Chiral Monomers with Minimal Functional Group Linkages for Suspension Co-polymerization: A Suzuki Coupling Approach

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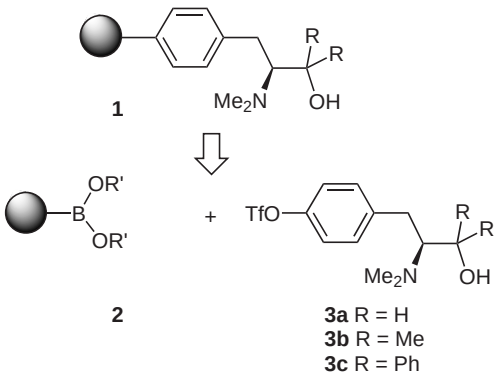
Abstract: A new strategy for the synthesis of chiral monomers for co-polymerization with styrene is described. Suzuki coupling of 4-vinylphenylboronic acid with chiral aryl triflates **5** and **13**, and subsequent elaboration has resulted in chiral monomers **9** and **10**. One of these monomers **10** has subsequently been incorporated into a polystyrene gel-type resin **16** with a functional group loading of 0.48 mmolg^{-1}.

Key words: palladium, polymers, amino alcohols, ligands, asymmetric catalysis

Supported reagents and catalysts have found increasing use in synthesis due to their ease of handling and general applicability to automated parallel synthesis.[1] A number of polystyrene supported chiral catalysts have been reported and these have been shown to catalyze reactions such as the asymmetric addition of diethylzinc to aldehydes, asymmetric epoxidation and dihydroxylation reactions, and the asymmetric reduction of ketones.[2] Traditionally, two approaches to the synthesis of functionalized polystyrenes with side-chain chirality have been used. In the first, modification of an existing polystyrene backbone leads to an appended chiral functionality.[2] Grafting a chiral ligand offers the advantages of a pre-determined polymer structure (degree of cross-linking, surface area, pore size) and may allow an estimation of the ligand/catalyst loading through assuming complete conversion of a known mmolg^{-1} loading of the tether functionality. However, the principle disadvantage of this approach is that the tethering functionality (typically ether, amine, ester or amide) remains and may therefore affect the reaction to be catalyzed. In the second approach a chiral monomer is copolymerized with styrene to generate polystyrene with the desired side-chain chirality.[2c,3] With polymerization, any additional functionality beyond the desired chiral ligand which is present in the side-chain (ether, amine etc.) results from the synthesis of the chiral monomer. A derivation of this approach makes use of chiral cross-linking agents and a number of examples of this strategy have appeared in the recent literature.[2c,4] Overall, the polymerization of chiral monomers has received less attention from the synthetic community due in part to the difficulty in achieving the required suspension polymerization with standard laboratory apparatus.[5]

Supported chiral 1,2-amino alcohols have been used extensively in the asymmetric addition of dialkylzinc reagents to aryl aldehydes.[2a,b,6] However, a number of weaknesses in the synthesis of supported chiral amino alcohols have been identified.[7] The first is that tethering of the amino alcohol to the support is frequently achieved through either the amine or alcohol functionality, hence affecting the catalytic activity with respect to the corresponding solution phase analogue. This almost always leads to a lowering of the observed enantioselectivity of a particular catalytic system. This has been overcome recently through the use of a chloro-(2-chloro)trityl polystyrene resin, in place of the traditional Merrifield resin, which has been shown to eliminate the reduction in enantioselectivity through the formation of a highly hindered ether linkage to the solid support.[7a] Secondly, the incorporation of polar chiral side-chains may reduce the swelling capacity of the resin in solvents, such as toluene, in which the diethylzinc addition is most readily performed.[7b] Finally, and in order to be truly useful e.g. for use in automated synthesis or continuous flow reactors, the resins must retain high levels of enantioselective induction through several cycles of usage and hence any linkage unit must be unreactive under a range of conditions.[7c] We felt that a C-C bond linkage between the chiral side-chain and polystyrene resin might successfully overcome these difficulties and would offer a new and exciting strategy for the synthesis of side-chain chiral polymers.[8]



Scheme 1 Functionalisation of a modified polystyrene resin to give a supported amino alcohol.

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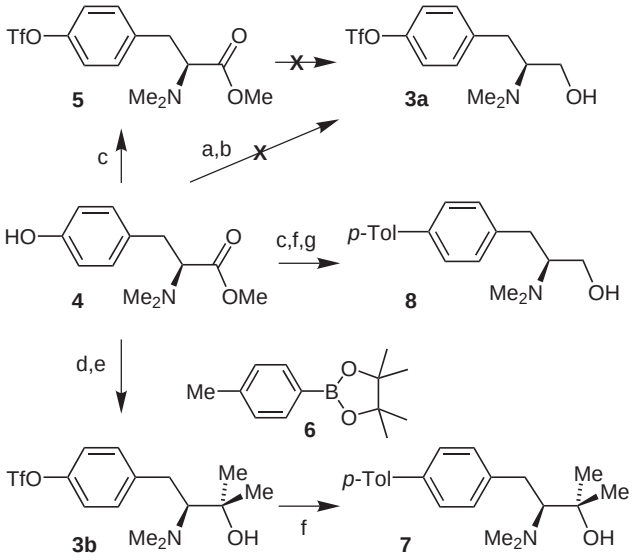
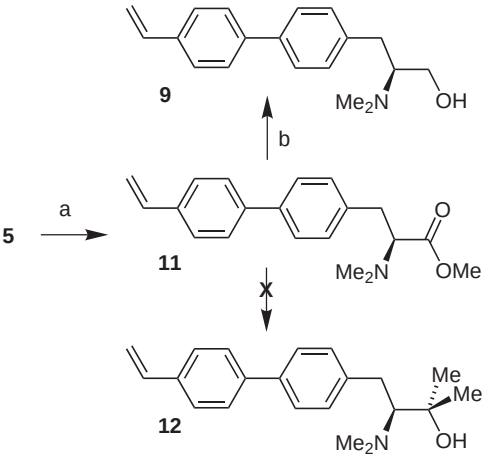
As part of a program directed towards the synthesis of supported chiral catalysts and auxiliaries we became interested in the synthesis of tyrosine-derived chiral amino alcohols **1** (Scheme 1, R = H, Me etc.) and their derivatives.[9] We were initially attracted by the literature precedent for Suzuki couplings carried out on supported boronic esters[10] (although the number of coupling reactions involving the use of aryl triflates as required by the strategy outlined in Scheme 1, are rather more limited).[10b,11] Using this analysis we hoped to access the desired chiral amino alcohols through coupling of a boronic acid/ester functionalized polystyrene **2**, with a triflate precursor such as **3**. Our strategy would deviate significantly from this literature precedent in that we would not be using a linker between the boronic acid functionality and the polystyrene backbone, but would be reliant upon functionalization of the polystyrene core itself, e.g. though lithiation[12] and reaction with a suitable boronic acid or ester.[8,13]



Scheme 2 Model coupling reactions for amino alcohol attachment to a polystyrene core. *Reagents and Conditions:* (a) $LiAlH_4$, Et_2O, –78 °C (57%); (b) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, 0 °C to r.t. (17%); (c) $(CF_3SO_2)_2O$, py, CH_2Cl_2, 0 °C (87%); (d) MeMgI, Et_2O, reflux (81%); (e) $PhN(SO_2CF_3)_2$, Et_3N, CH_2Cl_2, 0 °C (74%); (f) **6**, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3 (2 N aq), DMF, 80 °C (50% alcohol **3b**, 66% ester **5**); (g) $LiBH_4$, THF, r.t. (65%).

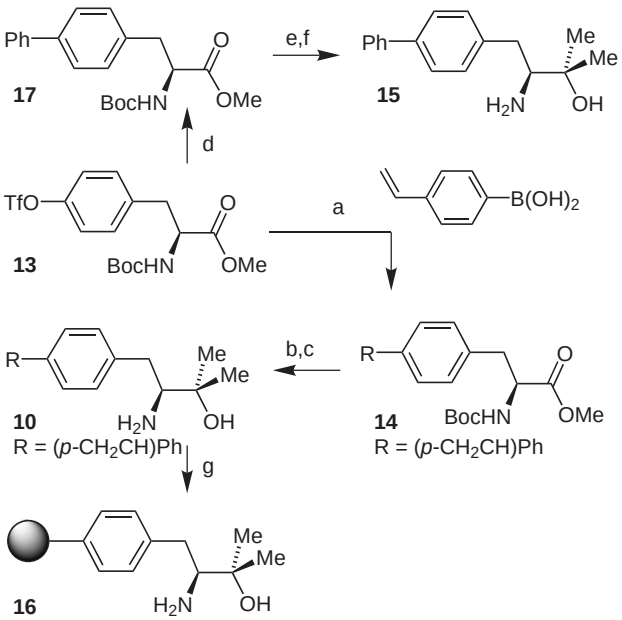
Two routes to the simplest amino alcohol coupling partner **3a** from amino ester **4**[14] were pursued (Scheme 2). But both routes were plagued by low conversion to the desired amino alcohol **3a** in the second step. However, synthesis of gem-dimethyl derivative **3b** proceeded smoothly, with Grignard addition to ester **4** followed by selective triflation of the phenol giving **3b** in 53% overall yield from L-tyrosine methyl ester. To model coupling to the polystyrene backbone, Suzuki couplings of **3b** and also the triflate of ester **4**, with 4-methylphenyl boronic ester (**6**),[15] were carried out using Giroux's coupling conditions.[16] The low yields associated with the solution phase Suzuki coupling of these chiral *N*,*N*-dimethyl amino alcohol and amino ester derivatives suggested that this would not be a particularly viable strategy for the synthesis of well-defined supported chiral amino alcohols.[13]



Scheme 3 Synthesis of monomer **9**. *Reagents and Conditions:* (a) 4-vinylphenylboronic acid, $K_3PO_4\cdot H_2O$, $PdCl_2(dppf)\cdot CH_2Cl_2$, DME, 80 °C (82%) *or* 4-vinylphenyl-boronic acid, $PdCl_2(dppf)\cdot CH_2Cl_2$, Na_2CO_3 (2 N aq), DMF, 80 °C (71%); (b) $NaBH_4$, THF/MeOH, reflux (78%).

In pursuit of an alternative approach to the desired functionalized polystyrene resins, chiral monomers **9** and **10** were synthesized as outlined in Schemes 3 and 4, respectively. Triflate **5** could be coupled with 4-vinylphenylboronic acid to give the Suzuki product **11** in excellent yield (82%). This was readily reduced to give the parent monomer **9**. However, disappointing preliminary results in the enantioselective addition of diethylzinc to a range of aromatic aldehydes catalyzed by the solution phase analogue **8** meant that polymerization of monomer **9** was not pursued. Direct conversion of **11** to the gem dimethyl analogue **12** was not possible due to significant levels of concomitant anionic polymerization.[17]

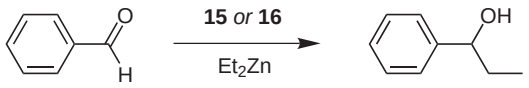
Since the *N*,*N*-dimethylated tyrosinol analogues appeared to be somewhat unstable with respect to aerial oxidation, a Suzuki coupling approach towards the primary amino alcohols was sought. A wide range of conditions for the Suzuki coupling of triflate **13**[18] to 4-vinylphenylboronic acid were investigated, and tetrakis(triphenylphosphine) palladium(0) generated in situ was found to give the highest isolated yield of coupled product **14**.[19,20] Conversion to the gem dimethyl derivative **10** was achieved in two steps; Grignard addition,[21] followed by aqueous acid deprotection.[22] The optical purity of the intermediate gem dimethyl carbamate was assessed as >99.8%ee by comparison with a racemic sample by chiral HPLC. A solution phase analogue **15** of the anticipated polymer supported amino alcohol **16** was synthesized in an analogous manner. Thus Suzuki coupling gave biphenyl derivative **17**,[18] and Grignard addition followed by TFA deprotection yielded the desired amino alcohol **15**.[23]



Scheme 4 Synthesis of polymer **16** and its solution phase analogue **15**. *Reagents and Conditions:* (a) 4-vinylphenylboronic acid, $Pd(OAc)_2$, PPh_3, K_2CO_3, $PhCH_3$, 85 °C (61%); (b) MeMgI, Et_2O, reflux (82%); (c) HCl (3 N aq), MeCN, r.t. (87%); (d) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_2CO_3, $PhCH_3$, 85 °C (55%); (e) MeMgI, Et_2O, reflux (77%); (f) CF_3CO_2H, CH_2Cl_2, r.t. (87%); (g) i. H_2O, PVA, 125 °C; ii. H_2CCHPh, divinylbenzene, AIBN, THF/toluene, 0 °C to 80 °C (53%).

The utility of this route for the synthesis of functionalised polystyrene resins was ultimately demonstrated by the suspension co-polymerization of **10** with styrene in the presence of the cross-linking agent divinylbenzene. Optimization of conditions for this procedure, led to the use of a THF/toluene solvent mixture to promote the solubilization of monomer **10** and poly(vinylalcohol) (PVA) to stabilize the suspension.[4,24,25] Elemental analysis confirmed that the amino alcohol monomer had been successfully incorporated to produce the functionalized polymer **16**, and the functional group loading was determined to be 0.48 $mmolg^{-1}$. The polystyrene resin **16** was found to have a negligible surface area in the dry state as determined by N_2 adsorption and application of BET theory, thus indicating a gel-type resin.

Table 1 Amino Alcohol Catalyzed Addition of Diethyl Zinc to Benzaldehyde



Catalyst	mol%	Solvent	Yield	%ee[a]
15	5	$PhCH_3$	77	50 (*R*)
16	10	$PhCH_3$	72	56 (*S*)
16	10	hexane	80	51 (*S*)

[a] Major enantiomer indicated in parentheses.

Preliminary results (Table 1) using amino alcohols **15** and **16** to catalyse the addition of diethylzinc to benzaldehyde have shown that equivalent levels of enantioselectivity may be obtained from both, although a slightly higher catalyst mol% is required with the polymer supported catalyst in order to achieve this. Curiously, the sense of enantioselectivity is consistently overturned when the polymer supported amino alcohol is employed, a result which is observed whether the polymer is swollen in hexane, or toluene. At this relatively low ligand loading (0.48 $mmolg^{-1}$), it is possible that site isolation may lead to an alternative mechanism for the reaction catalysed by the supported metal-ligand complex.[26]

This new approach to the synthesis of styrene-like monomers for suspension polymerisation is particularly attractive due to the ready availability of a wide range of coupling partners that may be linked with 4-vinylphenylboronic acid via a Suzuki reaction. The procedure is unique in that it allows the synthesis of monomers which lack a linking functionality, but in which the side-chain chirality is attached through a robust and inert carbon-carbon linkage. This approach will also allow the synthesis of a range of bead morphologies (gel-type, macroporous etc.) to be investigated.

Acknowledgment

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(19) The conditions previously optimised for the coupling of methyl ester **5** and 4-vinylphenylboronic acid were found to give incomplete conversion to Suzuki product **14** resulting in a tricky separation of unreacted triflate **13** and product **14**.
(20) Methyl (2*S*)-2-*N*-(*tert*-butoxycarbonyl)-3-[*p*-(*p*-vinylphenyl)phenyl]-propanoate (**14**), R_f [CH_2Cl_2:MeOH (95:5)] 0.92; mp 110 °C; $[\alpha]_D$ +61.6 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$ solution)/cm^{-1} 3429, 3365, 2979, 1740, 1712, 1498, 1366, 1166, 756; δ_H (250 MHz, $CDCl_3$) 7.57–7.44 and 7.25–7.17 (8 H, m), 6.75 (1 H, dd, *J* = 17.6 Hz, 10.9 Hz), 5.78 (1 H, dd, *J* = 17.6 Hz, 0.9), 5.27 (1 H, dd, *J* = 10.9 Hz, 0.9 Hz), 5.02 (1 H, d, *J* = 7.7 Hz), 4.62 (1 H, d, *J* = 7.9 Hz), 3.73 (3 H, s), 3.19–3.05 (2 H, m), 1.42 (9 H, s); δ_C (62.9 MHz, $CDCl_3$) 172.2, 155.0, 139.9, 139.3, 136.4, 136.2, 135.0, 129.6 (2 C), 126.9 (4 C), 126.5 (2 C), 113.8, 79.9, 54.2, 52.2, 37.8, 28.2 (3 C); *m/z* (FAB) 382 ([M + H]$^+$, 7%), 326 (25), 193 (25), 154 (100), 57 (28); HRMS (FAB) $C_{23}H_{28}NO_4$ [M + H]$^+$ requires 382.2018, found 382.2004.
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(22) (3*S*)-3-*N*-(*tert*-Butoxycarbonyl)-2-methyl-4-[*p*-(*p*-vinylphenyl)phenyl]-butan-2-ol, R_f [CH_2Cl_2/MeOH (90:10)] 0.51; mp 150–151 °C; $[\alpha]_D$ –69.0 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$ solution)/cm^{-1} 3377, 2980, 1669, 1529, 1172, 757; δ_H (200 MHz, $CDCl_3$) 7.52–7.45 and 7.29–7.26 (8 H, m), 6.76 (1 H, dd, *J* = 17.5 Hz, 10.8 Hz), 5.79 (1 H, d, *J* = 17.5 Hz), 5.27 (1 H, d, *J* = 10.8 Hz), 4.66 (1 H, d, *J* = 9.2 Hz), 3.74–3.70 (1 H, m), 3.12 (1 H, d, *J* = 13.8 Hz), 2.68 (1 H, d, *J* = 13.8 Hz), 2.58 (1 H, br s), 1.30 (15 H, m); δ_C (50.3 MHz, $CDCl_3$) 156.5, 140.4, 138.6, 138.2, 136.4 (2 C), 129.6 (2 C), 127.0 (2 C), 126.8 (2 C), 126.6 (2 C), 113.8, 79.4, 72.9, 60.3, 35.5, 28.1 (3 C), 27.5, 26.5; *m/z* (FAB) 382 ([M + H]$^+$, 2%), 373 (5), 309 (9), 301 (14), 193 (43), 57 (100); HRMS (FAB) $C_{24}H_{32}NO_3$ [M + H]$^+$ requires 382.2382, found 382.2399.
(3*S*)-3-Amino-2-methyl-4-[*p*-(*p*-vinylphenyl)phenyl]-butan-2-ol (**10**), R_f [CH_2Cl_2/MeOH (90:10)] 0.23; mp 114–115 °C; $[\alpha]_D$ –44.2 (*c* 0.5, MeOH); IR ($CHCl_3$ solution)/cm^{-1} 3402, 3343, 3280, 2976, 1497, 1389; δ_H (200 MHz, CD_3OD) 7.57–7.44 and 7.32–7.28 (8 H, m), 6.75 (1 H, dd, *J* = 17.8 Hz, 10.8 Hz), 5.79 (1 H, d, *J* = 17.8 Hz), 5.22 (1 H, d, *J* = 10.8 Hz), 3.02 (1 H, dd, *J* = 13.2 Hz, 2.7 Hz), 2.88 (1 H, dd, *J* = 10.7 Hz, 2.7 Hz), 2.34 (1 H, dd, *J* = 13.2 Hz, 10.7 Hz), 1.27 (3 H, s), 1.23 (3 H, s); δ_C (62.9 MHz, CD_3OD) 139.6, 138.7, 138.0, 136.0, 135.8, 128.9 (2 C), 126.1 (2 C), 126.0 (2 C), 125.8 (2 C), 112.1, 71.5, 61.3, 37.1, 24.7, 22.9; *m/z* (FAB) 282 ([M + H]$^+$, 56%), 264 (17), 222 (19), 193 (100), 88 (31), 43 (27); HRMS (FAB) $C_{19}H_{24}NO$ [M + H]$^+$ requires 282.1858, found 282.1858; Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98, found C, 80.59; H, 8.16; N, 4.73.
(23) (3*S*)-4-Biphenyl-3-*N*-(*tert*-butoxycarbonyl)-2-methyl-butan-2-ol, R_f [hexane/EtOAc (80:20)] 0.14; mp 137–138 °C; $[\alpha]_D$ –61.2 (*c* 1.0, $CHCl_3$);IR ($CHCl_3$ solution)/cm^{-1} 3442, 2980, 1700, 1503, 1368, 1169; δ_H (250 MHz, $CDCl_3$) 7.58–7.25 (9 H, m), 4.65 (1 H, d, *J* = 9.6 Hz), 3.80–3.69 (1 H, m), 3.13 (1 H, dd, *J* = 14.2 Hz, 3.4 Hz), 2.71 (1 H, br s), 2.62 (1 H, d, *J* = 14.2 Hz), 1.41–1.25 (15 H, m); δ_C (62.9 MHz, $CDCl_3$) 156.3, 141.0, 139.0, 137.9, 129.5, 128.6 (3 C), 126.9 (5 C), 79.2, 72.8, 60.2, 35.3, 28.1 (3 C), 27.4, 26.5; *m/z* (FAB) 356 ([M + H]$^+$, 19%), 300(57), 282(75), 167(100), 57(91); HRMS (FAB) $C_{22}H_{30}NO_3$ [M + H]$^+$ requires 356.2225, found 356.2225; Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94, found C, 73.82; H, 8.24; N, 4.06.
(3*S*)-3-Amino-4-biphenyl-2-methyl-butan-2-ol (**15**), R_f [CH_2Cl_2/MeOH (90:10)] 0.23; mp 65–66 °C; $[\alpha]_D$ –40.2 (c 1.0, $CHCl_3$); IR (nujol)/cm^{-1} 3404, 3341, 3270, 1487, 754; δ_H (200 MHz, CD_3OD) 7.60–7.54 and 7.44–7.29 (9 H, m), 3.03 (1 H, d, *J* = 13.4 Hz), 2.89 (1 H, d, *J* = 11.0 Hz), 2.35 (1 H, dd, *J* = 13.4 Hz, 11.0 Hz), 1.28 (3 H, s), 1.24 (3 H, s); δ_C (50.3 MHz, CD_3OD) 142.3, 140.7 (2 C), 130.8 (2 C), 129.9 (2 C), 128.2 (3 C), 127.9 (2 C), 73.5, 63.2, 39.0, 26.6, 24.8; m/z (FAB) 256 ([M + H]$^+$, 85%), 238 (35), 196 (20), 167 (100), 88 (24), 43 (28); HRMS (FAB) $C_{17}H_{22}NO$ [M + H]$^+$ requires 256.1701, found 256.1706.
(24) Suzuki, T.; Narisada, N.; Shibata, T.; Soai, K. *Polym. Adv. Technol.* **1999**, *10*, 30.
(25) A dry 500 mL 3-necked flask equipped with overhead stirrer, condenser and septum was charged with distilled water (135 mL) which was subsequently degassed and purged with argon. PVA (675 mg, 87–89% hydrolysed, average MW = 85000–146000) was added and the reaction mixture was stirred at 125 °C for 10 minutes before being cooled to 0 °C. Two further dry flasks were separately charged with THF (50 mL) and toluene (50 mL), each being degassed and purged with argon. The amino alcohol monomer **10** (1.84 g, 6.55 mmol) was added to the THF ensuring dissolution before addition of the toluene. AIBN (211 mg, 1.28 mmol), styrene (9.94 mL, 86.7 mmol) and divinylbenzene (5.25 mL, 29.5 mmol) were then added to the organic phase with each of the monomers being washed with 1% aqueous NaOH (10 mL) and water (2 × 10 mL) immediately prior to use. The monomer phase was added via cannulation over a period of 10 minutes to the cooled aqueous phase which was stirred at 350 RPM. The height of the paddle impeller was positioned ~ 3 cm below the surface of the reaction mixture as this depth was found to visually reduce horizontal flow. Stirring was then continued at 0 °C

for 1 hour. The reaction mixture was then heated to 80 °C with constant stirring at 350 RPM under argon for 18 hours. The polymer beads were collected by filtration through a 100 micron mesh sieve and washed with water (500 mL), THF (500 mL) and methanol (500 mL). The polymeric material was then dried under reduced pressure at 40 °C to constant mass and sieved between 500 and 100 micron mesh sieves affording cross-linked amino alcohol polymer(**16**) as colourless free flowing beads (3.40 g, 23%), IR (KBr disc)/ cm^{-1} 3446, 3025, 2923, 1601, 1493, 1452, 758, 698; Anal. Calcd. for polymer: C, 90.69; H, 7.81; N, 0.70, found C, 89.74; H, 8.05; N, 0.67, loading = 0.48 $mmolg^{-1}$; N_2 BET adsorption < 10 m^2g^{-1}; resin swelled to 5.2 times its own volume in CH_2Cl_2.

A significant proportion of the polymeric product was found to contain larger colourless beads mixed with plastic residue which were retained in the 500 micron mesh sieve (4.34 g, 30%), IR (KBr disc)/cm^{-1} 3446, 3025, 2918, 1601, 1493, 1452, 758, 699; Anal. Calcd. for polymer: C, 90.69; H, 7.81; N, 0.70, found C, 89.89; H, 8.08; N, 0.70, loading = 0.50 $mmolg^{-1}$; N_2 BET adsorption < 10 m^2g^{-1}; resin swelled to 4.7 times its own volume in CH_2Cl_2.

(26) For a discussion of the mechanism of catalysis by primary amine containing amino alcohols, see: Itsuno, I.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304.