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# Combinatorial Synthesis of Dihydropyridone Libraries and their Derivatives

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**Abstract:** Polymer-supported quench methodology has been used for parallel purification of combinatorial libraries of dihydropyridones and their derivatives. The dihydropyridone scaffold was assembled via a solution phase Lewis acid catalyzed, hetero-Diels-Alder reaction. Further modifications allow for the rapid generation of subsequent aminopiperidine and acyl-aminopiperidine libraries utilizing a library from library approach. © 1998 Published by Elsevier Science Ltd. All rights reserved.

## Introduction

The use of combinatorial chemistry for both lead generation and lead optimization of biologically active compounds has become ubiquitous in the pharmaceutical industry. In a relatively short period of time a variety of methodologies have been developed or redefined for use in the rapid parallel synthesis of small molecule libraries.[1] Solid-phase methods were popularized first, by offering the ability to synthesize huge libraries using a variety of specialized techniques.[1,2] Because of the substantial time investment involved with method development, the low quantities of product produced, the lack of analytical tools to characterize intermediates, and the need for an attachment point, many chemists have returned to solution-phase methods for library generation.[3-9] A variety of imaginative techniques have been developed to rapidly purify the many reactions of a solution-phase library in a parallel fashion. Some of these techniques include acid/base extraction,[4] fluorous-phase extraction,[5] polymer-supported reagents[6] and catalysts,[7] solid-phase-extraction (SPE),[4,8] and polymer-supported quench/scavenging reagents (PSQ).[9]

One of our approaches to the synthesis of compound libraries for biological screening has been to focus on methodology for the synthesis of heterocyclic scaffolds which would allow for variation of appended functionality. Particular attention is paid to the formation of carbon-carbon bonds, and a library from library[2e] approach allows for peak efficiency.

Synthesis of the 2,3-dihydro-4-pyridone scaffold via the reaction of imines with Danishefsky's diene offers the challenge of forming carbon-carbon bonds and an opportunity to explore the modification of the

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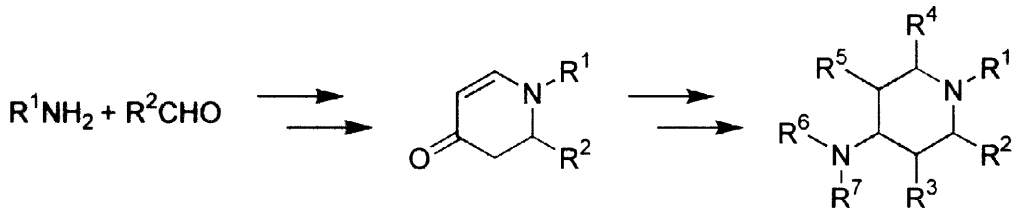
resultant functionality. A diverse array of imines are possible from a plethora of available aldehydes and primary amines, and the dihydropyridone scaffold itself offers numerous opportunities for further elaboration, adding up to five new sites of diversity (Scheme 1).[10]

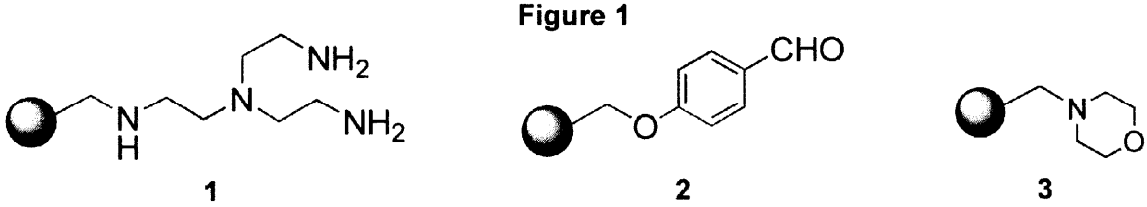
**Scheme 1**




The precedence for forming dihydropyridone rings in this manner dates back to the early '80s when Danishefsky reported that aldehyde-derived imines react with electron-rich dienes in the presence of a Lewis acid to form 1,2-disubstituted 2,3-dihydro-4-pyridones.[11] This was later applied to amino acid imines, with sterically hindered amino acids providing good asymmetric induction.[12] Although this is a formal hetero-Diels-Alder reaction, it has been shown to proceed through a tandem Mannich/Michael mechanism.[13] A solid phase route to dihydropyridones was recently reported, taking advantage of a polymer bound hydroxybenzaldehyde imine.[14] We also recently disclosed a solid phase synthesis of dihydropyridones from polymer-bound amino acid imines.[15] A variety of Lewis acids provided acceptable yields of dihydropyridones, but the purities obtained after cleavage were inconsistent and generally unsatisfactory. Encouraged by the results obtained from PSQ studies ongoing in our laboratories, we decided to pursue a more efficient solution-phase route to this ring system and its derivatives. Not only does a solution-phase synthesis eliminate the loading, deprotection, and cleavage steps from the synthesis, but the diversity of the library can be broadened since there is no need for an attachment point.

Kobayashi has recently reported excellent yields for the solution-phase synthesis of dihydropyridones from imines and Danishefsky's diene, with $Yb(OTf)_3$ as a catalyst and an excess of diene to drive the reaction to completion.[16] However, a convenient method for removing the excess diene is necessary for this solution-phase route to be successful in generating combinatorial libraries. Polymer-supported quench reagents are useful for removing excess starting materials and byproducts from solution-phase reactions.[9] For example, the polyamine resin **1** will remove excess isocyanates, the aldehyde resin **2** removes excess primary amines in the presence of

**Figure 1**




**1** **2** **3**

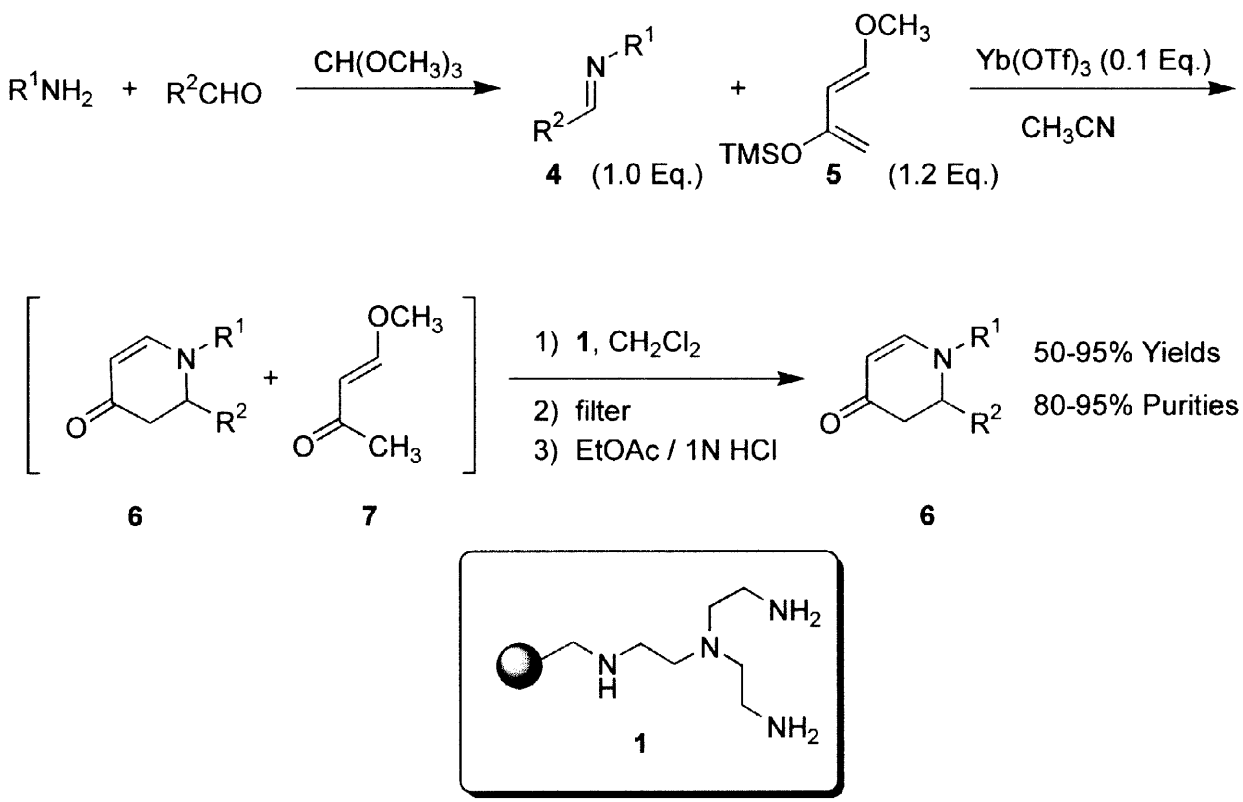
secondary amine products in a reductive amination reaction, and the morpholine resin **3** serves as an acid sponge. The feature of polymer-supported quench which makes it ideal for solution-phase library generation is that a simple filtration is all that is necessary to workup and purify all of the reactions in a library.

We describe herein the combinatorial synthesis and purification of dihydropyridone libraries and their derivatives using polymer-supported quench methodology.

## Results and Discussion

**Dihydropyridone libraries.** Scheme 2 outlines the solution-phase synthesis of dihydropyridones from imines using $Yb(OTf)_3$ as the Lewis acid catalyst in the Diels-Alder reaction. The procedure reported by the Affymax group[17] works well for synthesizing libraries of imines in solution. An equimolar mixture of aldehyde and primary amine is stirred for about one hour in trimethylorthoformate, then the solvent is evaporated. After evaporating from an inert solvent such as 1,2-dichloroethane, the resulting imines **4** are used directly in the subsequent Lewis acid catalyzed hetero-Diels-Alder reaction. Using an excess of Danishefsky's diene in the $Yb(OTf)_3$ catalyzed Diels-Alder reaction yields a mixture of the desired 1,2-disubstituted 2,3-dihydro-4-pyridone **6** and 4-methoxy-3-buten-2-one (**7**), resulting from competing hydrolysis of the excess diene.

**Scheme 2**



As anticipated, polymer-supported quench methodology is ideal for the purification of this reaction when used for library synthesis. Not only does the poly-amine resin **1** remove the diene byproduct **7**, but if the reaction does not go to completion, this resin also removes any unreacted imine **4**.[18] Therefore, after a simple filtration followed by an acidic aqueous workup to remove the ytterbium triflate, good yields of very pure dihydropyridone products are obtained. The yields can range from 40 to 90 percent and the purities typically range from 80 to 99 percent for biased arrays.

A variety of imine functionality is tolerated in the cyclization. Imines derived from alkyl, arylalkyl, and pyridyl amines, as well as those from halogen, alkoxy, acyloxy, and trifluoromethyl substituted anilines have all been used successfully. Most aromatic aldehydes worked well, including those substituted with alkyl, halogen, alkoxy, acyloxy, nitro, and trifluoromethyl groups. Cyclohexane carboxaldehyde is acceptable, but if both the amine and aldehyde components of the imine are aliphatic, the Diels-Alder reaction must be run immediately following imine formation. In addition to the range of substituents discussed here, many imines derived from our proprietary library of amines and aldehydes also worked well. These Diels-Alder reaction conditions are not applicable, however, if the imine is insoluble in acetonitrile. In this instance the Lewis acid catalyzed hydrolysis of the diene is faster than dissolution of the imine. In addition, some building blocks which contained carboxylic acid or alcohol functionalities did not afford clean dihydropyridone products. A few examples of imines made from nitroanilines also gave lower yields and purities. It is possible that aniline-derived imines can also function as dienes in a competing Diels-Alder reaction.[19]

In an attempt to eliminate the aqueous workup we briefly examined a recently reported polymer-bound scandium catalyst for the cyclization.[20] Simple filtration of the PSQ resins would also remove the catalyst. However, under these conditions, the reaction rate for diene hydrolysis was competitive with the Diels-Alder reaction, and even large excesses of diene did not drive reactions to completion. Therefore, large amounts of polymer-supported quench resin were needed to remove **7** as well as the unreacted imine **4**, and the purity of the products was less than that using a soluble ytterbium catalyst. We have not investigated a recently disclosed soluble polymeric scandium catalyst,[7a] due to the likelihood that the large volumes of solvent needed to precipitate the catalyst would not be practical for automation.

To demonstrate the utility of this methodology, a small four by ten array of dihydropyridones was synthesized using a representative group of building blocks shown in Figure 2. Each of ten primary amines was condensed with four aromatic aldehydes to provide 40 imines possessing a variety of electronic properties. The group of imines was then subjected to the standard Diels-Alder reaction conditions and purification protocol outlined in Scheme 2, and the yields and purities of the individual compounds in the array are listed in Table 1. The yields obtained in this array are quite admirable, averaging 64 percent, but most noteworthy are the exceptionally high purities, most being above 95 percent. Products from some of the lower-yielding reactions are obtained in high purity because **1** removes both the diene byproduct **7** and starting imine **4**. The yields and purities of the four dihydropyridones derived from the N-methylpyrrole amine building block **F** were quite low

**Figure 2**

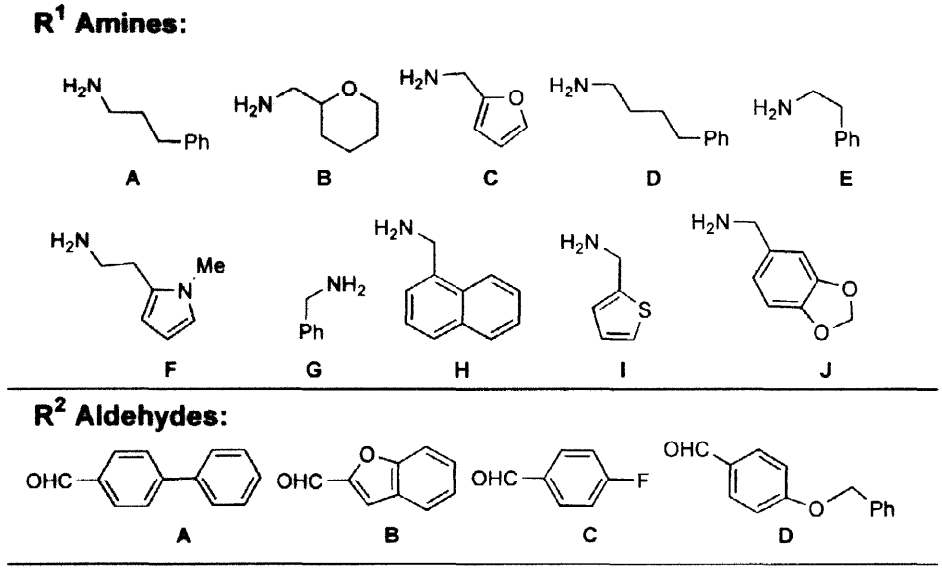
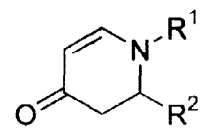



**Table 1: Dihydropyridone Array (Yields & Purities)**



| Compd No. | $R^1$ | $R^2$ | Yield | Purity | Mass (M+1) | Compd No. | $R^1$ | $R^2$ | Yield | Purity | Mass (M+1) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6AA | A | A | 75 | 99 | 368 | 6FA | F | A | 60 | 53 | 357 |
| 6AB | A | B | 74 | 98 | 332 | 6FB | F | B | 46 | 66 | 321 |
| 6AC | A | C | 71 | 98 | 310 | 6FC | F | C | 23 | 32 | 299 |
| 6AD | A | D | 71 | 97 | 398 | 6FD | F | D | 66 | 37 | 387 |
| 6BA | B | A | 74 | 99 | 348 | 6GA | G | A | 73 | 99 | 340 |
| 6BB | B | B | 74 | 97 | 312 | 6GB | G | B | 66 | 98 | 304 |
| 6BC | B | C | 49 | 93 | 290 | 6GC | G | C | 65 | 99 | 282 |
| 6BD | B | D | 65 | 99 | 378 | 6GD | G | D | 73 | 99 | 370 |
| 6CA | C | A | 70 | 96 | 330 | 6HA | H | A | 41 | 84 | 390 |
| 6CB | C | B | 70 | 90 | 294 | 6HB | H | B | 61 | 86 | 354 |
| 6CC | C | C | 52 | 97 | 272 | 6HC | H | C | 75 | 97 | 332 |
| 6CD | C | D | 65 | 93 | 360 | 6HD | H | D | 73 | 97 | 420 |
| 6DA | D | A | 60 | 96 | 382 | 6IA | I | A | 67 | 96 | 346 |
| 6DB | D | B | 69 | 99 | 346 | 6IB | I | B | 67 | 94 | 310 |
| 6DC | D | C | 70 | 99 | 324 | 6IC | I | C | 56 | 89 | 288 |
| 6DD | D | D | 67 | 98 | 412 | 6ID | I | D | 69 | 97 | 376 |
| 6EA | E | A | 51 | 91 | 354 | 6JA | J | A | 39 | 97 | 384 |
| 6EB | E | B | 69 | 97 | 318 | 6JB | J | B | 68 | 97 | 348 |
| 6EC | E | C | 66 | 99 | 296 | 6JC | J | C | 69 | 95 | 326 |
| 6ED | E | D | 70 | 99 | 384 | 6JD | J | D | 68 | 99 | 414 |

in comparison with the others. Multiple products were obtained in these four reactions which were not characterized. This four by ten array was run in a manual fashion in capped 2-dram vials without the use of an inert atmosphere. However, the process has since been automated, using a liquid handling robot to dispense reagents and perform the aqueous extractions, yielding similar results. The robot can also be used for serial filtrations. We have also taken advantage of Polyfiltronic's 96-well PKP™ filter plates for running eight by twelve arrays. Here one can take advantage of a parallel filtration process.

**Acyl-aminopiperidine libraries.** As mentioned earlier, the dihydropyridone scaffold **6** possesses functionality that can be further elaborated. Realizing that the carbonyl could function as a latent amine, the 1-benzyl-2-phenyl substrate **9** was synthesized on a larger scale, and chemoselective reduction of the double bond was accomplished with L-Selectride™ (Scheme 3). Using the reductive amination procedure published by Kaldor and coworkers,[9] the resulting 4-piperidone **10** was condensed with a representative group of ten amines (Scheme 3, A-J) to yield ten aminopiperidenes **11**. This reductive amination protocol uses an excess of amine to quantitatively pre-form the imine which is then reduced with the commercially available polymer-supported borohydride resin. Either aldehyde resin **2** or **7** can be used to remove the excess primary amine in the presence of the secondary amine product. Each aminopiperidine **11** was then acylated with a variety of eight acid chlorides (1.2 eq. of acid chloride, Scheme 3, A-H) using the polymer-supported morpholine **3** as an acid sponge and resin **1** to remove the excess acid chloride. To remove any unreacted aminopiperidine, the isocyanate resin **8** was also used. The result of this three step sequence was an eight by ten array of eighty acyl-aminopiperidenes **12**. The yields for this array were quite respectable, averaging 48 percent. The purities, however, were remarkable for the two step process, most of which were between 80 and 90 percent (84 percent average, see Table 2). As anticipated, mixtures of diastereomers were typically obtained, and the yield and purity tables reflect the combined diastereomeric products. No attempts were made to isolate and characterize individual diastereomers.

By scaling up syntheses of individual piperidones, subjecting each to these reductive amination conditions with a variety of amines, and acylating each resulting aminopiperidine with several acid chlorides, one can quickly generate a large library of acyl-aminopiperidines **12** plus a smaller library of aminopiperidine intermediates **11**. We have indeed taken this type of approach, running various two-dimensional arrays in an automated fashion. The yields and purities obtained in the above array were typical for the arrays using commercial amines and acid chlorides. We have also used many proprietary amines in this sequence with similar success.

**Libraries from Libraries.** In an attempt to take the libraries from libraries approach to an extreme, we are currently optimizing the five step sequence outlined in Scheme 4. Rather than scale up a handful of intermediates and carry them on in a combinatorial fashion as described above, the idea here is to carry a

## Scheme 3

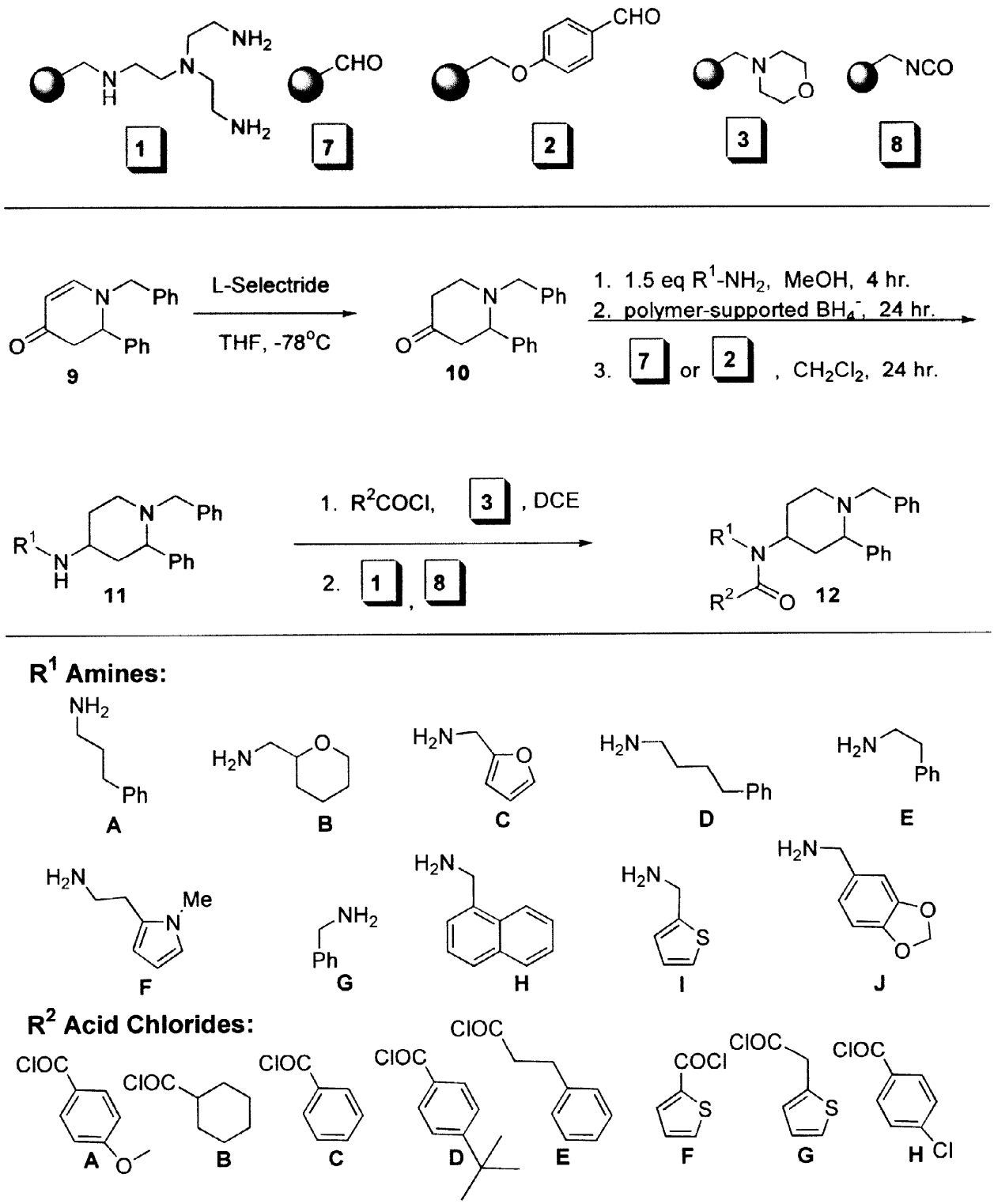
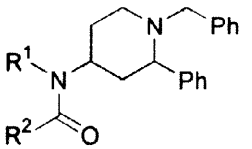
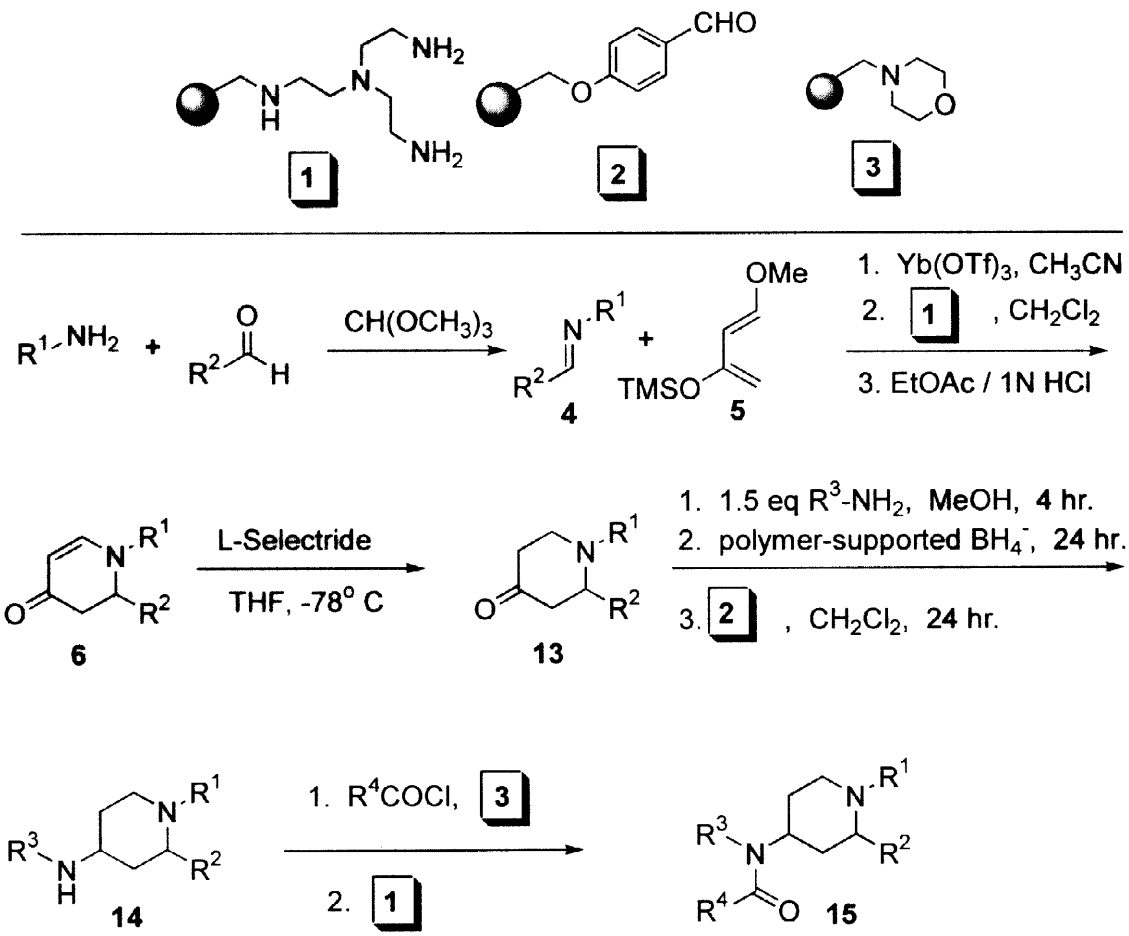

NH2
N
H
N
NH2
1
CHO
7
CHO
O
2
N
O
3
NCO
8
N
Ph
Ph
O
9
L-Selectride
THF, -78°C
N
Ph
Ph
O
10
1. 1.5 eq R1-NH2, MeOH, 4 hr.
2. polymer-supported BH4-, 24 hr.
3. 7 or 2 , CH2Cl2, 24 hr.
R1
N
H
N
Ph
Ph
11
1. R2COCl, 3 , DCE
2. 1 , 8
R1
N
R2
O
N
Ph
Ph
12
R1 Amines:
NH2
Ph
A
H2N
O
B
H2N
O
C
H2N
Ph
D
H2N
Ph
E
H2N
Me
N
F
NH2
Ph
G
H2N
H
H2N
S
I
H2N
O
O
J
R2 Acid Chlorides:
ClOC
O
A
ClOC
B
ClOC
C
ClOC
D
ClOC
E
COCl
S
F
ClOC
S
G
ClOC
Cl
H

**Table 2: Acyl-Aminopiperidine Array (Yields & Purities)**




| Compd. No. | $R^1$ | $R^2$ | Yield (%) | Purity (%) | Mass (M+1) | Compd. No.. | $R^1$ | $R^2$ | Yield (%) | Purity (%) | Mass (M+1) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12AA | A | A | 10 | 85 | 519 | 12AE | A | E | 39 | 82 | 517 |
| 12BA | B | A | 33 | 80 | 499 | 12BE | B | E | 58 | 83 | 497 |
| 12CA | C | A | 18 | 84 | 481 | 12CE | C | E | 55 | 82 | 479 |
| 12DA | D | A | 36 | 87 | 533 | 12DE | D | E | 60 | 82 | 531 |
| 12EA | E | A | 37 | 84 | 505 | 12EE | E | E | 58 | 86 | 503 |
| 12FA | F | A | 26 | 85 | 508 | 12FE | F | E | 65 | 62 | 506 |
| 12GA | G | A | 60 | 84 | 491 | 12GE | G | E | 62 | 83 | 489 |
| 12HA | H | A | 46 | 81 | 541 | 12HE | H | E | 59 | 84 | 539 |
| 12IA | I | A | 53 | 81 | 497 | 12IE | I | E | 24 | 85 | 495 |
| 12JA | J | A | 58 | 79 | 535 | 12JE | J | E | 61 | 83 | 533 |
| 12AB | A | B | 8 | 89 | 495 | 12AF | A | F | 38 | 86 | 495 |
| 12BB | B | B | 48 | 83 | 475 | 12BF | B | F | 62 | 83 | 475 |
| 12CB | C | B | 44 | 82 | 457 | 12CF | C | F | 57 | 85 | 457 |
| 12DB | D | B | 33 | 85 | 509 | 12DF | D | F | 60 | 87 | 509 |
| 12EB | E | B | 44 | 86 | 481 | 12EF | E | F | 51 | 88 | 481 |
| 12FB | F | B | 48 | 82 | 484 | 12FF | F | F | 56 | 88 | 484 |
| 12GB | G | B | 49 | 86 | 467 | 12GF | G | F | 35 | 85 | 467 |
| 12HB | H | B | 48 | 91 | 517 | 12HF | H | F | 57 | 85 | 517 |
| 12IB | I | B | 38 | 82 | 473 | 12IF | I | F | 75 | 84 | 473 |
| 12JB | J | B | 44 | 83 | 511 | 12JF | J | F | 55 | 85 | 511 |
| 12AC | A | C | 30 | 84 | 489 | 12AG | A | G | 32 | 90 | 509 |
| 12BC | B | C | 47 | 83 | 469 | 12BG | B | G | 59 | 89 | 489 |
| 12CC | C | C | 40 | 84 | 451 | 12CG | C | G | 52 | 86 | 471 |
| 12DC | D | C | 41 | 84 | 503 | 12DG | D | G | 58 | 86 | 523 |
| 12EC | E | C | 44 | 86 | 475 | 12EG | E | G | 54 | 84 | 495 |
| 12FC | F | C | 39 | 85 | 478 | 12FG | F | G | 58 | 83 | 498 |
| 12GC | G | C | 42 | 87 | 461 | 12GG | G | G | 54 | 91 | 481 |
| 12HC | H | C | 45 | 79 | 511 | 12HG | H | G | 62 | 85 | 531 |
| 12IC | I | C | 52 | 83 | 467 | 12IG | I | G | 63 | 84 | 487 |
| 12JC | J | C | 49 | 83 | 505 | 12JG | J | G | 58 | 83 | 525 |
| 12AD | A | D | 26 | 83 | 545 | 12AH | A | H | 37 | 84 | 523 |
| 12BD | B | D | 63 | 85 | 525 | 12BH | B | H | 60 | 76 | 503 |
| 12CD | C | D | 57 | 85 | 507 | 12CH | C | H | 27 | 84 | 485 |
| 12DD | D | D | 58 | 88 | 559 | 12DH | D | H | 51 | 85 | 537 |
| 12ED | E | D | 67 | 87 | 531 | 12EH | E | H | 48 | 89 | 509 |
| 12FD | F | D | 59 | 85 | 534 | 12FH | F | H | 53 | 81 | 512 |
| 12GD | G | D | 63 | 89 | 517 | 12GH | G | H | 57 | 85 | 495 |
| 12HD | H | D | 45 | 90 | 567 | 12HH | H | H | 51 | 84 | 545 |
| 12ID | I | D | 49 | 81 | 523 | 12IH | I | H | 59 | 82 | 501 |
| 12JD | J | D | 44 | 85 | 561 | 12JH | J | H | 50 | 82 | 539 |

**Scheme 4**

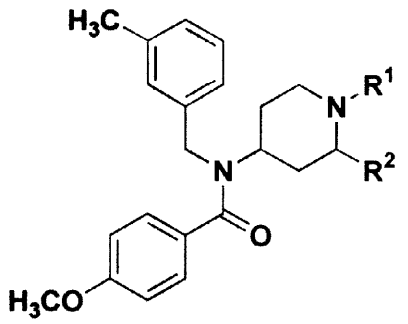

1
2
3
CH(OCH3)3
4
5
1. Yb(OTf)3, CH3CN
2. 1 , CH2Cl2
3. EtOAc / 1N HCl
6
L-Selectride
THF, -78° C
13
1. 1.5 eq R3-NH2, MeOH, 4 hr.
2. polymer-supported BH4-, 24 hr.
3. 2 , CH2Cl2, 24 hr.
14
1. R4COCl, 3
2. 1
15
R1 Amines:
A
B
C
D
R2 Aldehydes:
A
B
R3 Amine:
R4 Acid Chloride:

dihydropyridone library through three additional synthetic steps, collect an intermediate library at each step, and ultimately produce a library of acyl-aminopiperidines **15** . Thus, the overall process would encompass a five step synthetic sequence without any purifications other than PSQ and aqueous workups, the formation of one carbon-carbon bond and three carbon-nitrogen bonds, and the generation of four independent libraries from one sequence, with the final library of compounds possessing four sites of diversity.

To demonstrate the viability of this approach, a small two by four by one by one array was carried out to generate eight acyl-aminopiperidines (Scheme 4). As described earlier, four amines were condensed with each of two aldehydes, and the resulting imines were converted to the corresponding dihydropyridones. The key step in this sequence is the conjugate reduction, considering the utility of the other four steps in the sequence have already been demonstrated. The reduction of the eight dihydropyridones was carried out at -78° C, using a manual operation and 2-dram vials equipped with septa-caps and flea-bars. Following an oxidative aqueous workup, the eight piperidone products **13** were obtained with minimal byproducts. A small amount of the saturated alcohol product resulting from over reduction of the ketone was observed. Using a single amine in the reductive amination procedure previously described in Scheme 3, the piperidones were converted to eight aminopiperidines **14** with no adverse consequences. Finally, employing the PSQ purified acylation procedure, the array of eight acyl-aminopiperidines **15AA-DB** were obtained in excellent yields and purities for the overall five step sequence. The yields were consistently around 50 percent and the purities were consistently around 80 percent (Table 3). To reiterate, these results are for a five step sequence using only PSQ purifications and aqueous workups, with the potential to generate four compound libraries, the last of which possesses four sites of diversity. We are quite excited about the promise of this five step synthetic sequence for library generation, and plan to take full advantage of its potential.

In conclusion, we have demonstrated the utility of polymer-supported quench methodology for the efficient purification of 1,2-disubstituted 2,3-dihydro-4-pyridones and their acyl-aminopiperidine derivatives. In addition, a five step synthetic sequence has been developed offering the potential to yield four independent libraries of dihydropyridones, piperidones, aminopiperidines, and acyl-aminopiperidines using only PSQ purifications and aqueous workups. Polymer-supported quench is another powerful tool at the disposal of the organic chemist allowing the efficient generation of combinatorial libraries in solution.

**Table 3: Libraries from Libraries (Purities and Yields)**




| Compd. No. | R1 | R2 | Yield (%) | Purity (%) | Mass (M+1) |
|---|---|---|---|---|---|
| 15AA | A | A | 53 | 76 | 535 |
| 15BA | B | A | 52 | 73 | 549 |
| 15CA | C | A | 48 | 82 | 593 |
| 15DA | D | A | 46 | 78 | 557 |
| 15AB | A | B | 56 | 80 | 491 |
| 15BB | B | B | 58 | 76 | 505 |
| 15CB | C | B | 49 | 78 | 549 |
| 15DB | D | B | 34 | 83 | 513 |

## Experimental Section

### General.

Unless otherwise indicated, all reactions were run in capped glass vials, without the use of an inert atmosphere, and were shaken on an orbital shaker. THF was distilled from sodium and benzophenone. Other reagents and anhydrous solvents were commercially available and used without further purification. The polymer-supported quench resins **1**, **2**, **3**, and **8** were purchased from Novabiochem and used without further purification. Proton NMR spectra were recorded on a Varian Gemini 2000 spectrometer using a field strength of 300 MHz with samples dissolved in $CDCl_3$. HPLC analysis was achieved using a Thermo Separation Products Spectra System P2000 pump, AS3000 autosampler, and UV1000 detector at 214 nm. Mass spectra were recorded on a VG

Trio-2 mass spectrometer. LC/MS analysis was achieved using a Micromass Platform LC. Automated liquid handling was performed using TECAN RSP 5052 robots.

**General Procedure for the Preparation of 2,3-Dihydro-4-pyridones 6.**

To a solution of amine (1.0 mmol) in anhydrous trimethyl orthoformate (5.0 mL) was added neat aldehyde (1.0 mmol) via syringe. The resulting solution was shaken for 1.5 hrs, then evaporated to dryness with a stream of nitrogen. Each sample was dissolved in 1,2-dichloroethane (5 mL), a one mL aliquot (0.1 mmol of imine to be used in the next reaction) was removed, and each sample was evaporated again and used without further purification. To the 2-dram vials of imine (0.1 mmol from previous reaction) was added a solution of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene, **5**, 1.2 mL, 1.0 M in anhydrous acetonitrile, 0.12 mmol) followed by a solution of $Yb(OTf)_3$ (1.0 mL, 0.01 M in anhydrous acetonitrile, 0.01 mmol) via electronic manual pipetter. The resulting solution was shaken for 1 h, and then polymer-supported tris(2-aminoethyl)amine (**1**, 100 mg, 3.4 mmol/g) and anhydrous dichloromethane (1.0 mL) were added. After shaking for 4 h, the slurry was filtered through a plug of glass wool and washed with dichloromethane (2 X 1.0 mL). The combined organic phases were evaporated to dryness with a stream of nitrogen. The residue was dissolved in ethyl acetate (2.0 mL), and washed with 1.0 N HCl (aq., 2.0 mL). Brine (2.0 mL) was added and the organic layer was transferred to a new tared vial. The aqueous phase was back extracted with ethyl acetate (2 X 1.0 mL). The combined organic phases, when evaporated to dryness with a stream of nitrogen, gave the title compounds typically as vicious oils: for HPLC and mass spec. data see Table 1.

**Preparation of 1-benzyl-2,3-dihydro-2-phenyl-4-pyridone (9).**[21]

To a stirred solution of benzyl amine (2.0 mL, 18 mmol) in anhydrous trimethyl orthoformate (50 mL) was added neat benzaldehyde (1.9 mL, 18 mmol) via syringe. The resulting solution was stirred for 3 h, then concentrated. The resulting oil was concentrated from 1,2-dichloroethane (2 X 50 mL), and stored under vacuum overnight to yield 3.6 g (quantitative) of benzylidenebenzylamine[21] as a clear oil which was used without further purification. Solid $Yb(OTf)_3$ (1.1 g, 1.8 mmol) was added in one portion to a stirred solution of benzylidenebenzylamine (3.6 g, 18 mmol) in anhydrous acetonitrile (100 mL) followed by 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (4.3 mL, 22 mmol). The resulting orange solution was stirred for 1 h, then concentrated. The resulting oil was partitioned between EtOAc (300 mL) and 1.0 M HCl (100 mL). The organic layer was washed with brine (2 X 100 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (50% EtOAc/hexanes) gave 3.9 g (81%) of the title compound as a light orange viscous oil: $^1$H NMR ($CDCl_3$) δ 7.40-7.22 (m, 9H), 7.13 (m, 2H), 5.08 (d, J = 8 Hz, 1H), 4.50 (t, J = 8 Hz, 1H), 4.34 (d, J = 15 Hz, 1H), 4.12 (d, J = 15 Hz, 1H), 2.85 (dd, J = 17, 8 Hz, 1H), 2.68 (dd, J = 17, 8 Hz, 1H).

**Preparation of 1-benzyl-2-phenyl-4-piperidone (10).**[21,22]

A solution of L-Selectride™ (15.1 mL, 1.0 M in THF, 15 mmol) was added dropwise to a cooled (-78° C) solution of **9** (3.6 g, 14 mmol) in dry THF (80 mL). The resulting solution was stirred at -78° C for 30 min, the dry ice bath was removed, and the solution was stirred an additional 30 min. Saturated sodium bicarbonate (50 mL) was added, the resulting slurry was stirred for 30 min, then the organic layer was concentrated. EtOAc (300 mL)was added, and the aqueous layer was drained. The organic layer was washed with brine (2 X 100 mL), dried over $MgSO_4$, and concentrated to a dark oil. Flash chromatography (20% EtOAc/hexanes) gave 1.8 g (48 %) of the title compound as a clear oil: $^1$H NMR ($CDCl_3$) δ 7.48-7.20 (m, 10H), 3.83 (d, J = 14 Hz, 1H), 3.58 (dd, J = 11, 4 Hz, 1H), 3.21 (m, 1H), 2.94 (d, J = 14 Hz, 1H), 2.67 (m, 2H), 2.54 (m, 1H), 2.33 (m, 2H).

**General procedure for the preparation of aminopiperidines 11 and 14.**

To a 2-dram screw cap glass vial was added 1.0 mL of piperidone solution (0.33 M in anhydrous methanol, 0.33 mmol) and 0.5 mL of primary amine solution (1.0 M in anhydrous methanol, 0.5 mmol). The vial was capped and the resulting solution was shaken for 4 h. Approximately 250 mg (2.5 mmol $BH_4^-$ / g resin, 0.63 mmol) of Amberlite™ IRA-400 borohydride resin (Aldrich Chemicals) was added, and the resulting slurry was shaken for 24 h. Approximately 120 mg (3.0 mmol / g resin, 0.36 mmol) of polystyrene-linked 4-hydroxybenzaldehyde resin and 1.5 mL of dichloromethane was added, and the resulting slurry was shaken overnight. The slurry was filtered through a glass wool plug, washed with dichloromethane (2 X 1.0 mL), and then the solvent was evaporated with a stream of nitrogen. The residue was dissolved in dichloromethane and evaporated again. After drying overnight in a vacuum oven at room temperature, the title compounds were obtained.

**General procedure for the preparation of acyl-aminopiperidines 12.**

To 80 wells of a Polyfiltronics 96-well PKP™ filter plate (2 mL/well capacity) was added approximately 40 mg (3.4 mmol/g, 0.14 mmol) of polymer-supported morpholine resin **3**.[23] Using a liquid handling robot, 0.5 mL of each of the 10 aminopiperidine solutions (0.082 M in 1,2-dichloroethane, 0.041 mmol/well) was added in turn to the 8 individual wells in rows 1-10. Then 0.2 mL of each of the 8 acid chloride solutions (0.23 M in 1,2-dichloroethane, 0.045 mmol/well) was added in turn to the 10 individual wells in columns 1-8 of the plate. The plate was capped with a cap-mat, secured to an orbital shaker and shaken overnight. To the resulting slurries was added polymer-supported tris(2-aminoethyl)amine (**1**, 40 mg, 3.4 mmol/g, 0.14 mmol) and polymer-supported isocyanate (**8**, 20 mg, 1.1 mmol/g, 0.02mmol) followed by an additional 0.4 mL of 1,2-dichloroethane. The resulting plate was shaken for an additional 24 h, then the slurries were filtered into a 96-well collection plate (2 mL / well), and washed with methanol (2 X 0.2 mL). Using a liquid handling robot, the solutions were transferred into tared vials, and evaporated with a stream of nitrogen to yield the title compounds: for HPLC and mass spec. data see Table 2.

**General procedure for the preparation of piperidones 13.**

In septa-capped 2-dram vials evacuated and filled with argon, a solution of L-Selectride™ (1.1 Eq., 1.0 M in THF) was added in one portion to a cooled (-78° C) solution of 2,3-dihydro-4-pyridone **6** (0.1-0.2 mmol) in dry THF (3 mL). The resulting solution was stirred at -78° C for 30 min, the dry ice bath was removed, and the solution was stirred an additional 30 min. Nine percent $H_2O_2$ (2 mL) was added, and the resulting solution was stirred for 2 h, then partially evaporated with a stream of nitrogen. The resulting solution was extracted with $CHCl_3$ (4 mL). The organic layer was washed with water (3 X 2 mL), then transferred to clean tared vials. Evaporation yielded the title compounds.

**General procedure for the preparation of acyl-aminopiperidines 15.** Using capped 2-dram vials instead of 96-well PKP™ filter plates, the acylation procedure used to prepare acyl-aminopiperidenes **12** gave the title compounds. For LC / MS data see Table 3.

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23. For this small scale array a large excess of polymer-suported amine and morpholine resins were used out of convenience of measuring the resin, but it is not normally necessary to use a large excess.