Supported *N*-Methylmorpholine *N*-Oxide as an Efficient and Readily Recyclable Co-oxidant in the TPAP Oxidation of Alcohols

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Received 2 June 2001

Key words: alcohols, oxidations, polymer-supported, ruthenium, solid-phase synthesis

As the chemical community comes under continued pressure to develop production methods based on cleaner technologies, attempts to establish more industrially applicable methodology are on the increase. Among other factors, these developing methods should combine efficiency, cost reduction, and more environmentally acceptable advances.¹ In attempts to satisfy, at least, some of these set criteria and in a drive to prepare a library of specific solid phase reagents, we have recently reported a flexible and novel synthesis of a polymer-supported amine N-oxide.² Moreover, this Argogel based resin was found to be a highly efficient promoter of the Pauson-Khand (P-K) annulation process, giving good to excellent yields of cyclopentenones in remarkably fast times under very mild reaction conditions. In an effort to enhance the overall efficacy and wider applicability of the supported *N*-oxide, a higher loading polymer bound reagent, based on the readily available morpholinomethyl polystyrene (Merrifield-type) resin, was prepared.³ Likewise, this was also found to be an excellent promoter of the P-K cyclisation.

In terms of highly desirable processes for more environmentally benign oxidation of alcohols, the efficient and selective methods developed by Griffith and Ley, which employ only catalytic quantities of tetrapropylammonium perruthenate (TPAP),⁴ along with a stoichiometric co-oxidant, appear to offer an attractive and readily utilisable technique for employment on small to large scales. More recently, to enhance the applicability of this general oxidative strategy, Ley and co-workers have modified the TPAP protocol and developed the polymer supported perruthenate (PSP) technique.⁵ Specifically, the PSP reagent can be used in both stoichiometric quantities or, like the solution phase reaction, in catalytic amounts when used in tandem with a co-oxidant such as trimethylamine N-oxide (TMANO) or N-methylmorpholine N-oxide (NMO) in the presence of molecular sieves. With regards to the latter approach, whilst only sub-stoichiometric quantities of the ruthenium-based reagent are used, the process still results in the presence of amine by-products (from the 1.0 - 1.5 equivalents of the requisite co-oxidant) which require to be removed and are normally discarded. On consideration of these issues, it was envisaged that our recently established poly-*N*-methylmorpholine *N*-oxide (PNMO) reagent could be applied as a co-oxidant within the TPAP oxidation of alcohols in an efficient and potentially recyclable fashion.⁶

To initiate our studies, preparation of the requisite polymer supported amine *N*-oxide was attempted using the commercially available polymer supported morpholine based resin **1**. This was readily achieved by either utilising the *N*-phenylsulfonyloxaziridine of Davis^{3a,b,7} or, importantly, using the commercially available oxidant MCPBA. As shown in Scheme 1, this oxidation process provided the required polymer supported morpholine *N*-oxide **2** with high theoretical loading.



Scheme 1 Reagents and conditions: (a) N-(phenylsulfonyl)phenyloxaziridine (4 equiv.), CH_2Cl_2 , r.t., 4 h. (b) MCPBA (3 equiv.), CH_2Cl_2 , r.t., 4 h.

With the required polymer supported N-oxide 2 in hand, we turned our attention to the application of this resin bound reagent as a co-oxidant in the TPAP oxidation of alcohols. Initially, we found that these oxidations were really rather sluggish. For example, with benzyl alcohol 3, only a 49% yield of benzaldehyde 4 was obtained after 24 hours, with the mass balance being made up by starting alcohol. Importantly however, although the initial oxidations were not proceeding to completion, they did at least demonstrate that the PNMO resin was acting as a co-oxidant within the TPAP reaction mixture. To further probe the preliminary oxidative processes, the conversion of Ecinnamyl alcohol 5 to E-cinnamaldehyde 6 was followed by GC. Perhaps unsurprisingly based on previous studies,⁴⁻⁶ it was observed that conversion of the alcohol to the aldehyde initially occurs rapidly and up to 40% within 15 minutes. However, after a further 48 hours only a 60% conversion was achieved.

Abstract: A readily available, polymer supported amine *N*-oxide has been prepared and shown to be a practicable, efficient, selective, and readily recyclable co-oxidant in the TPAP oxidation of alcohols.

In most solution and solid phase TPAP processes, it is necessary and, indeed, standard practice to introduce activated molecular sieves in order to achieve optimal rates and efficiencies of oxidation; the sieves act as a general dehydrating agent as water has a retarding effect upon the reaction rate.⁴⁻⁶ Despite this, it was envisaged that the hydrophobic nature of the polystyrene-based resin would discourage hydration of the key ruthenium species thus negating any requirement for molecular sieves.⁸ Nevertheless, on addition of activated 4Å molecular sieves to the reaction mixture, prior to introduction of the TPAP, the desired oxidation processes proceeded much more efficiently. Using the conditions illustrated in Scheme 2, a range of alcohols were tested and the results are presented in Table 1. As can be seen, the oxidation of activated alcohols (Entries 1-4) proceed exceedingly well⁹ and even the secondary alcohols 11 and 13 (Entries 5 & 6) gave the ketones 12 and 14 in reasonable to good yields. The oxidation of non-activated primary alcohols proceeds somewhat less efficiently.



Scheme 2

Having established that this solid supported co-oxidant is particularly effective in the TPAP oxidation of benzylic and allylic alcohols, we next investigated whether any selectivity would occur in the reactions of activated and unactivated alcohols. Pleasingly, using our developed protocol, reaction of 1 equivalent of *para*-methoxybenzyl alcohol **7** in the presence of 1 equivalent of 1-decanol **15** delivered a 71% yield of *para*-methoxybenzaldehyde **8** compared to only 13% yield of decanal **16** (with an 84% yield of returned starting material, 1-decanol **15**), after only 30 minutes (Scheme 3).

With an efficacious and selective oxidative protocol in hand, to exploit the recoverable nature of the supported amine and establish the full efficiency of this methodology, the recycling of the solid phase species was explored. LETTER

Table 1TPAP Oxidations of a Range of Alcohols with Solid Phase*N*-Oxide 2 as the Co-oxidant.



First of all, it should be noted that during the series of oxidations already described, on completion of reaction and following filtration, the spent amine resin is admixed with the used molecular sieves. Furthermore, re-activated sieves would be required for each successive oxidation process. Since the resin was unlikely to be stable to the vigorous conditions used for dehydration of the sieves, re-



Scheme 3

Synlett 2001, No. 8, 1257-1259 ISSN 0936-5214 © Thieme Stuttgart · New York

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cycling of the resin/sieve mixture did not seem to be practicable. To circumvent these practical issues, a reaction system was devised whereby the amine N-oxide resin 2 and the molecular sieves were separated from the outset by an additional porous frit. More specifically, the N-oxide resin is placed in a fritted filter tube and this is then capped (leaving sufficient head space) with the second porous frit. In turn, the resin is swollen with DCM and, subsequently, the molecular sieves are introduced. On completion of the alcohol oxidation with TPAP, draining of the product mixture and washing of the resin is followed by simple removal of the spent molecular sieves. In due course, the amine resin is ready for re-oxidation and further use within the same double fritted reaction vessel. Using this technique with *E*-cinnamyl alcohol **5** as the substrate, the excellent yield of the corresponding aldehyde 6 was maintained through five cycles (Table 2). It is also worth noting that resin oxidised with either Davis' reagent or MCPBA were effective throughout this recycling study.10

Table 2 TPAP Oxidations of a *E*-Cinnamyl Alcohol 5 with Recycled Resin 2 as the Co-oxidant.

Ph	соорон S	TPAP (20 mol%) Activated 4Å Mol. Sieves DCM, r.t., 24 h				
	Run	1	2	3	4	5
	Yield (%)	85	81	83	83	79
	O-PNMO ^a					
	Yield (%)	97	94	91	90	90
	M-PNMO ^b					

^aO-PNMO refers to oxaziridine (Davis' reagent) oxidised resin. ^bM-PNMO refers to MCPBA oxidised resin.

In conclusion, a readily accessible, high loading polymer supported amine *N*-oxide **2** has been prepared, in one simple step from two commercially available reagents, the morpholinomethyl polystyrene resin and MCPBA, or the same resin and the routinely prepared Davis oxaziridine. In turn, protocols have been developed which allow this *N*-oxide resin to be utilised as an efficient co-oxidant in the TPAP oxidation of alcohols. It was found that the resin gave rise to high product yields in the oxidation of allylic and benzylic alcohols and showed good chemoselectivity for activated alcohol systems in competitive reactions. Importantly, both the Davis reagent and MCPBA oxidised resins could be readily recycled without loss in activity.

Acknowledgement

We thank AstraZeneca Pharmaceuticals for studentship support (P.D.R) and Strategic Research Funding (W.J.K.) and the University of Strathclyde for financial support. We are also indebted to the EPSRC Mass Spectrometry Service, University of Wales, Swansea, for analyses.

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- (6) It should be noted that both Markó and Ley have developed techniques for the TPAP oxidation of alcohols where oxygen has been employed as the co-oxidant. In these protocols elevated temperatures (70–85 °C in toluene) are more usually required: (a) Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Chellé-Regnaut, I.; Urch, C. J.; Brown, S. M. J. Am. Chem. Soc. 1997, 119, 12661. (b) Lenz, R.; Ley, S. V. J. Chem. Soc., Perkin Trans. 1 1997, 3291. (c) Hinzen, B.; Lenz, R.; Ley, S. V. Synthesis 1998, 977.
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- (9) Representative experimental procedure: PNMO resin 2 (2.86 mmol g⁻¹ based on microanalysis, 150 mg, 0.43 mmol) was weighed into an Alltech fritted filter tube. This was then swollen in DCM (2 mL) for 30 minutes before addition of activated 4Å molecular sieves (225 mg). The reaction vessel was then shaken for a further 30 minutes followed by addition of p-methoxybenzyl alcohol 7 (29.7 mg, 0.215 mmol), as a solution in DCM (2 mL), and TPAP (15.1 mg, 0.043 mmol). The reaction vessel was then shaken for 24 hours before draining and washing of the resin with DCM $(10 \times 2mL)$, filtration through a silica pad, and evaporation to dryness. Purification by silica gel column chromatography gave pmethoxybenzaldeyde 8 (28.0 mg, 95% Yield). IR (DCM): 1683, 1600, 1511, 1315, 1264, 1160, 1018, 828 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 9.89 (s, 1H), 7.84 (d, 2H, J = 9.5 Hz), 7.01 (d, 2H, J = 9.5 Hz), 3.89 (s, 3H) ppm.
- (10) Initially, it had been anticipated that the PNMO resin might sequester the catalytic quantity of TPAP introduced, which would, in turn, allow this transition metal loaded polymer species to be recycled for use in further catalytic oxidative processes. However, it was apparent that, on draining the reaction mixture, quantities of the TPAP residues were being leached from the resin. Furthermore, after re-oxidation of the spent resin, reaction with benzyl alcohol with no additional TPAP failed to give any oxidised organic product after 24 hours.

Article Identifier:

1437-2096,E;2001,0,08,1257,1259,ftx,en;D11801ST.pdf