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p-Benzyloxybenzylamine (BOBA) Resin. A New Polymer-Supported Amine Used in Solid-Phase Organic Synthesis

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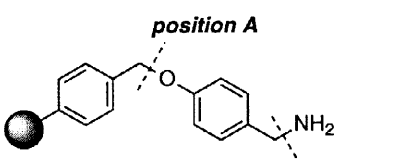
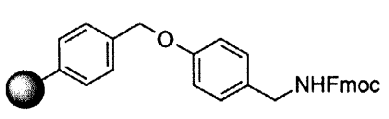
Abstract: *A new type of polymer-supported amine, p-benzyloxybenzylamine (BOBA) resin, has been developed. BOBA resin is readily prepared from Merrifield's resin in two steps. Polymer-supported imines prepared from aldehydes and BOBA resin reacted with silyl enolates in the presence of a catalytic amount of Yb(OTf)3 to afford the corresponding adducts. Cleavage from the polymer support was carried out using TMSOTf or DDQ to give different types of products in good yields.* © 1998 Elsevier Science Ltd. All rights reserved.

Polymer-supported amines are useful not only in solid-phase peptide synthesis but also in the preparation of many biologically important nitrogen-containing compounds. Although several polymer-supported amines have already been reported, "traces" of the polymer supports remained on the nitrogen atoms after cleavage from the supports in most cases.[1] "Traceless" linker resins such as Rink and Seiber amide resins have been developed,[2] however, rather long transformations are needed for their preparation. Moreover, strong acidic conditions are often required for cleavage from these resins. To solve these problems, we designed *p*-benzyloxybenzylamine (BOBA) resin (**1**). Resin **1** could be readily prepared, and cleavage at two possible positions under different conditions was expected. Namely, while cleavage at position A could occur under weak acidic conditions, cleavage at position B could take place under oxidative conditions. In this paper, we report the preparation and use of **1** in solid-phase organic synthesis.



BOBA Resin (**1**)



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BOBA resin (**1**) was prepared according to Scheme 1. Chloromethylated polystyrene resin **2** (Merrifield's resin, 1% cross-linked) was treated with *p*-hydroxybenzamide in the presence of sodium hydroxide in dimethylsulfoxide (DMSO). Formation of amide resin **3** was monitored using Swollen-Resin Magic Angle Spinning (SR-MAS) NMR[3] and IR spectra. Amide resin **3** was treated with borane•dimethysulfide in DME under reflux conditions to afford **1** in a high yield. The loading of **1** was calculated from the loading of FMOC derivative **4**, determined by the FMOC release UV assay.[4]

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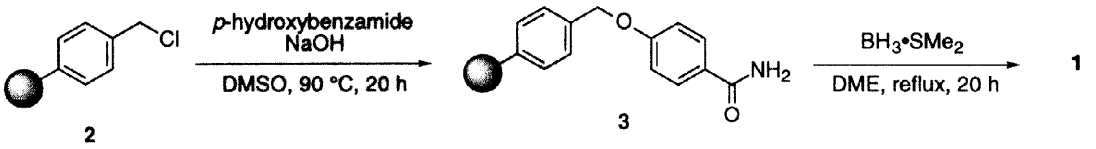
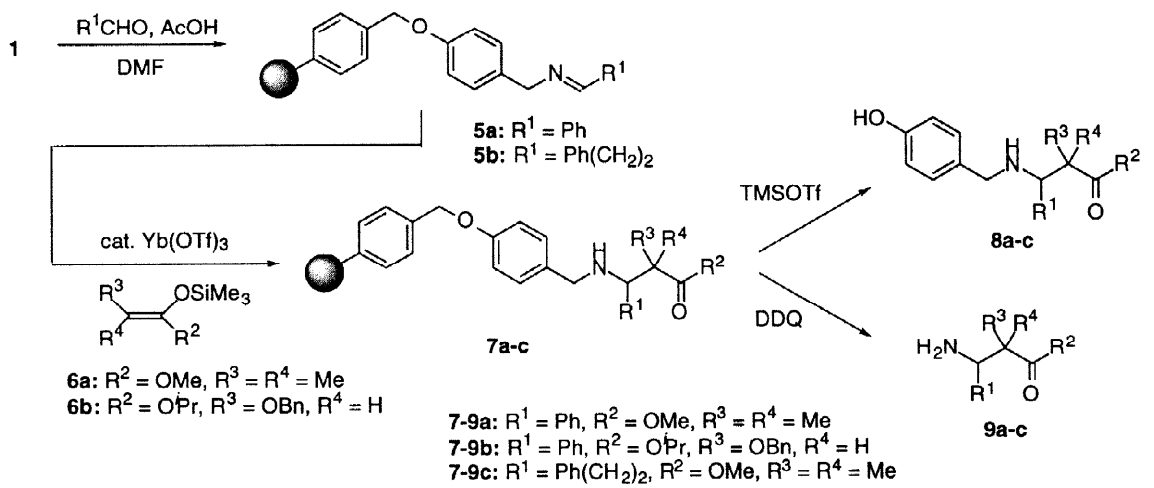


Scheme 1. Preparation of BOBA Resin (**1**)

BOBA resin (**1**) thus prepared was evaluated in imine formation[5] and successive Mannich-type (imino aldol) reactions (Scheme 2).[6] Benzaldehyde was treated with **1** in the presence of acetic acid in dimethylformamide (DMF). Imine formation was confirmed by IR spectra. Polymer-supported imine **5a** was then treated with silyl enolate **6a** in the presence of 20 mol% of $Yb(OTf)_3$ in dichloromethane at room temperature (rt) for 20 h. After the reaction, some cleavage methods were tested. When trifluoroacetic acid (TFA) was used, cleavage occured at 60 °C for 3 h to afford amino ester **8a** in a 73% yield. In the case using more acidic trifluoromethanesulfonic acid (TfOH), the cleavage took place at rt. It is noted that amino ester **8a** was obtained in an 82% yield when trimethylsilyl triflate (TMSOTf),[7] a less acidic Lewis acid, was used at rt. On the other hand, while no product was obtained by using TFA or TfOH at the cleavage from the support in the reaction of **5a** with silyl enolate **6b**, the desired adduct **8b** was produced in a 78% yield by using TMSOTf. Decomposition of the adduct was observed under strong acidic conditions using TFA or TfOH. We next tried to cleave free amino esters directly from the polymer support under oxidative conditions. After several trials, 2,3-dichlor-5,6-dicyano-1,4-benzoquinone (DDQ) was found to be quite effective for the cleavage.[8] Although the desired adduct (**9a**) was obtained in an 18% yield in dichloromethane, it was found that choice of solvents was essential in this cleavage, and that the yield was improved to 63% when benzene was used as a solvent.



Scheme 2. Imine Formation and Mannich-type Reactions Using BOBA Resin

We then examined the preparation of polymer-supported imine **5b** (a representative aliphatic imine) and its reactions with a silyl enolate. It is known that imines derived from aliphatic aldehydes are unstable and are difficult to isolate. On the other hand, polymer-supported imine **5b** was identified by IR spectra after a usual work up. **5b** was treated with **6a** in the presence of 30 mol% $Yb(OTf)_3$ in dichloromethane at rt to afford the desired amino ester (**8c**) in a 45% yield after cleavage from the support using TMSOTf. Although the yield

was moderate, interesting solvent effects in the Mannich-type reaction were found at this stage. The yield was improved to 73% when an acetonitrile-dicloromethane (1:1) solvent was used, while only a 36% yield of **8c** was obtained using acetonitrile as a solvent.

Several examples of the Mannich-type reactions of polymer-supported imines based on BOBA resin with silyl enolate **6a** are summarized in Table 1. In all cases using imines derived from aromatic, aliphatic, and heterocyclic aldehydes, the reactions proceeded smoothly in the presence of 30 mol% $Yb(OTf)_3$ in acetonitrile-dichloromethane (1:1) at rt. While (*N*-4-hydroxy benzyl)amino esters (**8**) were obtained by using TMSOTf as a cleavage reagent, free amino esters (**9**) were produced when DDQ was employed in the cleavage from the polymer support.

Table 1. Synthesis of **8** and **9** Using BOBA Resin and Silyl Enolate **6a**

R^1	Yield of **8** (%)	Yield of **9** (%)
Ph	98	84
p-ClPh	60	50
p-MePh	82	73
2-pyridyl	59	64
c-C_6H_{11}	77	81

In summary, a new type of polymer-supported amine, BOBA resin (**1**), has been developed. BOBA resin is readily prepared and cleaved at two positions under different conditions (Lewis acidic conditions and oxidative conditions). Further progress using BOBA resin in other solid-phase organic syntheses is now in progress.

Preparation of BOBA Resin (1): To 4-hydroxybenzamide (5.60 g, 40.8 mmol) in DMSO (65 ml) was added NaOH (1.80 g, 45 mmol) at rt. The mixture was stirred for 1 h at 90 °C, and chloromethylated polystyrene resin **2** (1%-cross linked, 15 g, 1.0 mmol/g) was added to the mixture at rt. The mixture was stirred for an additional 3 h at 90 °C. The resin was washed with water, THF, and ether and dried under reduced pressure to afford the amide resin (**3**). The amide resin thus prepared was treated with BH_3•SMe_2 (7.5 ml) in DME (300 ml). The mixture was stirred under reflux conditions for 20 h and then quenched by adding water. The resin was treated with 10% NaOH aq. (50 ml) in THF (200 ml) for 10 h at rt and washed with water, THF, and ether. The resin was dried under reduced pressure to afford BOBA resin (**1**, 0.87 mmol/g, 94%).

A Typical Experimental Procedure for Mannich-type Reactions: BOBA resin (**1**, 400 mg, 0.35 mmol) was washed with DMF and an aldehyde (1.75 mmol) and glacial AcOH (1% v/v) were added to the resin suspended in DMF (5 ml). The suspension was agitated for 1h and the resin was subsequently washed with DMF. This treatment was repeated for complete formation of the imine. The resin was washed with CH_2Cl_2 and dried under reduced pressure to give the imine resin (**5**). To this imine resin thus obtained and $Yb(OTf)_3$ (0.11 mmol) in CH_2Cl_2/CH_3CN = 1/1 (12 ml) was added a silyl enolate (1.15 mmol) at rt. The mixture was stirred for 20 h at this temperature and saturated $NaHCO_3$ aq. was then added. The resin (**7**) was washed with water, THF, and ether and dried under reduced pressure.

Cleavage from the Polymer Support Using TMSOTf: The resin (**7**) was treated with TMSOTf (3.5 mmol) in CH_2Cl_2 (12 ml) at rt for 3 h and saturated $NaHCO_3$ aq. was then added. The aqueous layer was

extracted with CH_2Cl_2. The combined organic layer was washed with saturated NaCl aq. and dried over Na_2SO_4. After removal of the solvents, the crude product was purified by preparative TLC to afford the amino ester (**8**).

Cleavage from the Polymer Support Using DDQ: The resin (**7**) was treated with DDQ (1.15 mmol) in benzene (12 ml) at rt for 3 h and 5% aqueous ascorbic acid and saturated $NaHCO_3$ aq. were then added. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with saturated NaCl aq. and dried over Na_2SO_4. After removal of the solvents, the crude product was purified by preparative TLC to afford the traceless amino ester (**9**).

References

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1. (a) Green, J. *J. Org. Chem.* **1995**, *60*, 4287-4290. (b) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029-7030. (c) Look, G. C.; Schullek, J. R.; Holmes, C. P.; Chinn, J. P; Gordon E. M.; Gallop, M. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 707-712. (d) Runland, B.; Bhandari, A.; Gordon E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253-254.
2. For the traceless cleavage of amines, see (a) Katritzky, A. R.; Xie, L.; Zhang G. *Tetrahedron Lett.* **1997**, *38*, 7011-7014. (b) Boyd, E. A.; Chan, W. C.; Loh, Jr. V. M. *Tetrahedron Lett.* **1996**, *37*, 1647-1650.
3. Kobayashi, S.; Akiyama, R.; Furuta, T.; Moriwaki, M. *Molecules* **1998**, *2*, 35-39.
4. Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makofske, R. C.; Change, C. -D. *Int. J. Pept. Protein Res.* **1973**, *13*, 35-42.
5. For the preparation of polymer-supported aldimines, see Ref. 1, and (a) Dewitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody D. M. R.; Pavia M. R. *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6909-6913. (b) Pátek, M.; Drake, B.; Lebi, M. *Tetrahedron Lett.* **1995**, *36*, 2227-2230. (c) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588-7590. (d) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47-50. (e) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937-2940.
6. (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233-234. (b) Kobayashi, S. *Synlett* **1994**, 689-701. (c) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809-2812. (d) Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783-7786.
7. For the use of TMSOTf in TFA, see Yajima, H.; Fujii, N.; Funakoshi, S.; Watanabe, T.; Murayama, E.; Okata, A. *Tetrahedron* **1988**, *44*, 805-819.
8. For the cleavage of alcohols from the polymer-supports using DDQ, see (a) Deegan, T. L.; Gooding, O. W.; Baudart, S.; Porco, Jr. J. A. *Tetrahedron Lett.* **1997**, *38*, 4973-4976. (b) Egusa, K.; Fukase, K.; Nakai, Y.; Kusumoto, S. *The 74th Annual Meeting of the Chemical Society of Japan*, Kyoto, 1998, 1E6 14.