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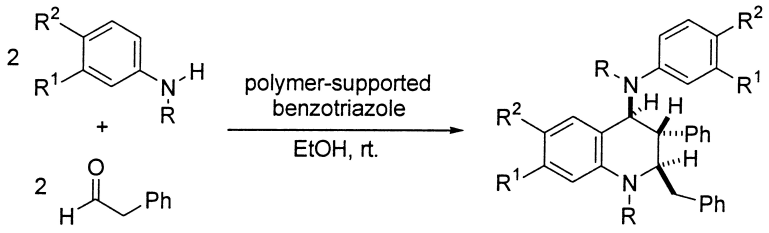

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Polymer-Supported Benzotriazoles as Catalysts in the Synthesis of Tetrahydroquinolines by Condensation of Aldehydes with Aromatic Amines

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Four polymer-supported benzotriazoles were prepared by linkage of 5-(hydroxymethyl)benzotriazole and benzotrizaole-5-carboxylic acid with Wang resin, Merrifield resin, and (monomethoxy)poly(ethylene glycol). The solid-phase and liquid-phase syntheses of tetrahydroquinolines were achieved by two-pair coupling reactions of aldehydes and aromatic amines using these polymer-supported benzotriazoles as the promoters. The ether-type benzotriazole prepared by loading 5-(hydroxymethyl)benzotriazole onto Merrifield resin turned out to be the catalyst of choice. Thus, a series of tetrahydroquinoline products were obtained in high purity by simple filtration, and the resin was recovered for reuse without loss of activity.

Introduction

Combinatorial chemistry[1] using polymer-bound reagents and catalysts[2] to build small-molecule libraries has become an efficient tool for accelerating the drug discovery process. Tetrahydroquinolines (THQs) belong to an important heterocyclic system of medicinal and industrial interests.[3] Many general methods for the synthesis of THQs in solution phase have been developed.[3,4] A solid-phase synthesis of THQs has been carried out by using a condensation reaction of three components that include benzaldehyde, aniline, and an alkene.[5a−c] Since one of the reagents is immobilized on a solid support, an additional step is required for cleavage of the THQ product from the polymeric support. On the other hand, strategies that allow automatic release of polymeric support for recycle in the desired transformations are attractive. In the synthesis of THQs, such a strategy has been applied by using polymer-supported microencapsuled scandium triflate as the catalyst.[5d]

We have recently reported a one-pot synthesis of THQs using a two-pair coupling reaction of phenylacetaldehydes and aromatic amines by the promotion of 1*H*-benzotriazole (BtH).[6] This synthesis involves the initial formation of *N*-(α-aminoalkyl)benzotriazole from which the *N*-aryliminium ion is generated, and the Bt^- counteranion promotes isomerization to give the corresponding enamine. Coupling of the *N*-aryliminium ion and enamine intermediates thus affords the THQ products. BtH plays both roles as nucleophile and general base in this reaction sequence.[7] Such tandem reactions, occurring under mild conditions, offer great potential for combinatorial synthesis on structurally defined templates. Indeed, polymer-bound benzotriazoles have recently been developed to generate a library of amines.[8] We demonstrate herein the use of polymer-supported benzotriazoles as catalysts for the generation of a THQ library.

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Results and Discussion

Preparation of Polymer-Supported Benzotriazoles P1−P4 (Scheme 1). Benzotriazole-5-carboxylic acid (**4**) was subjected to esterification, NH protection, and reduction to give alcohol **5**.[8c] The corresponding benzyl ether of **5** was prepared, and the trityl group was removed to give 5-(benzyloxymethyl)benzotriazole **6**. On the other hand, alcohol **5** was treated with CBr_4 and Ph_3P to afford the corresponding bromide **7**. Bromination of *N*-trityl-5-methylbenzotriazole also provided compound **7** in an efficient manner.

Treatment of acid **4** with $SOCl_2$ gave the corresponding acid chloride, which could be anchored onto Wang resin to give **P1** with a loading of 0.33 mmol/g on the basis of elemental analyses of nitrogen content. The polymer-bound benzotriazole **P2** was similarly prepared by linkage of the acid chloride with (monomethoxy)poly(ethylene glycol) (MeO-PEG-OH, average molecular weight of ∼5000). The IR absorptions at 3452 and 1722 cm^{-1} were attributable to the NH and ester functionalities. By use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) as the dehydrating agent, a direct coupling of acid **4** with MeO-PEG-OH in the presence of Et_3N/DMPA was less effective to give **P2**. The ^1H NMR spectrum of **P2** in DMSO-d_6 showed the signals at δ 4.21 (2 H, br s, $MeOCH_2$) and 4.56 (2 H, br s, $BtCO_2CH_2$), in addition to three aromatic protons.

According to the known procedure,[8c] alcohol **5** was treated with NaH and reacted with Merrifield resin to give the ether-type resin **P3** after removal of the trityl group. The loading was estimated to be 0.83−0.97 mmol/g on the basis of nitrogen content. The PEG-bound benzotriazole **P4** was prepared by linkage of bromide **7** with the sodium salt of monomethoxy-PEG-OH_{5000}, followed by removal of the trityl group. The diagnostic $BtCH_2O$ group of **P4** appeared at δ 4.63 (2 H, br s) in the ^1H NMR spectrum. The loading of benzotriazole moieties in the PEG-bound benzotriazoles **P2** and **P4** was rather low (≤0.15 mmol/g).

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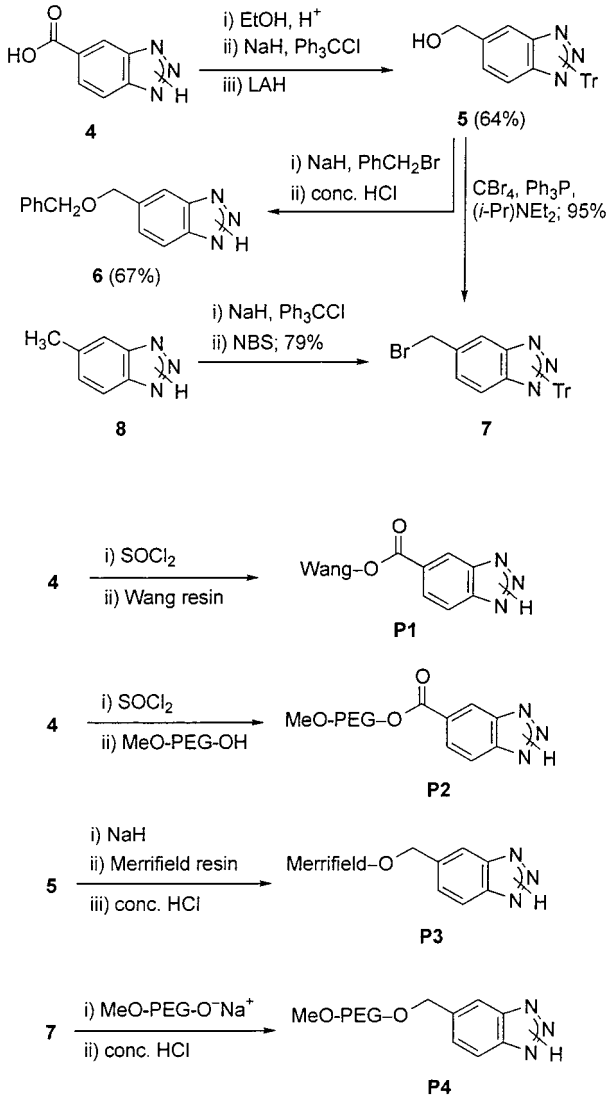
Scheme 1



The ester functionality at the 5-positions of **P1** and **P2** would impart a small inductive effect (−I), and the acidity of **P1** and **P2** might slightly increase by comparison with the parent BtH (pK_a of ∼8.2).[7] On the other hand, the electron-donating alkyl groups at the 5-positions of **P3** and **P4** would somewhat intensify the nucleophilicity of benzotriazole. Thus, the polymer-bound benzotriazoles **P1**−**P4** would still meet the electronic requirements of BtH itself to serve as the suitable catalysts in the two-pair coupling reactions for the synthesis of THQs. The PEG-bound benzotriazoles **P2** and **P4** could be used as soluble polymeric matrices in the liquid-phase combinatorial synthesis.[9] When **P2** and **P4** are used, the progress of reactions could be monitored by TLC and NMR analyses.

Synthesis of Tetrahydroquinolines Using Polymer-Bound Benzotriazoles as Catalysts (Scheme 2). We chose the facile two-pair coupling reaction of 3-methoxyaniline (**1c**) and phenylacetaldehyde (**2a**) as a model to test the viability and efficacy of the polymer-supported benzotriazoles **P1**−**P4** (Table 1). For comparisons, the reactions using ethyl benzotriazole-5-carboxylate (**4a**) and 5-(benzyloxymethyl)-benzotriazole (**6**) as surrogates were also investigated (entries 2 and 3 in Table 1). When the ester-type benzotriazole **4a** (20 mol %) was used as a promoter, the condensation reaction of **1c** and **2a** in EtOH solution at 25 °C gave the

Scheme 2

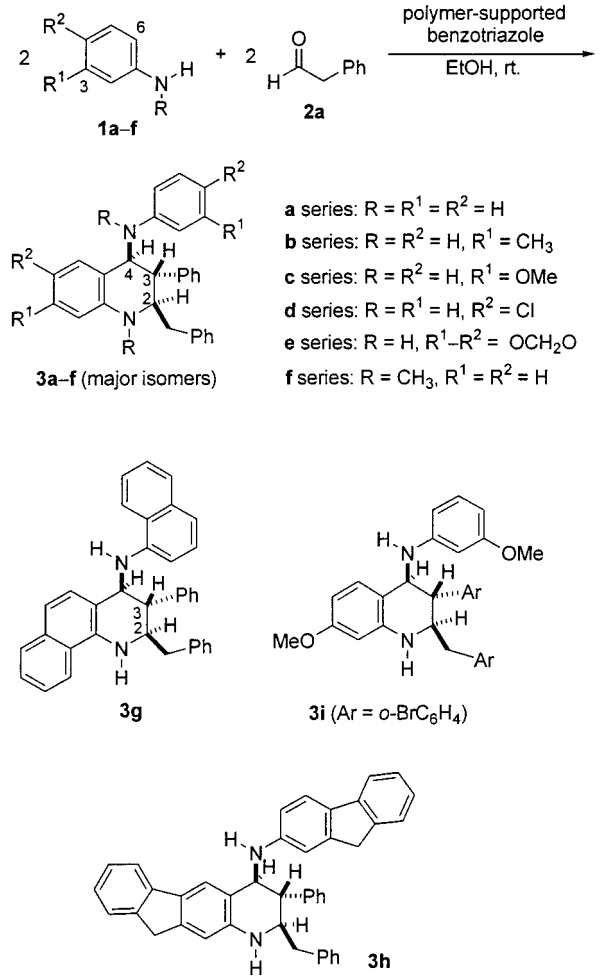


Table 1. Condensation of 3-Methoxyaniline (**1c**) and Phenylacetaldehyde (**2a**) Using Various Benzotriazole Derivatives as Promoters To Give Tetrahydroquinoline **3c**[a]

entry	promoter (mol %)	reaction time (h)	yield[b] (%)	ratio of isomers[c]
1	BtH (20)	1	78	95:5
2	**4a**[d] (20)	8	74	73:27
3	**6** (20)	1	90	97:3
4	**P1** (20)[e]	3	64	95:5
5	**P2** (10)[f]	6	30	96:4
6	**P2** (20)[f]	6	38	87:13
7	**P2** (20)[g]	4	61	92:8
8	**P3** (20)[h]	3	84	100:0
9	**P4** (20)[i]	4	57	100:0

[a] The reactions were performed in EtOH with 10−20 mol % of catalyst at room temperature. [b] Yields of isolated products with purity greater than 95% according to the ^{1}H NMR analyses. [c] The ratio of major (2,3-trans-2,4-cis) isomer to minor (2,3-cis-2,4-cis) isomer was determined by the ^{1}H NMR analysis. [d] The ethyl ester of benzotriazol-5-carboxylic acid (**4**). [e] The Wang resin supported benzotriazole with a loading of 0.33 mmol/g was used. [f] The MeO-PEG-OH supported benzotriazole with a loading of 0.045 mmol/g was used. [g] The MeO-PEG-OH supported benzotriazole with a loading of 0.086 mmol/g was used. [h] The Merrifield resin supported benzotriazole with a loading of 0.90 mmol/g was used. [i] The MeO-PEG-OH supported benzotriazole with a loading of 0.15 mmol/g was used.

Table 2. Synthesis of THQs **3a**−**i** in EtOH at 25 °C Using Merrifield Resin Supported Benzotriazole **P3** (20 mol %) as the Promoter

entry	arylamine	aldehyde	reaction time (h)[a]	products[b]	yield (%)	ratio of isomers	comparison[c] yield (ratio of isomers)
1	**1a**	**2a**	16	**3a**	84	84:16	86 (76:24)
2	**1b**	**2a**	5	**3b**	88	82:18	78 (80:20)
3	**1c**	**2a**	3	**3c**	84	100:0	78 (95:5)
4	**1d**	**2a**	24	**3d**	88	75:25	80 (77:23)
5	**1e**	**2a**	5.5	**3e**	89	100:0	88 (100:0)
6	**1f**	**2a**	6	**3f**	88	100:0	68 (100:0)
7	**1g**	**2a**	5	**3g**	83	100:0	88 (100:0)
8	**1h**	**2a**	5	**3h**	82	100:0	78 (100:0)
9	**1c**	**2b**	2.5	**3i**	87	100:0	85 (100:0)

[a] The solid-phase synthesis was slower than that using 1*H*-benzotriazole as the promoter. Approximately half of the listed reaction time is required for the corresponding reaction using 1*H*-benzotriazole as the promoter. [b] The THQ products had a high purity (>95%) as indicated by HPLC analyses. [c] The data are adapted from ref 6 for the corresponding reactions using 1*H*-benzotriazole (20 mol %) as the promoter.

desired THQ **3c** in 74% yield as a mixture of two isomers (2,3-trans-2,4-cis/2,3-cis-2,4-trans = 73:27). The yield and stereoselectivity were somewhat lower than the BtH-catalyzed reaction[6] (entry 1 in Table 1). On the other hand, the reaction promoted by the ether-type benzotriazole **6** (20 mol %) gave THQ **3c** in high yield (90%) and high stereoselectivity (94% de). Neither **4a** nor **6** were recovered for reuse.

When the polymer-bound catalysts **P1**−**P4** (10−20 mol %) were used, THQ **3c** was also formed by coupling equal molar amounts of amine **1c** and aldehyde **2a** at room temperature in a reasonable period (3−6 h). The two-pair coupling reactions were generally conducted in EtOH. The ether-type benzotriazole **P3** anchored onto Merrifield resin turned out to be the best catalyst to give THQ **3c** in 84% yield as a single isomer with 2,3-trans-2,4-cis configuration. By simple filtration, the polymer-bound catalyst **P3** was easily recovered and reused with equal efficiency. The reactions using PEG-bound benzotriazoles **P2** and **P4** afforded only 30−61% of THQ **3c**, not so high-yielding as one might anticipate for a liquid-phase synthesis. Using CH_2Cl_2 as a cosolvent in the reaction did not improve the yield of **3c**. The low yield might be due to low loadings (≤0.15 mmol/g) in **P2** and **P4**. The reaction mixture was concentrated and triturated with Et_2O to give precipitates of **P2** and **P4**, which were recovered by filtration.

When Merrifield resin supported benzotriazole **P3** (20 mol %) was used as the promoter, a small library of THQs was established (Table 2). The arylamines included anilines **1a**−**f**, 1-naphthylamine (**1g**), and 2-fluorenamine (**1h**). The aldehyde counterparts included phenylacetaldehdye and *o*-bromophenylacetaldehyde (**2b**). The reactions of anilines **1b**, **1c**, and **1e** containing C-3 substituents (Me, OMe, or methyleneoxy) occurred exclusively at C-6 rather than C-2 positions presumably because of the steric effect of C-3 substituents. By comparison, the reactions using BtH as the promoter[6] were also shown in Table 2. Both the parent BtH and the polymer-bound benzotriazole **P3** appeared to be effective promoters for the synthesis of THQs. The advantage of using **P3** resided on its facile recovery by simple filtration and ensuring high purity of THQ products.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 or 500 MHz; ^{13}C NMR spectra were recorded at 75 or 100 MHz. $CDCl_3$ ($\delta_H = 7.24$ and $\delta_C = 77.0$ (central line of triplet)) was used as an internal standard in ^{1}H and ^{13}C NMR spectra, unless otherwise stated. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. HPLC (Waters, model M-45) analysis was performed on a Li-chromsorb Si-60 column using UV detection at $\lambda = 254$ nm. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on silica gel (70−230 mesh); gradients of EtOAc and hexane were used as eluents.

THF was distilled from sodium benzophenone ketyl under N_2. NaH (60% dispersed in mineral oil) was washed with anhydrous hexane before use. Wang resin (0.65 mmol/g, Sigma), Merrifield resin (2% cross-linked, 2−2.5 mequiv Cl/g, 200−400 mesh, Acros Organics), and monomethoxy-PEG-OH (average molecular weight ∼5000, Aldrich) were used. Wang and Merrifield resins were dried under reduced pressure before use. Monomethoxy-PEG-OH was dried by azeotropical removal of water with refluxing acetonitrile.

The isomers of THQ products have been separated by chromatography and fully characterized as reported in ref 6.

Poly(*p*-alkoxybenzyl)benzotriazole-5-carboxylate (P1). To a solution of benzotriazole-5-carboxylic acid (**4**) (0.5 g, 3 mmol) in CH_2Cl_2 (15 mL) was added thionyl chloride (0.5 g, 4.2 mmol). After the mixture was stirred at 25 °C for 5 h, excess $SOCl_2$ was removed under reduced pressure and the resulting solution of acid chloride was added to a mixture of Wang resin (1.5 g, 0.98 mmol) and DMAP (0.1 g, 0.09 mmol). After that, Et_3N (1.1 mL, 8 mmol) was added, and the mixture was refluxed for 12 h. The resin was filtered, washed successively with water (10 mL × 2), EtOH (10 mL × 2), and CH_2Cl_2 (10 mL × 2). After it was dried, white resin **P1** (1.5 g) was obtained. IR (KBr): 1716, 1614, 1362, 1245, 1067 cm^{-1}. Elemental analyses (two measurements) showed a nitrogen content of 1.30−1.47%, equivalent to a loading of 0.33 mmol/g on average.

Methoxy-PEG-OH Benzotriazole-5-carboxylate (P2). An acid chloride was prepared by stirring acid **4** (0.82 g, 5 mmol) with $SOCl_2$ (5 mL) for 6 h. After removal of excess $SOCl_2$ under reduced pressure, a solution of MeO-PEG-

OH_{5000} (5 g, 1 mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (25 mL) was added. The mixture was cooled in an ice bath, and Et_3N (510 mg, 5 mmol) was added. After it was stirred for 48 h at room temperature, the mixture was concentrated to about 5 mL. Triturating with Et_2O (35 mL) gave precipitates, which were filtered and washed successively with Et_2O (20 mL), 2-propanol (30 mL), EtOAc/hexane (1:9, 30 mL), and Et_2O (20 mL). After they were dried, white powders of **P2** (4.89 g) were obtained. IR (KBr): 3453, 2889, 1722, 1469, 1282, 1114 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (1 H, s), 7.94 (2 H, s), 4.56 (2 H, br s, $BtCO_2CH_2$), 4.21 (2 H, br s, $MeOCH_2$). Elemental analyses (four measurements) showed a nitrogen content of 0.32−0.44%, equivalent to a loading of 0.086 mmol/g on average.

Another preparation using **4** and MeO-PEG-OH_{5000} in a molar ratio of 1.5:1 gave **P2** with a loading of 0.045 mmol/g (on an average of 0.31−0.52% nitrogen content from four measurements).

5-[(Polystyrene-bound)methoxymethyl]benzotriazole (P3).[8c] According to the known procedure,[8c] linkage of the sodium salt of **5** (1.95 g, 5 mmol) with Merrifield resin (2 g, 4−5 mmol), followed by removal of the trityl group with concentrated HCl, gave resin **P3** (2.18 g). Elemental analyses (including two measurements of **P3** and two measurements of its trityl precursor) showed a nitrogen content of 3.49−4.10%, equivalent to a loading of 0.90 mmol/g on average.

5-[(Methoxy-PEG-oxy)methyl]benzotriazole (P4). A suspension of monomethoxy-PEG-OH_{5000} (1.25 g) was treated with NaH (7.5 mg, 0. 3 mmol) in anhydrous THF (40 mL) at 25 °C for 5 h. A solution of *N*-trityl-5-bromomethylbenzotriazole (**7**) (227 mg, 0.5 mmol) and tetrabutylammonium iodide (12 mg, 0.03 mmol) in THF (10 mL) was added. The mixture was refluxed for 16 h, and the TLC analysis indicated complete consumption of the bromide **7**. The reaction mixture was cooled, and THF was removed under reduced pressure. To the thick mass was added Et_2O (25 mL). The resins were collected by filtration and washed successively with Et_2O (10 mL × 3) and 2-propanol (10 mL × 3). White powders of *N*-trityl-5-[(methoxy-PEG-oxy)-methyl]benzotriazole (1.23 g) were obtained after drying as a mixture of N_1-, N_2- and N_3-trityl isomers according to the ^1H NMR analysis.

After they were stirred with concentrated HCl (2.5 mL) in THF/MeOH (25 mL, v/v = 3:2) at 25 °C for 5 h, the powders were collected by filtration, washed successively with Et_2O (10 mL × 3) and 2-propanol (10 mL × 3), and dried to give **P4** (1.04 g). IR (KBr): 3441, 3009, 2886, 1645, 1470, 1283, 1250, 1110 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 7.90−7.79 (2 H, m), 7.37 (1 H, s), 4.63 (2 H, s, $BtCH_2O$). Elemental analyses (including two measurements of **P4** and two measurements of its trityl precursor) showed a nitrogen content of 0.61−0.66%, equivalent to a loading of 0.15 mmol/g on average.

Representative Procedure for the Formation of THQs Using Polymer-Supported Benzotriazoles as Catalysts. 1. Liquid-Phase Synthesis. PEG-bound benzotriazole **P2** (0.92 g, 0.083 mmol) was dissolved in hot EtOH (5 mL) and then cooled to room temperature. A solution of phenylacetaldehyde (50 mg, 0.42 mmol) in EtOH (1 mL) was added. After the mixture was stirred for 5 min, a solution of 3-methoxyaniline (56 mg, 0.46 mmol) in EtOH (1 mL) was added. The mixture was stirred at room temperature for 6 h, while the progress of reaction was monitored by TLC analysis (EtOAc/hexane = 3:7). The mixture was concentrated to about 1 mL and triturated with Et_2O (10−15 mL) to give precipitates. After the mixture was cooled in an ice bath, the solids were filtered and washed successively with Et_2O (15 mL), 2-propanol (15 mL), EtOAc/hexane (1:9, 15 mL), and Et_2O (10 mL) to give **P2** (>97% recovery). The filtrate was concentrated and chromatographed on a silica gel column by elution with EtOAc/hexane (1:9) to give THQ product **3c** [59% yield of 2,3-trans-2,4-cis isomer (56 mg) and 2% yield of 2,3-cis-2,4-cis isomer (5 mg)]. The recovered **P2** catalyst was reused for the other two cycles to give similar results.

2. Solid-Phase Synthesis. A mixture of 3-methoxyaniline (**1c**, 123 mg, 1 mmol), phenylacetaldehyde (**2a**, 120 mg, 1 mmol), and polymer-bound benzotriazole **P3** (196 mg, 0.20 mmol) in EtOH solution (2 mL) was stirred at room temperature (25 °C) for 3 h. The resins were filtered and washed successively with EtOH (5 mL × 2), CH_2Cl_2 (5 mL × 2), and Et_2O (5 mL × 2). The filtrate was concentrated to give THQ product **3c** (205 mg, 84% yield) with the 2,3-trans-2,4-cis configuration. Resin **P3** (194 mg, 99% recovery) was recovered and reused to give similar results.

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