COMMUNICATION

Development of a polymer bound Wittig reaction and use in *multi-step* organic synthesis for the overall conversion of alcohols to β-hydroxyamines

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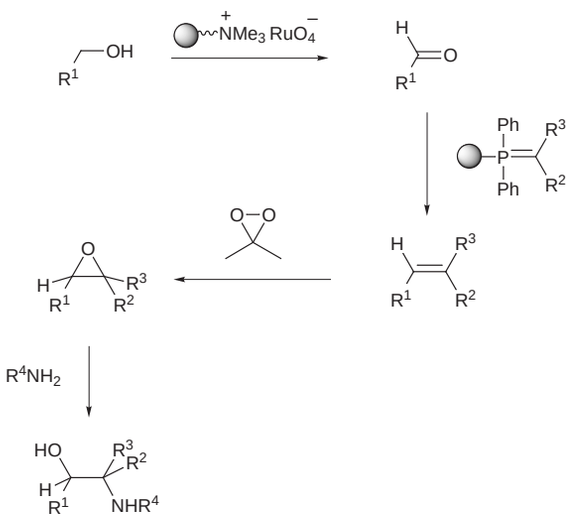
An efficient combinatorial access to β-hydroxyamines suitable for automation is achieved by the mild oxidation of alcohols to aldehydes by polymer supported perruthenate (PSP), the subsequent clean olefination of the obtained aldehydes by polymer supported Wittig reagents followed by the epoxidation of the olefins by dimethyldioxirane (DMDO), and the final aminolysis of the epoxides with various amines is described.

In the preceding two papers[1] we demonstrated the use of a combination of polymer supported reagents to effect clean *multi-step* organic synthesis leading to products with potential application in combinatorial chemistry. Here we continue the ideas by developing polymer supported Wittig reagents[2] which when reacted with aldehydes, which in turn may be derived from alcohols by oxidation with polymer supported perruthenate,[1a,3] afford alkenes. These are prepared in excellent yields and require only simple filtration to obtain pure products which are useful for further synthetic transformations. In order to exemplify potential applications many of these alkenes were converted in essentially quantitative yields to epoxides using dimethyldioxirane.[4] Once again pure products are obtained simply by removing solvent by evaporation. Likewise these epoxides were themselves excellent precursors for further steps such as the reaction with amines to produce β-hydroxyamines since these are considered as privileged structures in many pharmaceutical and agrochemical products (Scheme 1).



Scheme 1

The carbonyl compounds that were subjected to the polymer supported Wittig olefination are given in Fig. 1. As we have shown previously, with the exception of pentan-3-one **N** they all

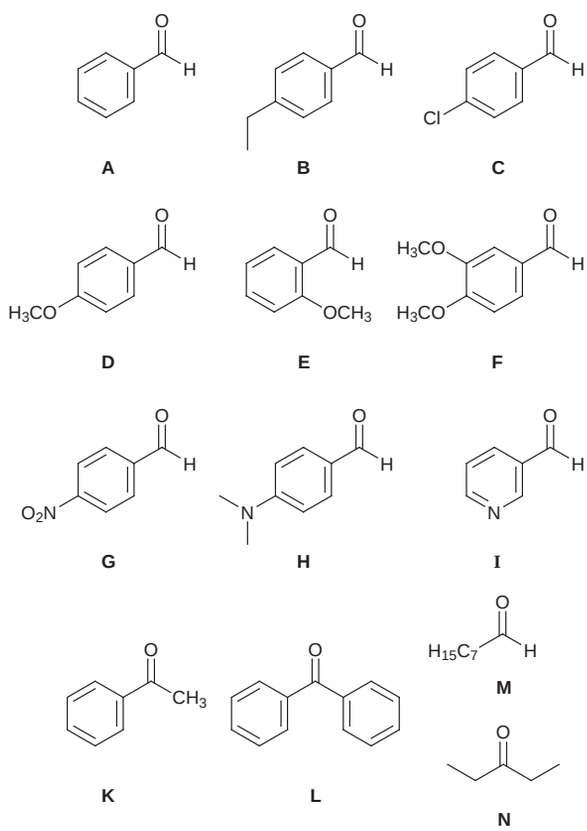
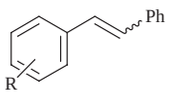
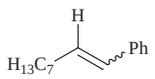
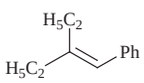
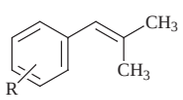
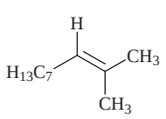
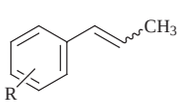
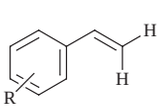
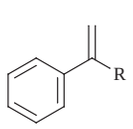
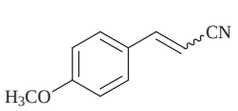
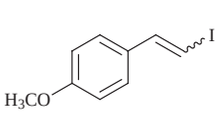


Fig. 1

can be prepared from their corresponding alcohol precursors in excellent yields and high purities by PSP oxidation.[1a,3] Although a diphenylphosphine derivatised polystyrene was developed to perform Wittig olefinations in the early 1970s[2a–d] and many examples have been reported since,[2e] a protocol which allows automation of the process and therefore opens up a combinatorial access to olefins has not been disclosed. However the phosphonium salt formation on such a polymer supported triphenylphosphine has recently been exploited as a linking procedure in solid phase synthesis.[5]

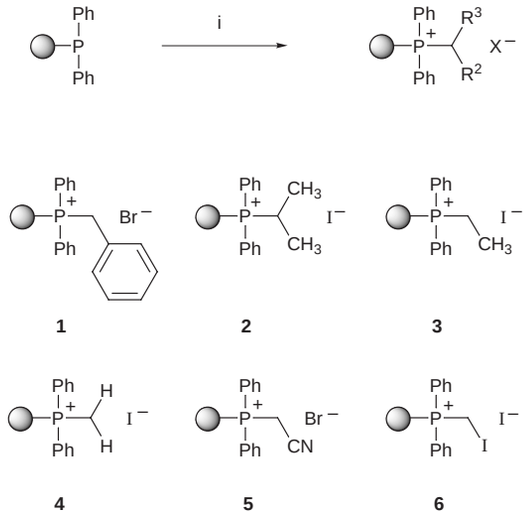
For this study a set of six Wittig reagents was prepared according to a literature procedure[6] starting from commercial diphenylphosphine derivatised polystyrene (Scheme 2). Thus to the support (1–2 g, 3–6 mmol phosphine) suspended in dry DMF (10–20 ml) was added 2–4 equivalents of the alkyl halide. The slurry was stirred for 48 hours at 50–70 °C. Eventually the support was carefully filtered off under argon and extensively washed with dry toluene (40 ml), dry dichloromethane (40 ml) and dry diethyl ether (60 ml). The grey to brown powders were dried *in vacuo*. According to the weight increase the loading was

Table 1 Summary of polymer supported Wittig olefinations

Entry	Wittig reagent	Carbonyl compound	Olefin	GLC Conversion [a] (%)	Isolated yield (%) (*cis*:*trans*)
1	**1**	**A**–**G**, **I**		>98	88–100 (2:1–1:3)
2		**M**		97	87 (1:3)
3		**N**		50 [b]	— [c]
4	**2**	**C**, **F**, **H**, **I**		⩾99	70–95
5		**M**		>99	— [c]
6	**3**	**D**–**F**		>99	77–90 (3:1–6:1)
7	**4**	**D**, **F**, **I**		>99	83–99
8		**K**, **L**		>99	— [c], >99
9	**5**	**D**		~92 [d]	80 (1:3)
10	**6**	**D**		50 >95	— (3:1) [e] — (2:1) [f]

All olefins were satisfactorily identified by their ^{1}H and ^{13}C NMR spectra and where possible by comparison with authentic samples. [a] GLC Conversions determined after 20 min reaction time. [b] After 28 h. [c] Yields not determined due to partial loss of the volatile product during evaporation. [d] After 24 h. [e] 1 g resin per mmol aldehyde, the crude product consists of 45% of iodoolefin (4-methoxy-β-iodostyrene), 3% of the deiodinated olefin (4-methoxystyrene), ~1% of 4-methoxyethynylbenzene and 48% starting material. [f] 3 g resin per mmol aldhyde, the crude product consists of 69% of 4-methoxy (2-iodovinyl)benzene, 7% of 4-methoxystyrene and 21% of presumably 4-methoxyethynylbenzene.

estimated to be in the range of 1.8–3.0 mmol phosphonium salt per gram support. The choice of the base and the solvent for the deprotonation of the phosphonium salt as well as the subsequent olefination step was evaluated and the procedure was carefully optimised. With a view to automating the process all steps were carried out in a column technique manner. Hence in a typical experiment a syringe equipped with a sintered Teflon frit was charged with the polymer supported phosphonium salt (300 mg, 0.54–0.9 mmol phosphonium salt). The support was placed under an argon atmosphere and washed with dry THF (8 ml). Addition of a 1 M solution of sodium bis(trimethylsilyl)amide (NaHMDS) in THF (1.8 ml) at room temperature effected the generation of the ylide within 30 minutes. Excess base was carefully removed by extensive washing of the reddish brown to black support with dry THF (25 ml). Eventually the support was resuspended in dry THF (3 ml) and the carbonyl compound (0.25–0.3 mmol) was added at room temperature. According to GLC analysis the olefination reaction was generally complete within 20–40 minutes (conversion >95%). The olefin containing solution was collected together with additional support washings (15 ml of dry THF) and filtered over a small amount of silica gel (0.5–1 g). Evaporation *in vacuo* furnished the crude olefins. Some examples are summarised in Table 1. While aliphatic and benzylic aldehydes as well as phenones were rapidly converted to furnish olefins of high purity (>90%) and in good to excellent yields (70–100%), pentan-3-one **N** reacted only very slowly. In general the observed *cis*:*trans* ratios were in accordance with those reported in literature.[2e,6,7] However, some examples with the phosphonium salt **1** showed a slightly enhanced *trans*-selectivity. The olefination with the cyanomethylene ylide was slow yet very clean. Neither the use of a larger excess of ylide

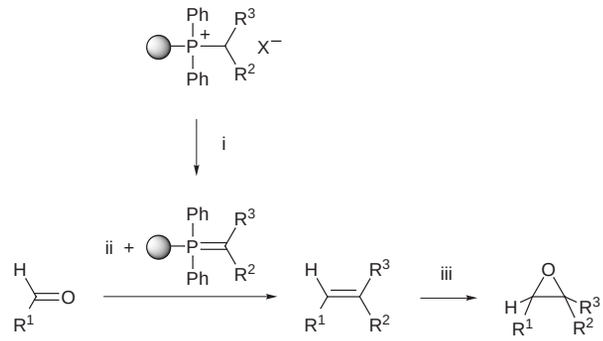


Scheme 2 *Reagents and conditions*: i, for **1**–**5** 2–4 equivalents alkyl halide, DMF, 50–70 °C, 48 h, for **6** 4 equiv. diiodomethane, DMF, rt, 16 h

nor elevated temperatures greatly affected the rate of the reaction. In the case of the polymer supported iodomethylphosphonium salt **6** the olefination proceeded less cleanly. In all experiments the isolated iodoolefin contained various amounts of the corresponding deiodinated Wittig product[8] together with another side product which is considered to be the corresponding acetylene.

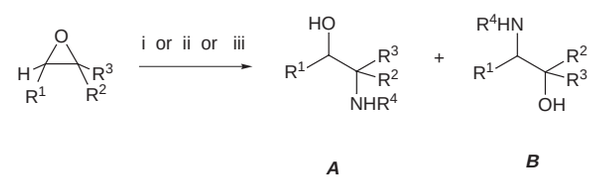
Epoxidation of some of the above olefins (0.1 mmol) was achieved by the addition of a ~0.075 M solution of dimethyldioxirane (DMDO) in acetone (2 ml) at room temperature. In general within two hours conversion was complete according to GLC analysis. Stilbenes reacted slightly slower than styrene derivatives. 4-Nitrostilbene was the slowest needing 18 hours for complete conversion. Work-up simply consisted of evaporation of excess reagent and solvent. Pure epoxides were obtained in nearly quantitative yields (Table 2).

Finally, the aminolysis is exemplified with the above epoxides using either ammonia, cyclohexylamine or piperazine as amine (Scheme 3). Typically the epoxide (0.1 mmol) was dissolved in either methanol or ethanol (1 ml) and a large excess (25–100



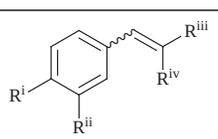
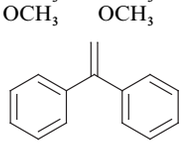
Scheme 3 *Reagents and conditions*: i, 2 equiv. NaHMDS in THF, rt, 30–60 min; ii, THF, rt, 20–40 min, iii, ~2 equiv. DMDO in acetone, rt, 40–120 min

equiv.) of the amine was added. The reaction mixture was stirred at 75 °C. While most of the epoxides were converted into their corresponding β-hydroxyamines in less than 24 hours (GLC analysis), the sterically hindered 1,1-dimethyl-2-(3,4-dimethoxyphenyl)oxirane needed considerably longer reaction times. Work up consisted of the evaporation of the solvent and the excess of amine followed by careful drying. In the case of piperazine the excess of reagent was removed under high vacuum (0.2 torr) at 40 °C within 12 hours. In general the purity of the obtained amino alcohols exceeded 85%. Some examples are given in Table 3. While stilbene derivatives (Table 3, entries 1–4) furnished a nearly 1 : 1 mixture of the two regioisomeric β-hydroxyamines ***A*** and ***B*** (Scheme 4), styrene oxides (Table 3, entries 5–8) opened to give preferentially regioisomer ***B***.



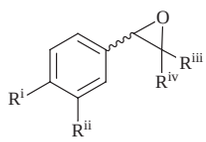
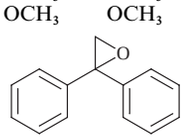
Scheme 4 *Reagents and conditions*: 0.1 mmol epoxide in: i, 0.75 ml methanol + 0.75 ml sat. aq. NH_3; ii, 10 mmol cyclohexylamine in 1 ml methanol; iii, 2.5–5.0 mmol piperazine in 2 ml ethanol; all at 75 °C, for reaction times see Table 3

Table 2 Some examples of the epoxidation with DMDO of olefins obtained from the polymer supported Wittig reaction

Entry	Olefin				GLC Conversion[a] (%)	Isolated yield (%)
						
	R^i	R^{ii}	R^{iii}	R^{iv}		
1	H	H	H	Ph	>99	95[b]
2	Cl	H	H	Ph	>99[c]	87[b]
3	OCH_3	H	H	Ph	>99	100[b]
4	NO_2	H	H	Ph	>99[d]	100[b]
5	OCH_3	OCH_3	H	H	>99	96
6	OCH_3	H	H	CH_3	>99	98[b]
7	OCH_3	OCH_3	H	CH_3	>99	100[b]
8	OCH_3	OCH_3	CH_3	CH_3	>99	100
9					>99	100

All epoxides were satisfactorily identified by their ^1H and ^{13}C NMR spectra and where possible by comparison with authentic samples. [a] *Reaction conditions*: ~2 equiv. of DMDO in acetone, rt, GLC conversions determined after 40 min reaction time. [b] As the alkene was obtained as a *cis* : *trans* mixture the epoxide was isolated as a mixture of two racemic diastereoisomers. [c] After 120 min (~80% after 40 min). [d] 4 equiv. DMDO, 24 h.

Table 3 Summary of some examples of the aminolysis of epoxides with ammonia, cyclohexylamine and piperazine

		GLC Conversion[a] (reaction time) with					
		NH_3		Cyclohexylamine		Piperazine	
Entry	Epoxide	% (h)	ratio ***A*** : ***B***[b]	% (h)	ratio ***A*** : ***B***[b]	% (h)	ratio ***A*** : ***B***[b]
							
	R^i R^{ii} R^{iii} R^{iv}						
1	H H H Ph	97 (30)	*c*	98 (44)	*c*	99 (6)	*c*
2	Cl H H Ph	95 (20)	1 : 1[c]			99 (6)	1 : 1[c]
3	OCH_3 H H Ph			99 (48)	1 : 2[c]		
4	NO_2 H H Ph					99 (7)	2 : 1[c]
5	OCH_3 OCH_3 H H					>99 (16)	1 : 2
6	OCH_3 H H CH_3	99 (8)	<1 : 10[c]			99 (6)	<1 : 10[c]
7	OCH_3 OCH_3 H CH_3			99 (20)	1 : 9[c]		
8	OCH_3 OCH_3 CH_3 CH_3	99 (72)	~1 : 5	17 (72)	—[d]	62 (72)	—[d]
9						98 (24)	>10 : 1

All β-hydroxyamines were satisfactorily identified by their ^1H, ^{13}C NMR as well as their high resolution mass spectra. Where possible the obtained NMR spectra were compared with literature data. [a] For reaction conditions see Scheme 4. [b] The constitution of the two regioisomers ***A*** and ***B*** is given in Scheme 4. [c] Isolated as racemic *erythro*/*threo* mixtures. [d] Ratio not determined.

In summary we have elaborated an efficient procedure for the clean preparation of β-hydroxyamines starting from alcohols using polymer supported reagents in combination with solution chemistry. Throughout the whole process work-up is achieved by mere filtration and evaporation. We believe this work, together with the preceding two communications, further illustrates the power of using polymer bound reagents to effect clean *multi-step* organic synthesis for potential application in combinatorial chemistry programmes.

Acknowledgements

We are grateful to the Swiss National Science Foundation (Fellowship to M. H. B.), the BP endowment and the Novartis Research Fellowship (to S. V. L.) for financial support.

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Paper 8/03612H
Received 14*th May* 1998
Accepted 16*th June* 1998