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# Preparation of an amine *N*-oxide on solid phase: an efficient promoter of the Pauson–Khand reaction

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**A novel, recyclable polymer-supported amine *N*-oxide has been prepared and shown to be a good promoter of the Pauson–Khand reaction under mild conditions, affording good to excellent yields of cyclopentenones.**

The field of solid phase chemistry, as applied to organic synthesis, has grown exponentially in recent years.[1] Immobilising either reagents or substrates on a polymeric support provides two complementary methods which both offer significant advantages over traditional solution phase methods. The use of polymer supported reagents[2] affords a clean approach to solution phase chemistry, whereby a reagent may be removed by filtration, aiding facile product purification. Alternatively, by establishing the substrate molecule on solid phase, excess reagents may be used to drive the reaction to completion, with the work-up procedures remaining as simple washing and filtration steps. Furthermore, this approach is highly compatible with the preparation of combinatorial libraries.

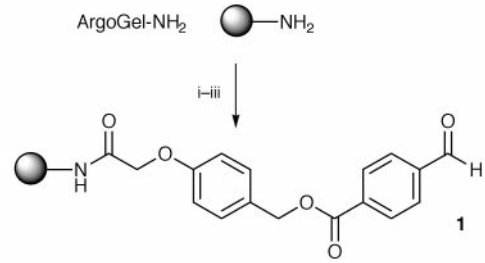
In recent years, the preparation of libraries of small organic molecules on solid phase has emerged as a powerful strategy in the drug discovery process.[3] However, these combinatorial methods are not only limited to drug discovery; recently they have also been applied to the discovery of novel compounds for a variety of purposes, most notably in the search for new asymmetric catalysts and reagents.[4] In this regard, based on our drive to further develop our chiral *N*-oxide mediated asymmetric versions[5] of the Pauson–Khand (P–K) reaction,[6] we envisioned that preparing an amine *N*-oxide on solid phase would provide a convenient polymer-supported promoter for this cobalt-mediated annulation process. More importantly, a controlled and adaptable synthetic strategy, which allowed for the incorporation of functional diversity, would also permit the preparation of libraries of chiral amine *N*-oxides. In turn, these mild oxidants could be used to further refine our methodology for inducing asymmetry in the P–K cyclisation process. Herein, we report our initial studies in this area, specifically, the preparation of an amine *N*-oxide on solid phase, and demonstrate the efficiency of this species as the first such supported promoter of the P–K reaction.

To initiate our studies, we needed to develop a flexible synthesis of solid supported tertiary amines and the corresponding *N*-oxides. We chose to generate tertiary amines *via* reductive amination of solid supported aldehydes which are, in turn, attached to the support *via* an acid labile, carboxylic acid releasing linker. Thus, ArgoGel-$NH_2$[7] was functionalised with the hydroxymethylphenoxyacetic acid linker in a two step process, followed by attachment of 4-formylbenzoic acid to the linker *via* standard esterification conditions (Scheme 1) to give **1**.

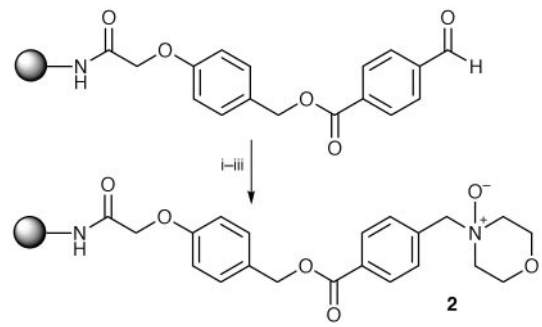
The supported aldehyde **1** was then aminated with morpholine, catalysed by acetic acid, and the intermediate reduced with acetoxyborohydride to give the tertiary amine (Scheme 2). At this stage, following TFA cleavage from the support, the amine product was analysed by NMR; clean reductive amination had occurred under the reaction conditions shown. It should also be noted that, in the initial amination stage, the use of less equivalents of amine, more acid, or shorter reaction times all ultimately led to large quantities of by-products derived from carbonyl reduction.

The supported amine was then oxidised using the *N*-sulfonyl oxaziridine reported by Davis,[8] cleanly furnishing the desired *N*-oxide **2** (Scheme 2). Following cleavage of the *N*-oxide from a known amount of resin the overall yield for this five step process was calculated† to be 51%.‡

Having established a flexible approach to the solid phase *N*-oxide **2**, its use as a promoter in the P–K reaction was then evaluated by reacting a series of cobalt complexes with norbornene. To our delight, all reactions were complete in under 30 min at room temperature, cleanly affording cyclopentenones **3** in good to excellent yields (Table 1).§ Additionally, a significant practical advantage over the more traditional P–K protocols was found in that, on reaction work-up, the oxidised cobalt residues remained bound to the resin, allowing the cyclopentenone products to be isolated in > 95% purity simply by filtration and removal of the solvent *in vacuo*. In due course, a variety of alkene substrates were also examined. These reactions also proceeded rapidly and in good yield (Table 2) with even the normally less reactive alkenes, 2,5-dihydrofuran

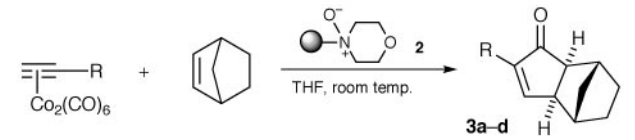



**Scheme 1** *Reagents and conditions*: i, 4-formylphenoxyacetic acid, HATU, $Pr^i_2NEt$, DMF, room temp., 2 h; ii, $Bu_4NBH_4$, $CH_2Cl_2$, room temp., 16 h; iii, 4-formylbenzoic acid, diisopropylcarbodiimide, DMAP, DMF, room temp., 16 h.



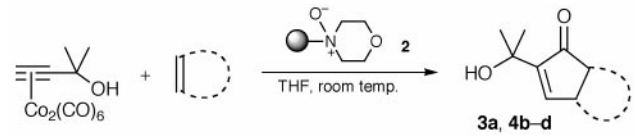

**Scheme 2** *Reagents and conditions*: i, morpholine (10 equiv.), AcOH (1 equiv.), $CH_2Cl_2$, room temp., 7 h; ii, $Bu_4NBH_4$ (10 equiv.), AcOH (20 equiv.), $CH_2Cl_2$, room temp., 16 h; iii, *N*-(phenylsulfonyl)phenyloxaziridine (4 equiv.), $CH_2Cl_2$, room temp., 3 h.

**Table 1** Solid phase *N*-oxide promoted P-K reactions




| R | *t*/min | Product | Yield (%) |
|---|---|---|---|
| $Me_2(OH)C$ | 30 | **3a** | 91 |
| Ph | 15 | **3b** | 99 |
| $Me_3Si$ | 15 | **3c** | 59 |
| $Bu^t$ | 30 | **3d** | 74 |

**Table 2** P–K reactions with a selection of alkenes




| Alkene | *t*/min | Product | Yield (%) |
|---|---|---|---|
| Norbornene | 30 | **3a** | 91 |
| Norbornadiene | 30 | **4b** | 95 |
| 2,5-Dihydrofuran | 30 | **4c** | 79 |
| Cyclopentene | 30 | **4d** | 51 |

and cyclopentene, efficiently affording the desired products **4c** and **4d.**¶

In all cases, the bound cobalt residues could be subsequently removed from the resin by washing with a 2:1 mixture of THF and 1 M HCl, the amine then being regenerated from its hydrochloride salt by washing with a 10% solution of $Pr^i_2NEt$ in DMF. This facile recovery of the amine opens up the possibility for recycling the polymer supported *N*-oxide by simply re-treating the resin with the Davis reagent. Indeed, this was shown to be the case. As illustrated by the reaction between the dimethylpropargyl alcohol complex and norbornene with recycled supported *N*-oxide **2**, the excellent yield and short reaction time is maintained through five cycles, demonstrating the durability of the tethered amine (Table 3).

In conclusion, we have achieved the synthesis of an amine *N*-oxide on solid phase and found it to be a highly efficient and re-usable promoter of the Pauson–Khand reaction, affording cyclopentenones in high purity without the need for column chromatography. Furthermore, due to the nature of the synthetic route, this methodology allows for a diverse set of *N*-oxides to be leveraged on solid phase. The application of this methodology to the preparation of a library of chiral *N*-oxides and the use of other resins, to allow higher loading for the polymer supported reagent, is currently under investigation and will be reported in due course.

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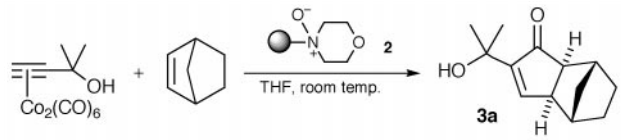
**Table 3** P–K reactions using recycled *N*-oxide




| Run | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| *t*/min | 30 | 30 | 30 | 30 | 30 |
| Yield (%) | 91 | 72 | 77 | 74 | 86 |

EPSRC Mass Spectrometry Service, University of Wales, Swansea, for analyses.

## Notes and references

† The cleaved *N*-oxide was analysed by $^1$H NMR using *p*-nitrophenol as an internal standard.

‡ To the best of our knowledge, only one other polymeric *N*-oxide, poly(vinylpyridine *N*-oxide), has been described. Besides practical concerns, this material has the disadvantage of being less adaptable and, in turn, less utilisable as a basis for the generation of a library of supported *N*-oxides (ref. 9).

§ Representative experimental procedure: Amine *N*-oxide resin **2** (1.12 g, 0.447 mmol) was swelled in THF (15 ml) for 10 min. Norbornene (35 mg, 0.372 mmol) and hexacarbonyl(2-methylbut-3-yn-2-ol)dicobalt (24.3 mg, 0.066 mmol) were added sequentially and the reaction shaken at room temperature for 30 min. The solvent was drained and the resin washed with THF (10 × 2 ml) and $CH_2Cl_2$ (10 × 2 ml). The combined filtrates were then evaporated *in vacuo* to afford **3a** as a white crystalline solid (12.3 mg, 91% yield). The product was >95% pure as indicated by $^1$H NMR analysis.

¶ Cyclopentenones **4c** and **4d** required purification by column chromatography.

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