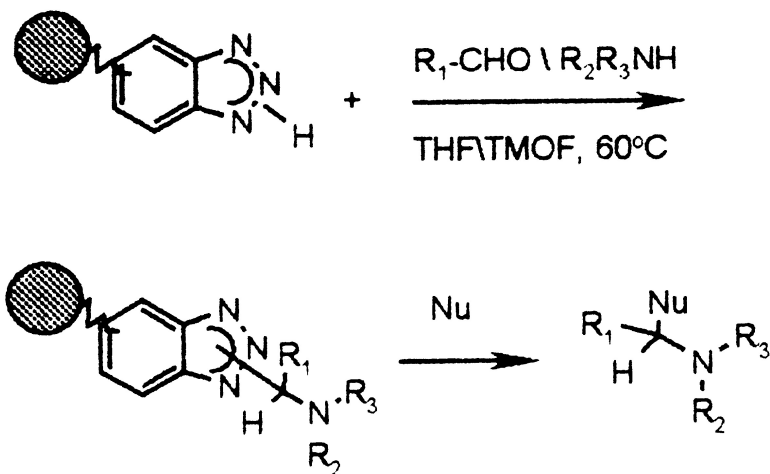Article

Solid-Supported Benzotriazoles: Synthetic Auxiliaries and Traceless Linkers for the Combinatorial Synthesis of Amine Libraries

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Solid-Supported Benzotriazoles: Synthetic Auxiliaries and Traceless Linkers for the Combinatorial Synthesis of Amine Libraries[1]

Alfredo Paio,* Alessio Zaramella, Rafael Ferritto, Nadia Conti, Carla Marchioro, and Pierfausto Seneci

GlaxoWellcome Medicines Research Centre, Via Fleming 4, 37135 Verona, Italy

This paper describes the successful transfer of benzotriazole-based chemistry on solid support. The strategy followed to anchor this peculiar heterocycle on solid phase and the full analytical characterization of the various supported benzotriazoles are herein described. The chemistry assessment process on solid phase, the preparation of discrete libraries by parallel synthesis, the semiautomated purification procedures, and the complete analytical characterization of the library components are also presented and discussed.

Introduction

A growing interest in developing solid phase synthetic strategies[2] for preparing highly differentiated small drug-like molecules in a combinatorial library format[3] has been witnessed during the past few years. The development of new linkers[2c,4] has increased the compound diversity obtainable from solid phase chemistry, especially regarding small organic molecules: the so-called traceless linkers,[5] which leave no residual tethering on cleaved compounds, are particularly appealing to the combinatorial chemist. Recent advances in the use of solid-supported reagents[6] have opened new routes leading to library synthesis, both in solution and on solid phase. We disclose herein the successful application of resin-bound benzotriazoles, which can be seen both as supported synthetic auxiliaries or as novel traceless linkers, to the preparation of highly functionalized amine libraries. This work was inspired from well-known benzotriazole chemistry in solution:[7] the resin-bound benzotriazoles herein described are novel, the only precedent being the use of supported *N*-hydroxy benzotriazoles[8] mainly as activating agents for amide bond formation or related reactions.

A supported benzotriazole should provide access to chemical diversity contained within combinatorial libraries: as outlined in Scheme 1, the resin-bound benzotriazole **1** should react with aldehydes **2** in the presence of secondary amines, amides, thioamides, sulfonamides (**3,** Scheme 1),[9] or alcohols (**4,** Scheme 1)[10] to give, respectively, supported adducts **5** and **6**. Each adduct should release in solution highly substituted derivatives **7** and **8** by reaction with nucleophiles such as hydride ion, Grignard reagents, and carbanions as described in classical organic chemistry.[11]

The synthesis of supported benzotriazoles and their usefulness to prepare libraries of highly substituted and potentially bioactive amines is herein discussed. The reactivity of various aldehydes and amines with supported benzotriazoles is reported as well as the semiautomated purification procedures of final library compounds which are suitable for parallel synthesis.[12]
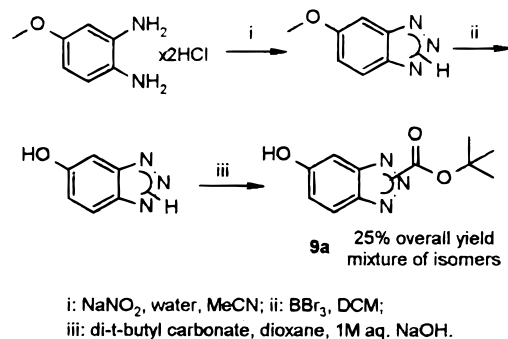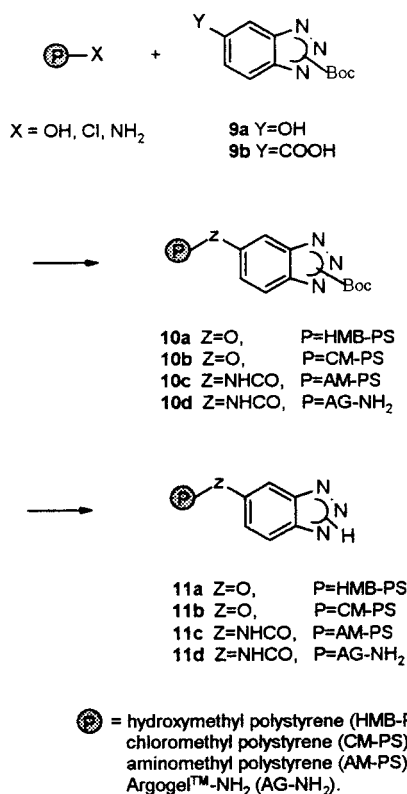
Scheme 1
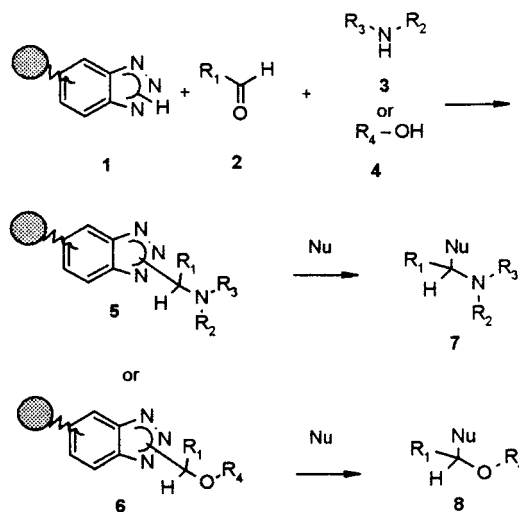
Results and Discussion

Supporting the Benzotriazoles. Attempts of anchoring benzotriazoles onto polystyrene resins were started using both an *in house* prepared and a commercially available compound. The connection between the polymer and the heterocycle was examined because often harsh reducing agents or organometallic reagents such as Grignard reagents are used during the synthesis. Two strategies were followed and are reported in Scheme 2, top: the preparation of 5-hydroxy benzotriazole, according to literature procedures,[13] followed by the *N*-Boc protection to afford compound **9a** with a moderate overall yield. Coupling of the phenolic function of **9a** with the resin was planned to anchor the compound via a stable ether bond. As an alternative, commercially available 5-benzotriazole carboxylic acid was transformed into its *N*-Boc derivative **9b** (Scheme 2, bottom) to be coupled via an amide bond onto the resin, providing that the amide bond would not interfere with the nucleophilic cleavage. Both **9a** and **9b** were used as mixtures of *N*-Boc isomers, as monitored by ¹H NMR (most likely as a mixture of 1-*N*-Boc and 3-*N*-Boc). For this reason, starting from

Table 1. Anchoring of **9a** (Entries 1, 2) and **9b** (Entries 3, 4) onto Different Resins
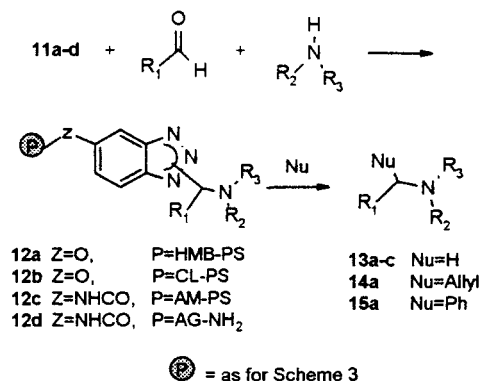
entry	resin[a]	coupling conditions	^{1}H MAS NMR[b] 10a−d	FT-IR bands, (cm^{-1})[b,c]	elemental analysis (%) 10/11a−d
1	HMB−PS	Ph$_3$P/DEAD/THF	confirmed	1747	>95%
2	CM-PS	NaH/DMF	confirmed	1754	>95%
3	AM-PS	DIC/DMAP/DMF	confirmed	1750, 1640	>95%
4	AG-NH$_2$	DIC/DMAP/DMF	confirmed	1750, 1649	>95%

[a] See Scheme 3 for abbreviations. [b] See Supporting Information. [c] Peaks for compounds **10a−d**; the disappearance of the Boc band (1760−1755 cm^{-1}) monitored the formation of **11a−d**.

Scheme 2

9a 25% overall yield mixture of isomers

i: NaNO$_2$, water, MeCN; ii: BBr$_3$, DCM; iii: di-t-butyl carbonate, dioxane, 1M aq. NaOH.

9b

Scheme 3

X = OH, Cl, NH$_2$ 9a Y=OH   9b Y=COOH

10a Z=O,   P=HMB-PS
10b Z=O,   P=CM-PS
10c Z=NHCO, P=AM-PS
10d Z=NHCO, P=AG-NH$_2$

11a Z=O,   P=HMB-PS
11b Z=O,   P=CM-PS
11c Z=NHCO, P=AM-PS
11d Z=NHCO, P=AG-NH$_2$

= hydroxymethyl polystyrene (HMB-PS), chloromethyl polystyrene (CM-PS), aminomethyl polystyrene (AM-PS), Argogel™-NH$_2$ (AG-NH$_2$).

Scheme 1, the substituents on the triazole are indicated with a generic linkage to the ring.

Compounds **9a** and **9b** were successfully anchored onto different polystyrene-based resins (Scheme 3 and Table 1). Compound **9a** was loaded onto hydroxymethyl polystyrene (HMB-PS, entry 1, Table 1) using Mitsunobu solid phase
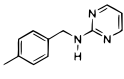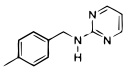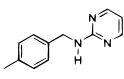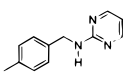
Scheme 4

12a Z=O,   P=HMB-PS
12b Z=O,   P=CL-PS
12c Z=NHCO, P=AM-PS
12d Z=NHCO, P=AG-NH$_2$

13a-c Nu=H
14a   Nu=Allyl
15a   Nu=Ph

= as for Scheme 3

conditions[14] and onto chloromethyl polystyrene (CM-PS, entry 2, Table 1) using nucleophilic substitution conditions, obtaining supported compounds **10a** and **10b**, respectively. Compound **9b** was hooked onto aminomethyl polystyrene (AM-PS, entry 3, Table 1) and onto Argogel-NH$_2$ (AG-NH$_2$, entry 4, Table 1) using conventional peptide coupling conditions thereby obtaining amide-linked derivatives **10c,d**. The solid phase coupling reactions were followed by FTIR,[15] and the relevant peaks observed are reported in Table 1; the yields were calculated via elemental analysis[16] (N), always observing a near quantitative loading (Table 1). For compounds **10c,d**, the quantitative coupling was also monitored following the disappearance of the resin free amino group by means of the colorimetric Kaiser test.[17] Supported derivatives **10a−d** were analytically characterized by ^{1}H MAS NMR.[18]

Boc deprotection to give **11a−d** (Scheme 3) was performed with 30% TFA/DCM and monitored by FTIR (disappearance of the carbamate signals, see Table 1). Benzotriazoles **11a−d** were characterized by ^{1}H MAS NMR, and yields were determined via elemental analysis (Table 1). The loading of compound **11a** was also estimated through its Fmoc protection, deprotection with 20% piperidine/DMF, and UV−Fmoc quantitation.[19] The result (>90% loading) was consistent with elemental analysis results (>95%, Table 1).
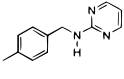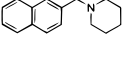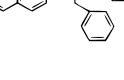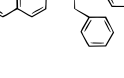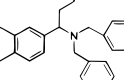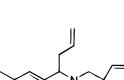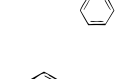
Chemistry Assessment on Solid Phase. The chemistry assessment process aimed to prepare secondary and tertiary amines from benzotriazoles[9a] on solid phase was started on compounds **11a−d** (Scheme 4) to select from them the best supported reagent (hydrophobic or hydrophilic polystyrene resins, ether or amide bonds). The outcome of the significant experiments is reported in Table 2. The four supported benzotriazoles performed similarly in terms of purity and yields using sodium borohydride as a nucleophilic cleavage agent (entries 1−4, Table 2). In particular, compounds **11c,d**

Table 2. Performance Evaluation of the Different Supported Benzotriazoles **11a−d**

entry	product	resin[a]	adduct formation[b]	cleavage conditions[c]	¹H NMR results	HPLC/MS purity
1	**13a**	HMB-PS **11a**	A	A1	confirmed	65% a/a[d]
2	**13a**	CM-PS **11b**	A	A1	confirmed	70% a/a[d]
3	**13a**	AM-PS **11c**	A	A1	confirmed	77% a/a[d]
4	**13a**	AG-NH₂ **11d**	A	A1	confirmed	55% a/a[d]

[a] See Scheme 3 for abbreviations. [b] A: THF/TMOF 2/1, room temperature, 15 h. [c] A1: NaBH₄/THF, 60 °C, 15 h. [d] Crude from reaction.

Table 3. Chemistry Evaluation of Supported Benzotriazoles **11a−d**

entry	product	resin[a]	adduct formation[b]	cleavage conditions[c]	¹H NMR results[d]	HPLC/MS purity
1	**13a**	AM-PS	A	A1	confirmed	77% a/a[e]
2	**13b**	AM-PS	A	A1	confirmed	40% a/a[e]
3	**13c**	AM-PS	B	A1	confirmed	55% a/a[e]
4	**13c**	AM-PS	B	A1	confirmed	89% a/a[f]
5	**14a**	AM-PS	B	B1	confirmed	100% a/a[f]
6	**14a**	AM-PS	C	B1	confirmed	75% a/a[f]
7	**15a**	AM-PS	B	C1	confirmed	95% a/a[f]

[a] See Scheme 3 for abbreviations. [b] A: THF/TMOF 2/1, room temperature, 15 h; B: THF/TMOF 2/1, 60 °C, 15 h; C: dioxane/TMOF 2/1, 60 °C, 15 h. [c] A1: NaBH₄/THF, 60 °C, 15 h; B1: allylMgCl/THF/TMOF, 40 °C, 15 h; C1: PhMgBr/THF/TMOF, 40 °C, 15 h. [d] See Supporting Information. [e] Crude from reaction. [f] After SCX (strong cation-exchange resin) purification.

afforded clean amines, thus confirming the compatibility of the amide bond to the cleavage conditions with sodium borohydride (see also entries 1−4, Table 3) and with Grignard reagents (entries 5−7, Table 3). Supported ben-

zotriazole **11c** was thus selected and used in all the following experiments also because of the ready commercially available 5-benzotriazole carboxylic acid.

A detailed chemical assessment used a few selected

Scheme 5

11c

12c

= AM-PS

16–30
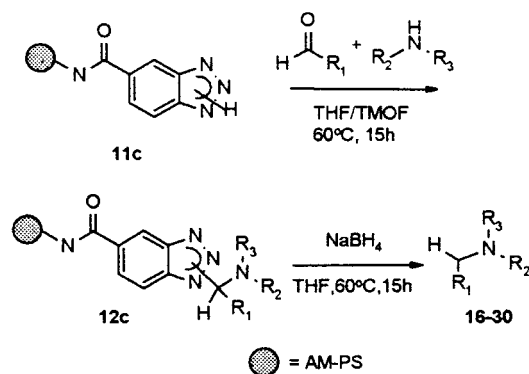
aldehydes and amines, optimizing the adduct formation on solid phase and the cleavage via hydride ion (entries 1–4, Table 3) or Grignard addition (entries 5–7, Table 3). Major issues to solve were incomplete adduct formation on solid phase, resulting in the presence of a primary alcohol in the crude product from hydride ion quenching; the formation of complexes between the borates and the final amines from hydride ion quenching; and the purification of the final amines from alcohols (hydride ion quenching), hydrocarbons (Grignard quenching), and/or inorganic salts and complexes (both cleavage conditions).

THF/trimethyl orthoformate (TMOF) or dioxane/TMOF at 60 °C over 15 h using 10 and 12 equiv of aldehyde and amine, respectively, was identified as the best reaction conditions for adduct formation (B and C, Table 3). Sodium borohydride at 60 °C in THF over 15 h (A1, Table 3) and allylmagnesium chloride or phenylmagnesium bromide in THF/TMOF at 40 °C over 15h (B1 and C1, Table 3) were determined, respectively, as the best cleavage conditions. The supported adduct obtained with benzaldehyde and dibenzyl-amine was stored for 15 days in a CaCl$_2$ desiccator and showed neither loss of loading nor formation of impurities: its cleavage using optimized condition C1 (Table 3) gave comparable yields to the same freshly prepared adduct. Significant improvements for product purification were obtained via a combination of aqueous extractions (Na$_2$CO$_3$ or NH$_4$Cl/DCM) and strong cation exchange (SCX) resins capturing solid phase extractions (entries 4–7, Table 3). The average yield of the whole synthesis (two chemical steps and two purifications) ranged between 30 and 50% of pure final compounds (see Experimental Section and Supporting Information for more details).

Library Preparation. The synthesis of arrays of compounds by manual parallel synthesis using sodium borohydride and allylmagnesium chloride as cleaving agents was our next step. Aldehydes and amines with different reactivity were selected to test the optimized conditions for both the hydride and Grignard cleavage on a wider reagents panel.

A first 15-membered array (library **1**, Scheme 5, Table 4) evaluated the reactivity of eight aldehydes with dibenzyl-amine and of eight amines with 2-naphthaldehyde using sodium borohydride as the cleavage agent. Compound **16** was prepared twice as a standard (Table 4) in order to evaluate the process robustness under library production conditions; no significant differences between the two preparations were observed in terms of both yield and purity.

The following optimized conditions were used: aldehyde (10 equiv), amine (12 equiv), THF/TMOF 2/1 at 60 °C, 15 h for the adduct formation; sodium borohydride (20 equiv), THF at 60 °C, 15 h for the reductive cleavage; aqueous extraction (aqueous Na$_2$CO$_3$/DCM) and strong cationic exchange (SCX) resin capturing for the semiautomated sample purification. More details are reported in the Experimental Section. Good reactivity was observed with aromatic, heteroaromatic, and aliphatic aldehydes, giving the desired products with comparable overall yields (20–50%) and purities (60–90% a/a by HPLC/MS, Table 4, compounds **16–19**, **21–23**). The only exception was 5-bromo-2-furan-carboxaldehyde which did not produce compound **20** due to aldehyde polymerization during adduct formation. The reactivity profile of amines was worse: some aliphatic amines failed to react (Table 4, compounds **25**, **26**, and **29**) while four others, including low reacting 2-amino pyridine, gave the expected products varying from acceptable to good overall yields (25–65%) and purities (80–90% a/a by HPLC/MS, Table 4, compounds **24**, **27**, **30**, **16**). Compound **28** was obtained with low yield and purity (Table 4). The observed variability in the amine monomers reactivity can be attributed to their different nucleophilicity, as reported for the related solution phase chemistry.[9a] Different amines, though, might require ad hoc optimized conditions. The introduction of more significant chemical diversity via general synthetic routes is considered one of the major issues in developing solid phase chemistry for library synthesis.

Another 15-membered array was prepared using the same aldehydes and amines (library **2**, Scheme 6, Table 5) with allylmagnesium chloride as the cleavage agent (30 equiv THF/TMOF at 40 °C, 15 h) followed by purification of the final compounds (aqueous NH$_4$Cl/DCM extraction and SCX resin capturing). The adduct formation was performed as seen for the first array, and compound **31** was prepared twice as a standard (Table 5) for the method robustness evaluation. Once again, a good reactivity for the various aldehydes was observed, obtaining the desired products with moderate overall yields (20–50% with the exception of compound **35**) and from good to high purities (55–100% a/a by HPLC/MS, Table 5, compounds **31–34** and **36–38**). Amines showed the same behavior seen for the previous array, with additional poor or nonreactivity of primary amines. Only two compounds were obtained with moderate yields (25–40%) and high purities (95–100 a/a by HPLC/MS, Table 5, compounds **42** and **31**). Compound **43** was obtained with low yield and purity (Table 5).

Conclusions

In summary, we have successfully anchored benzotriazoles onto different polymeric supports, and we have transferred an example of Katritzky's chemistry to solid phase. New opportunities to generate small organic molecule combinatorial libraries should arise from these findings which prove the usefulness of **11a–d** as supported synthetic auxiliaries. The application of purification procedures[12] amenable to parallelization, such as aqueous/organic solvents extractions, phase separations, and strong cation-exchange resin purifications, to this chemistry afforded high quality final com-

Table 4. Library **1** (NaBH$_4$ Cleavage)

aldehyde rehearsal				amine rehearsal			
compound number	product	yield[a]	HPLC/MS purity[b]	compound number	product	yield[a]	HPLC/MS purity[b]
16	(structure)	45	90	**24**	(structure)	60	82
17	(structure)	26	61	**25**	(structure)	-	-
18	(structure)	22	82	**26**	(structure)	-	-
19	(structure)	41	79	**27**	(structure)	65	91
20	(structure)	-	-	**28**	(structure)	25	27
21	(structure)	24	60	**29**	(structure)	-	-
22	(structure)	47	90	**30**	(structure)	55	86
23	(structure)	30	75	**16**	(structure)	50	86

[a] Calculated as w/w yield after SCX purification. [b] Calculated as area/area percentage.

Scheme 6
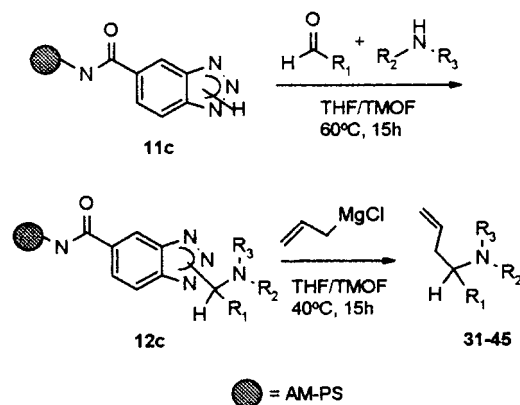
pounds. Further experiments to expand this new solid phase chemistry are currently ongoing in our laboratories, and their results will be communicated soon. Among them, the exploitation of **11a−d** as novel traceless linkers through further functionalization of resin bound adducts and subsequent cleavage is in progress.

Experimental Section

Materials. All the individual solid phase reactions were carried out in glass vials (Wheaton), and the resin washings were carried out on Extract Clean Tube syringes (Alltech or IST). Reagents were purchased from Aldrich, Sigma, Fluka, Acros, or Janssen and used without further purification. The polypropylene syringes as well as the Meltblown polypropylene microtiter plate (MBPP) for phase separation were purchased from Whatman. The SCX cartridges were purchased from Varian and the microtiter plate Bioplate SPE-SCX was purchased from Whatman; both were washed with methanol before being used. The polystyrene resins used were purchased from Novabiochem, Polymer Laboratories, and Argonaut Technologies Inc.

General Methods. All the solid phase reactions at room temperature were stirred on an orbital shaker unless otherwise stated; those that required heating were performed in a heating block without stirring. The manual parallel synthesis, in which heating is involved in the two chemical steps, was carried out on the Flexchem from Robbins Scientific while for parallel purification the HiTOPS device developed by Affymax Research Institute and sold by Whatman/Polyfiltronic was used. Concentration of the cleavage solutions and of solutions from purification procedures was performed on a Speed Vac Plus SC210A (Savant).

Infrared spectra were recorded on a FTIR spectrophotometer on solid compound (KBr disk) unless otherwise stated and are reported in wavenumbers (cm^{-1}). All the NMR spectra were acquired at 25 °C, referred to the residual solvent line, and reported in ppm: ^{1}H NMR spectra were obtained in CDCl$_3$, unless otherwise stated, at 500 MHz

Table 5. Library **2** (Allyl Magnesium Chloride Cleavage)

aldehyde rehearsal				amine rehearsal			
compound number	product	yield[a]	HPLC-MS purity[b]	compound number	product	yield[a]	HPLC-MS purity[b]
31		33	100	**39**		-	-
32		48	100	**40**		-	-
33		45	100	**41**		-	-
34		41	55	**42**		26	94
35		-	-	**43**		22	13
36		36	81	**44**		-	-
37		20	100	**45**		-	-
38		11	75	**31**		40	100

[a] Calculated as w/w yield after SCX purification. [b] Calculated as area/area percentage.

while ^{1}H MAS NMR spectra were obtained in CD_2Cl_2 at 400 MHz using the Nano-probe.

All the HPLC/MS data were obtained using the HP1100 liquid chromatography system equipped with diode array detector (Hewlett-Packard, Germany) coupled with the mass spectrometer Platform II (Micromass Ltd., U.K). The autosampler was a Gilson 233XL (Gilson, France). All samples were analyzed by flow injections mass spectrometry and by liquid chromatography mass spectrometry (HPLC/MS), both performed with the same equipment. Flow injections analysis was obtained by infusing 20 μL of each sample into the mass spectrometer by an autosampler. The mass spectrometer worked in positive electrospray ionization mode (ES$^+$) with a 3.8 kV capillary voltage. The mobile phase was water/acetonitrile 50/50 with 0.1% of TFA, and the flow rate was 25 μL/min. The mass range of 80−800 amu was scanned in compressed centroid acquisition mode with 5.0 s scan time.

The chromatographic separations were obtained using a Supelcosil ABZ+ Plus column (Supelco, USA), 3.3 cm × 0.46 cm, 3 μm. The mobile phase was water (A) and acetonitrile (B): initially from 20% to 90% of B in 8 min, and then 5 min with 90% of B. The reequilibration time between two injections was 3 min. The flow rate was 0.8 mL/min. All samples were injected using a Gilson XL233 autosampler. The injection volume was 20 μL. Diode array chromatograms were collected using a large bandwidth (from 220 to 350 nm).

The mass spectrometer was set in positive electrospray ionization mode (ES$^+$) with 3.6 kV capillary voltage; the mass range of 170−800 amu was scanned in compressed centroid acquisition mode with 3.5 s scan time. All acquired data were processed using the MassLynx software with the OpenLynx Diversity tools (Micromass Ltd, U.K.).

Preparation of *N-tert*-Butyloxycarbonyl-5-hydroxy-

benzotriazole 9a. A solution of di-*tert*-butylcarbonate (3.14 g, 14.4 mmol) in dioxane (20 mL) in 30 min was added dropwise to a solution of 5-hydroxy-benzotriazole[13] (0.97 g, 7.2 mmol) in dioxane/1 M NaOH 4/6 (40 mL). After being stirred for 2 h at room temperature, the solution was diluted with water (50 mL), acidified to pH 3 with 2 N HCl, and then extracted with ethyl acetate (2 × 100 mL). The organic phase was washed with brine, dried (MgSO$_4$), and then concentrated to dryness.

The crude was purified by flash chromatography (cyclohexane/ethyl acetate 7/3) affording **9a** as a yellowish foam (0.78 g, 3.32 mmol, yield 46%) characterized as follows: ^{1}H NMR (DMSO-d_6) δ 10.53 (s, 0.4H), 10.03 (s, 0.6H), 7.97, 7.82 (m, m, 1H), 7.34, 7.29 (m, m, 1H), 7.25, 7.00 (m, m, 1H), 1.68 (s, 9H).

Preparation of *N-tert*-Butyloxycarbonyl-5-benzotriazole Carboxylic Acid 9b. A solution of di-*tert*-butylcarbonate (18 g, 80 mmol) in dioxane (40 mL) in 30 min was added dropwise to a solution of commercially available 5-benzotriazole carboxylic acid (10 g, 60 mmol) in dioxane/1 M NaOH 4/6 (100 mL). After being stirred for 2 h at room temperature, the solution was diluted with water (100 mL), acidified to pH 3 with 2 N HCl, and then extracted with ethyl acetate (2 × 250 mL). The organic phase was washed with brine, dried (MgSO$_4$), and then concentrated to a small volume (60 mL). Addition of cyclohexane (350 mL) under vigorous stirring caused precipitation of the product which was filtered, washed with cyclohexane, and dried to give pure **9b** as a pale yellow solid (12.2 g, 46.4 mmol, yield 76%), mp 264−266 °C: ^{1}H NMR (DMSO-d_6) δ 13.4 (bs, 1H), 8.71, 8.61 (m, m, 1H), 8.29 (m, 1H), 8.10−8.08 (m, 1H), 1.71 (s, 9H).

Supporting 5-Hydroxy-*N*-Boc-Benzotriazole 9a on Hydroxymethyl Polystyrene (HMB-PS): Preparation of 10a. A typical procedure is as follows: a 25% v/v solution of diethylazodicarboxylate (0.316 mL, 2 mmol) in dry THF (0.95 mL) was added at 0 °C to a magnetically stirred mixture of hydroxymethyl polystyrene resin (Novabiochem, 100−200 mesh, 1% cross-linked, batch A19390; loading: 0.87 mmol/g; 0.460 g, 0.4 mmol), **9a** (0.47 g, 2 mmol), and triphenylphosphine (0.524 g, 2 mmol) in dry THF (2 mL). After warming to room temperature, the reaction mixture was stirred for 15 h. The mixture was filtered and the resin washed with THF (3 mL) and DCM (3 mL) for five repeating cycles. The resin was then dried under vacuum, and the supported benzotriazole **10a** was characterized by FTIR (Nujol: 1747, C=O), ^{1}H MAS NMR (δ 8.00−7.3 (m, 3H), 1.39 (m, 9H)), and elemental analysis (N: theoretical 3.05%, found 2.95%, yield > 95%).

Supporting 5-Hydroxy-*N*-Boc-Benzotriazole 9a on Chloromethyl Polystyrene (CM-PS): Preparation of 10b. A typical procedure is as follows: NaH (80% in mineral oil, 0.09 g, 3 mmol) was added at 0 °C to a mixture of chloromethyl polystyrene resin (Polymer Laboratories, 75−150 μm, 1% cross-linked, batch CMS035; loading: 1.09 mmol/g; 0.55 g, 0.6 mmol) and **9a** (0.66 g, 2.8 mmol) in dry DMF (3.5 mL). After 30 min the mixture was warmed to room temperature and gently stirred for an additional 15 h. The mixture was filtered and the resin washed with DMF

(3 mL), MeOH (3 mL) and DCM (3 mL), for five repeating cycles. The resin was then dried under vacuum, and the supported benzotriazole **10b** was characterized by FTIR (Nujol: 1754, C=O), ^{1}H MAS NMR (δ 8.00−7.3 (m, 3H), 1.39 (m, 9H)), and elemental analysis (N: theoretical 3.7%, found 3.62%, yield > 95%).

Supporting *N*-Boc-5-Benzotriazole Carboxylic Acid 9b on Aminomethyl Polystyrene (AM-PS): Preparation of 10c. A typical procedure is as follows: diisopropyl carbodiimide (1.06 mL, 6.75 mmol) and catalytic DMAP (0.066 g, 0.54 mmol) were added at room temperature to a mixture of aminomethyl polystyrene resin (Polymer Laboratories, 75−150 μm, 1% cross-linked, batch AMS009; loading: 0.9 mmol/g; 3 g, 2.7 mmol) and benzotriazole **9b** (3.55 g, 13.5 mmol) in dry DMF (18 mL). The mixture was gently shaken for 15 h at room temperature, and reaction completion was monitored via the colorimetric Kaiser test.[15] After filtration the resin was washed with DMF (15 mL), MeOH (15 mL), and DCM (15 mL) for five repeating cycles. The resin was then dried under vacuum, and the supported benzotriazole **10c** was characterized by FTIR (1750, C=O, 1640, C=O amide), ^{1}H MAS NMR (δ 8.0−7.3 (m, 3H), 1.49 (m, 9H)), and elemental analysis (N: theoretical 4.13%, found 4.01%, yield > 95%).

Supporting *N*-Boc-5-Benzotriazole Carboxylic Acid 9b on Argogel-NH$_2$ (AG-NH$_2$): Preparation of 10d. A typical procedure is as follows: diisopropyl carbodiimide (0.34 mL, 2.15 mmol) and DMAP (0.021 g, 0.172 mmol) were added at room temperature to a mixture of Argogel-NH$_2$ resin (Argonaut Technologies Inc., 164 average μm, batch 00043; loading: 0.43 mmol/g; 2 g, 0.86 mmol) and **9b** (1.13 g, 4.3 mmol) in dry DMF (10 mL). The mixture was gently shaken for 15 h, and reaction completion was monitored via the colorimetric Kaiser test. After filtration the resin was washed with DMF (12 mL), MeOH (12 mL), and DCM (12 mL) for five repeating cycles. The resin was then dried under vacuum, and the supported benzotriazole **10d** was characterized by FTIR (Nujol: 1750, C=O, 1649, C=O amide), ^{1}H MAS NMR (δ 8.50−8.0 (m, 3H), 1.49 (m, 9H)), and elemental analysis (N: theoretical 2.16%, found 2.07%, yield > 95%).

General Procedure for Boc Deprotection of Supported *N*-Boc-Benzotriazoles 10a−d: Preparation of 11c. The resin **10c** (3 g, 2.7 mmol) was treated with 30% TFA/DCM (30 mL) and stirred at room temperature for 3 h. The reaction was monitored by FTIR (disappearance of the C=O carbamate stretching). After filtration the resin was washed with DCM (30 mL), MeOH (30 mL), and DCM (30 mL) for five repeating cycles. The resin was then dried under vacuum, and the supported benzotriazole **11c** was characterized by FTIR (1636, C=O amide) and elemental analysis (N: 4.46%, found 4.37%, yield >95%).

Supported benzotriazoles **11a**, **11b**, and **11d** were prepared using similar experimental procedures.

(4-Methylbenzyl)pyrimidin-2-yl-amine 13a (Entry 1, Table 3). 1. Adduct Formation 12c. A mixture of supported **11c** (0.1 g, 0.087 mmol), 4-methylbenzaldehyde (0.104 g, 0.87 mmol), and 2-aminopyrimidine (0.1 g, 1.044 mmol) in THF/TMOF 2/1 (1 mL) was stirred at 25 °C over 15 h. The

resin was filtered, washed with THF (2 mL), and DCM (2 mL) for five repeating cycles, and dried under vacuum.

2. Cleavage with Sodium Borohydride. A mixture of the adduct **12c** (0.1 g, 0.087 mmol) and sodium borohydride (0.033 g, 0.87 mmol) in dry THF was heated at 60 °C for 15 h. Methanol (1 mL) was added, and heating was prolonged for further 60 min (breaking of amine−borane complexes). The exhausted resin was then washed with a mixture 1/1 MeOH/DCM (2 × 2 mL) and filtered off. The organic solution was concentrated to dryness affording a crude mixture (0.12 g) which was submitted to purification.

3. Purification of the Crude. The residue (0.12 g) was taken up with DCM (2 mL) and extracted with saturated aqueous Na_2CO_3. The two layers were separated with a phase-separation polypropylene syringe, and the recovered DCM layer was evaporated to dryness. The residue was taken up with methanol (2 mL) and purified through an SCX column by elution with 2 M NH_3/MeOH. After concentration at reduced pressure, the amine **13a** (0.0074 g, 43% yield) was recovered as a brownish solid, mp 112−114 °C (lit. 122−123 °C):[11] ^{1}H NMR (CDCl$_3$) δ 8.3 (d, 2H), 7.26 (m, 2H), 7.15 (m, 2H), 6.56 (m, 1H), 4.60 (s, 2H), 2.35 (s, 3H); MS *m/z* 200 (M + H)[+]; LC/MS (DAD) 77% a/a purity.

Dibenzyl-naphthalen-2-yl-methylamine 13c (Entry 4, Table 3). 1. Adduct Formation 12c. A mixture of supported **11c** (0.1 g, 0.087 mmol), 2-naphthylaldehyde (0.135 g, 0.87 mmol), and *N,N*-dibenzylamine (0.2 g, 1.04 mmol) in THF/TMOF 2/1 (1 mL) was heated at 60 °C over 15 h. After cooling at room temperature, the resin was filtered, washed with THF (2 mL) and DCM (2 mL) for five repeating cycles, and dried under vacuum.

2. Cleavage with Sodium Borohydride and Purification. The obtained adduct **12c** was processed following the same procedure reported for **13a**, obtaining the amine **13c** (0.013 g, yield 45%) as a solid, mp 64−65 °C (lit. 73−74 °C):[20] ^{1}H NMR (CDCl$_3$) δ 7.86 (m, 3H), 7.62 (m, 1H), 7.47 (m, 5H), 7.41 (m, 1H), 7.36 (m, 5H), 7.27 (m, 2H), 3.83 (bs 2H), 3.71 (bs, 4H); MS *m/z* 338 (M + H)[+]; LC/MS (DAD) 89% a/a purity.

Dibenzyl-(1-naphthalen-2-yl-but-3-enyl)amine 14a (Entry 5, Table 3). 1. Adduct Formation 12c. The same procedure already described for **13c** was used.

2. Cleavage with Allylmagnesium Chloride. A mixture of adduct **12c** (0.1 g, 0.087 mmol) and allylmagnesium chloride (2 M THF solution, 1.3 mL, 2.61 mmol) in dry TMOF (0.7 mL) was heated at 40 °C for 15 h. The exhausted resin was then washed with DCM (2 × 2 mL) and filtered off. The DCM solution was then purified according to the following procedure.

3. Purification of the Crude. The DCM solution was extracted with saturated aqueous NH_4Cl, the two layers were separated with a phase-separation polypropylene syringe, and the recovered DCM layer was evaporated to dryness. The residue was taken up with methanol (2 mL) and purified through an SCX column by elution with 2 M NH_3/MeOH. After concentration at reduced pressure the amine **14a** (0.016 g, 48% yield) was recovered as a solid, mp 66−68 °C: ^{1}H NMR (CDCl$_3$) δ 7.85 (m, 2H), 7.64 (bs, 2H), 7.49−7.4 (m, 3H), 7.41 (d, 4H), 7.33 (t, 4H), 7.24 (m, 2H), 5.83 (m, 1H),

5.07 (m, 2H), 3.99 (m, 1H), 3.84 (d, 2H), 3.30 (d, 2H), 2.96 (m, 1H), 2.73 (m, 1H); MS *m/z* 378 (M + H)[+]; LC/MS (DAD) 100% a/a purity.

Library 1 (Sodium Borohydride Cleavage, Compounds 16−30, Table 4). 1. Adduct Formation and Cleavage. The same procedures (methods B−A1, Table 3) reported for individual compounds using sodium borohydride as cleavage reagent were adopted for the parallel preparation of the discrete array (25 mg of AM-PS resin for each library individual), carried out on the Flexchem device.

2. Purification of the Crudes. The residues were taken up with DCM (0.7 mL each) and extracted with saturated aqueous Na_2CO_3 (0.7 mL each), then the two layers were separated in parallel, on the HiTOPS device (cleavage block), using a MBPP (Meltblown polypropylene) microtiter plate bearing an hydrophobic polypropylene membrane with 10 μm pore size. The DCM layers were recovered into a deep 96 well plate and evaporated to dryness in a vacuum centrifuge. The residues were taken up with methanol (1 mL) and purified in parallel, as above, using an SPE-SCX 96 well plate. The samples were collected into a 96 deep well plate by elution with NH_3/MeOH. After concentration at reduced pressure in a vacuum centrifuge the purity of the recovered amines was controlled by LC/MS (on the entire set) and by ^{1}H NMR on a few samples (see Supporting Information for more details).

Library 2 (Grignard's Cleavage, Compounds 31−45, Table 5). 1. Adduct Formation and Cleavage. The same procedures (methods B−B1, Table 2) reported for the preparation of the individual compounds using Grignard reagents as cleavage reagents were adopted for the parallel preparation of the discrete array (25 mg of AM-PS resin for each library individual), carried out on the Flexchem device.

2. Purification of the Crudes. The DCM solutions (0.7 mL each) were extracted with saturated aqueous NH_4Cl (0.7 mL), and the two layers were separated in parallel using a MBPP microtiter plate as described previously. The DCM layers were recovered into a 96 deep well plate and evaporated to dryness in a vacuum centrifuge, as previously described. The residues were taken up with methanol (1 mL) and purified in parallel using an SPE-SCX 96 well plate as described previously. The samples were collected into a 96 deep well plate by elution with 2 M NH_3/MeOH and concentrated at reduced pressure in a vacuum centrifuge. The purity of recovered amines was controlled by LC/MS (on the entire set) and by ^{1}H NMR on a few representative samples (see Supporting Information for more details).

Supporting Information Available. ^{1}H MAS NMR and FTIR spectra of **10a−d** and **11c**; ^{1}H NMR and HPLC/MS spectra of **13a** (entry 1, Table 3), **13c** (entry 4, Table 3), **14a** (entry 5, Table 3), **15a** (entry 7, Table 3); ^{1}H NMR and HPLC/MS spectra of **18**, **19**, **24**, **30** (library **1**, Table 4) and

37, **38**, **42**, **31** (library **2**, Table 5). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) After the submission of this manuscript, a similar contribution from Prof. A. R. Katritzky and co-workers (*J. Comb. Chem.* **1999**, *1* (2), 173−176) disclosed the first supported 1*H*-benzotriazole chemistry in this journal.

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