SOLID-PHASE TRACELESS SYNTHESIS OF SELECTED NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS. THE ENCORE TECHNIQUE FOR DIRECTED SORTING OF MODULAR SOLID SUPPORT

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The acid lability of electron-rich *N*-benzylanilines has been exploited in a linker for the traceless solid-phase synthesis of benzimidazoles, 2-aminobenzimidazoles, quinoxalinones and tetrahydroquinoxalines. The target compound precursors were assembled on a solid-phase support derivatized with either a benzylamine or a benzhydrylamine linker. Exposure to an acidic reagent caused cleavage of the C(benzyl)–N(aniline) bond, releasing the product with only a hydrogen atom on the descending nitrogen. The Encore technique for directed sorting on SynPhase Lanterns has been developed and applied to combinatorial synthesis of generic drug discovery libraries.

Keywords: Heterocycles; Solid-phase synthesis; Combinatorial libraries; Benzimidazoles; Quinoxalines; Benzylamine linkers.

In 1963 Bruce Merrifield introduced his ingenious concept of the solid-phase peptide synthesis[1]. The carboxy terminal amino acid was attached to a solid support *via* an ester linkage. The ester allowed immobilization of the amino acid to the solid support and also protected the carboxylic function, an inherent part of a peptide. Since then, numerous ester linkages for tethering carboxylic acids have been developed, mostly for peptide synthesis (reviewed in refs[2,3]). The ester linker was used in early combinatorial syntheses of heterocyclic compounds. The target compounds contained a carboxylate function, often tolerated but generally an undesired feature of the heterocycle. To make the solid-phase synthesis "clean", new linkers have been developed that allow for a traceless synthesis, meaning the target compound does not carry any trace (*i.e.*, functional groups) of the linker

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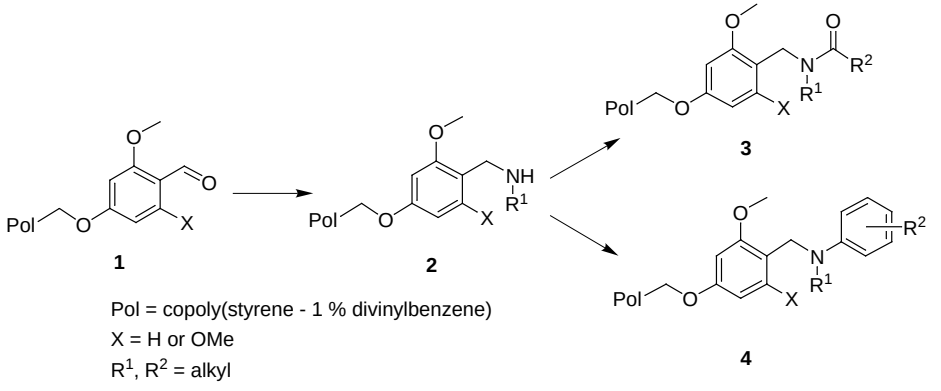
that was used to tether the first building block(s) to the solid support. Since with notable exceptions the C–H bond is an inherent feature of organic compounds, the general traceless linker, referred to as a C–H linker, leaves only a hydrogen atom on the carbon used for the attachment to the solid support. For aromatic and heteroaromatic compounds, two linkers, silyl-based[4–13] and triazene[14–19], were developed.

However, the C–H linker is not the only approach for the traceless synthesis of organic molecules. Most (if not all) interesting organic compounds do contain a heteroatom in their structures and the heteroatom in particular serves as a convenient way for tethering the first building block to a solid-supported linker. (A widespread concept of making compound devoid of any residual linker functionality is cyclative cleavage (see *e.g.*, ref.[41]).) Similar to C–H linkers, N–H linkers provide very practical traceless routes to compounds whose integral part is a nitrogen atom. One of the very useful linkers that allows cleavage of the C–N bond of the target compound, leaving the N–H part on the descending molecule, is the benzylamine linker derived from the aldehyde resin **1**, introduced independently by three groups[20–22]. The linker was originally developed for the synthesis of amides **3** (BAL, backbone amide linker[22]) *via* reductive amination followed by acylation of the secondary resin-bound amine **2** (Scheme 1). In order to cleave the C–N bond, the nitrogen was acylated. Nevertheless, we observed that an electron-rich benzyl group attached to the polymer-supported aniline nitrogen was cleaved with the same efficiency, thus extending the applicability of the aldehyde resin **1** to *N*-benzylanilines **4**, where the aryl group instead of the acyl group is attached to the secondary amine nitro-



SCHEME 1
Access to resin-bound acid-sensitive *N*-benzylamides and *N*-benzylanilines

gen. Since the nitrogen atom is an integral part of many heterocyclic systems, we developed several synthetic routes for a traceless combinatorial synthesis of nitrogen-containing heterocycles. Attachment and cleavage of anilines have also been reported[51–54]. Preliminary results have been published elsewhere[23–26].

However, our ultimate task was to develop chemical routes applicable to combinatorial synthesis of generic libraries for drug discovery. The most efficient approach to the synthesis of sizable compound libraries (tens of thousands of compounds) is the split-and-pool method[27–29], and particularly the directed sorting approach, introduced for the first time by Frank[30] and later rediscovered by others[31–34]. The directed sorting method intentionally prepares each selected compound from the combinatorial array only once, the abundance of compounds in the split-and-pool method is driven by statistics due to the random distribution of pooled solid-phase particles.

The directed sorting method requires recording the chemical history of individual particles (or containers of particles). Houghten T-bags were labeled by an alphanumeric code readable by a chemist[35], color coding was used by Guiles *et al.*[36]. Radiofrequency tagging[31,32] or optical encoding[33,34] enabled computer-assisted reading of the tag and automation of the process of directed sorting. We have developed a simple method for tracking the chemical history on SynPhase Crowns referred to as necklace coding[37]. A similar concept was recently reported by Furka *et al.*[38,39]. Individual crowns were strung on a stainless steel wire and the position of a crown on the string (necklace) encoded the previous chemical history (spatially addressable split procedure).

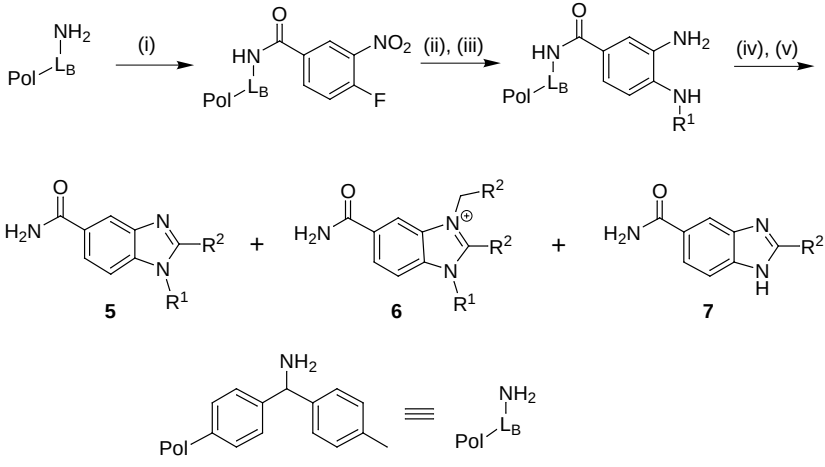
Recently, Mimotopes (Dunedin, Victoria, Australia, www.mimotopes.com) introduced an alternative support for solid-phase organic synthesis, the SynPhase Lanterns. The lantern is a modular grafted polypropylene mold and its shape resembles a lantern. A 50-μ layer of polystyrene is grafted onto the surface of lanterns. The surface layer is functionalized and the solid-phase organic reactions take place in this layer. Two lantern sizes are available, L-Series Lantern (5 × 5 mm in size) with a loading of 15 μmol and D-Series Lantern (5 × 12.5 mm in size) with 35 μmol.

Here we wish to report a simple and practical technique for the synthesis of combinatorial libraries that combines the advantages of (i) the directed sorting method for the synthesis of compound libraries, (ii) the novel modular solid-phase support, the lanterns, and (iii) our necklace coding concept[37]. Tracking the chemical history is based on a combination of three different encoding techniques: necklace coding is employed for the first

combinatorial step, color-coding for the second step, and reaction-vessel coding in the third combinatorial step. Consequently, this method is referred to as the Encore technique (**E**ncoding by a **N**ecklace, **Co**lor, and **Re**action vessel).

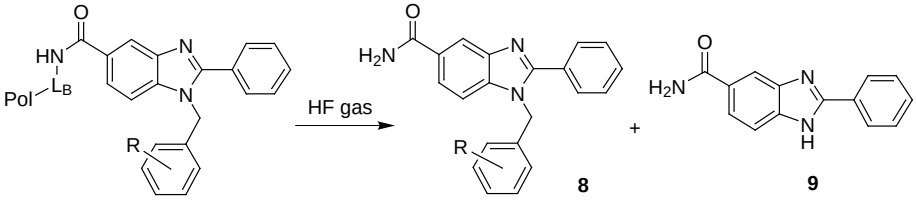
RESULTS AND DISCUSSION

During the production of a benzimidazole library synthesized on a polymer-supported *p*-methylbenzhydrylamine linker (L_B) according to the Scheme 2, essentially identical with the route recently described by Mayer *et al.*[40], we consistently observed two side-products **6** and **7** in addition to benzimidazole **5**. One side-product was identified as an alkylated benzimidazolium salt **6**, reported for the first time by Zaragoza[41] and also described by Wu *et al.*[42]. The second side product was caused by acidolytic cleavage of a benzyl-type substituent yielding a 1-unsubstituted benzimidazole **7**. The side reaction was promoted by the presence of electron-donating substituents (Scheme 3, Table I) and inspired us to explore the use of a benzyl group attached to a benzimidazole nitrogen as a linker for the traceless synthesis of benzimidazoles and related heterocycles.



(i) 4-fluoro-3-nitrobenzoic acid, DIC, HOBt, DMF, 16 h; (ii) amine, DMF or DMSO, 16 h; (iii) $SnCl_2 \cdot H_2O$, NMP, 16 h; (iv) aldehyde, DMF, 16 h; (v) gaseous HF, 2 h

SCHEME 2
Solid-phase synthesis of benzimidazoles

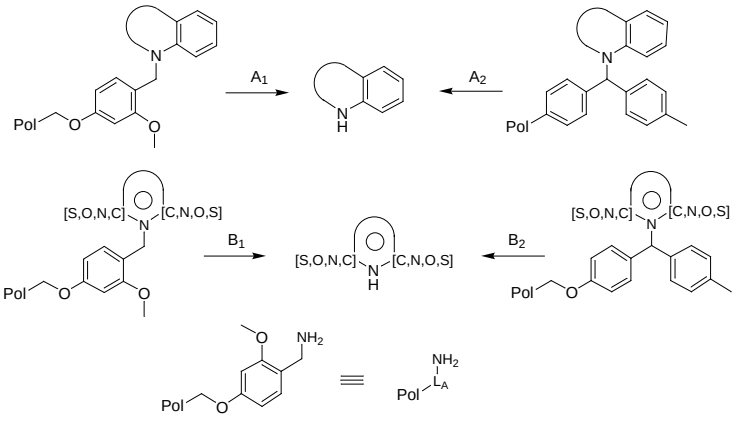


SCHEME 3
Cleavage of *N*-benzyl group by gaseous HF

The common concept of traceless solid-phase synthesis of benzimidazoles and related nitrogen-containing heterocyclic compounds is based on the acid lability of an electron-rich benzyl or benzhydryl group attached to an aniline-type nitrogen (routes A in Scheme 4). Similar acid lability of a benzyl group attached to a nitrogen that was part of a heteroaromatic ring (routes B) was reported by Bilodeau and Cunningham[43] for the synthesis of imidazoles. Analogously, thiazoles[44] have been prepared on the Rink linker. Our synthetic scenario included a step-by-step building of the precursor of the targeted heterocycles (the alternative concept is based on decorating a pre-formed derivatized scaffold (heterocycles) attached to the solid support (see, *e.g.*, a review[55])) on the benzylamine linker (L_A)- or benzhydrylamine linker (L_B)-derivatized solid support, followed by cleaving the C(benzyl/benzhydryl)–N(aniline) bond and releasing the compound from the resin. Depending on the kind of heterocycle and particular route, the cyclization was performed either on the resin prior to cleavage, or in solution following the cleavage.

TABLE I
Composition of crude products after HF cleavage

R	**8**, %	**9**, %
H	>99	<1
4-OH	>99	<1
2-OMe	66	34
2-Naphthyl	83	17



SCHEME 4
General concept of traceless synthesis

Syntheses on the Benzylamine Linker

Reductive Amination

Common intermediates for the syntheses were resin-bound secondary amines **2**, efficiently prepared from the aldehyde linker by reductive alkylation (Scheme 1). The conditions for reductive alkylation have been optimized for a large set of diverse amines (more than a hundred) including α-amino acid esters for the synthesis of quinoxalines and β-amino alcohols for the synthesis of tetrahydroquinoxalines. A typical protocol consisted of pre-incubation with an amine, followed by reduction using $NaBH(OAc)_3$ in AcOH/DMF (refs[23,45]). Increased yields were observed after repeated Schiff base formation and reduction.

Optical integrity of amino acids during reductive amination was addressed by Boojamra *et al.*[20,46]. They minimized the racemization of amino acid esters during on-resin reductive amination by adding the reducing agent and the amino acid ester to the aldehyde resin at the same time. Kung and Swayze[47] did not observe any racemization of β-amino alcohols after reductive amination. At this time, we did not address the racemization during reductive alkylation; except ethanolamine, racemic amino alcohols were used.

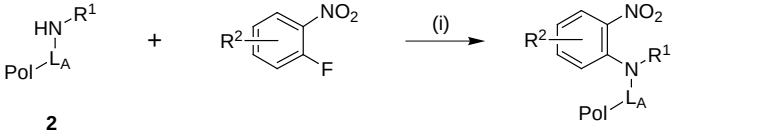
In order to assess the purity and yield of the product of reductive amination, the resin-bound secondary amine was reacted with Fmoc-Cl.

Fmoc-derivatized secondary amine was released upon exposure to an acidic cleavage reagent (TFA, gaseous HCl, gaseous HF) and the purity of the product was evaluated by analytical HPLC. As a convenient way of quantification of the secondary amine, the Fmoc group was cleaved by piperidine and the product spectrometrically quantified, taking the advantage of a high molar absorption coefficient (8 100) at relatively long wavelength (302 nm).

N-Benzylanilines

The aryl substituent was introduced *via* an aromatic nucleophilic substitution of activated aryl halides, 1-fluoro-2-nitrobenzenes (Scheme 5). The product, cleaved from the resin and analyzed, will not reveal an incomplete nucleophilic substitution because the unsubstituted secondary benzyl amine is stable in TFA. Therefore, in order to evaluate the conversion of the secondary amine, a sample of the resin-bound intermediate **10** was reacted with Fmoc-Cl. Any unreacted secondary amine was derivatized and the corresponding Fmoc-amine was detected after cleavage from the resin.

The rate of the nucleophilic substitution depends on the nucleophilicity and steric accessibility of the resin-bound amine, as well as on the character of substituent(s) on the 2-fluoronitrobenzene. Aliphatic amines provided complete conversion at elevated temperature (75 °C), 1-fluoro-2-nitrobenzenes having an additional electron-withdrawing group did not require elevated temperature. In order to optimize the nucleophilic displacement in the case of amino acid esters, we tested a less sterically demanding linker (4-(4-formylphenoxy)butanoic acid), several solid supports (polystyrene resin, Tentagel, Chiron's SynPhase Crowns), and various solvents (DMF, NMP, DMSO, THF, alcohols, ionic liquid). We did not observe any substantial differences in the rate of nucleophilic substitution for different solid



2

(i) 1 M amine, DMSO, for temperature and time, see Tables I and II

10a, R^1 = alkyl
10b, R^1 = CHR^1 - COOMe
10c, R^1 = CHR^1 - CH_2 - OH

SCHEME 5
Arylation of the secondary amine

supports or linkers. The best conversion was observed in DMSO at 75 to 90 °C, with premature cleavage from the resin observed at higher temperatures. Typical results for amino acid esters and amino alcohols are summarized in Tables II and III. It is worth mentioning that incomplete

TABLE II
Reaction of resin-bound amino acid esters with 1-fluoro-2-nitrobenzenes

Entry	Amine	1-Fluoro-2-nitrobenzene	Time day	Temperature °C	Conversion %
1	H-Gly-OMe	4-CF_3	1	25	50
2	H-Gly-OMe	4-CF_3	1	75	>99
3	H-Gly-OMe	4,5-diCl	1	75	90
4	H-Leu-OMe	4-CF_3	1	75	8
5	H-Ala-OMe	4-CF_3	3	75	65
6	H-Leu-OMe	4-NO_2	3	75	77
7	H-Lys-OMe	4-NO_2	3	75	84
8	H-Val-OMe	5-F-4-NO_2	3	75	90

TABLE III
Reaction of resin-bound amino alcohols with 1-fluoro-2-nitrobenzenes

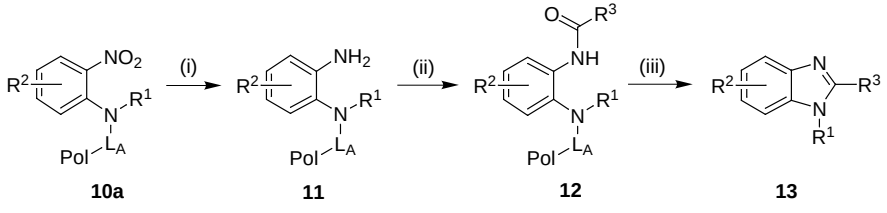
Entry	Amine	1-Fluoro-2-nitrobenzene	Time day	Temperature °C	Conversion %
1	glycinol	H	1	75	>99
2	glycinol	4-CF_3	1	75	>99
3	glycinol	4,5-diCl	1	75	>99
4	glycinol	4-Br	1	75	>99
5	phenylalaninol	H	1	75	32
6	phenylalaninol	4-CF_3	1	75	98
7	phenylalaninol	4,5-diCl	1	75	97
8	phenylalaninol	4-Br	1	75	37
9	phenylalaninol	4-F	1	75	32

nucleophilic displacement does not compromise the purity of the target compound; only the yield is affected.

The next chemical transformation was dependent on the type of heterocyclic system synthesized.

Benzimidazoles

For the synthesis of benzimidazoles, the nitro group of **10a** was reduced with tin(II) chloride and the aniline nitrogen of **11** was acylated with acids to yield a linear precursor of benzimidazoles **12** (Scheme 6). When compound **12** was cleaved from the resin by TFA, acylaniline was obtained that, upon overnight exposure to AcOH at elevated temperature, cyclized to target benzimidazoles **13**. Since AcOH cleaved the linear precursor from the resin, for practical reasons, we exposed the resin-bound intermediate to AcOH and achieved cleavage and cyclization to **13** at the same time.



(i) $SnCl_2 \cdot H_2O$, NMP, rt, overnight; (ii) acid chloride, DIEA, DCM, rt, overnight;(iii) AcOH, 80°C, overnight

SCHEME 6
Synthesis of benzimidazoles

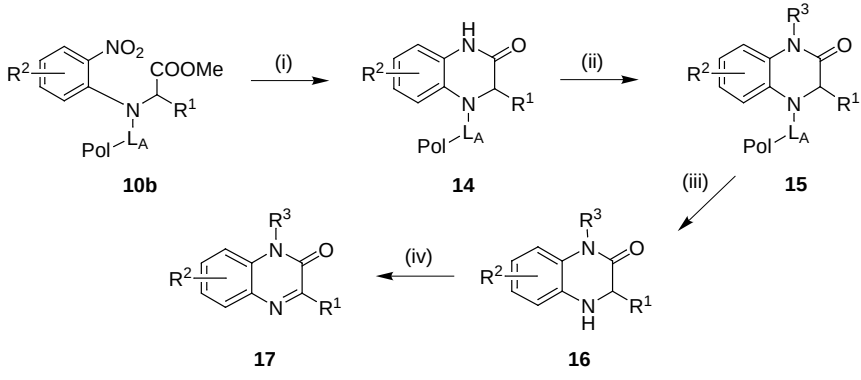
Quinoxalinones

The aldehyde linker was reductively aminated with an amino acid ester and the corresponding resin-bound secondary amine treated with 1-fluoro-2-nitrobenzenes to yield **10b** (Scheme 7). However, in this case the nucleophilic substitution was considerably slower due to the electron-withdrawing effect of the neighboring carboxylate. An additional strong electron-withdrawing group on 1-fluoro-2-nitrobenzene was required to obtain acceptable yield of nucleophilic displacement with a sterically demanding R^1 substituent.

In the next transformation, the nitro group was reduced with tin(II) chloride. At this stage, the intermediate spontaneously cyclized and formed

dihydroquinoxalinone **14** on resin. Interestingly, after 2 h reduction of resin-bound intermediates prepared using 1-fluoro-2,4-dinitrobenzene and 1,5-difluoro-2,4-dinitrobenzene, only the nitro group ortho to the amino substituent was reduced.

The amide nitrogen of **14** was further derivatized by alkylation to yield dihydroquinoxalinones **15** with three points of diversification. Several bases were tested and BEMP in DMF provided the purest product, while KHMDS left some starting material (<10%). Upon cleavage, dihydroquinoxalines **16** were isolated which underwent air oxidation to quinoxalinones **17**.



(i) $SnCl_2 \cdot H_2O$, NMP, rt, 2 h; (ii) BEMP, alkyl halide, DMF, rt, 2 h; (iii) TFA or gaseous HCl or gaseous HF, rt, 2 h; (iv) air oxidation, MeOH, rt, overnight

SCHEME 7
Synthesis of quinoxalinones

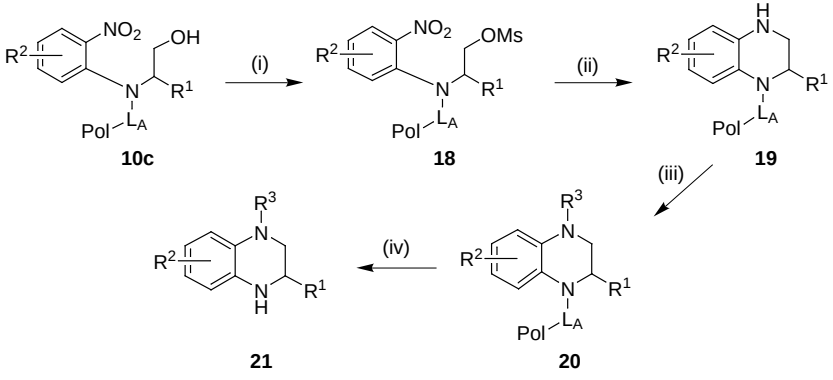
Tetrahydroquinoxalines

We performed the reductive alkylation procedure on the aldehyde resin with β-amino alcohols in order to cyclize the linear precursor **10c** (Scheme 8) to tetrahydroquinoxalines on the resin. The nucleophilic substitution proceeded more smoothly when compared with the amino acid esters on resin; however, the combination of amino alcohols having bulky side chains with 1-fluoro-2-nitrobenzenes lacking additional electron-withdrawing groups proceeded sluggishly (Table III).

In order to convert the hydroxy functionality into a good leaving group, the resin-bound nitroanilines **10c** were reacted with mesyl chloride to yield

18. Upon reduction of the nitro group with tin (II) chloride, spontaneous cyclization to **19** was observed. The only exception was an intermediate prepared with ethanolamine; the analytical HPLC revealed incomplete cyclization and the resin had to be heated overnight (40 °C) to force the ring closure.

As in the previous case, the cyclized tetrahydroquinoxaline **19** was further derivatized by acylation to yield **20**. Interestingly, when the target acylated compound was treated with gaseous HF to cleave the product from the resin, partial cleavage of the acyl group was observed. Cleavage by TFA afforded the expected product **21** only.

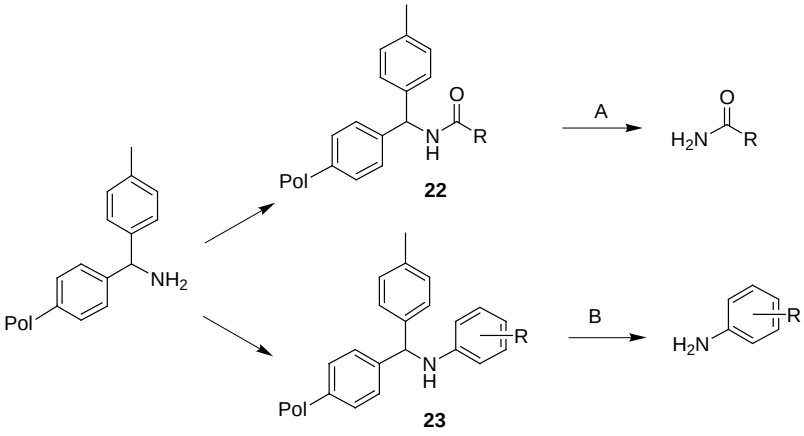


(i) MsCl in pyridine or MsCl, proton sponge in DCM, rt, 1 h; (ii) $SnCl_2 \cdot H_2O$, NMP, rt, 2 h; (iii) acyl chlorides, anhydrides or isocyanates in DCM or NMP, 16 h; (iv) TFA or gaseous HF,rt, 2 h

SCHEME 8
Synthesis of tetrahydroquinoxalines

Syntheses on the Benzhydrylamine Linker

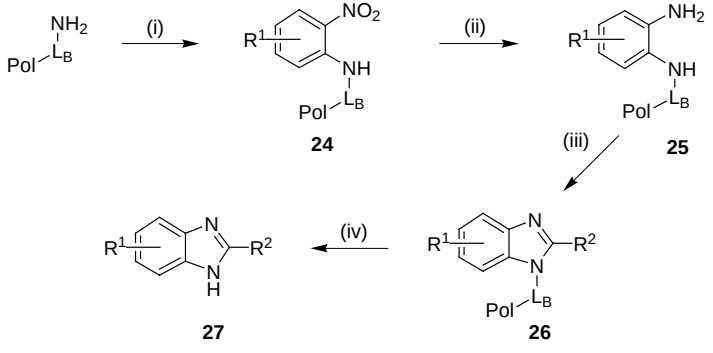
The *p*-methylbenzhydrylamine linker, developed for the synthesis of carboxamides (Scheme 9, route A), was used for the traceless synthesis of nitrogen-containing heterocyclic compounds in an analogous manner to the benzylamine linker (route B). The C–N bond of intermediates **22** and **23** was acidolytically cleaved (Scheme 9); however, the increased acid stability required the use of gaseous HF (ref.[48]). In order to cleave the target compounds with TFA, the more acid-labile Rink linker[49] was used.



SCHEME 9
Cleavage of carboxamides and anilines from the benzhydrylamine linker

Benzimidazoles

To prove the concept of a traceless synthesis on the benzhydrylamine linker, benzimidazoles were synthesized with two combinatorial steps according to Scheme 10. The *p*-methylbenzhydrylamine resin was reacted with 1-fluoro-2-nitrobenzenes, the nitro group of the resin-bound nitro-



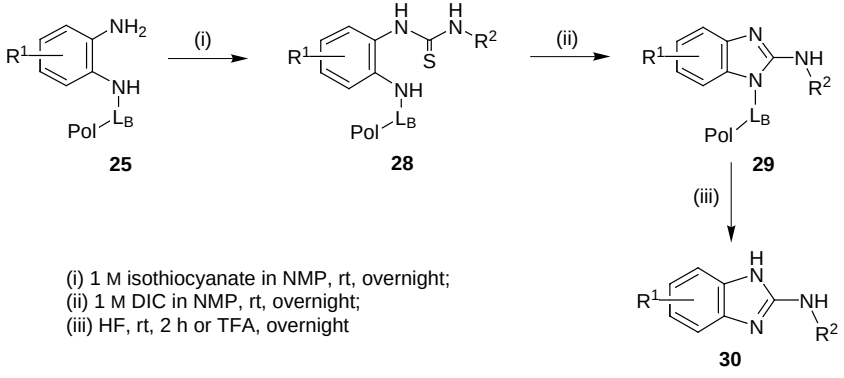
(i) 1-fluoro-2-nitrobenzene, DMF, rt, overnight; (ii) $SnCl_2 \cdot H_2O$, NMP, rt, overnight; (iii) aldehyde in DMF, rt, overnight; (iv) gaseous HF, 2 h

SCHEME 10
Synthesis of traceless benzimidazoles with two combinatorial steps

aniline **24** was reduced with tin(II) chloride, and the 1,2-phenylenediamine **25** was cyclized to benzimidazole **26** with an aldehyde. The product **27** was cleaved from the resin with gaseous HF (ref.[48]).

2-Aminobenzimidazoles

We have already reported combinatorial solid-phase synthesis of 2-(arylamino)benzimidazoles[37]. The *p*-methylbenzhydrylamine resin was acylated with the first building block, 4-fluoro-3-nitrobenzoic acid, and acidolytic cleavage released the target compounds as carboxamides. An alternative approach leading to a traceless solid-phase synthesis was developed using the *p*-methylbenzhydrylamine and Rink linkers (Scheme 11). The first two steps to resin-bound intermediate **25** were identical to those in Scheme 10. The 1,2-phenylenediamine **25** was then reacted with isothiocyanates, and the resulting thiourea **28** was cyclized to 2-(arylamino)benzimidazoles **29** by DIC. The product **30** was released by cleavage with gaseous HF.

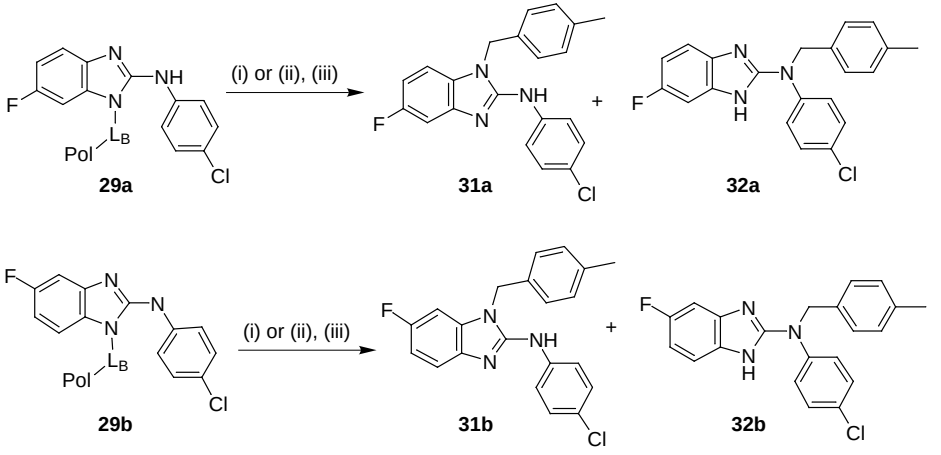


SCHEME 11
Synthesis of 2-(arylamino)benzimidazoles

For the synthesis on Lanterns, the aminomethyl-derivatized Lanterns were acylated with the Fmoc-4-[(γ-carboxypropyl)oxy]-4-methoxybenzhydrylamine (Bachem Bioscience, King of Prussia, PA) and the product was cleaved with TFA.

Attempts to further derivatize the two-diversity-point benzimidazoles by alkylation yielded, depending on the reaction conditions, either *N*-exo- or *N*-endo-alkylated product. In order to unambiguously determine the posi-

tional isomers, we prepared two model compounds from 2,4-difluoro-1-nitrobenzene and 1,4-difluoro-2-nitrobenzene (Scheme 12). When alkylation with an electrophile was performed in the presence of potassium car-



(i) 1 M alkyl halide, K_2CO_3, in DMF, 75 °C, overnight; (ii) 0.5 M alkyl halide, 1% BTPP, DMF, rt, overnight; (iii) TFA, 1 h

SCHEME 12
Alkylation of 2-(arylamino)benzimidazoles

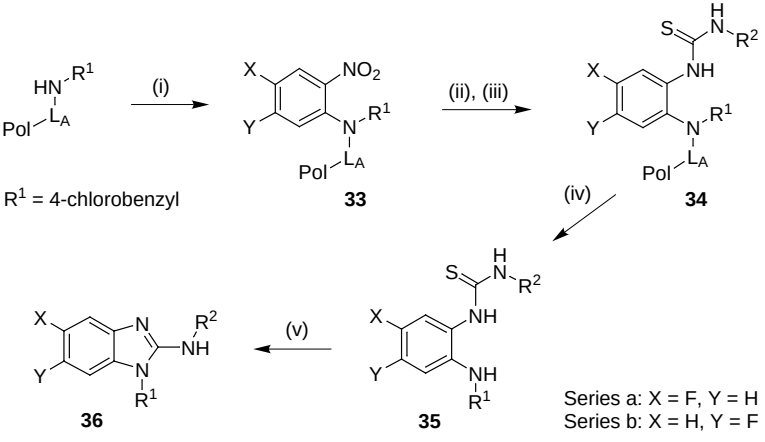
bonate, the major products **31a** and **31b** were separated by analytical HPLC (two peaks on co-injection). However, when a phosphazene base BTPP was used at low concentration, both major alkylated products **32a** and **32b** were undistinguishable by HPLC and NMR. Interestingly, increased concentration of the phosphazene base BTPP increased the amount of ring-alkylated product (Table IV).

As an independent proof of the ring-alkylated structure, we synthesized the model compounds **31a** and **31b** using an alternative protocol (Scheme 13). The synthesis started with the reductive amination procedure, using 4-chlorobenzylamine as the first building block. The secondary amine was then reacted with 2,4-difluoro-1-nitrobenzene and 1,4-difluoro-2-nitrobenzene, yielding the nitroanilines **33**. After reduction of the nitro group, the thiourea **34** was formed by reaction with an isothiocyanate. In order to cyclize to benzimidazoles, the linear precursors **34** were cleaved from the resin to yield **35** which was treated with DIC in solution. Products **31** pre-

pared by alkylation of benzimidazoles **29** were found identical to cyclized benzimidazoles **36** from this route, thus independently proving the structure of product.

TABLE IV
Alkylation of 2-(arylamino)benzimidazoles **29**

Entry	Base	Concentration %	Yield, %			
			31a	**32a**	**31b**	**32b**
1	BTPP	16	68	31	59	31
2	BTPP	8	69	30	67	31
3	BTPP	4	69	30	68	31
4	BTPP	2	32	66	43	55
5	BTPP	1	5	95	4	96
6	K_2CO_3	NA	87	4	85	3



(i) 1,4-difluoro-2-nitrobenzene (series a) and 2,4,-difluoro-1-nitrobenzene (series b), DMSO, 75 °C, overnight; (ii) $SnCl_2 \cdot H_2O$, NMP, rt, overnight, (iii) 4-chlorophenyl isothiocyanate in DMF, rt, overnight; (iv) TFA, rt, 2 h; (v) DIC, ethyl acetate, rt, overnight

SCHEME 13
Alternative route to alkylated 2-(arylamino)benzimidazoles

Combinatorial Synthesis Using the Encore Technique

The traceless solid-phase synthesis of heterocyclic compounds was developed for preparation of generic lead discovery libraries. So far we have been using a "classic" library synthesis on resin beads using the split-split approach[50]. To take advantage of the directed sorting approach and recently introduced modular solid-phase support, SynPhase Lantern, we developed a new method for tracking the history of individual solid-phase particles during combinatorial synthesis. The Encore technique combines three different coding methods: sequential position on a necklace (Fig. 1) for the first combinatorial step, color coding of individual necklaces for the second combinatorial step, and reaction vessel coding as the indication of the identity of the last building block. The Encore method does not require redistribution of solid-phase particles after each combinatorial step. In fact, the particles are handled on an individual basis only once during the synthesis, when the particles are organized into a linear sequence to form the necklace.

As proof of concept, a model synthesis of a small combinatorial array of 27 benzimidazoles according to Scheme 6 is reported. The chemical route included three combinatorial steps, and three building blocks were used in each step (Fig. 2). In order to determine the structure of the benzimidazole on any lantern, the chemical history (*i.e.*, building block reacted with any

FIG. 1
SynPhase Lanterns and their stringing (white, virgin aminomethylated; blue, colorized by bromophenol blue; yellow and orange, after reductive alkylation with two different amines)

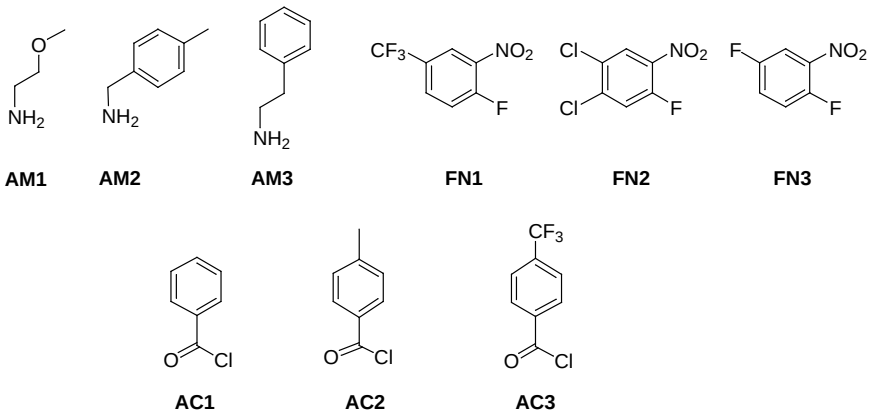


FIG. 2
Structure of building blocks for the benzimidazole Lantern synthesis

particular lantern) was recorded (Fig. 3). The first combinatorial step was performed in three reaction vessels charged with 9 lanterns each. The first building block was encoded by the position on the string (necklace). With 27 lanterns, nine identical three-lantern necklaces were made. The next step was performed on three necklaces, as three intermediates of each combination of the first and second building blocks were required for the reaction with three acids. The necklaces were labeled with color tags and one reaction vessel was charged with necklaces of the same color. After the second combinatorial step, necklaces were rearranged for the last combinatorial step with acids, each reaction vessel contained three necklaces of different color. The reaction vessel defined the last building block.

After the synthesis was completed, lanterns were placed into individual reaction vessels and products were cleaved by AcOH. The structure was confirmed by LC/MS, the purity of crude products is listed in Table V. Following the proof of concept with a small library, a sizable library of 24 576 compounds (in a 32 × 32 × 24 format) is currently in production using a different chemical protocol.

Conclusion

We have developed practical routes for the traceless synthesis of some nitrogen-containing heterocycles that are based on the acid lability of an electron-rich benzyl group attached to an aniline nitrogen. Work is in prog-

ress to expand the set of accessible heterocycles. A simple combination of three coding techniques, referred to as Encore technique, was developed and used for combinatorial synthesis on SynPhase Lanterns.

TABLE V
Purity of benzimidazoles (%)

Step# 1 BB Step# 2 BB	**AM 1** **FN 1**	**AM 1** **FN 2**	**AM 1** **FN 3**	**AM 2** **FN 1**	**AM 2** **FN 2**	**AM 2** **FN 3**	**AM 3** **FN 1**	**AM 3** **FN 2**	**AM 3** **FN 3**
Step# 3 BB: **AC1**	82	80	83	83	86	75	85	83	78
Step# 3 BB: **AC2**	80	80	83	81	84	77	86	83	81
Step# 3 BB: **AC3**	82	82	90	83	88	72	85	85	75

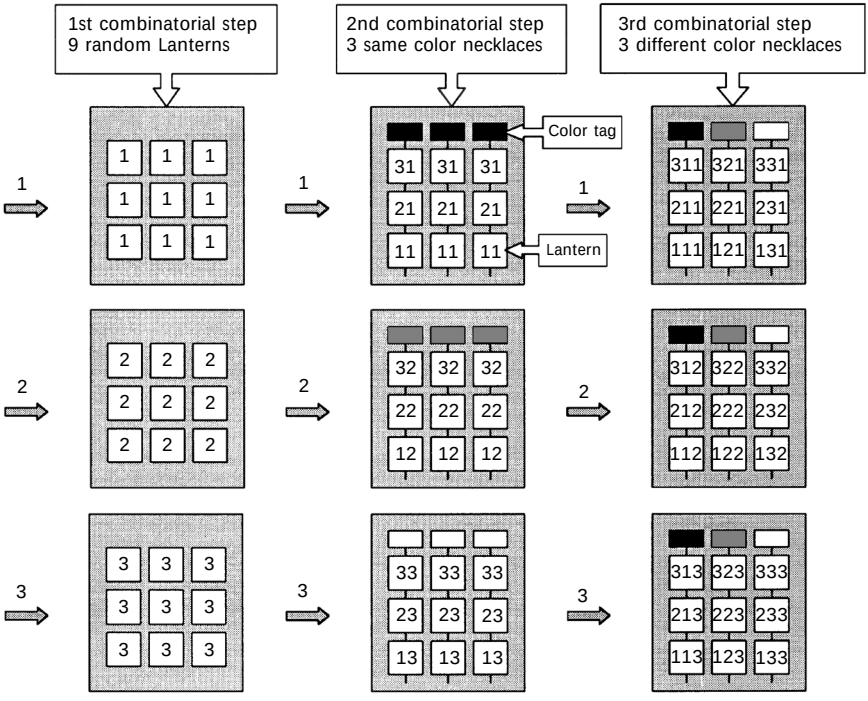


FIG. 3
Logistics of the synthesis (Large box represents individual reaction vessel. Sequential numbers 1, 2, and 3 indicate individual building blocks for any combinatorial step; consequently, a target compound labeled, *e.g.*, 322 was made using building blocks number 3, 2, and 2 in the 1st, 2nd, and 3rd combinatorial steps, respectively)

EXPERIMENTAL

General

The following abbreviations were used: BEMP, 2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine; BTPP, (*tert*-butylimino)tris(1-pyrrolidinyl)-phosphorane; DCM, dichloromethane; DIC, *N*,*N*′-diisopropylcarbodiimide; DIEA, *N*,*N*-diisopropylethylamine; Fmoc, fluorenylmethyloxycarbonyl; HOBT, 1-hydroxybenzotriazole; KHMDS, potassium hexamethyldisilazane; Ms, mesyl; NMP, *N*-methylpyrrolidin-2-one; TFA, trifluoroacetic acid.

Solvents were purchased from Burdick & Jackson (Muskegon, MI, U.S.A., www.vwrsp.com) or EM Science (Gibbstown, NJ, U.S.A., www.emscience.com) and used without further purification. Chemicals were obtained from Aldrich (Milwaukee, IL, U.S.A., www.sigma-aldrich.com). The (4-(4-formyl-3-methoxyphenoxy)butanoyl) resin was obtained from Novabiochem (Laufelfingen, Switzerland, www.nova.ch), and the *p*-methylbenzhydrylamine resin from Advanced ChemTech (Louisville, KY, U.S.A., www.peptide.com). Both solid phase supports were copoly(styrene–1% divinylbenzene) resins. SynPhase Lanterns were purchased from Mimotopes (Dunedin, Victoria, Australia, www.mimotopes.com). Synthesis was carried out on Domino Blocks in polypropylene syringes fitted with polypropylene frits (Torviq, Tucson AZ, U.S.A., www.torviq.com). Labquake Tube Rotator (Thermolyne, Dubuque, Iowa, U.S.A., www.barnsteadthermolyne.com) was used for gentle but efficient tumbling of resin slurry and lanterns during reactions.

All reactions were carried out at room temperature (25 °C) unless stated otherwise. The volume of wash solvent was 10 ml per 1 g of resin or 30 ml per 100 lanterns. For washing, both resin and lanterns were shaken with the fresh solvent for at least 1 min before changing the solvent. Washing protocol for both resin and lanterns was identical except for omission of MeOH in washing cycles of lanterns. After manually adding any reagent solution, the resin or lanterns were shaken well by hand. Resin and lantern-bound intermediates were dried in a stream of nitrogen for prolonged storage.

Unless stated otherwise, a sample of resin (10 mg) was treated with TFA for the analysis of an intermediate, TFA was evaporated by a stream of nitrogen, product extracted into 0.5 ml of MeOH, and analyzed on HPLC.

HPLC analysis was performed on a Waters HPLC system consisting of a 600S controller, a 626 pump, a 2 700 sample manager and a 2 487 dual wavelength UV detector (Milford, MA, U.S.A., www.waters.com). The column used was a 4.6 × 30 mm, Phenomenex Prodigy ODS (Torrance, CA, U.S.A., www.phenomenex.com). HPLC mobile phases consisted of 0.05% TFA in HPLC-grade water (A) and HPLC-grade acetonitrile (B). A gradient was performed from 0 to 100% B in 5 min at 1.0 ml/min. Flow-injection mass spectrometry was performed with a system consisting of a Shimadzu LC-10AD HPLC pump, a Gilson 215 autosampler, and a PE/Sciex API-150EX single quadrupole mass spectrometer (Foster City, CA, U.S.A., www.appliedbiosystems.com). A 5 μl sample from each well was injected into a flow of 0.5% formic acid in methanol at 0.7 ml/min. The Turbo IonSpray source was employed with an ion spray current of 5 kV and a temperature of 350 °C. ^{1}H NMR spectra were obtained on a Varian Gemini 500 MHz instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. All compounds were measured as TFA or HF salts.

Reductive Alkylation (Resin **2**)

A polypropylene 10-ml fritted syringe was charged with 500 mg of the 4-(4-formyl-3-methoxyphenoxy)butanoyl resin (degree of substitution 0.8 meq/g). A 0.5 M solution (5 ml) of amine in 10% AcOH/dry DMF was added to the resin and kept on a tumbler for 1 h. A 1 M solution (2.5 ml) of $NaBH(OAc)_3$ (0.53 g) in 5% AcOH/dry DMF was added to the syringe, and the syringe was closed with the plunger and punctured with a needle just below the plunger (hydrogen gas evolved). The vented syringe with resin was shaken in upright position on a shaker at room temperature for 3 h.

The resin was washed three times with 5% AcOH/dry DMF, the Schiff base formation was repeated for 2 h, and reduction was carried out overnight at room temperature. The resin was washed three times with 5% AcOH/DMF, 3 × DMF, neutralized with 20% piperidine/DMF for 5 min, and washed three times with DMF, three times with THF, three times with DCM, three times with MeOH.

Evaluation of loading: A weighed sample of dry resin was placed into a 2.5-ml polypropylene syringe equipped with a porous disc and 1 ml of a 0.5 M solution of Fmoc-Cl and DIEA in DCM was added. The syringe was kept on a tumbler for 30 min. The resin was washed five times with DCM and three times with DMF, 1 ml of 50% piperidine/DMF was added, the resin was shaken for 10 min, and the solution and three DMF washes were collected and pooled. The solution was diluted with DMF and its absorbance measured at 302 nm. The substitution was calculated according to the formula.

$$\text{Substitution (meq/g)} = \frac{\text{absorbance} \times \text{volume (ml)} \times \text{dilution (ml)}}{8\,100 \times \text{weight of resin (g)}}$$

Evaluation of purity: A sample of Fmoc-Cl treated resin (see above) was placed into an HPLC vial and product was cleaved with TFA for 30 min. TFA was evaporated with a stream of nitrogen, and the product was extracted into 0.5 ml MeOH. Analytical HPLC was run and product detected at 280 nm.

Nucleophilic Substitution (Resin **10**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of resin **2**, and the resin was washed three times with dry DMSO. A 1 M solution (5 ml) of substituted 2-fluoronitrobenzene and DIEA (125 µl) in dry DMSO was added, and the reaction was carried out. Reaction time and temperature for representative amines and 1-fluoro-2-nitrobenzenes is given in Tables II and III. The resin was washed five times with DMSO, three times with DMF, three times with DCM, three times with MeOH.

A sample of the resin was treated with Fmoc-Cl as described above, the product was cleaved with TFA and its purity analyzed on HPLC.

Nucleophilic Substitution (Resins **24**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of *p*-methylbenzhydrylamine resin, the resin was washed 3 × DMF, neutralized with 20% piperidine/DMF, and washed three times with DMF, three times with dry DMSO. A 1 M solution (5 ml) of substituted 1-fluoro-2-nitrobenzene and DIEA (125 µl) in dry DMSO was added, and the reaction

was carried out at 75 °C overnight. The resin was washed five times with DMSO, three times with DMF, three times with DCM, three times with MeOH.

For the synthesis on Lanterns, the aminomethyl-derivatized Lanterns were acylated with the Fmoc-4-[(γ-carboxypropyl)oxy]-4′-methoxybenzhydrylamine (Bachem Bioscience, King of Prussia, PA, U.S.A., www.bachem.com).

Reduction of the Nitro Group (Resins **11**, **14**, **19**, and **25**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of resin **10**, and the resin was washed three times with NMP "degassed" with argon. A 2 M solution (5 ml) of tin(II) chloride dihydrate in NMP was "degassed" with argon, added to the resin, and the syringe was kept on a tumbler for 2 h or overnight. The resin was washed five times with DMF, three times with DMF–water (3 : 2), three times with DMF, three times with MeOH, three times with DCM, three times with MeOH.

Acylation of Amino Group (Resins **12** and **20**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of resin **11** or **19**, and the resin was washed three times with DMF. A 0.5 M solution (5 ml) of acid chloride and 0.5 M DIEA in DMF was added to the resin and the syringe was kept on a tumbler for 5 h. The resin was washed five times with DMF, three times with DCM, three times with MeOH.

Synthesis of Benzimidazoles **13**

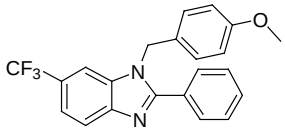
Dry resin **12** (50 mg) was placed into a glass vial, 0.5 ml of AcOH was added and the slurry was shaken in an incubator at 60 °C overnight. The resin was filtered off, washed twice with AcOH, and AcOH was evaporated. The structure and properties of benzimidazoles **13** are given in Fig. 4 and Table VI. ^{1}H NMR spectra (500 MHz, DMSO-d_6) of **13a**: 3.68 (s, 3 H); 5.57 (s, 2 H); 6.82 (d, 2 H, J = 9); 6.91 (d, 2 H, J = 9); 7.57 (m, 3 H); 7.72 (d, 1 H, J = 8.5); 7.76 (d, 2 H, J = 7); 7.93 (d, 1 H, J = 7); 8.08 (s, 1 H); **13b**: 3.67 (s, 3 H); 5.53 (s, 2 H); 6.82 (d, 2 H, J = 9); 6.89 (d, 2 H, J = 9); 7.39 (t, 2 H); 7.79 (q, 2 H); 7.95 (s, 1 H); 8.00 (s, 1 H); **13d**: 5.66 (s, 2 H); 6.95 (d, 2 H, J = 7); 7.26 (m, 3 H); 7.89 (d, 2 H, J = 9); 7.95 (d, 2 H, J = 9); 7.98 (s, 1 H); 8.07 (s, 1 H); **13g**: 5.68 (s, 2 H); 6.81 (d, 2 H, J = 8); 6.89 (d, 2 H, J = 8); 7.91 (d, 2 H, J = 7); 7.97 (d, 2 H, J = 7); 7.98 (s, 1 H); 8.05 (s, 1 H).

Alkylation of Amide (Resin **15**)

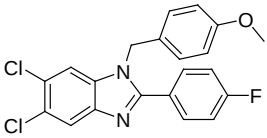
A polypropylene 5-ml fritted syringe was charged with 100 mg of resin **14** and the resin was washed three times with dry DMF. A 1 M solution of electrophile and a phosphazene base BEMP in DMF was added. The syringe was left on a tumbler overnight. The resin was washed three times with DMF, three times with DCM, three times with MeOH.

Synthesis of Dihydroquinoxalinones **16** and Quinoxalinones **17**

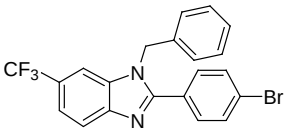
A polypropylene fritted syringe was charged with 50 mg of dry resin **15** and exposed to gaseous HF for 2 h in a dedicated gas cleavage apparatus (Torviq, Tucson, AZ, U.S.A., www.torviq.com). The product was extracted three times with MeOH under nitrogen, extracts were pooled and MeOH evaporated in a stream of nitrogen to obtain dihydroquinoxalinone **16**. An air-open solution of **16** in MeOH was stirred overnight at ambient



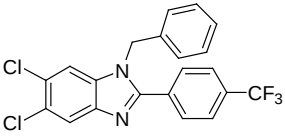
13a



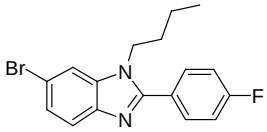
13b



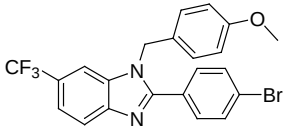
13c



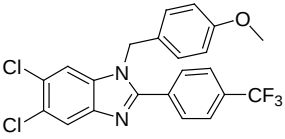
13d



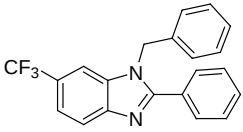
13e



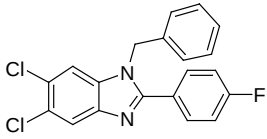
13f



13g



13h



13i

FIG. 4
Structure of benzimidazoles **13**

TABLE VI
Benzimidazoles **13**

Compound	*Rt*, min	Purity, %	Yield, %	Mw	$[M + H]^+$
13a	6.9	82	54	382	383.1
13b	7.7	94	70	400	400.9
13c	8.1	88	30	430	431.1
13d	8.7	91	64	420	421.1
13e	5.8	96	72	346	347.0
13f	8.0	85	48	460	461.3
13g	8.6	90	71	450	451.1
13h	7.0	90	46	352	353.0
13i	7.8	96	74	370	371.1

temperature to prepare the quinoxalinones **17**. The structure and properties of compounds **16** and **17** are given in Fig. 5 and Table VII. ^{1}H NMR spectra (500 MHz, DMSO-d_6) of **17a**: 7.59 (s, 1 H); 7.62 (d, 1 H, *J* = 8); 7.92 (d, 1 H, *J* = 8); 8.32 (s, 1 H); **17b**: 2.65 (s, 3 H); 8.16 (s,

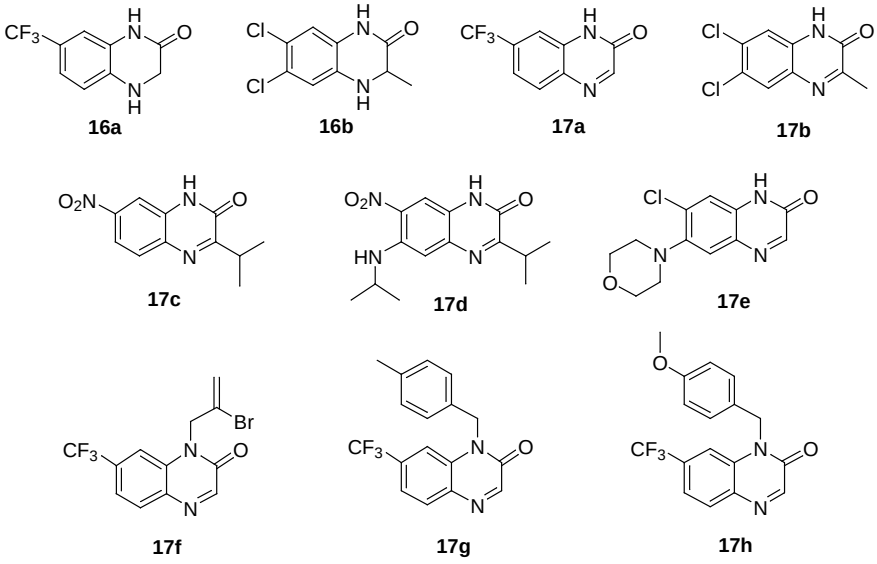


FIG. 5
Structure of dihydroquinoxalinones **16** quinoxalinones **17**

TABLE VII
Dihydroquinoxalinones **16** and quinoxalinones **17**

Compound	*Rt*, min	Purity, %	Yield, %	Mw	$[M + H]^+$
16a	4.9	nt[a]	nt[a]	216	217.2
16b	5.5	nt[a]	nt[a]	230	231.1
17a	4.8	87	80	214	215.1
17b	5.4	99	77	228	229.0
17c	5.4	84	76	233	234.2
17d	5.5	92	69	292	293.2
17e	4.0	89	53	279	280.3
17f	6.7	85	82	332	332.9
17g	6.9	89	91	318	319.0
17h	7.3	90	78	334	335.0

[a] nt stands for not tested.

1 H); 8.39 (s, 1 H); **16a**: 4.01 (s, 2 H); 6.76 (d, 1 H, *J* = 8); 7.12 (d, 1 H, *J* = 8); 7.20 (s, 1 H); **16b**: 1.25 (d, 3 H, *J* = 6); 4.04 (q, 1 H, J_1 = 6, J_2 = 7); 6.87 (s, 1 H); 7.09 (s, 1 H); **17d**: 0.78 (d, 3 H, *J* = 7); 0.95 (d, 3 H, *J* = 7); 1.22 (d, 3 H, *J* = 7); 1.24 (d, 3 H, *J* = 7); 3.65 (m, 1 H); 3.88 (m, 1 H); 7.38 (s, 1 H); 7.60 (s, 1 H); **17e**: 2.97 (m, 4 H); 3.74 (m, 4 H); 7.33 (s, 1 H); 7.49 (s, 1 H); 8.15 (s, 1 H); **17f**: 5.22 (s, 2 H); 5.71 (s, 1 H); 5.95 (s, 1 H); 7.72 (d, 1 H, *J* = 8); 7.79 (s, 1 H, *J* = 8); 8.06 (d, 1 H); 8.45 (s, 1 H); **17g**: 2.21 (s, 3 H); 5.47 (s, 2 H); 7.11 (d, 2 H, *J* = 8); 7.15 (d, 2 H, *J* = 8); 7.65 (d, 1 H, *J* = 8); 7.70 (s, 1 H); 8.04 (d, 1 H, *J* = 8); 8.46 (s, 1 H); **17h**: 3.85 (s, 3 H); 5.48 (s, 2 H); 6.87 (d, 2 H, *J* = 9); 7.24 (d, 2 H, *J* = 9); 7.65 (d, 1 H, *J* = 8); 7.79 (s, 1 H); 8.05 (d, 1 H, *J* = 8); 8.48 (s, 1 H).

Mesylation (Resin **18**)

A polypropylene 5-ml fritted syringe was charged with 100 mg of resin **10c**, the resin was washed three times with pyridine, and a 1 M solution of mesyl chloride in pyridine was added. The syringe was left on a tumbler for 2 h. The resin was washed three times with pyridine, three times with DMF, three times with DCM, three times with MeOH.

Synthesis of Tetrahydroquinoxalines **21**

A glass vial was charged with 50 mg of dry resin **20** and 2 ml of TFA was added. The resin was gently shaken for 2 h, then filtered off and washed twice with TFA. The extracts were pooled and TFA was evaporated in a stream of nitrogen. The structure and properties of compounds **21** are given in Fig. 6 and Table VIII. ^{1}H NMR spectra (500 MHz, DMSO-d_6) of **21a**: 3.28 (q, 2 H, J_1 = 3, J_2 = 11); 3.39 (m, 2 H); 6.52 (d, 1 H, *J* = 8); 6.75 (s, 1 H); 6.77 (d, 1 H, *J* = 8); **21b**: 1.12 (d, 3 H, *J* = 6); 2.84 (q, 1 H, J_1 = 8, J_2 = 11); 3.30 (q, 1 H, J_1 = 3, J_2 = 11); 3.41 (m, 1 H); 6.55 (d, 1 H, *J* = 8); 6.78 (s, 1 H); 6.80 (d, 1 H, *J* = 8); **21c**: 2.83 (q, 1 H, J_1 = 8.5, J_2 = 14); 2.89 (q, 1 H, J_1 = 8.5, J_2 = 19); 3.01 (q, 1 H, J_1 = 5, J_2 = 13); 3.27 (q, 1 H, J_1 = 2, J_2 = 12); 3.88 (m, 1 H); 5.72 (d, 2 H, *J* = 2); 6.94 (d, 1 H, *J* = 9); 7.24 (m, 3 H); 7.31 (d, 2 H, *J* = 6); 7.34 (d, 1 H, *J* = 9); 7.38 (s, 1 H).

Thiourea Formation (Resins **28** and **34**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of resin **25**, and the resin was washed three times with NMP. A 1 M solution (5 ml) of phenyl isothiocyanates in NMP was added, and the reaction was carried out at ambient temperature overnight. The resin was washed three times with NMP, three times with DCM, three times with MeOH.

Cyclization to 2-(Arylamino)benzimidazoles (Resin **29**)

A polypropylene 10-ml fritted syringe was charged with ≈500 mg of resin **28** and the resin was washed three times with NMP. A 1 M solution (5 ml) of DIC in NMP was added, and the reaction was carried out at ambient temperature overnight. The resin was washed three times with NMP, three times with DCM, three times with MeOH.

Alkylation of Benzimidazole (Resins **31** and **32**)

Procedure A: A polypropylene 5-ml fritted syringe was charged with 100 mg of resin **29**, the resin was washed three times with dry DMF, and 50 mg of anhydrous K_2CO_3 and 2 ml of a 1 M solution of an electrophile in DMF were added. The syringe was shaken in an incu-

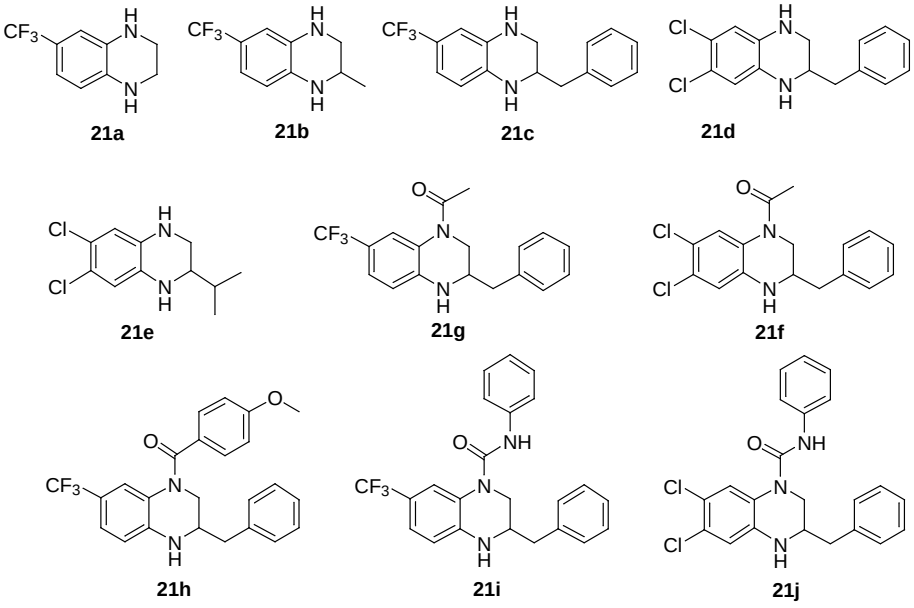


FIG. 6
Structure of tetrahydroquinoxalines **21**

TABLE VIII
Tetrahydroquinoxalines **21**

Compound	*Rt*, min	Purity, %	Yield, %	Mw	$[M + H]^+$
21a	3.6	85	79	202	203.1
21b	4.4	84	86	216	216.1
21c	7.2	87	91	292	292.2
21d	7.2	87	76	292	293.2
21e	6.7	84	88	244	245.1
21f	7.5	95	83	334	335.0
21g	7.1	94	79	334	335.1
21h	8.6	91	81	426	427.1
21i	8.0	89	96	411	412.1
21j	8.4	85	93	411	412.1

bator at 75 °C overnight. The resin was washed three times with DMF, three times DCM, three times MeOH.

Procedure B: A polypropylene 5-ml fritted syringe was charged with 100 mg of resin **29**, the resin was washed three times with dry DMF, and 2 ml of a 0.5 M solution of an electrophile and phosphazene base BTPP in DMF were added (for concentration of the BTPP base see Table IV). The syringe was left on a tumbler overnight. The resin was washed three times with DMF, three times with DCM, three times with MeOH.

Synthesis of 2-(Arylamino)benzimidazoles **30**

The protocol for cleavage and isolation of 2-(arylamino)benzimidazoles **30** (for structure and properties see Fig. 7 and Table IX) is identical to the protocol for tetrahydroquinoxalines **21**. ^{1}H NMR spectra (500 MHz, DMSO-d_6) of **30a**: 7.27 (t, 2 H); 7.44 (d, 1 H, J = 8); 7.49 (d, 1 H,

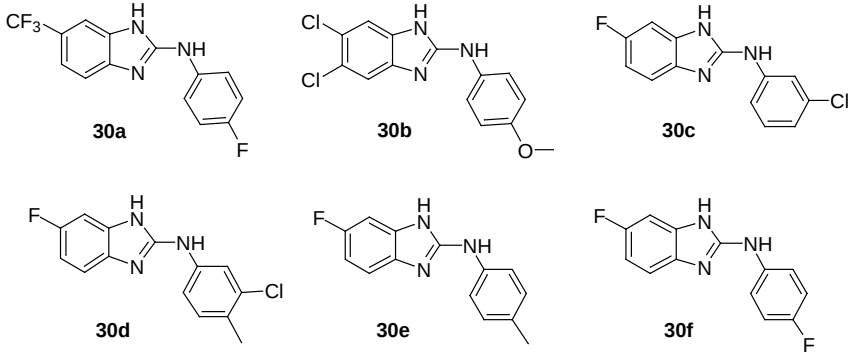


FIG. 7
Structure of 2-(arylamino)benzimidazoles **30**

TABLE IX
2-(Arylamino)benzimidazoles **30**

Compound	*Rt*, min	Purity TFA[a], %	Purity HF[a], %	Mw	$[M + H]^+$
30a	4.4	89	91	295.1	296.1
30b	4.6	79	87	307.1	308.1
30c	4.2	81	98	261.1	262.1
30d	4.4	81	84	nt[b]	nt[b]
30e	4.3	92	95	241.1	242.1
30f	4.4	87	93	261.1	262.1

[a] Indicates the method of cleavage; [b] nt stands for not tested.

J = 8); 7.61 (s, 1 H); 7.67 (q, 2 H); **30c**: 7.11 (t, 1 H); 7.26 (m, 1 H); 7.34 (d, 1 H, *J* = 8); 7.4 (m, 2 H); 7.50 (m, 1 H); 7.63 (s, 1 H); **30d**: 2.33 (s, 3 H); 7.06 (t, 1 H); 7.23 (d, 1 H, *J* = 9); 7.34 (d, 2 H, *J* = 9); 7.38 (q, 1 H); 7.43 (d, 1 H, *J* = 9); 7.66 (s, 1 H).

Synthesis of 2-(Arylamino)benzimidazoles **36**

A 10 mg sample of the resin **34** was cleaved with 0.5 ml of TFA for 1 h, TFA was evaporated in a stream of nitrogen, and the product was extracted into 1 ml of ethyl acetate. The ethyl acetate was extracted three times with 5% K_2CO_3 in water, dried with anhydrous $MgSO_4$, 15.6 μl DIC was added, and the reaction mixture was kept at ambient temperature overnight.

Acylation of Lanterns with the Aldehyde Linker

A 20-ml syringe was charged with 100 aminomethylated SynPhase Lanterns. The lanterns were washed three times with DMF, neutralized with 20% piperidine/DMF for 5 min, and washed seven times with DMF. 4-(4-Formyl-3-methoxyphenoxy)butanoic acid (5 mmol, 1.19 g) and HOBt (5 mmol, 0.675 g) were dissolved in 15 ml DMF, DIC (5 mmol, 0.782 ml) was added, and the solution was left for 5 min. The syringe with lanterns was charged with the solution and kept on a tumbler overnight. Lanterns were washed five times with DMF, three times with THF, three times with DCM, dried in a stream of nitrogen and kept in a freezer.

Evaluation of loading: One lantern was placed into a 2.5-ml syringe, a solution of L-alanine *tert*-butyl ester hydrochloride (90 mg, 0.5 mmol) in 1 ml of 5% AcOH/dry DMF was added, and the syringe was left on a tumbler for 30 min. A solution of $NaBH(OAc)_3$ (58 mg, 0.5 mmol) in 0.5 ml dry DMF was added, the syringe was punctured at the top with a needle, and shaken in upright position for 2 h. The lantern was washed three times with 5% AcOH/dry DMF. The incubation with L-alanine *tert*-butyl ester hydrochloride was repeated for 30 min and the reduction with $NaBH(OAc)_3$ overnight. The lantern was washed twice with 5% AcOH/DMF, three times with DMF, twice with 5% DIEA/THF, twice with THF, and 1 ml of a 0.5 M solution of Fmoc-Cl (130 mg) and DIEA (85 μl) in DCM were added. The lantern was shaken for 30 min and washed with three times with DCM, three times with DMF, three times with THF, three times with DCM. A solution of 50% piperidine/DMF (1 ml) was added, the lantern was shaken for 10 min, and the solution and three DMF washes were collected and pooled. The solution was diluted with DMF to 10 ml and absorbance was measured at 302 nm. The substitution was calculated according to the formula.

$$\text{Substitution (μmol/lantern)} = \frac{\text{absorbance} \times \text{volume (ml)} \times \text{dilution (ml)} \times 1\,000}{8\,100 \times \text{number of lanterns}}$$

Typical substitution was 9–11 μmol/lantern.

Synthesis on SynPhase Lanterns Using the Encore Technique

Twenty-seven aminomethyl lanterns acylated with the 4-(4-formyl-3-methoxyphenoxy)-butanoic acid were split into three syringes, and the first combinatorial step, the reductive amination, was performed using three amines (Fig. 3) on 9 lanterns. All protocols for lanterns and resin were identical. After finishing the first combinatorial step, nine identical necklaces were formed, each containing three lanterns, one from each syringe. Lanterns

were strung on a Teflon rope (Teflon Chemware Beading, Cole-Parmer, Vernon Hills, IL, U.S.A., www.coleparmer.com) and individual necklaces were labeled with three different color tags (Mimotopes, Dunedin, Victoria, Australia, www.mimotopes.com), one color for three necklaces. Three necklaces of the same color were placed into three syringes and the next combinatorial step, the nucleophilic substitution with three 1-fluoro-2-nitrobenzenes, was performed. The nitro group was reduced with tin(II) chloride and necklaces were reorganized such that each syringe contained three necklaces labeled with different color tags. The last combinatorial step, the acylation, was performed with three acid chlorides. The lanterns were washed and dried, then distributed into individual wells of 96-well plate, and the product was cleaved from lanterns and cyclized in AcOH.

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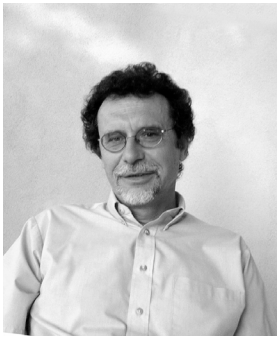

Viktor Krchňák was born in Brno, Moravia, where he studied chemistry at Masaryk University. After receiving his Ph.D. in organic chemistry while working with Prof. Zdeněk Arnold, Institute of Organic Chemistry and Biochemistry, Prague, his research interest focused on solid-phase synthesis. In the Peptide Department of Léčiva Pharmaceuticals, Prague, he developed solid-phase commercial production of peptides and initiated a research program of synthetic peptide antigens for antibody detection. In 1992 he joined Selectide Corporation, Tucson, Arizona, and since then his research interests have included combinatorial chemistry and solid-phase synthesis methodology. After a short sabbatical at Houghten Pharmaceuticals, San Diego, he returned to Tucson to build a high throughput combinatorial chemistry unit at Systems Integration Drug Discovery Company (SIDDCO). He also started his own company, Torviq, developing novel tools for solid-phase chemistry. This paper discusses some of the research activities of his former New Concepts Development group at SIDDCO. In addition to chemistry and instrumentation, he enjoys listening to baroque music, loves to drive historical sport cars, and landscape photography.