Versatile Acylation of *N*-Nucleophiles Using a New Polymer-Supported 1-Hydroxybenzotriazole Derivative

Iuliana E. Pop,[†] Benoît P. Déprez,[†] and André L. Tartar*[,‡]

CEREP, 1 rue du Pr. Calmette, 59 019 Lille Cédex, France and Chimie des Biomolécules, URA CNRS 1309, Institut Pasteur de Lille, Faculté de Pharmacie,1 rue du Pr. Calmette, 59 019 Lille Cédex, France

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The synthesis of a new polymer-supported coupling reagent derived from 1-hydroxybenzotriazole is described. An aminomethylated polystyrene was functionalized by reaction with 3-nitro-4-chlorobenzenesulfonyl chloride (**2**) followed by treatement with hydrazine hydrate, to give the polymeric *N*-benzyl-1-hydroxybenzotriazole-6-sulfonamide (**4**).The polymeric reagent **4** was shown to be highly efficient for the synthesis of amides. The efficiency of **4** could be attributed to its high acidity, conferred by the sulfonyl moiety. The procedure for amide synthesis involves the formation of an activated ester on the derivatized polymer followed, in a second step, by treatment with an amine to generate the amide in solution. Simple filtration allows the separation of the product from the polymeric reagent which in this case plays the role of leaving group. An optimization study of this two-step procedure was performed. As amides are obtained in solution free of reaction byproducts, this method can be used in an automated procedure to recover them directly into a 96 well plate, ready to be used in high throughput screening assays. Thus **4** was shown to be particularly suitable for the high throughput parallel synthesis of amides libraries.

Introduction

Recent advances in molecular biology and automation have led to a dramatic increase in the throughput of the biological screening. Consequently, the rapid generation of large arrays of chemically diverse compounds has become a major tool in the search for novel lead structures. Large numbers of oligomeric compounds have been synthesized rapidly by repetitive coupling reactions, using both solid phase techniques and automated synthesizers which were developed for peptide and oligonucleotide synthesis during the past three decades. The limited number of building blocks from which they stem limits their chemical diversity. In this context, the synthesis of diverse small organic molecules has received much attention during the recent years.

One of the major difficulties encountered during the synthesis of large chemical libraries is conciliating the need for highly diverse arrays of compounds with their heterogeneous behavior either from physical or from chemical points of view. Organic synthesis by solid phase methods is therefore emerging as a powerful tool for clean generation of structurally diverse small organic molecules. Tethering starting materials or reagents to an insoluble polymer allows great simplifications in all handling steps, rendering the automation process readily feasible. Heterocycles as benzodiazepines, diketopiperazines, and hydantoins were synthesized on insoluble polymers.[1−3] A wide range of organic reactions such as Mitsunobu,[4] Still,[5,6] Heck,[7,8] Horner−Emmons[9] have already been performed on solid phase. However, insoluble polymers can also be used not only as supports for the growing molecule but also as tethers for reagents or catalysts. In this case, unlike classical solid phase syntheses, the reagents remain attached to the insoluble matrix, while the desired product generated in solution is easily recovered by filtration. Reagents such as nitrophenol,[10−13] HOBt (1-hydroxybenzotriazole),[14−16] carbodiimides,[17,18] DMAP (4-(dimethylamino)pyridine)[19] or triphenylphosphine,[20−22] which have been synthesized on polymeric beads, should meet a renewed interest for the synthesis of small organic molecules, especially for two- or three-step routes.

Taking into account that commercially available amines and carboxylic acids give access to a wide structural diversity space, our aim was to design a reaction scheme

[†] CEREP.
[‡] Institut Pasteur de Lille.
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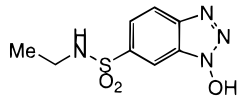
for the synthesis of large arrays of amides, easily implementable in a robotic system. The need for a clean activation procedure led us first to focus on the use of the previously described polymeric carbodiimide.[18] No additional soluble reagent is needed when activating acids with this polymeric carbodiimide. Nevertheless, we encountered two major difficulties associated with this functionalized polymer. The described synthesis of this polymeric reagent lacks reproducibility and is not easily monitored, neither is the final reagent easily characterized.[23] Considering these difficulties, we decided to develop a procedure involving a soluble activating reagent and a polymeric nucleophile, likely to form reactive isolable esters with most of the carboxylic acids. Polymeric nitrophenol and 1-hydroxybenzotriazole (HOBt) were already used in peptide synthesis; however, the most successful for the amide bond creation was a HOBt-containing polymer.[10−16] HOBt is well known for its efficiency in coupling amino acids, improving reactions kinetics, and decreasing racemization. On these bases, our interest has been devoted to the synthesis of an improved polymer-supported HOBt.

The previously described[14] functionalization of polystyrene beads via a Friedel−Crafts alkylation is rather delicate and moreover, is limited to aryl-containing polymers. Our aim was to design a more versatile anchoring scheme of the HOBt moiety, suitable for any kind of amino-functionalized polymer such as polyethylene oxide-grafted polystyrene, polymethacrylate, functionalized polyethylene, or polypropylene. In this paper we describe the synthesis and evaluation of a new polymer-supported HOBt derivative, and we explore the reactivity of this polymeric coupling reagent toward a variety of carboxylic acids and *N*-nucleophiles.

Results and Discussion

Highly efficient HOBt-derived soluble coupling reagents have recently been reported.[24−27] The increased effectiveness of these novel coupling reagents was obtained by incorporating electron-withdrawing substituents on the benzotriazole ring (although, in the case of the 1-hydroxy-7-azabenzotriazole (HOAt) an intramolecular base catalysis was also suspected). In this context, incorporating an electron-withdrawing substituent in the polymer-supported benzotriazole ring was expected to enhance its reactivity. Syntheses of several HOBt derivatives were already described.[28] Among them, *N*-ethyl-1-hydroxybenzotriazole-6-sulfonamide (**1**) was selected for the derivatization of an aminofunctionalized polymer. Indeed, a polymer-supported derivative



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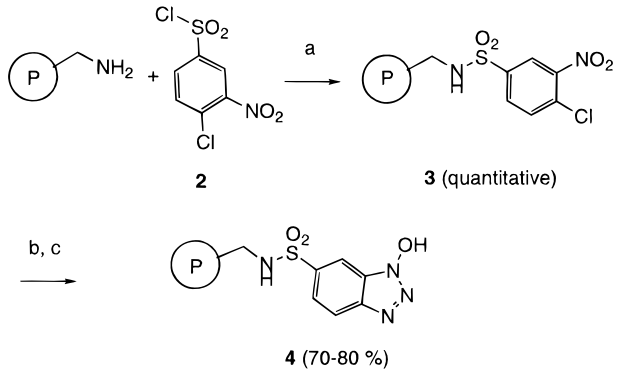
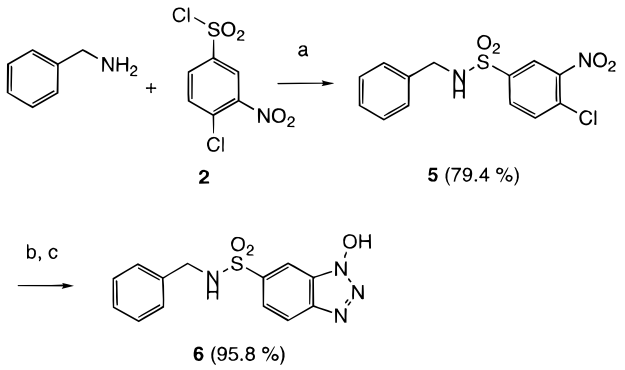
of **1** is not only easy to obtain from commercially available materials, but also allows the introduction of the required electron-withdrawing group. An aminomethylated divinylbenzene cross-linked polystyrene charged with 1.6 mmol of amino-groups/g was reacted with the sulfonyl chloride **2** at room temperature in the presence of Et_3N to give the sulfonamide-derivatized polymer **3** (Scheme 1). The reaction went to completion within 5 h, as determined by a quantitative ninhydrin test.[29] Reacting **3** with hydrazine hydrate under reflux of ethanol and subsequent treatment with a dioxane solution of hydrochloric acid afforded the polymer-bound 1-hydroxybenzotriazole-6-sulfonamide (**4**) under neutral form. The loading of **4** was determined by acetylation of the hydroxyl groups on the polymer followed by aminolysis of the polymer-bound activated ester with benzylamine and subsequent quantification of the unreacted amine in the reaction mixture. A substitution level of 0.8−1 mmol of hydroxyl-groups/g of polymer was found.

Scheme 1[a]



[a] (a) Et_3N, CH_2Cl_2, rt, 5 h; (b) NH_2NH_2, EtOH, reflux, 5 h; (c) HCl, dioxane.

Scheme 2[a]



[a] (a) Et_3N, CH_2Cl_2, rt, 2.5 h; (b) NH_2NH_2, EtOH, reflux, 5 h; (c) aqueous HCl, pH 0.9.

In order to evaluate its properties, the soluble *N*-benzyl-1-hydroxybenzotriazole-6-sulfonamide (**6**) was also synthesized (Scheme 2). pK_a and ^1H NMR studies were performed to compare the acidities of the following compounds: **6**, HOBt (**7**), HOSu (1-hydroxysuccinimide) (**8**), and 2-nitrophenol (**9**). The pK_a values found for **7**−**9** were in good agreement with the literature.[30] Both the pK_a and chemical shifts of the hydroxyl proton indicated a higher acidity of **6** (Table 1). This is explained by the strong electron-withdrawing effect induced by the sulfonyl moiety. The acidity of **6** ($pK_a = 3.59$) is close to that

(23) The synthesis and use of a polymer-bound carbodiimide cationic derivative, which seems to overcome these difficulties, was meanwhile reported.[18]

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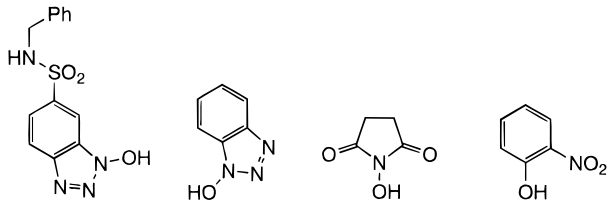
Table 1. pK_a Values and Chemical Shift of the Acid Proton for 6−9



6 **7** **8** **9**

compd	pKa	chemical shift (ppm)[a]
6	3.59	14.0
7	4.64	13.6
8	6.00	11.0
9	7.15	10.6

[a] ^{1}H NMR spectra were performed in C_6D_6.

of HOAt (pK_a = 3.47), which is known to be a highly efficient coupling reagent in the peptide synthesis. According to the general assumption that the electrophilicity of an active ester is related to the acidity of the parent alcohol,[30] these findings should indicate a great effectiveness of **4** in promoting amide bond formation.

General Optimization of Amides Synthesis Using the Polymeric Reagent 4. Our aim was to adapt the use of **4** to the coupling of the largest array of carboxylic acids and *N*-nucleophiles, in the view of its further use in parallel combinatorial synthesis. Synthesis of amides using **4** requires a two-step procedure: first, the esterification of the polymer-bound HOBt with the carboxylic acid by the mean of a soluble activating reagent. After removal of the reagent in excess, the next step involves the reaction of the *N*-nucleophile and subsequent release of the acylated product in a soluble form (Scheme 3). Systematic optimization of both steps was performed. DMF was found to be the solvent of choice for the synthesis, according to the solubility studies performed on a representative cross section of a large set of compounds (about 700 carboxylic acids and 700 amines): 86% of the amines were soluble at 0.1 M concentration in DMF while only 55% were soluble at the same concentration in CH_2Cl_2, and 84% of the carboxylic acids were soluble at 0.75 M concentration in DMF. Moreover, DMF is easily handled in an automated process, due to its high boiling point and viscosity.

A. Activation Step. The soluble activating reagent, activating time, and excess of reagents were studied to define a general procedure to activate carboxylic acids *via* the polymer-bound reagent **4**.

1. Choice of the Soluble Activating Reagent. The use of activating reagents, such as HBTU (2-(1*H*-benzotriazole-1-yl)tetramethyluronium hexafluorophosphate) or BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate), that generate nucleophilic species likely to compete with the nucleophilic polymer was avoided. Preliminary studies were performed using DCC (*N*,*N*′-dicyclohexylcarbodiimide), DIC (*N*,*N*′-diisopropylcarbodiimide), and PyBrOP (bromotrispyrrolidinophosphonium hexafluorophosphate). Difficulties were encountered when using DCC because of the poorly soluble dicyclohexylurea generated during the activation. Thus, the separation of the polymer from the reagents in excess and byproducts becomes difficult and requires large volumes of solvents. This problem could be only partially overcome using DIC (data not shown). On the contrary, PyBrOP is highly soluble, as well as the byproducts generated during the activation. PyBrOP was shown to be highly effective for difficult couplings in the field of peptide synthesis.[31,32] It was thus selected and submitted to further experimentation to determine the most suitable activating conditions.

2. Optimization of the Activation Step Using PyBrOP as Soluble Activating Reagent. To this aim, three acids were used: 5-methyl-2-nitrobenzoic acid (**a**), 2-(*p*-toluoyl)benzoic acid (**b**), and diphenylacetic acid (**c**). The efficiency of the activation was determined in each case by the amount of amide formed upon reaction of the resulting polymer-bound species with benzylamine. Single and double activation procedures were tested, as well as different amounts of acid with respect to the polymer-bound reagent **4** (Table 2). The best results were obtained when using a double activation procedure (entries 3, 5, and 8 in Table 2). Attempts to improve the activation by increasing the activation time were unsatisfactory (entries 1, 3, and 5 in Table 3). The reaction time was optimized to allow the reaction of less reactive species and to minimize the decomposition of the polymer-bound esters.[33] The conditions for an effective activation when using PyBrOP as soluble activating reagent were found to be: 2 × 3 h activating time using 3 equiv of acid for each activation step.

B. Coupling Step. Optimization of the Coupling Time. The reaction time of the polymer-bound esters with *N*-nucleophiles was then investigated. In initial experiments, reactions of benzylamine and 2-aminobenzothiazole with the polymer-bound active ester of 5-methyl-2-nitrobenzoic acid (**10a**) were used to determine the optimum coupling time. While benzylamine was quantitatively acylated within 1 h, used under the same conditions, 2-aminobenzothiazole reacted more slowly, a maximal conversion of 68% being obtained after 25 h. In the meantime, 20% of the activated ester was decomposed, as indicated by the presence of free carboxylic derivative in the solution (Table 4). The optimum coupling time was found to be 20 h. Further increase of the coupling time was not likely to improve coupling yields, as we have previously shown[33] that in the absence of nucleophile, 62% of the polymer-bound ester is hydrolyzed in DMF solution during that period of time.

C. Scope of the Method. Commercially available carboxylic acids and *N*-nucleophiles (about 700 different structures in each group) were divided into several classes, according to criteria based on structural and reactivity parameters. Representative structures were chosen for each class and were tested under the conditions previously defined, to establish the range of applicability of this method to the synthesis of amides.

1. Reactivity of Carboxylic Acids toward the Polymer-Bound Reagent 4. The following compounds were chosen to investigate the reactivity of the different

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(32) Coste, J.; Frérot, E.; Jouin, P. *Tetrahedron Lett.* **1991**, *32*, 1967.

(33) Stability studies of the polymer-bound activated ester **10a** showed that, in suspension in neat DMF and in the presence of *N*-ethyldiisopropylamine, 62% of **10a** is decomposed during 25 h to give the starting polymer **4** and the free carboxylic acid in solution. Stored under appropriate conditions, the activated esters of **4** were quite stable. After storage in dry form for two months at +4 °C and under nitrogen, **10a** still gave quantitative yield when reacted with phenethylamine.

Scheme 3

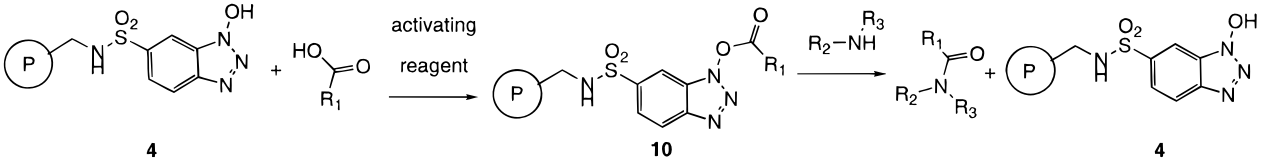
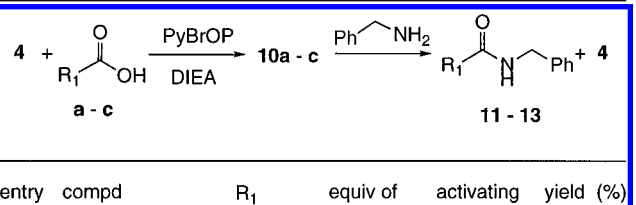
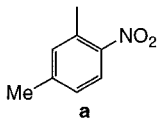
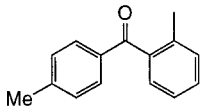
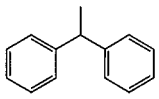


Table 2. Influence of the Quantity of Acid on the Activation Step[a]



entry	compd	R_1	equiv of acid	activating time (h)	yield (%)
1			2	3	40
2	**11**		2+2	3+3	47
3		**a**	3+3	3+3	84
4	**12**		3+1	3+3	80
5		**b**	3+3	3+3	87
6			2	3	18
7	**13**		2+2	3+3	27
8		**c**	3+3	3+3	50

[a] For each activation step, 0.27 M DMF solutions of acids and an equimolar quantity of PyBrOP with respect to the acid were used. For the coupling step, 0.16 M DMF solutions of benzylamine were used, in equimolar quantity with respect to the polymer-bound ester.

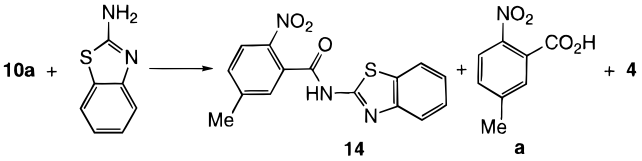
Table 3. Influence of the Reaction Time on the Activation Step[a]

entry	compd	equiv of acid	activating time (h)	yield (%)
1	**11**	3 + 3	5 + 15	33
2	**11**	3 + 3	3 + 3	84
3	**12**	3 + 3	5 + 15	73
4	**12**	3 + 3	3 + 3	87
5	**13**	3 + 3	5 + 15	13
6	**13**	3 + 3	3 + 3	50

[a] For each activation step, 0.27 M DMF solutions of acids and an equimolar quantity of PyBrOP with respect to the acid were used. For the coupling step, 0.16 M DMF solutions of benzylamine were used, in equimolar quantity with respect to the polymer-bound ester.

classes of carboxylic acids toward the reagent **4**: the benzoic-type acids **a**, **b**, and **d**, possessing different substituents on the aromatic ring; acids **e** and **f**, for which the carboxyl moiety is linked to a hindered aliphatic carbon; acid **g**, possessing a nucleophilic group, and acids **c** and **h**, containing an acidic α proton (Table 5). Their reactivity was estimated by quantifying the amount of amide formed upon reaction of the corresponding polymer-bound esters with benzylamine. Very good yields in

Table 4. Conversion and Decomposition of the Polymer-Bound Ester 10a during Coupling With 2-Aminobenzothiazole[a]



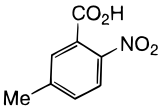
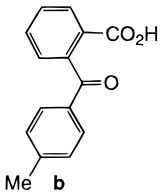
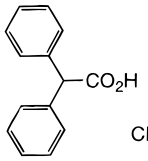
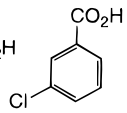
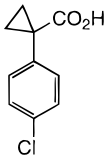
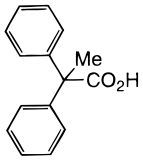
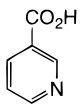
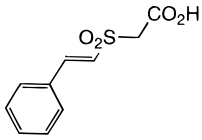
time (min)	5	10	20	30	60	90	1500	2940
compd **14** (%)[b]	7.6	16.7	25.2	32.5	44.9	45.9	68.3	68.0
acid (%)[c]	1.3	1.6	2.0	2.6	4.0	4.8	17.7	19.5

[a] **10a** was obtained under the optimized activating conditions previously defined. For the coupling step, 0.16 M DMF solution of 2-aminobenzothiazole, in equimolar quantity with respect to **10a** was used. [b] Yield was determined by HPLC using calibration curves. [c] Free acid found in the solution due to the decomposition of **10a**, determined by HPLC using calibration curves.

isolated amide were obtained when reacting benzoic type acids **a**, **b**, and **d**, as well as sterically hindered acids **e** and **f** (entries 1, 2, and 4−6 in Table 5). Moderate yields were obtained when activating acids **c** and **g**, while no reaction took place for acid **h** (entries 3, 7, and 8 in Table 5). For the polymer-bound esters of acids **c** and **h**, under the basic conditions of the activation, the acidity of the α proton is likely to be responsible for the formation of a ketene, in which the polymer plays the role of leaving group. For the nicotinic acid **g**, the nucleophilic pyridine ring is likely to be acylated, leading to the cleavage of the activated ester bond. In this latter case, the activation could be improved to 55% by reducing the activation time at 1 h (when activating 2 × 3 h, only 37% yield in isolated amide was obtained). It is noteworthy that carboxylic acids showing particular reactivities as **c**, **g**, and **h**, which should be eliminated when synthesizing a library of amides by this method, represent about 25% of the commercially available carboxylic acids. Nevertheless, the large number of the commercially available carboxylic acids tolerated by this chemistry would allow the synthesis of a very large numbered library of amides.

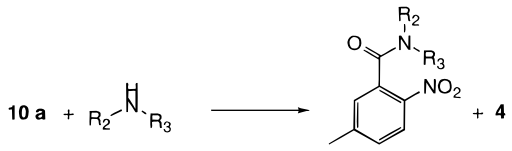
2. Reactivity of *N*-Nucleophiles toward the Polymer-Bound Activated Esters 10. In the next step, compounds belonging to different classes of *N*-nucleophiles were tested to determine their reactivity toward the polymer-bound esters. *N*-nucleophiles were reacted with the polymer-bound ester **10a**. Reactions were followed by HPLC, and conversions were determined using calibration curves (Table 6). Good conversions and excellent purities were obtained when coupling phenethylamine, *N*,*O*-dimethylhydroxylamine, 2-amino-5-methyl-1,3,4-thiadiazole, ethyl 4-aminobenzoate, benzophenonehydrazone, and 5-nitroindazole (entries 1−6 in Table 6). Only traces of free acid generated by decomposition of the polymer-bound ester or nonreacted nucleophile were in some cases detected in the reaction mixture. Interestingly, coupling of 5-nitroindazole (entry 6 in Table 6) required the presence of a base, due to the fact that in this particular case the reactive species is

Table 5. Synthesis of Amides Using Carboxylic Acids a−h and Benzylamine[a]

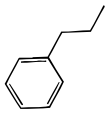
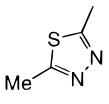
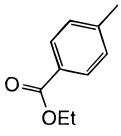
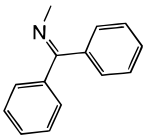
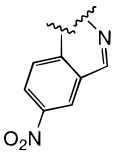
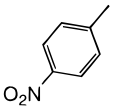
entry	1	2	3	4	5	6	7	8
acid	 **a**	 **b**	 **c**	 **d**	 **e**	 **f**	 **g**	 **h**
compd	**11**	**12**	**13**	**15**	**16**	**17**	**18**	-
yield (%)	84	87	50	85	81	86	55[b]	na[c]

[a] Syntheses were performed under the previously defined conditions (unless otherwise noted). [b] Activation was performed under the following conditions: 1 × 1 hours using 3 × 3 equiv of acid. [c] No activation took place.

Table 6. Reaction of Polymer-Bound Ester 10a with Different *N*-Nucleophiles



19 - 25

entry	1	2	3	4	5	6	7	8	9
R_2	H	CH_3	H	H	H	H	H	H	H
R_3									
compd	**19**	**20**	**21**	**22**	**23**	**24**	**25**	-	-
conversion (%)[b]	82	85	91	44	69	80[c]	17	nr[d]	nr

[a] Reactions were performed under the previously defined conditions. 0.4 M solutions of acids and 0.1 M solutions of amines in DMF were used. [b] Conversions were determined by HPLC using calibration curves. [c] No reaction occured when coupling was performed in the absence of base. 80 % conversion was obtained when 1 equiv of DIEA was added to the reaction mixture during coupling. [d] No reaction.

the anion formed by deprotonation. 2-Aminopyridine showed only a poor reactivity (entry 7 in Table 6), while 4-nitroaniline and 2-aminopyrimidine did not react with **10a** (entries 8 and 9 in Table 6). Thus highly deactivated anilines, 2-aminopyrimidines, or 2-aminopyridines should be eliminated as being too poor nucleophiles to generate amides by this method. Results in Table 6 show that a large variety of *N*-nucleophiles: primary and secondary amines, moderately deactivated anilines, as well as other nucleophiles such as hydrazones can be succesfully used for the synthesis of amides, good to excellent purities of the crude products being obtained.

A small library of amides was synthesized under the optimized conditions (Table 7). In most cases good yields in isolated products were obtained. An excellent selectivity for the amide formation was found when coupling an amino alcohol (entries 6 and 10 in Table 7). No traces of ester or polymeric species were found in these cases in the reaction mixture, the amide being the sole product. Satisfactory yields were also obtained when coupling some less usual *N*-nucleophiles (entries 1−4 and 9 in Table 7), which introduce a larger diversity into the amide library.

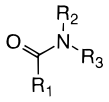
Conclusion

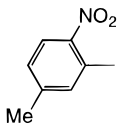
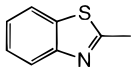
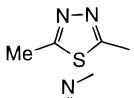
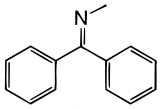
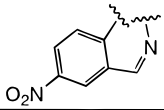
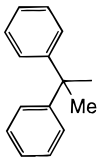
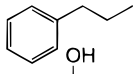
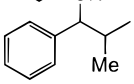
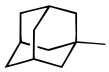
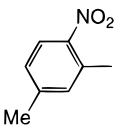
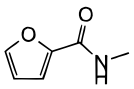
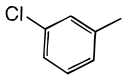
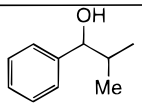
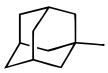
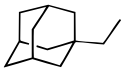
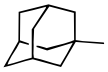
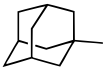
A novel HOBt derivative-tethered polymer has been synthesized. This polymer was designed for the rapid and clean synthesis of large combinatorial arrays of amides and related compounds. Optimization studies of this two-step synthesis, carried out on a wide variety of carboxylic acids and *N*-nucleophiles, allowed the choice of standard reaction conditions. Amides generated in solution showed in most cases good to excellent purities. This should allow their direct use in the biological screenings, without purification. The chemistry described in this work should be of broad utility in the multiple simultaneous synthesis of amide libraries in a soluble form.

Experimental Section

General Methods. All commercial reagents and solvents were used without further purification. The aminomethylated divinylbenzene cross-linked polystyrene used to synthesize **4** was obtained as described,[18] starting from a Merrifield resin (1.7 mmol/g) purchased from Fluka. The PyBrOP was purchased from Nova Biochem. Melting points are uncorrected.

Table 7. Synthesis of Amides Using Various Carboxylic Acids and *N*-Nucleophiles



entry	amide	R_1	R_2	R_3	yield (%)
1	**14**		H		55
2	**21**		H		70
3	**23**		H		70
4	**24**				77
5	**26**		H		82
6	**27**		H		74
7	**28**		H		64
8	**29**		H		50
9	**30**		H		50
10	**31**		H		79
11	**32**		H		79
12	**33**				72
13	**34**		H		70
14	**35**		H		51
15	**36**		Et		85
16	**37**		H		65
17	**38**		H		65

HPLC analyses were performed using a 250 × 4 mm^2 reversed-phase Vydac C18 5 μm column. A gradient starting from 100% H_2O/0.05% TFA and going to 100% H_2O/80% CH_3CN/0.0425% TFA within 30 min at 1 mL/min flow rate was used. Elemental analyses were determined by Service Central d'Analyse, Vernaison, France.

Polymer-Bound 1-Hydroxybenzotriazole-6-sulfonamide (4). 4-Chloro-3-nitrobenzenesulfonyl chloride (**2**) (59.0 g, 230.7 mmol) in CH_2Cl_2 (800 mL) was added to an aminomethylated divinylbenzene cross-linked polystyrene (47.2 g, 76.9 mmol) preswollen with CH_2Cl_2 (300 mL). Et_3N was added (32 mL, 230.7 mmol), and the reaction mixture was gently stirred at room temperature. After 5 h the resin was filtered, washed with CH_2Cl_2 (1500 mL), DMF (1000 mL), DMF/water (1/1, V/V, 1000 mL), water (1500 mL), 95% EtOH (1000 mL), and diethyl ether (1000 mL) and dried at room temperature to give the polymer **3**, for which a coupling level of 99% of the amino groups was determined using a quantitative ninhydrin procedure.[29] Polymer **3** (67.2 g) was then treated with hydrazine hydrate (134 mL) in 95% EtOH (200 mL). The reaction mixture was gently stirred under reflux. After 5 h, the resin was washed with EtOH (1500 mL), water (1500 mL), DMF/water (1/1, V/V, 500 mL), DMF (500 mL), CH_2Cl_2 (500 mL), 1% HCl in dioxane (1000 mL), dioxane (500 mL), and diethyl ether (500 mL) and was dried at room temperature to give 59.6 g (95.6% yield with respect to the starting aminomethylated resin) of polymer **4**.

Substitution Level of Polymer 4. Samples of polymer **4** were introduced into six tubes (30 mg, 37.0 μmol theoretical, in each tube) and suspended into 0.2 mL of 2 M acetic anhydride in CH_2Cl_2. After shaking for 2.5 h at room temperature, the six samples were washed with DMF (20 mL) and diethyl ether (8 mL) and dried under vacuum at room temperature. The acetylated resins were reacted with different amounts of 0.195 M benzylamine in DMF (19.5 μmol, 29.25 μmol, 33.15 μmol, 35.1 μmol, 46.8 μmol, and 58.5 μmol). After shaking at room temperature for 4 h, the polymeric beads were filtered, and the solutions were diluted with DMF. The amount of unreacted amine was determined for each reaction mixture using a quantitative ninhydrin test.

***N*-Benzyl-4-chloro-3-nitrobenzenesulfonamide (5).** A mixture of benzylamine (5.45 mL, 50 mmol) and Et_3N (6.95 mL, 50 mmol) in CH_2Cl_2 (300 mL) was added dropwise to a solution of 4-chloro-3-nitrobenzenesulfonyl chloride (12.8 g, 50 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 2.5 h. The solvent was removed by rotary evaporation, leaving a yellow powder which was taken up in EtOAc (300 mL), washed with water (3 × 200 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give 12.95 g (79.4%) of crude *N*-benzyl-4-chloro-3-nitrobenzenesulfonamide (**5**): mp 90 °C; C18 RP HPLC (215/254 nm) t_R = 29.7 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61−8.67 (t, J = 6.26 Hz, NH, 1H), 8.30 (d, J = 2.0 Hz, ArH, 1 H), 8.01−7.97 (dd, J = 2.0, 8.46 Hz, ArH, 1 H), 7.95−7.92 (d, J = 8.45 Hz, ArH, 1 H), 7.27−7.19 (m, ArH, 5 H), 4.12 (d, J = 6.24 Hz, CH_2, 2 H); ^{13}C NMR δ 147.9, 141.9, 137.70, 133.8, 132.2, 129.9, 129.07, 128.7, 128.1, 124.9, 47.1.

***N*-Benzyl-1-hydroxybenzotriazole-6-sulfonamide (6).** To a solution of **5** (12 g, 36.7 mmol) in 95% EtOH (400 mL) was added hydrazine hydrate (80 mL), and the mixture was stirred under reflux. After 5 h, the solvent was removed by rotary evaporation to give a dark yellow oil which was taken up in water (500 mL) and acidified with aqueous HCl (pH 0.9). The crude product precipitated and was separated by filtration and dried under vacuum to give 10.7 g (95.8%) of crude **6**. Upon crystallization from EtOH (113 mL)/water (100 mL), the

product was obtained as pale yellow crystals (9.2 g, 86.8% yield): mp 200−205 °C; C18 RP HPLC (215/254 nm) t_R = 22.3 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.12 (s, OH, 1 H), 8.42 (t, J = 6.3 Hz, NH, 1 H), 8.20−8.17 (dd, J = 8.8, 0.5 Hz, ArH, 1 H), 8.09 (m, ArH, 1 H), 7.78−7.75 (dd, J = 1.6, 8.8 Hz, ArH, 1 H), 7.25−7.14 (m, ArH, 5 H), 4.06 (d, J = 6.3 Hz, CH_2, 2 H); ^{13}C NMR δ 144.6, 140.54, 138.1, 129.0, 128.5, 127.9, 127.80, 122.9, 121.5, 110.5, 47.1; TOF-MS m/z 304.5 (M^+). Anal. Calcd for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.95; N, 18.42; O, 15.79; S, 10.53. Found: C, 50.87; H, 3.91; N, 18.10; O, 15.59; S, 10.71.

pK_a Measurements for Compounds 6, 7, 8, and 9. 2 mM hydroalcoholic solutions (9% MeOH in water) of **6**−**9** were prepared. These solutions (15 mL) were titrated with aqueous NaOH (2 mM), and the pH was followed using a 3 M KCl/AgCl electrode. pK_a values were determined from the titration plots.

General Procedure for the Preparation of Polymer-Bound Activated Esters 10. One equivalent of PyBrOP and two equivalents of diisopropylethylamine with respect to the acid were used. The acid was taken up in a DMF solution of PyBrOP, and diisopropylethylamine was added next. The resin **4**, preswollen with DMF, was reacted with this mixture at room temperature for 3 h (unless otherwise noted). After the first activation step the resin was washed with DMF (three times). The second activation step was performed under the same conditions as the first one (unless otherwise noted), and the resin was washed with DMF (five times).

General Procedure for the Preparation of Compounds 11−38. One equivalent of *N*-nucleophile with respect to the resin **4** was generally used. The amine was taken up in DMF, and diisopropylethylamine was added to this solution if necessary. The polymer-bound activated ester was reacted with this mixture at room temperature. After 20 h, the supernatant was separated from the resin by filtration. The polymeric beads were washed with DMF (three times), the washing solutions were recovered and combined with the supernatant previously recovered, and the solvent was removed under vacuum. The residue was taken up in *tert*-butyl alcohol, and the solution was frozen and lyophilized to give the crude products (unless otherwise noted).

***N*-Benzyl-5-methyl-2-nitrobenzamide (11).** By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.087 g, 0.48 mmol) and PyBrOP (0.224 g, 0.48 mmol) in the presence of diisopropylethylamine (0.223 mL, 0.96 mmol) in DMF (1.5 mL) with the resin **4** (0.2 g, 0.16 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (17 μL, 0.16 mmol) in DMF (1 mL) at room temperature. The product was recovered by the general procedure to give 36.3 mg (84%) of crude **11**: mp 156 °C; C18 RP HPLC (215/254 nm) t_R = 20.5 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.15 (t, J = 5.80 Hz, NH, 1 H), 7.96 (d, J = 8.24 Hz, ArH, 1 H), 7.50−7.46 (m, ArH, 2 H), 7.37 (m, ArH, 4 H), 7.29−7.25 (m, ArH, 1 H), 4.46 (d, J = 5.95 Hz, CH_2, 2 H), 2.44 (s, CH_3, 3 H); MS(CI) m/z 271 (MH^+), 165, 106, 91. Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.37. Found: C, 66.66; H, 5.00; N, 10.18.

***N*-Benzyl-2-(*p*-toluoyl)benzamide (12).** By the general procedure, the reaction of 2-(*p*-toluoyl)benzoic acid (**b**) (0.115 g, 0.48 mmol) and PyBrOP (0.224 g, 0.48 mmol) in the presence of diisopropylethylamine (0.223 mL, 0.96 mmol) in DMF (1.5 mL) with the resin **4** (0.2 g, 0.16 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (17 μL, 0.16 mmol) in DMF (1 mL). The product was recovered by the general procedure to give 46.1 mg (87%) of crude **12**: mp 152 °C; C18 RP HPLC (215/254 nm) t_R = 25.3 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.74−7.71 (m, ArH, 1 H), 7.56−7.49 (m, ArH, 2 H), 7.27−7.07 (m, ArH, NH, 11 H), 4.49 (d, J = 15.47 Hz, CH_2, 1 H), 4.18 (d, J = 15.47 Hz, CH_2, 1 H), 2.24 (s, CH_3, 3 H); MS(CI) m/z 330 (MH^+), 223, 106, 91.

***N*-Benzyldiphenylacetamide (13).** By the general procedure, the reaction of diphenylacetic acid (**c**) (0.101 g, 0.48 mmol) and PyBrOP (0.224 g, 0.48 mmol) in the presence of diisopropylethylamine (0.223 mL, 0.96 mmol) in DMF (1.5 mL) with the resin **4** (0.2 g, 0.16 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (17.5 μL, 0.16 mmol) in DMF (1 mL). The product was recovered by the general procedure to give 24.1 mg (50%) of crude **13**: mp 125 °C; C18 RP HPLC (215/254 nm) t_R = 30.5 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.78 (t, J = 5.80 Hz, NH, 1 H), 7.35−7.19 (m, ArH, 15 H), 5.02 (s, CH, 1 H), 4.31 (d, J = 5.81 Hz, CH_2, 2 H); MS(EI) m/z 301 ($M^{\bullet+}$), 167, 91.

Preparation of *N*-(2-Benzothiazolyl)-5-methyl-2-nitrobenzamide (14). By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.652 g, 3.6 mmol) and PyBrOP (1.678 g, 3.6 mmol) in the presence of diisopropylethylamine (1.255 mL, 7.2 mmol) in DMF (5 mL) with the resin **4** (1.5 g, 1.2 mmol) gave the polymer-bound activated ester which was reacted with 2-aminobenzothiazole (0.162 g, 1.08 mmol) and diisopropylethylamine (0.376 mL, 1.08 mmol) in DMF (5 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in EtOAc (250 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), the solvent was removed by rotary evaporation, and the residue was taken up in *tert*-butyl alcohol (10 mL), frozen, and lyophilized to give 0.183 g (54%) of crude **14**: mp 205−210 °C (dec); C18 RP HPLC (215/254 nm) t_R = 28.9 min; ^{1}H NMR (600 MHz, DMF-d_7) δ 8.36 (d, J = 8.45 Hz, ArH, 1 H), 8.27 (d, J = 7.60 Hz, ArH, 1 H), 7.98 (d, J = 8.03 Hz, ArH, 1 H), 7.96 (d, J = 1.04 Hz, ArH, 1 H), 7.88 (dd, J = 8.44, 1.06 Hz, ArH, 1 H), 7.68 (td, J = 7.66, 1.16 Hz, ArH, 1 H), 7.58 (td, J = 7.63, 1.02 Hz, ArH, 1 H), 2.74 (s, CH_3, 3 H); MS(EI) m/z 313 ($M^{\bullet+}$), 267, 164, 149.

***N*-Benzyl-3-chlorobenzamide (15).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.279 g, 1.78 mmol) and PyBrOP (0.831 g, 1.78 mmol) in the presence of diisopropylethylamine (0.622 mL, 3.56 mmol) in DMF (3.80 mL) with the resin **4** (0.7 g, 0.59 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (64.9 μL, 0.59 mmol) in DMF (5.95 mL). The supernatant was collected and combined with the DMF solutions coming from the washings of the resin. This solution was concentrated by rotary evaporation. The residual solution was purified by preparative RP HPLC (column Vydac C18, 5 μm, 500 × 20 mm^2), using as eluents water/0.050% TFA and aqueous acetonitrile (80%)/0.045% TFA (grad) at 4 mL/min flow rate and detecting at 254/280 nm. The pure fractions were combined, and the solvent was removed by rotary evaporation to give 0.124 g (85%) of **15**: mp 89 °C; C18 RP HPLC (215/254 nm) t_R = 27.7 min; ^{1}H NMR (300 MHz DMSO-d_6) δ 9.18 (t, J = 5.83 Hz, NH, 1 H), 7.95 (t, J = 1.97, ArH, 1 H), 7.87 (dt, J = 1.38, 7.67, ArH, 1 H), 7.62 (ddd, J = 2.12, 7.99 Hz, ArH, 1 H), 7.52 (t, J = 7.83 Hz, ArH, 1 H), 7.38−7.32 (m, ArH, 4 H), 7.28−7.22 (m, ArH, 1 H), 4.50 (d, J = 5.98 Hz, CH_2, 2 H); MS(EI) m/z 245−247 ($M^{\bullet+}$), 139−141, 111−113, 106, 91. Anal. Calcd for $C_{14}H_{12}NOCl$: C, 67.88; H, 4.85; N, 5.66. Found: C, 67.69; H, 4.87; N, 5.77.

***N*-Benzyl-3-(4-chlorophenyl)-1-cyclopropanecarboxamide (16).** By the general procedure, the reaction of 3-(4-chlorophenyl)-1-cyclopropanecarboxylic acid (**e**) (94 mg, 0.48 mmol) and PyBrOP (0.224 g, 0.48 mmol) in the presence of diisopropylethylamine (0.223 mL, 0.96 mmol) in DMF (1.5 mL) with the resin **4** (0.2 g, 0.16 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (17.5 μL, 0.16 mmol) in DMF (1 mL). The product was recovered by the general procedure to give 37.2 mg (81%) of crude **16**: mp 107 °C; C18 RP HPLC (215/254 nm) t_R = 25.3 min; ^{1}H NMR (300 MHz, C_6D_6) δ 7.21−7.07 (m, ArH, 5 H), 7.05−7.00 (m, ArH, 2 H), 6.87−6.83 (m, ArH, 2 H), 5.40 (br s, NH, 1 H), 4.27 (d, J = 6.10 Hz, CH_2, 2 H), 1.88−1.84 (m, CH_2, 2 H), 0.81−0.77 (m, CH_2, 2 H); MS(EI) m/z 285−287 ($M^{\bullet+}$), 194−196, 180−182, 151−153, 91.

***N*-Benzyl-2,2′-diphenylpropionamide (17).** By the general procedure, the reaction 2, 2′-diphenylpropionic acid (**f**) (0.156 g, 0.69 mmol) and PyBrOP (0.322 g, 0.69 mmol) in the presence of diisopropylethylamine (0.241 mL, 1.38 mmol) in DMF (2 mL) with the resin **4** (0.4 g, 0.23 mmol) gave the polymer-bound activated ester which was reacted with benzylamine (25 μL, 0.23 mmol) in DMF (2 mL). The product was recovered by the general procedure to give 62.1 mg (86%) of crude **17**. mp 95−97 °C; C18 RP HPLC (215/254 nm) t_R =

32.1 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (t, J = 5.96 Hz, NH, 1 H), 7.33−7.15 (m, ArH, 15 H), 4.30 (d, J = 5.99 Hz, CH_2, 2 H), 1.90 (s, CH_3, 3 H);. MS(EI) m/z 315 ($M^{\bullet+}$), 181, 167, 103, 91, 77.

***N*-Benzylnicotinamide (18).** The reaction of nicotinic acid (**g**) (85 mg, 0.69 mmol) and PyBrOP (0.322 g, 0.69 mmol) in the presence of diisopropylethylamine (0.241 mL, 1.38 mmol) in DMF (2 mL) with the resin **4** (0.4 g, 0.23 mmol) twice for 1 h each time gave the polymer-bound activated ester which was reacted with benzylamine (25 μL, 0.23 mmol) in DMF (2 mL). The product was recovered by the general procedure to give 29.4 mg (60%) of crude **18** which was purified by preparative TLC (MN-Kieselgel G/UV_{254} glass plate; eluent: CH_2Cl_2/MeOH/H_2O/AcOH 9/1/0.1/0.05) to give 20.5 mg of **18**: mp 120−130 °C; C18 RP HPLC (215/254 nm) t_R = 17.8 min; ^{1}H NMR (300 MHz, DMF-d_7) δ 9.42 (br s, NH, 1 H), 9.38 (dd, J = 0.78, 2.30 Hz, ArH, 1 H), 8.93 (dd, J = 1.66, 4.81 Hz, ArH, 1 H), 8.54 (dt, J = 1.99, 7.94 Hz, ArH, 1 H), 7.75−7.70 (m, ArH, 1 H), 7.62−7.45 (m, ArH, 5 H), 4.80 (d, J = 5.93 Hz, CH_2, 2 H); MS(CI) m/z 213 (MH^+), 106, 91.

***N*-(2-(5-Methyl-1,3,4-thiadiazolyl))-5-methyl-2-nitrobenzamide (21).** By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.326 g, 1.8 mmol) and PyBrOP (0.839 g, 1.8 mmol) in the presence of diisopropylethylamine (0.627 mL, 3.6 mmol) in DMF (2.5 mL) with the resin **4** (0.75 g, 0.6 mmol) gave the polymer-bound activated ester which was reacted with 2-amino-5-methyl-1,3,4-thiadiazole (62 mg, 0.6 mmol) in DMF (2 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in EtOAc (150 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), the solvent was removed by rotary evaporation, and the residue was taken up in *tert*-butyl alcohol (10 mL), frozen, and lyophilized to give 0.106 g (71%) of crude **21**: mp 226 °C; C18 RP HPLC (215/254 nm) t_R = 22.9 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.03 (s, NH, 1 H), 8.12 (d, J = 8.34 Hz, ArH, 1 H), 7.64 (s, ArH, 1 H), 7.60 (d, J = 8.42 Hz, ArH, 1 H), 2.67 (s, CH_3, 3 H), 2.47 (s, CH_3, 3 H); MS(CI) m/z 279 (MH^+), 164.

Benzophenone (5-Methyl-2-nitrobenzoyl)hydrazone (23). By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.543 g, 3 mmol) and PyBrOP (1.398 g, 3 mmol) in the presence of diisopropylethylamine (1.05 mL, 6 mmol) in DMF (4 mL) with the resin **4** (1.25 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with benzophenone hydrazone (0.196 g, 1 mmol) in DMF (6 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in EtOAc (30 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation to give 0.253 g (70%) of crude **23** which was crystallized from EtOAc (4 mL) to give 99 mg of pure **23** (2 isomers 2.13/1): mp 204−206 °C; C18 RP HPLC (215/254 nm) t_R = 31.7 min; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.83 (s, NH, 1 H_a), 10.45 (s, NH, 1 H_b), 8.15 (d, J = 8.38 Hz, ArH, 1 H_b), 8.02 (d, J = 8.38, ArH, 1 H_a), 7.60−7.25 (m, ArH, 11 H_a, 10 H_b), 7.06 (d, J = 7.35, ArH, 1 H_b), 2.49 (s, CH_3, 3 H_b), 2.42 (s, CH_3, 3 H_a); MS(EI) m/z 359 ($M^{\bullet+}$), 195, 180, 165, 77. Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.19; H, 4.74; N, 11.70. Found: C, 69.83; H, 4.80; N, 11.88.

1-(5-Methyl-2-nitrobenzoyl)-5-nitroindazole (24). By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.652 g, 3.6 mmol) and PyBrOP (1.678 g, 3.6 mmol) in the presence of diisopropylethylamine (1.255 mL, 7.2 mmol) in DMF (5 mL) with the resin **4** (1.5 g, 1.2 mmol) gave the polymer-bound activated ester which was reacted with 5-nitroindazole (0.196 g, 1.2 mmol) and diisopropylethylamine (0.418 mL, 2.4 mmol) in DMF (3 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in EtOAc (250 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (12 mL), frozen, and lyophilized to give 0.273 g (77%) of **24**: mp 210−215 °C; C18 RP HPLC (215/254 nm) t_R = 31.3 min; ^{1}H NMR (600 MHz, DMF-d_7) δ 9.01 (d, J = 2.15 Hz, ArH, 1 H), 8.76 (d, J = 9.10 Hz, ArH, 1 H), 8.72 (s, ArH, 1 H), 8.68 (dd, J = 9.07, 2.21 Hz, ArH, 1 H), 8.35 (d, J = 8.48 Hz, ArH, 1 H), 7.92 (d, J = 1.09 Hz, ArH, 1 H), 7.80 (dd, J = 8.47, 1.14 Hz, ArH, 1 H), 2.76 (s, CH_3, 3 H); MS(CI) m/z 327 (MH^+), 280, 164.

***N*-Phenethyl-2,2′-diphenylpropionamide (26), *N*-((*β*)*R*-Hydroxy-(α)*S*-methylphenethyl)-5-methyl-2-nitrobenzamide (27), and 2,2′-Diphenylpropanilide (28).** By the general procedure, the reaction of 2,2′-diphenylpropionic acid (**f**) (1.627 g, 7.2 mmol) and PyBrOP (3.355 g, 7.2 mmol) in the presence of diisopropylethylamine (2.51 mL, 14.4 mmol) in DMF (18 mL) with the resin **4** (3 g, 2.4 mmol) gave the polymer-bound activated ester. The resin beads were washed with DMF (three times) and with CH_2Cl_2 (twice) and dried under vacuum. A portion of the polymer-bound activated ester (0.48 mmol) was reacted with phenethylamine (60.0 μL, 0.48 mmol) in DMF (4.8 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2, the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (12 mL), frozen, and lyophilized to give 129.5 mg (82%) of **26.** By the same procedure, reaction of the polymer-bound activated ester (0.48 mmol) with (1*R*,2*S*)-(−)-norephedrine (79.2 mg, 0.52 mmol) in DMF (4.8 mL) gave 128 mg (74%) of **27**. By the same procedure, reaction of the polymer-bound activated ester (0.48 mmol) with aniline (45.5 mg, 0.48 mmol) in DMF (4.8 mL) gave 82.6 mg (64%) of **28**. Data for compound **26**: mp 63−66 °C; C18 RP HPLC (215/254 nm) t_R = 32.3 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32−7.10 (m, NH, ArH, 16 H), 3.35 (m, CH_2, 2 H), 2.74 (t, J = 7.19 Hz, CH_2, 2 H), 1.83 (s, CH_3, 3 H); MS(EI) m/z 329 ($M^{\bullet+}$), 181, 167, 103, 91, 77. Data for compound **27**: mp 60−62 °C; C18 RP HPLC (215/254 nm) t_R = 29.9 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.31−7.23 (m, ArH, 11 H), 7.10 (m, ArH, 2 H), 6.94 (m, ArH, 2 H), 6.63 (d, J = 8.68 Hz, NH, 1 H), 5.41 (d, J = 4.59 Hz, OH, 1 H), 4.53 (m, CH, 1 H), 4.10 (m, CH, 1 H), 1.78 (s, CH_3, 3 H), 0.97 (d, J = 6.67 Hz, CH_3, 3 H); MS(EI) m/z 341 ($M^{\bullet+}$ − 18), 253, 181, 165, 103, 77. Data for compound **28**: mp 110 °C; C18 RP HPLC (215/254 nm) t_R = 32.2 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.19 (s, NH, 1 H), 7.62 (d, J = 1.24 Hz, ArH, 2 H), 7.38−7.24 (m, ArH, 12 H), 7.06 (t, J = 1.24 Hz, ArH, 1 H), 2.06 (s, CH_3, 3 H); MS(EI) m/z 301 ($M^{\bullet+}$), 181, 167, 103, 77.

***N*-(1-Adamantyl)-2,2′-diphenylpropionamide (29).** By the general procedure, the reaction of 2,2′-diphenylpropionic acid (**f**) (0.638 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with 1-adamantanamine chlorhydrate (0.15 g, 0.8 mmol) and diisopropylethylamine (0.139 mL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2, the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (20 mL), frozen, and lyophilized to give 0.144 g (50%) of **29**: mp 103−107 °C; C18 RP HPLC (215/254 nm) t_R = 38.9 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21−7.00 (m, ArH, 10 H), 5.65 (s, NH, 1 H), 1.84−1.45 (m, 18 H); MS(CI) m/z 360 (MH^+), 182, 135, 103.

***N*′-(5-Methyl-2-nitrobenzoyl)-2-furoichydrazide (30).** By the general procedure, the reaction of 5-methyl-2-nitrobenzoic acid (**a**) (0.608 g, 3.36 mmol) and PyBrOP (1.565 g, 3.36 mmol) in the presence of diisopropylethylamine (1.171 mL, 6.72 mmol) in DMF (5 mL) with the resin **4** (1.4 g, 1.12 mmol) gave the polymer-bound activated ester. The resin beads were washed with DMF (three times), with diethyl ether (twice) and dried under vacuum. A portion of the polymer-bound

activated ester (0.08 mmol) was reacted with 2-furoic hydrazide (10.1 mg, 0.08 mmol) in the presence of diisopropylethylamine (27.9 μL, 0.16 mmol) in DMF (0.5 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The crude product was purified by column chromatography (silica gel, pentane/EtOAc 1/1) to give 11.5 mg (50%) of **30**: mp 194−202 °C dec; C18 RP HPLC (215/254 nm) t_R = 18.7 min; ^{1}H NMR (300 MHz, DMSO-d_6) 10.61 (s, NH, 1 H), 10.57 (s, NH, 1 H), 8.04−8.01 (d, J = 8.30 Hz, ArH, 1 H), 7.93 (d, J = 3.16 Hz, ArH, 1 H), 7.58−7.55 (d, J = 8.39 Hz, ArH, 1 H), 7.52 (s, ArH, 1 H), 7.32−7.31 (d, J = 3.11 Hz, ArH, 1 H), 6.69−6.68 (q, J = 1.73 Hz, ArH, 1 H), 2.48 (s, CH_3, 3 H); m/z 290 (MH^+), 164, 149.

***N*-((*β*)*R*-Hydroxy-(α)*S*-methylphenethyl)-3-chlorobenzamide (31).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.279 g, 1.78 mmol) and PyBrOP (0.831 g, 1.78 mmol) in the presence of diisopropylethylamine (0.622 mL, 3.56 mmol) in DMF (3.80 mL) with the resin **4** (0.7 g, 0.59 mmol) gave the polymer-bound activated ester which was reacted with (1*R*,2*S*)-(−)-norephedrine (89.8 mg, 0.595 mmol) in DMF (5.95 mL). The product was recovered and purified by preparative RP HPLC, as described for compound **15**, to give 0.135 g (79%) of **31**: mp 140 °C; C18 RP HPLC (215/254 nm) t_R = 25.6 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37 (d, J = 8.32 Hz, NH, 1 H), 7.83 (t, J = 1.74 Hz, ArH, 1 H), 7.74 (dt, J = 7.67, 1.39 Hz, ArH, 1 H), 7.58 (ddd, J = 7.99, 1.08 Hz, ArH, 1 H), 7.48 (t, J = 7.80, ArH, 1 H), 7.40 (m, ArH, 2 H), 7.31 (m, ArH, 2 H), 7.24−7.18 (m, ArH, 1 H), 5.46 (d, J = 4.84 Hz, OH, 1 H), 4.71 (t, J = 5.13 Hz, CH, 1 H), 4.19−4.12 (m, CH, 1 H), 1.11 (d, J = 6.77 Hz, CH_3, 3 H); MS(CI) m/z 272−274 (M^+ − OH), 183−185, 139−141.

3-Chlorobenzanilide (32). By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.279 g, 1.78 mmol) and PyBrOP (0.831 g, 1.78 mmol) in the presence of diisopropylethylamine (0.622 mL, 3.56 mmol) in DMF (3.80 mL) with the resin **4** (0.7 g, 0.59 mmol) gave the polymer-bound activated ester which was reacted with aniline (55 mg, 0.595 mmol) in DMF (5.95 mL). The product was recovered and purified by preparative RP HPLC, as described for compound **15**, to give 0.109 g (79%) of **32**: mp 134−136 °C; C18 RP HPLC (215/254 nm) t_R = 28.6 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.36 (s, NH, 1 H), 8.02 (t, J = 1.83 Hz, ArH, 1 H), 7.93 (dt, J = 7.70, 1.38 Hz, ArH, 1 H), 7.80−7.76 (m, ArH, 2 H), 7.67 (ddd, J = 8.02, 1.08 ArH, 1 H), 7.58 (t, J = 7.86, ArH, 1 H), 7.41−7.34 (m, ArH, 2 H), 7.16- 7.10 (m, ArH, 1 H); MS(EI) m/z 231−233 ($M^{\bullet+}$), 139−141, 111−113.

***N*-(3-Chlorobenzoyl)piperidine (33).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.376 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with piperidine (79 μL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2, the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol , frozen, and lyophilized to give 0.128 g (72%) of **33**: mp 44−48 °C; C18 RP HPLC (215/200 nm) t_R = 27.1 min; ^{1}H NMR (300 MHz, CD_3CN) δ 7.48−7.39 (m, ArH, 3 H), 7.32−7.29 (m, ArH, 1 H), 3.63 (br s, 2 H), 3.29 (br s, 2 H), 1.72−1.52 (br m, 6 H); MS(CI) m/z 224−226 (MH^+), 188, 139−141. Anal. Calcd for $C_{12}H_{14}NOCl$: C, 64.42; H, 6.26; N, 6.26. Found: C, 64.38; H, 6.31; N, 6.18.

***N*-(1-Adamantyl)-3-chlorobenzamide (34).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.376 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with 1-adamantanamine chlorhydrate (0.15 g, 0.8 mmol) and diisopropylethylamine (0.139 mL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2 (30 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (20 mL), frozen, and lyophilized to give 0.161 g (70%) of **34**: mp 156−159 °C; C18 RP HPLC (215/200 nm) t_R = 34.7 min; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.83 (t, J = 1.75 Hz, ArH, 1 H), 7.76−7.74 (m, ArH, NH, 2 H), 7.57−7.55 (m, ArH, 1 H), 7.46 (t, J = 7.86 Hz, ArH, 1 H), 2.07 (s, CH, 9 H), 1.66 (s, CH, 6 H); MS(EI) m/z 289−291 ($M^{\bullet+}$), 232−234, 139−141, 111−113. Anal. Calcd for $C_{17}H_{20}NOCl$: C, 70.47; H, 6.91; N, 4.83. Found: C, 70.27; H, 6.99; N, 4.63.

***N*-*tert*-Butyl-3-chlorobenzamide (35).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.376 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with *tert*-butylamine (84 μL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2, the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (10 mL), frozen, and lyophilized to give 0.086 g (51%) of **35**: mp 99−101 °C; C18 RP HPLC (215/200 nm) t_R = 27.9 min; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.90 (s, NH, 1 H), 7.85 (t, J = 1.81 Hz, ArH, 1 H), 7.76 (dt, J = 7.72, 1.20 Hz, ArH, 1 H), 7.57 (m, ArH, 1 H), 7.47 (t, J = 7.86 Hz, ArH, 1 H), 1.38 (s, CH_3, 9 H); MS(EI) m/z 211−213 ($M^{\bullet+}$), 196−199, 156−158, 139−141, 111- 113. Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.62; N, 6.62. Found: C, 62.53; H, 6.64; N, 6.43.

***N*-Ethyl-*N*-phenyl-3-chlorobenzamide (36).** By the general procedure, the reaction of 3-chlorobenzoic acid (**d**) (0.376 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with *N*-ethylaniline (100 μL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2, the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (12 mL), frozen, and lyophilized to give 0.178 g (86%) of **36**: oil; C18 RP HPLC (215/254 nm) t_R = 29.9 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33−7.16 (m, ArH, 9 H), 3.86 (q, J = 7.10 Hz, CH_2, 2 H), 1.11 (t, J = 7.10 Hz, CH_2, 3 H); MS(EI) m/z 259−261 ($M^{\bullet+}$), 139−141, 120, 111−113. Anal. Calcd for $C_{15}H_{14}NOCl$: C, 69.36; H, 5.39; N, 5.39. Found: C, 69.11; H, 5.67; N, 5.42.

***N*-(1-Adamantyl)-1-adamantanacetamide (37).** By the general procedure, the reaction of 1-adamantanacetic acid (0.466 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with 1-adamantanamine chlorhydrate (0.15 g, 0.8 mmol) and diisopropylethylamine (0.139 mL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2 (50 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (25 mL), frozen, and lyophilized to give 0.170 g (65%) of **37**: mp 254−260 °C; C18 RP HPLC (215/200 nm) t_R = 39.1 min; ^{1}H NMR (300 MHz, CD_3OD) δ 7.14 (s, NH, 1 H), 2.05−1.97 (m, 12 H), 1.86 (s, CH_2, 2 H), 1.74−1.65 (m, 18 H); MS (EI) m/z 327 ($M^{\bullet+}$), 270, 151, 94, 79, 67, 135. Anal. Calcd for $C_{22}H_{33}NO$: C, 80.73; H, 10.09; N, 4.28. Found: C, 80.53; H, 10.23; N, 4.19.

***N*-(1-Adamantyl)cyclohexanecarboxamide (38).** By the general procedure, the reaction of cyclohexanecarboxylic acid (0.307 g, 2.40 mmol) and PyBrOP (1.118 g, 2.40 mmol) in the presence of diisopropylethylamine (0.837 mL, 4.80 mmol) in DMF (7 mL) with the resin **4** (1 g, 0.8 mmol) gave the polymer-bound activated ester which was reacted with 1-adamantanamine chlorhydrate (0.15 g, 0.8 mmol) and diisopropylethylamine (0.139 mL, 0.8 mmol) in DMF (4 mL). The supernatant was collected and combined with the DMF solutions used to wash the resin. DMF was removed by rotary evaporation. The residue was taken up in CH_2Cl_2 (50 mL), the solution was washed with 0.1 M aqueous $NaHCO_3$ (three times) and with 0.37 M aqueous HCl (three times) and dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The residue was taken up in *tert*-butyl alcohol (25 mL), frozen, and lyophilized to give 0.136 g (65%) of **38**: mp 189−192 °C; C18 RP HPLC (215/200 nm) t_R = 33.6 min; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.04 (s, NH, 1 H), 2.05 (tt, J = 11.50, 3.40 Hz, 1 H), 1.99 (s, 3 H), 1.90 (m, 6 H), 1.70−1.61 (m, 11 H), 1.31−1.13 (m, 5 H); MS (EI) m/z 261 ($M^{\bullet+}$), 206, 135, 94, 79, 67. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.16; H, 10.34; N, 5.36. Found: C, 77.82; H, 10.18; N, 5.20.

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Supporting Information Available: ^{1}H NMR spectra and HPLC chromatograms for all the compounds described in the Experimental Section (54 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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