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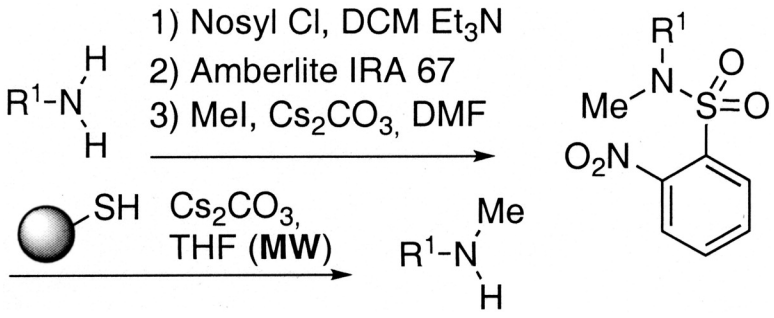

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Parallel Protocol for the Selective Methylation and Alkylation of Primary Amines

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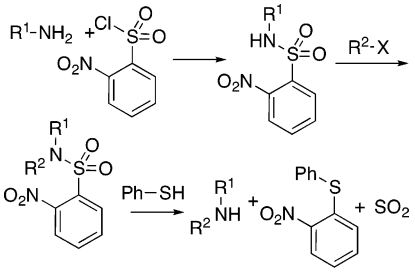
One of the still unresolved problems in parallel synthesis is the availability of a general and rapid method for the transformation of a primary amine into the corresponding secondary amine without the issue of polyalkylation. Following the Fukuyama method, which is based on the alkylation of *o*-nitrobenzenesulfonamides, followed by removal of the sulfonyl group, we have developed a simple protocol which can be easily applied to parallel synthesis making use of supported reagents and scavengers. To verify the robustness of the method, a small representative array of secondary amines have been prepared. Moreover, taking advantage of the possibility to use different supported reagents in the same pot, we also prepared, starting from primary amines, a series of differently substituted tertiary amines.

Introduction

The transformation of a primary into a secondary or tertiary amine is one of the most useful tools in organic chemistry.[1] Amines are structural moieties present in many drugs and in several natural products having biological activity. Moreover, the transformation of a primary amine group into the corresponding secondary or tertiary group may modulate the characteristics of the molecule. Simple methods for selective parallel alkylation of amines are requested to create libraries of basic nitrogen containing molecules. General synthetic methods[2] for the preparation of bisalkyl and trisalkyl amines include reductive amination,[3] amide reduction,[4] and direct N-alkylation.[5] Although several reductive protocols have been described for the alkylation of amines with aldehydes and ketones, these methods are not without limitations. The use of reducing agents is not compatible with several functional groups, and over-alkylation processes may compromise the result of the reaction.[5a] This is particularly true in the case of monomethylation of a primary amine. Formaldehyde is not easy to handle, and it generally gives variable amounts of the dimethylated compound.[6] Simple S_N2 alkylations give also over-alkylation, especially when MeI or other methylating agents are used.[7] A highly chemoselective process for the alkylation of amine based on the so-called cesium effect has been recently described,[8] but no examples of methylation have been reported using this method. Consequently, protection and activation of the nitrogen atom, followed by alkylation and deprotection, are often required to construct alkylated secondary amines. The Fukuyama method[9] is one of the most effective procedures reported in the literature. A primary amine is transformed into the corresponding *o*-nitrobenzenesulfonamide (nosylamide) which can be alkylated (methylated) with an alkyl halides or other SN-based substrates. The tertiary sulfonamide is subsequently deprotected to give the amine. This method has been largely employed, and a preparative version has been reported in *Organic Synthesis*.[10] However, all the intermediates must be purified by column chromatography, and the final secondary amine must be separated by the thioether deprotection product. It makes the procedure unsuitable for parallel synthesis.[11] For these reasons, the protocol has been recently applied to solid-phase synthesis methods,[12] while there are no examples of its application to parallel synthesis in a homogeneous phase. Since we have recently described one effective procedure for the deprotection of nosyl amides,[13] we though to study the possibility of developing a protocol for parallel alkylation of primary amines based on the Fukuyama reaction.

Scheme 1. General Scheme for Deprotection of Nosyl Amides.



Results and Discussion

The monomethylation of benzylamine **1** was selected as a model reaction to assess the influence of several bases,

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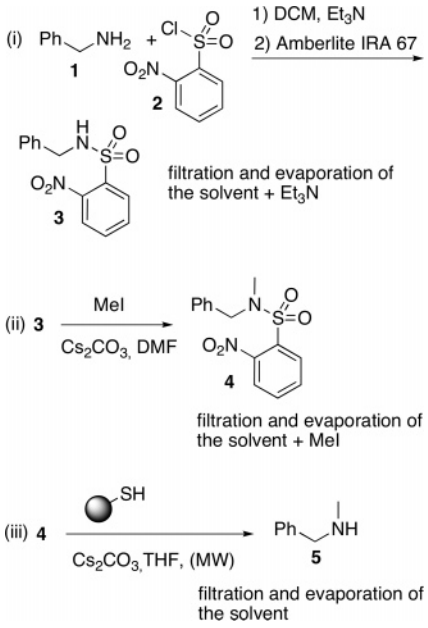
Scheme 2. General Procedure for Alkylation of Primary Amines with Supported Reagents.



solvents, reaction temperatures, and times. All steps of the formation of the sulfonamide, alkylation, and deprotection were examined to obtain pure products without chromatographic purification, aqueous workup, and other conditions that are not compatible with a parallel synthesis. The conventional method for the preparation of sulfonamides requires the use of a slight excess of the nosylchloride in DCM and the use of Et_3N as the base. These conditions were tried at first using a 1:1:3 ratio of the chloride, the amine, and Et_3N. After the mixture was stirred for 4 h at room temperature and the solid formed was filtered, evaporation of the solvent gave **3** in very good yields.

Unfortunately, the crude product **3** was contaminated with triethylammonium hydrochloride. This sideproduct could be removed by filtration of the crude DCM solution through a short path of silica gel and washing the filter cake several times with Et_2O. Since this procedure cannot be considered of general use, some alternative protocols were examined. With insoluble inorganic bases (such as Cs_2CO_3, Na_2CO_3, $NaHCO_3$, and NaOH), the conversion into the nosylamide **3** was not very good. On the other hand, with supported bases, such as PS-DIEA or PS-NMM, a large excess of the nosyl Cl was required for the complete transformation of the amine into the sulfonamide. The excess of nosyl Cl could be scavenged using PS-trisamine giving, after filtration of the base and the scavenger resins, sulfonamide **3** in almost quantitative yields with a purity higher than 95% (^{1}H NMR, 400 MHz). However, we found the Et_3N-based protocol more profitable, followed by the addition of an alkaline exchange resin (Amberlite IRA-67 free base) to the reaction mixture. The triethyammonium hydrochloride was neutralized, and the free Et_3N was reintegrated into the solution and removed, after filtration, by evaporation under vacuum (part i in Scheme 2).

Next, we examined the alkylation of **3** with MeI. An excess of MeI in DMF in the presence of Cs_2CO_3 at room-temperature gave product **4** in a 99% yield. It is worth noting that the product was isolated with a high level of purity after a simple filtration and DMF evaporation.[14] Sulfonamide **4** was finally treated with PS-thiophenol[15] (1.5 equiv) in THF at room temperature for 12 h. A second addition of 1.5 equiv of the resin was done, and the mixture was stirred for an additional 12 h. The ES/MS spectrum showed complete disappearance of the sulfonamide, and after filtration of the resin and evaporation of the solvent, the secondary benzylamine **5** was isolated in very good yields and purity (part iii in Scheme 2). This protocol was applied to the synthesis of several *N*-methyl amines, and the compounds obtained are collected in Chart 1, together with the yields of the isolated compounds.

The same protocol was applied to the alkylation of primary amines using different alkyl halides[16] (Table 1). A complete conversion of the intermediate was always obtained, although in same cases (see entries 3, 4, 5, 9, 10, and 12−15 in Table 1), more than 24 h of stirring at room temperature was required for a complete conversion. This problem could be solved by microwave (MW) irradiation of the reaction mixture. Two or three cycles of 2 min each at 100 °C (sealed vial, maximum internal pressure 200 psi) gave the required products in very good yields. In entries 4, 5, 13, and 14 in Table 1, an excess of the alkylating agent was required to give complete alkylation of the intermediate nosylamide. The excess of the halide was then removed with the same nucleophilic resin employed for deprotection of the sulfonamide. In any case reported in Table 1, the last step was

Chart 1

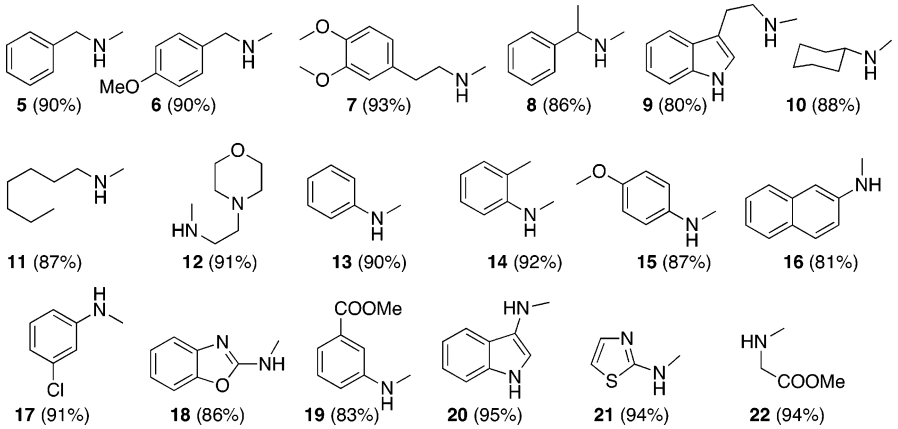
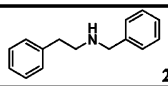
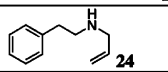
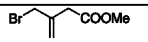
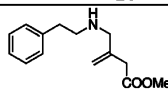
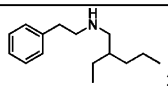
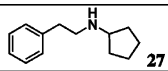
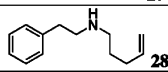
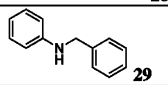
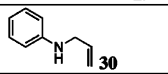
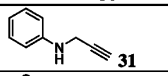
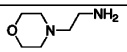
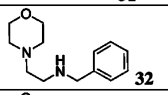
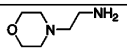
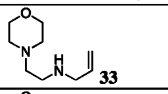
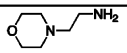
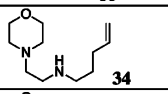
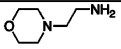
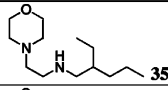
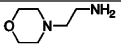
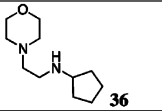
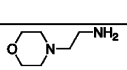
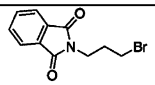
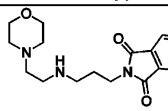


Table 1. Alkylation of Primary Amines

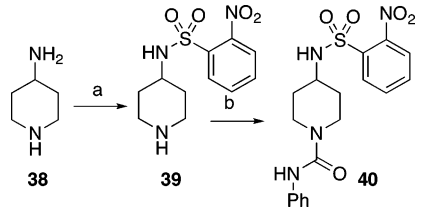
Entry	Amine	Alkylating agent	Cond.[a]	Product	Yield[b]
1	$Ph(CH_2)_2NH_2$	$PhCH_2Br$	A	 **23**	90
2	$Ph(CH_2)_2NH_2$	$CH_2=CHCH_2Br$	A	 **24**	94
3	$Ph(CH_2)_2NH_2$		B	 **25**	86
4	$Ph(CH_2)_2NH_2$		C	 **26**	88
5	$Ph(CH_2)_2NH_2$	cyclo-(C_5H_9)-I	C	 **27**	90
6	$Ph(CH_2)_2NH_2$	$CH_2=CH-(CH_2)_3Br$	A	 **28**	86
7	$Ph-NH_2$	$PhCH_2Br$	A	 **29**	88
8	$Ph-NH_2$	$CH_2=CHCH_2Br$	A	 **30**	91
9	$Ph-NH_2$		B	 **31**	92
10		$PhCH_2Br$	B	 **32**	86
11		$CH_2=CHCH_2Br$	A	 **33**	92
12		$CH_2=CH-(CH_2)_3Br$	B	 **34**	95
13			C	 **35**	91
14		cyclo-(C_5H_9)-I	C	 **36**	88
15			B	 **37**	85

[a] Conditions: A (i) nosyl Cl (1 equiv), Et_3N (3 equiv), DCM, room temp, (ii) alkylating agent (1 equiv), Cs_2CO_3 (1.2 equiv), DMF, 4 h, room temp, (iii) PS-thiophenol (1.5 equiv), DMF, room temp, 24 h; B (i) nosyl Cl (1 equiv), Et_3N (3 equiv), DCM, room temp, (ii) alkylating agent (1 equiv), Cs_2CO_3 (2 equiv), DMF, MW, 100 °C, 200 psi, 4 min, (iii) PS-thiophenol (2 equiv) DMF, room temp 24 h; C (i) Nosyll Cl (1 equiv), Et_3N (3 equiv), DCM, room temp, (ii) alkylating agent (2 equiv), Cs_2CO_3, DMF, MW, 100 °C, 200 psi, 4 min, (iii) PS-thiophenol (2.5 equiv), DMF, room temp, 24 h. [b] Yields of isolated and characterized products (see Supporting Information).

repeated as described in reaction iii in Scheme 2, giving amines **23**−**37** in good yields.

To assess the robustness of the procedure, we decided to prepare a small array of alkylated amines using a parallel synthesizer. At first, we chose compound **38** as the starting material (Scheme 3). The strategy proposed required the selective protection of the primary amine with nosyl Cl, then the functionalization of the nitrogen in the ring, followed by alkylation of the sulfonamides and deprotection. Compound **39** was prepared following the standard methodology, isolated, and purified by column chromatography on silica gel. The sulfonamide **39** was then submitted to acylation with PhNCO in the presence of a supported tertiary amine. Product

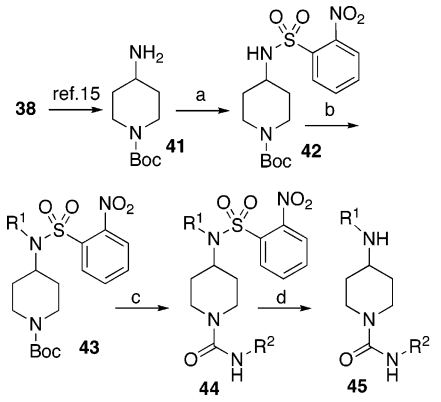
Scheme 3



(a)Nosyl Cl (1 equiv), Et_3N, DCM, room temp, 12 h. (b) PhNCO (1.2 equiv), Py, DCM, room temp, 12 h.

40 was formed in 60−70% yields together with several byproducts. We changed the conditions and the nature of the acylating agents and found that this reaction worked well

Scheme 4



R_1(*1-6*): *1* = CH_3-; *2* = CH_3CH_2-; *3* = CH_2=$CHCH_2$; *4* = CH_2=$CH(CH_2)_3$-; *5* = $PhCH_2$-; *6* = *p*-$MeOC_6H_4CH_2$-.
R_2(*1-2*); *1* = Ph- *2* = CH_3-CH_2-.

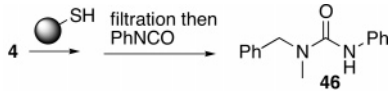
(a) Nosyl Cl, Et_3N, DCM, 6 h, room temp. (b) R^1(*1*−*6*)-X (X═Br or I), Cs_2CO_3, DMF, 40 °C, 24 h. (c) TFA/Et_3SiH (3/1), DCM, room temp, 2 h, followed by R^2(*1*−*2*)-NCO, PS-DIEA, and PS-Trisamine. (d) PS-thiophenol, THF, Cs_2CO_3, room temp, 24 h.

exclusively with few acyl chlorides or isocyanates. Aromatic isocyanates or acyl chlorides, such as phenyl or naphtyl isocyanate or benzoyl chloride, gave the acylated compounds in 60−80% yields and acceptable purity exclusively after column chromatography on silica gel. Moreover, alkyl isocyanates (e.g., butyl isocyanate or ethyl isocyanatoacetate) gave low yields (30−40%) of the expected products. Thus, the reaction on this scaffold was considered to be unsuitable as the first step of a parallel protocol.

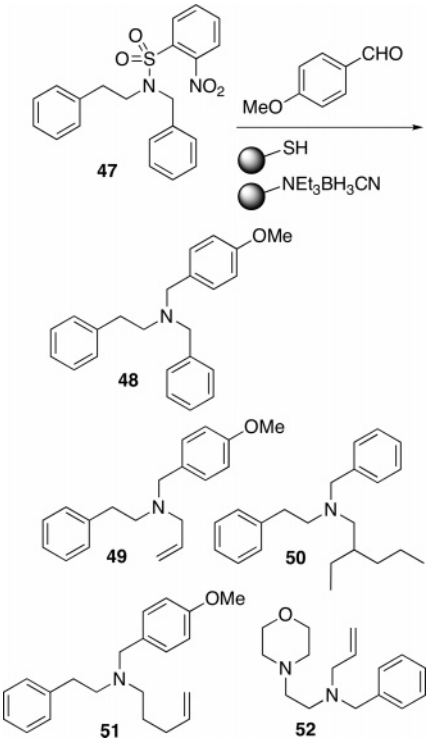
Then, we decided to start with the same scaffold having the secondary amine protected as Boc (**41** in Scheme 4). Differentiation between the primary and the secondary group was done using methyl isobutylketone (MIBK) for a temporary protection of the primary group, followed by an in situ reaction with Boc_2O for selective protection of the ring nitrogen.[17] Pure product **41** was obtained in a 65% yield after column chromatography on silica gel,[18] and then it was nosylated under standard conditions to give product **42**, which was divided in 12 vials, and submitted to the full procedure of alkylation, deprotection of the Boc, and acylation, followed by deprotection of the nosyl group.

Six different alkyl halides were reacted in the first step by stirring of the 12 vials for 24 h at 40 °C in DMF in the presence of Cs_2CO_3. The mixtures containing **43** were filtered; the solvent was evaporated, and a mixture of TFA/Et_3SiH (3:1) was added. After the mixture was stirred for 2 h at room temperature, the solvent was evaporated, and the residues were treated with the solutions containing the 2 different isocyanates in DCM in the presence of 3 equiv of PS-DIEA. After the mixture was stirred at room temperature for 12 h, PS-trisamine was added to scavenge the excess isocyanate. Chemset **44** was filtered, and the solvent was evaporated and treated with PS-thiophenol in THF and Cs_2CO_3. After 24 h at room temperature (and a second addition of PS-thiophenol after the first 12 h), the contents of the vials were filtered, and the solvent was evaporated to give chemset **45**. Passage through an SCX column, followed by elution with a solution of ammonia in methanol, gave products that were fully characterized.

Scheme 5



Scheme 6. Nosyl Deprotection and Reductive Amination.



To assess the versatility of such a protocol, we decided to investigate if it was possible to carry out the deprotection together with a contemporary functionalization of the secondary amine formed. The most trivial method of functionalization was to add an electrophile (PhNCO for example) to the THF solution containing the free secondary amine, coming from filtration of the PS-thiophenol resin. With this procedure, urea **46** was obtained in a 90% yield. Moreover we found that, when the sulfonamide **47** was treated with PS-thiophenol in the presence of supported PS-NEt_3CNBH_4 and an aromatic aldehyde, the corresponding tertiary amine **48** could be obtained in acceptable to good yields (Scheme 6). The procedure was repeated with different sulfonamides and aldehydes giving tertiary amines **49**−**52** in good yields. To force the reductive amination to completion, an excess of the aldeydes was required. Consequently, purification of the products by selective SCX extraction followed by elution with a methanolic solution of ammonia was needed.

In conclusion, the selective alkylation of a primary amine was carried out in a parallel mode using the supported reagents and scavengers by the use of a modification of the Fukuyama procedure. The present reaction provides an efficient alternative, in particular, for monomethylation of primary amines. As the last step of the reaction is compatible with the condition of reductive amination, the primary amine can be transformed into a tertiary amine with three different substituents in good yields with a simple purification by selective SCX extraction at the end.

Experimental Section

General Information. All commercially available reagents and solvents were used without further purification unless mentioned otherwise. Solution-phase reactions were monitored by analytical thin-layer chromatography (silica gel 60 F254 plates 0.25 mm) (TLC) and purified by column chromatography on silica gel 60. The supported reagents were obtained from either Argonaut or Novabiochem. Array syntheses were carried out with a Buchi-Syncore parallel synthesizer. MW-assisted reactions were carried out with a Discover apparatus for synthesis by CEM Corp. The purity of all the array members was observed by HPLC/MS spectra, which were recorded on a Agilent LC/MS system equipped with a Waters 120 ODS-BP column (C-18, 35 5 mm, 3 μ) or GC/mass analysis done with a Varian Saturn 2100 ion trap equipped with a 30 mt OV-101 capillary column. ^{1}H NMR spectra were obtained on Bruker 200 and 400 MHz spectrophotometers. Chemical shifts are quoted in parts per million and referenced to TMS and $CDCl_3$.

***N*-Methyl Benzylamine 5. General Procedure.** Benzylamine (0.068 mL, 0.63 mmol) was dissolved in dry DCM (3 mL), followed by the addition of Et_3N (0.19 mL, 1.9 mmol) and 2-nitrobenzenesulfonyl chloride (0.139 g, 0.63 mmol). The mixture was stirred at room temperature for 6 h. The mixture was filtered; DCM (6 mL) was added, and Amberlite IRA-67 (1.0 g, 2 mmol, previously washed with H_2O, MeOH, THF, and DCM) was added to the solution. The mixture shaken for 2 h. The resin was filtered off, and the solvent was evaporated under vacuum to give crude sulfonamide **3** (0.18 g, 98% yield) which was analyzed by ^{1}H NMR and HPLC-MS analysis. The crude was dissolved into dry DMF (5 mL); to this solution, Cs_2CO_3 (0.2 g, 0.616 mmol) and MeI (0.088 mL, 1.39 mmol) were added, and the mixture stirred at room temperature for 12 h. The mixture was filtered; the solvent was evaporated, and the residue was dissolved into dry $CHCl_3$. After 1 h of shaking in $CHCl_3$, the solution was filtered through a sintered glass disc (maximum pore size of 16−40 μm), and the solvent was evaporated to give pure compound **4** (0.18 g, 95% yield) which was analyzed by ^{1}H NMR and HPLC-MS analysis. The crude was dissolved into dry THF (5 mL), and to this solution, Cs_2CO_3 (0.38 g, 1.2 mmol) was added, followed by PS-thiophenol resin (0.4 g of a 1.41 mmol/g loading resin, 0.56 mmol). The mixture was shaken for 12 h at room temperature. The solid was filtered off, and Cs_2CO_3 (0.38 g, 1.2 mmol) and PS-Thiophenol resin (0.4 g of a 1.41 mmol/g loading resin, 0.56 mmol) were added to the solution. The mixture was shaken for 12 h and filtered, and then, the solvent evaporated to give compound **5** (0.067 g, 96% yield) which was analyzed by ^{1}H NMR and GC/MS analysis, in comparison with an authentic sample.[18]

***N*-Cyclopentyl-2-phenylethyl Amine 27. General Procedure for MW-Assisted Alkylation.** 2-Phenylethylamine (0.050 g, 0.413 mmol) was reacted with nosyl Cl as previously described. The crude sulfonamide was dissolved in DMF (5 mL) into a MW reaction tube, and Cs_2CO_3 (0.268 g, 0.826 mmol) added, followed by iodocyclopentane (0.201 g, 1.032 mmol). The tube was sealed, inserted inside a MW cavity (monomode irradiation), and heated at 100 °C and 200 psi for 2 min, followed by 2 min of rest and an additional 2 min of irradiation. The tube was cooled, the solvent diluted with DCM (10 mL) and the solid filtered off. The solvent was evaporated, and the crude was dissolved into dry THF (8 mL). Cs_2CO_3 (0.268 g, 0.826 mmol) was added, followed by PS-thiophenol (0.5 g of a 1.41 mmol/g loading resin, 0.75 mmol), and the mixture was shaken for 12 h at room temperature. The solid was filtered away, and to this solution, Cs_2CO_3 (0.266 g, 0.826 mmol) and PS-thiophenol resin (0.5 g of a 1.41 mmol/g loading resin, 0.75 mmol) were added. The mixture was shaken for 12 h and filtered, and the solvent was evaporated to give compound **27** (0.070 g, 90% yield) as an oil which was analyzed by ^{1}H NMR and ^{13}C NMR in comparison with literature data.[19]

2-Nitro-*N*-4-piperidinylbenzenesulfonamide 39. The product was obtained starting from 4-aminopiperidine (1.0 g, 10 mmol), nosyl Cl (2.2 g, 10 mmol), and Et_3N (3 mL, 30 mmol) in dry DCM (55 mL); it was stirred at room temperature for 2 h. Water was added, followed by EtOAc. The organic layer was separated, washed with HCl 2%, and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude was purified by column chromatography on silica gel (EtOAc/MeOH 20:1 as eluant) to give the desired compound **39** (2.46 g, 64% yield). A sample of **39** was transformed into the corresponding hydrochloride salt (**39**·HCl) by treatment with a solution of HCl in dry Et_2O (5 mL of a 6 M solution) to obtain a microanalytical sample. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70−1.90 (m, 4H), 2.02 (bs, 1H), 2.40−2.60 (m, 4H), 3.76 (m, 1H), 7.02 (bs, 1H), 7.90−8.20 (m, 3H), 8.42 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.7, 41.9, 46.7, 122.2, 124.8, 130.2, 133.4, 140.6, 148.7. MS (ES): 286 (M+). **39**·HCl Calcd for $C_{11}H_{16}ClN_3O_4S$: C, 41.06; H, 5.01; N, 13.06. Found C, 41.20; H, 5.05; N, 13.10.

4-(*o*-Nitrobenzensulfonylamino)-*N*-Boc-piperidine 42. Compound **42** was prepared, in the same manner as compound **39**, starting from **41** (1.0 g, 5 mmol), nosyl chloride (1.1 g, 5 mmol), and Et_3N (3 mL, 30 mmol) in dry DCM (45 mL). Workup and column chromatography on silica gel (EtOAc as eluant) afforded the desired compound **42** (1.15 g, 60% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.60−1.80 (m, 4H), 3.20−3.40 (m, 4H), 3.96 (m, 1H), 7.12 (bs, 1H), 7.90−8.20 (m, 3H), 8.40 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.5, 30.7, 41.0, 45.7, 79.7, 121.2, 128.8, 132.2, 134.4, 139.6, 146.7, 160.1. MS (ES): 408 (M^+ + Na). Calcd for $C_{16}H_{25}N_3O_6S$: C, 49.86; H, 6.01; N, 10.90. Found C, 49.75; H, 6.04; N, 10.87.

Chemset 45. Compound **42** was divided into 12 vials (25 mg each, 0.065 mmol) and dissolved in dry DMF (0.5 mL). Cs_2CO_3 (42 mg, 0.129 mmol) was added, followed by a solution containing R^1(*1*−*6*)X (0.100 mmol) in dry DMF (1 mL). The system was shaken for 24 h at 40 °C; then the mixture was cooled and filtered through a sintered glass disc (maximum pore size of 16−40 μm), and the DMF was evaporated under vacuum. The residue was dissolved in DCM (1 mL), and a mixture of TFA/Et_3SiH (24 μL, 0.21 mmol and 9 μL, 0.07 mmol) was added. After the mixture was stirred for 2 h at room temperature, the solvent was evaporated. To the residues, R^2(*1*−*2*)-NCO (0.1 mmol) dissolved in DCM (0.8 mL) was added in the presence of

PS-DIEA (0.26 gr of a 0.8 mmol/g loaded resin, 0.21mmol). The vials were stirred at room temperature for 12 h; then PS-trisamine (0.150 g of a1.1 mmol/gr loaded resin, 0.165 mmol) was added. After the mixture was stirred for 2 h, the contents of the vials were filtered through a sintered glass disc; the solution was recovered, and the solvent was evaporated under vacuum. The residue was dissolved in dry THF (1 mL); Cs_2CO_3 was added (42 mg, 0.129 mmol), followed by PS-thiophenol (0.1 g of a 1.41 mmol/g loading resin, 0.15 mmol), and the mixture was shaken for 12 h at room temperature. The solid was filtered off, and Cs_2CO_3 (42 mg, 0.129 mmol) and PS-thiophenol resin (0.1 g of a 1.41 mmol/g loading resin, 0.15 mmol) were added to this solution. The mixture was shaken for 12 h and filtered, and the solvent was evaporated. The residues were dissolved in dry MeOH (3 mL) and passed through a SCX cartridge (prepacked 6 mL tube). The column was washed several times with dry MeOH (18 mL) and dried under vacuum suction. The column was eluted with a solution of NH_3 in MeOH (10 mL of a 2 M solution, 20 mmol); the solvent was evaporated to give compounds **45**[(1−6), (1−2)]. The products were treated with a solution of HCl in dry Et_2O to form the corresponding solid hydrochlorides that were filtered and submitted to microanalysis.

***N*-Methyl-*N′*-phenyl-*N*-(phenylmethyl)urea 46.** Compound **4** (0.05 g, 0.165 mmol) was treated with PS-thiophenol (0.2 g of a 1.41 mmol/g loading resin, 0.3 mmol) in THF (5 mL) and Cs_2CO_3 (84 mg, 0.260 mmol) as previously described. The resin was filtered; PhNCO (0.025 g, 0.21 mmol) was added to this solution, and the mixture stirred at room temperature for 12 h. PS-trisamine (0.90 g of a 1.2 mmol/g loaded resin, 0.108 mmol) was added, and the mixture shaken at room temperature for 1 h. The resin was filtered, and urea **46** was isolated (32 mg, 82% yield) as a pure solid compound, as monitored by comparison with an authentic sample.[20]

***N*-(4-Methoxybenzyl)-*N*-benzyl-2-phenylethanamine 48.** The sulfonamide relative to amine **23** (0.039 g, 0.1 mmol) was dissolved in THF. To this solution, PS-thiophenol (0.18 g of a 1.41 mmol/g loaded resin, 0.25 mmol) and Cs_2CO_3 (0.05 g, 0.15 mmol) were added, followed by PS-NEt_3BH_3-CN (0.09 g of a 2 .0 mmol/g loaded resin, 0.18 mmol) and *p*-anisaldehyde (0.048 g, 0.35 mmol). The mixture was shaken at room temperature for 24 h; then additional PS-thiophenol (0.18 g) was added, and the mixture was stirred for 24 h. The mixture was filtered, and the solvent was evaporated. The residue was dissolved into DCM, and this solution was passed through an SCX cartridge (prepacked 6 mL tube), eluted with additional DCM, followed by a NH_3 in MeOH (10 mL of a 2 M solution, 20 mmol); the solvent evaporated to give compound **48** (25 mg, 77% yield) as an oil. The product was treated with a solution of HCl in dry ether to form the corresponding solid hydrochloride that was filtered and submitted to microanalysis. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (t, 2H, J = 7 Hz), 2.67 (t, 2H, J = 7 Hz), 3.62 (s, 2H), 3.68 (s, 3H), 3.83 (s, 2H), 6.80 (m, 2H), 7.20−7.40 (m, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4, 52.3, 55.6, 58.5, 59.8, 114.4, ,124.6, 124.7, 125.6, 127.7, 128.2, 128.4, 130.9, 138.4, 139.5, 150.1. **48**·HCl Calcd for $C_{23}H_{26}$-ClNO C, 75.08; H, 7.12; N, 3.81. Found C, 75.14; H, 7.09; N, 3.79.

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Supporting Information Available. Copies of ^{1}H NMR and mass spectra for representative library members without further purification and characterisation of products **6**−**37**, chemset **45**, and compounds **48**−**52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The residue from the DMF evaporation was treated with dry THF, and the solution was filtered to remove the trace of cesium salt that was soluble in DMF.
(15) PS-thiophenol is commercially available from Biotage Inc (former Argonaut Technologies) in the form of free thiol or from Novabiochem protected as trytyl. The Argonaut product can be used directly in the reaction, whereas the Novabiochem product must be deprotected with TFA-DCM before use. However, the activity of the −SH free resin may decrease after some time from the opening of the bottle. In this case, the resin must be treated with a solution of PPh_3 in deoxygenated THF before the use.

(16) Alkylation of nosylamides could be carried out also with alcohols and phenols under Mitsunobu conditions. However, we tried different conditions (as supported PPh_3 and *t*-budiazadicarboxylate (DBAD) or other conditions described for parallel Mitsunobu-type reaction), but the alkylated tertiary sulfonamides were always contaminated by azadicarboxylate or phosphine byproducts, requiring a chromatographic step for isolation. See: Gentles, R. G.; Wodka, D.; Park, D. C.; Vasudevan, A. *J. Comb. Chem.* **2002**, *4*, 442. Barret, A. G. M.; Roberts, R. S.; Schroder, *J. Org. Lett.* **2000**, *2*, 2999.

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