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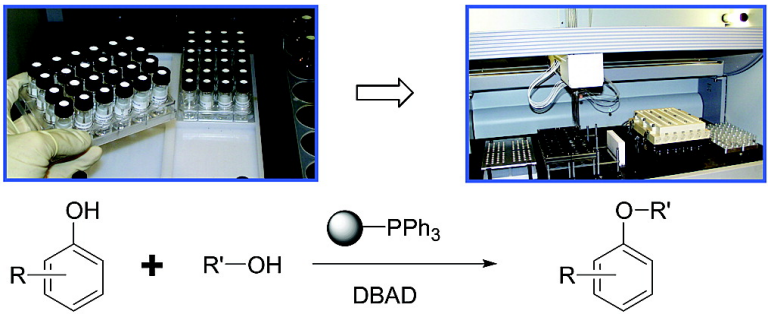

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Standardization Protocols and Optimized Precursor Sets for the Efficient Application of Automated Parallel Synthesis to Lead Optimization: A Mitsunobu Example

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A strategy has been developed for the efficient application of automated parallel synthesis to specific aspects of the lead optimization processes employed in drug discovery. The method involves the synthesis of collections of compounds using sets of precursors designed to encompass established medicinal chemistry principles and that have been concurrently optimized with respect to a specific chemical transformation. The strategy is illustrated using an automated Mitsunobu protocol employing sets of aliphatic alcohols and phenols as precursors. The former has been formatted to perform simple alkyl homologation exercises, with the latter being designed for use in diversity-based studies.

Introduction

It is estimated that currently existing drugs target in total around 500 distinct proteins.[1] It is anticipated however, that another 5000 or so targets[2] will shortly become available as a result of research related to the human genome project. This rapid increase in potential drug targets will necessitate a significant adaptation of the strategies applied to the interrelated activities of target validation and lead optimization. Correspondingly, an important goal in our laboratories is to significantly improve the efficiency of lead optimization programs by reducing the resources needed to design and perform many of the routine experiments that arise within most medicinal chemistry projects.

This objective arose as a result of an in-house analysis that suggested that the types of experiments frequently performed in early-phase discovery programs fall principally into two classes. The first involves experiments focused on optimizing leads where specific interactions between the ligand and target have been identified or can be assumed with some degree of confidence. These exercises typically follow traditional experimental designs involving the standard analogue strategies outlined by Wermuth,[3] Topliss,[4] and Craig,[5] as well as other related approaches.[6] The other main class of experiments involves leads where limited SAR exists and the strategy adopted requires the synthesis of a diverse set of analogues[7] with the purpose of identifying an unexpected group or functionality that addresses some deficiency in the lead structure.

After a review of a large number of both types of exercises, it became apparent that there existed a significant degree of redundancy in the basic experimental approaches being employed, particularly in regard to precursor selections. Importantly, the observed variability between precursor choices typically was not related to specific features of the target but reflected the personal preferences of the medicinal chemist. This ad hoc approach to experimental design required an associated ongoing chemistry development effort to validate precursor selections prior to synthesis, significantly extending project timelines. It was concluded, therefore, that it would be more efficient to format precursors principally by reactive functionality such that all members of a set could be validated once for use in a specific chemical transformation. Further formatting within such sets would allow experiments to be performed encompassing the medicinal chemistry strategies outlined above. It was reasoned that in the absence of compelling structural information on the target or supporting SAR data, such inventories would have wide application and should significantly shorten the time required for initial lead evaluations.

With this perspective, we thought to develop a series of automated medicinal chemistry experiments in which both the chemistry and the precursor selections have been co-optimized.

We undertook this work with an understanding that the application of automation to organic synthesis has historically met with limited success, despite significant developments in both chemical procedures and synthesis platforms.[8] However, two very notable exceptions involve the synthesis of oligonucleotides[9] and peptides.[10] In both cases, the synthesis is nearly always done using dedicated synthesizers employing highly optimized chemical procedures. Importantly, both chemistries employ relatively limited sets of monomers, the reactivity and physicochemical characteristics of which are well understood. It is apparent that the precursor inventories described above incorporate a reactivity element and could be formatted to accommodate additional physi-

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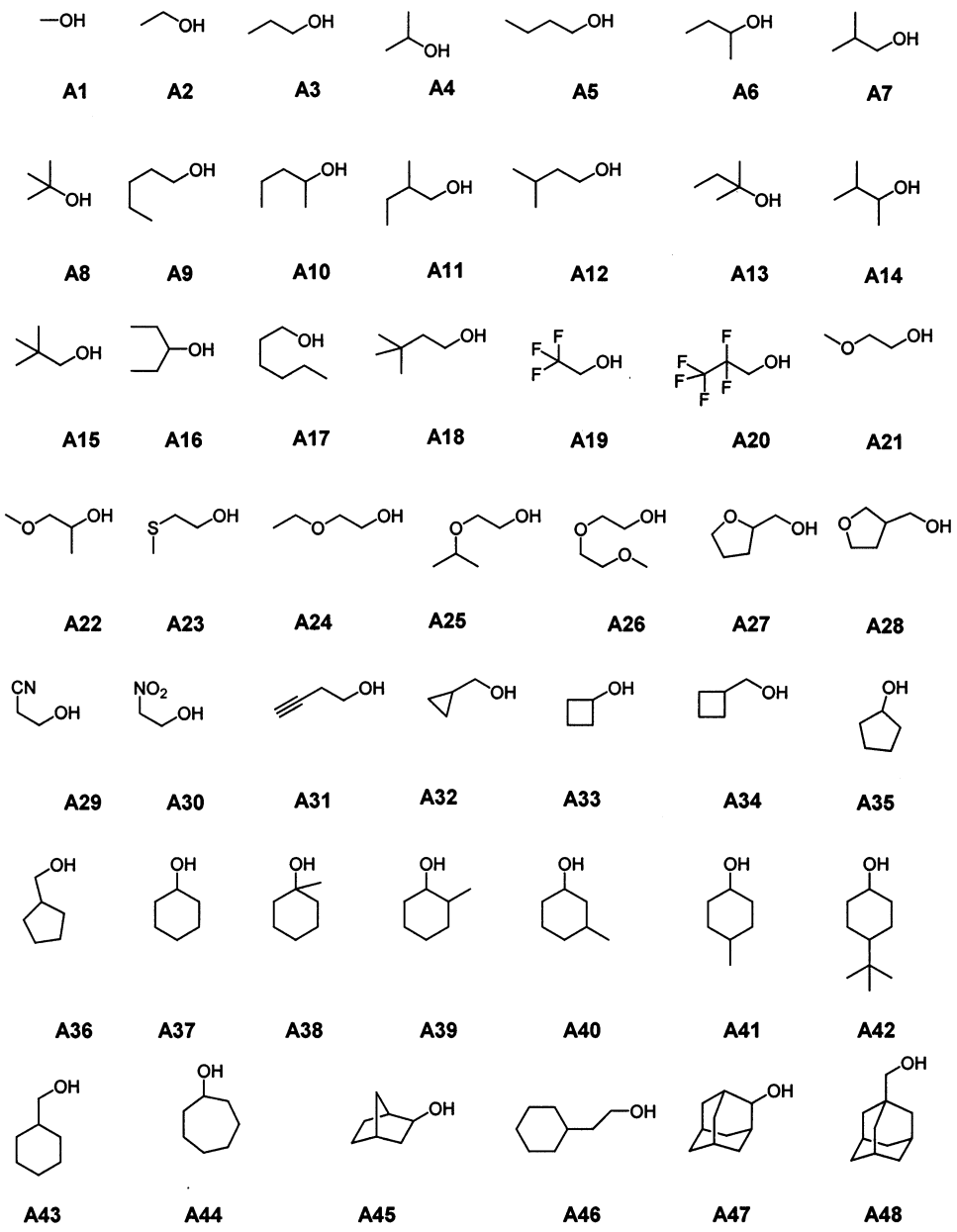


Figure 1. Original aliphatic alcohol collection.

cochemical restrictions. Correspondingly, we present below a description of the evolution of precursor sets that had been initially designed with respect to specific medicinal chemistry objectives and that have subsequently been modified to accommodate the reactivity and physicochemical requirements of a specific, automated chemical transformation, namely, the Mitsunobu reaction.

Precursor Set Design

The compound inventory discussed above consists of sets of compounds grouped primarily by reactive functionality. We will comment in future publications on the overall design of this inventory but limit ourselves here to a discussion of the characteristics of two precursor collections: a set of homologous aliphatic alcohols and a diverse set of phenols.

In the case of the former, we assembled a series of primary, secondary, and tertiary aliphatic alcohols containing the functionality typically employed to probe nonaromatic hydrophobic interactions.[11] Thus, the set consists of a homologous series of linear, branched, cyclic, and fused-cyclic analogues. In addition, a limited number of bioisosteric replacements of methylenes and various degrees of unsaturation have been included to expand the property space covered by the set. The collection is shown in Figure 1.

By contrast, we designed a set of structurally diverse phenols (Figure 2) based on compounds listed in the Available Chemicals Directory (ACD).[12] In selecting precursors, we decided to use a molecular weight cutoff of 210. This was based on an average molecular weight of 290 for compounds submitted to our group for derivatization and a desire that the bulk of the products synthesized be consistent with Lipinski's rule of five.[13] This reduced the ACD file of available phenols from an initial set of 13 453 down to 2288 compounds. Additionally, all radiolabeled phenols were removed, further reducing the set to 2125 compounds. This collection was then used to perform a cluster analysis[14] using

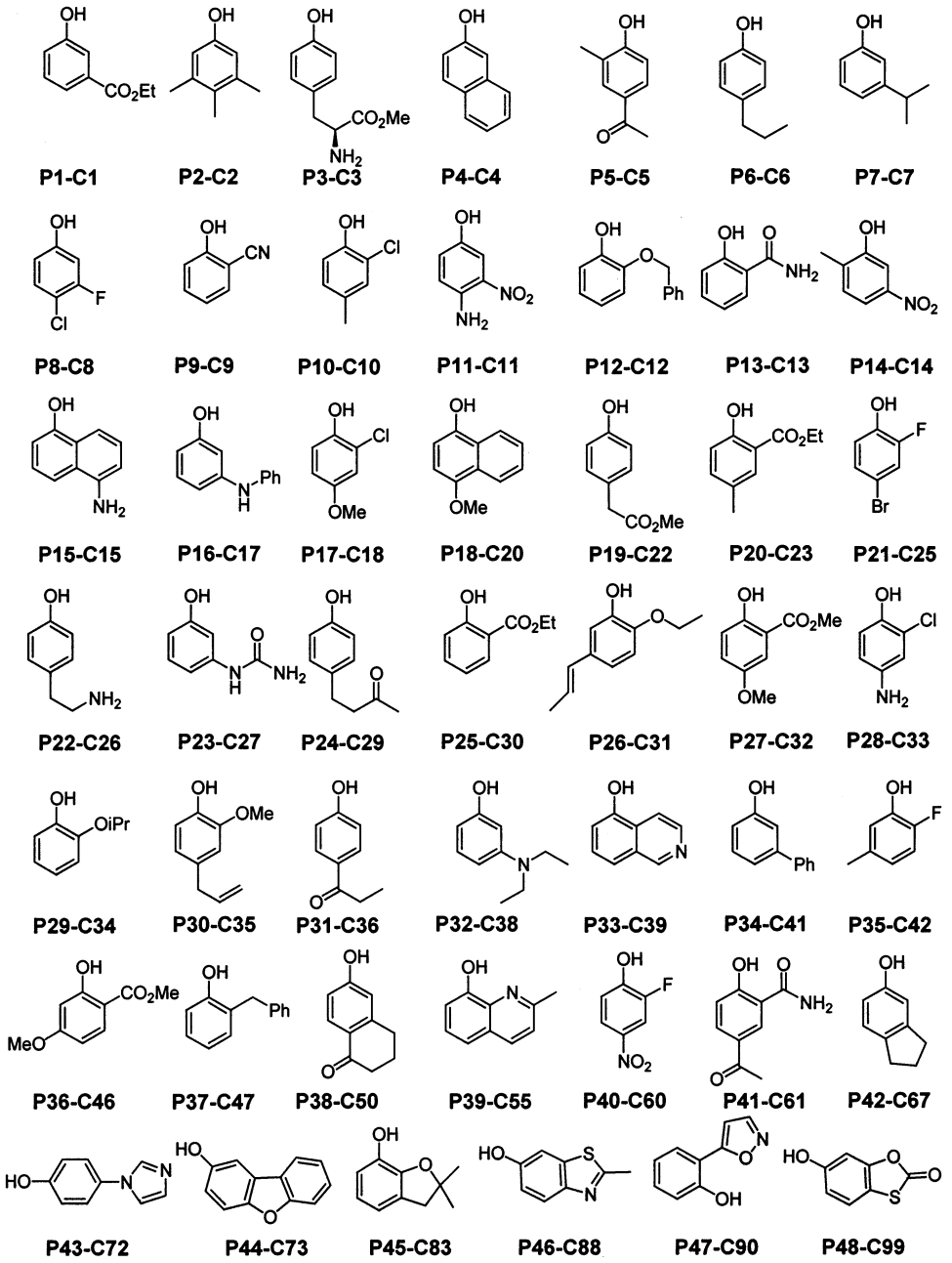


Figure 2. Diversity phenol collection.

as a basis a set of 100 clusters. This number was used on the basis of a subjective assessment of the homology between compounds grouped within a given cluster. An alternative analysis using smaller numbers of clusters resulted in significantly distinct structures being grouped together. The result of this 100-cluster-set analysis is shown in Figure 3, which depicts the population numbers associated with each cluster. This distribution was used as a reference with which to compare subsequent selections of compounds.

To this set we applied the selection process outlined in Table 1. We adopted a procedure that first involved removing compounds that were inappropriate from a medicinal chemistry perspective, sequentially excluding all alkylating reagents, Michael acceptors, excessively halogenated precursors, and phenols with long alkyl chain substituents. This, together with the elimination of radiolabeled precursors, resulted in the elimination of 312 compounds. We next

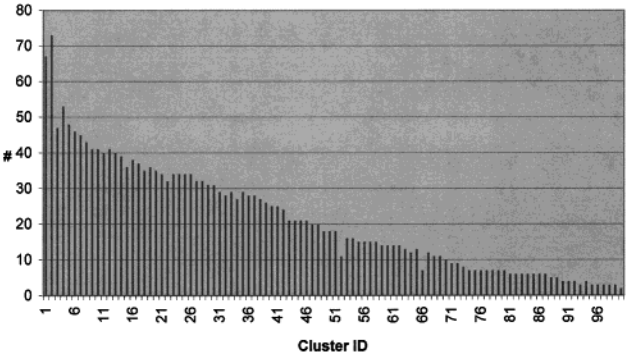


Figure 3. Commercially available phenols. MW < 210.

removed compounds that were anticipated to be problematic under the conditions of the Mitsunobu reaction, from either a chemo- or a regioselectivity perspective. This resulted in the elimination of sets of acids, aldehydes, *o*-aminophenols,

Table 1. Selection Criteria for Phenols

biological incompatibility filter	eliminated	chemical incompatibility filter	eliminated
alkyl halides	11	acids	337
deuterated phenols	65	aldehydes	121
tritiated phenols	24	*o*-aminophenols	70
^{13}C-labeled phenols	50	aliphatic alcohols	112
^{14}C-labeled phenols	54	sulfonamides	4
Si-containing phenols	1	thiols	18
sulfonic acids and esters	13	incompatible salts	26
polynitrophenols	19	poly-OH-phenols	47
polyhalogentated (>4) phenols	13	hydroxamic acids	7
Michael acceptors + long-chain alkyls	62	imides	4
totals	312		746

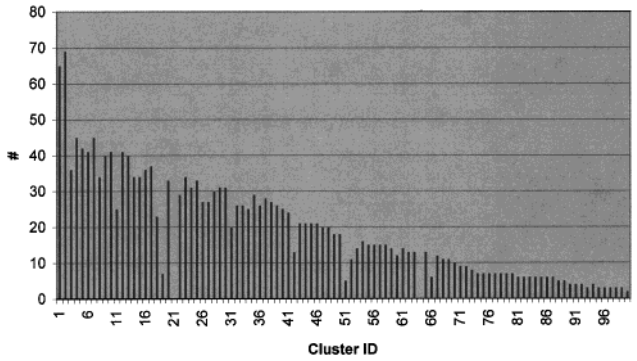


Figure 4. Biologically compliant phenols.

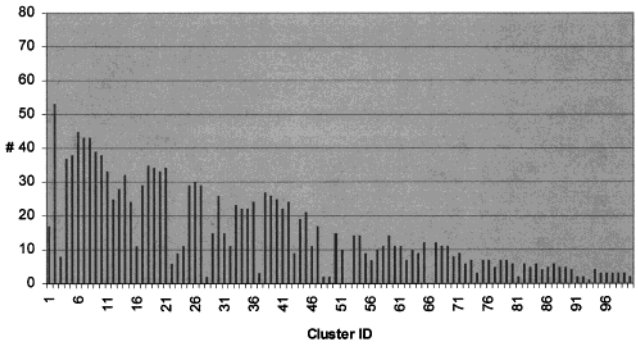


Figure 5. Commercially compliant phenols.

sulfonamides, polyhydroxylated phenols, hydroxamic acids, and a number of salts. This filter removed a further 746 compounds from the file and reduced the number of usable phenols to 1311. Table 1 lists the number of compounds excluded by each of the above-mentioned criteria.

An examination of the consequences of the removal of the above compounds was assessed by examining which clusters from the original distribution shown in Figure 3 were no longer represented in the residual selection. The distributions of the phenols left after removal of compounds with biological and chemical liabilities are shown in Figures 4 and 5, respectively. It is apparent that the biological compatibility filter excluded only two clusters, 21 and 64, corresponding respectively to sets of vinylnitro and substituted acrylonitrile compounds. The chemistry compatibility filter that had excluded a much larger number of compounds surprisingly also resulted in the loss of only two clusters, 52 and 66, corresponding to sets of 1,2-aliphatic hydroxyaminophenols and a class of triazole substituted phenols. However, a further restriction on our precursor set was the

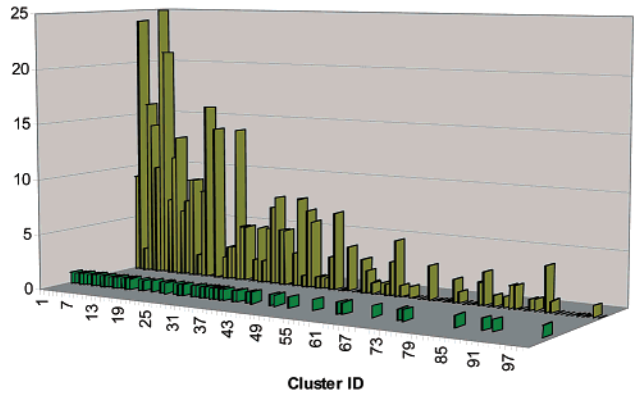


Figure 6. Commercial phenols and selected precursors.

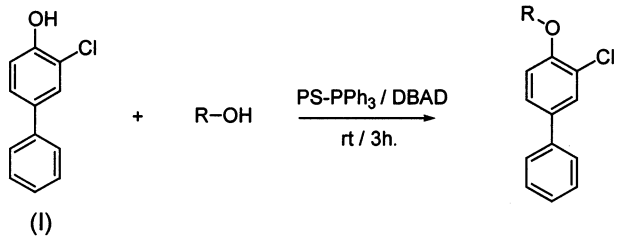
decision to limit compound selection based on multigram availability from major chemical vendors. This filter resulted in the elimination of 33 of the original 100 clusters, the distribution profile of the residual 64 clusters being shown as the taller columns at the rear of the plot in Figure 6. It is apparent that this restriction is the single most significant factor that impacts the range of diversity that can be accessed using the strategy outlined here, much more so than the elimination of compounds for reasons of biological or chemical compliance. However, given that ultimately we have to select only 48 compounds (i.e., the number that can be run on our automation platform), we planned to use reaction yield as a final filtering criterion. Therefore, we selected one member from each of the residual 64 clusters for the chemical optimization process outlined below. Ultimately, we would select 48 precursors based on the 48 highest yielding reactions. This would ensure that each compound selected originated from a different cluster of the original set of 100 clusters and should provide a set of reagents with a good overall reactivity profile.

With sets of focused aliphatic alcohols and diversity phenols identified, we proceeded to implement an automated chemistry protocol.

Results and Discussion

The Mitsunobu reaction has found extensive application in combinatorial chemistry,[16] providing a method for the generation of molecular diversity through the use of alcohols in combination with phenols and other acidic precursors.[17] While many articles have been published on the methodology of this reaction, we chose to follow a recently reported procedure that exploits resin-supported triphenylphosphine

Scheme 1



(I)

R-OH = A1, A14, A37 and A46

Primary Alcohols		Secondary Alcohols	
1. PS-PPh_3	2.2 eq.	1. PS-PPh_3	4.4 eq.
2. 3-Chloro-biphenyl-4-ol	1.0 eq.	2. 3-Chloro-biphenyl-4-ol	1.0 eq.
3. DBAD	1.6 eq.	3. DBAD	(1.6 x 2) eq.
4. Aliphatic Alcohol	1.25 eq.	4. Aliphatic Alcohol	(1.25 x 2) eq.

(PS−PPh_3) and di-*tert*-butylazodicarboxylate (DBAD) as the redox partners.[18] It had been demonstrated that this combination has distinct advantages in terms of ease of isolation of the products and seemed to be the most easily adaptable for implementation on our automation platform.

Consequently, a series of experiments was performed using the phenol **I** and the alcohols **A1**, **A14**, **A37**, and **A46** as shown in Scheme 1. Compound **I** was chosen because it is moderately deactivated, both electronically and sterically, and was therefore thought to be a suitably demanding chemical probe. The alcohols were chosen to be representative of the chemical reactivity and physicochemical properties displayed by the precursors shown in Figure 1. The purpose of these experiments was to identify optimal bench conditions prior to developing an automated procedure. This order of events gave us a performance target in subsequently developing the chemistry on the synthesizer, a strategy that allowed us to distinguish between the limitations of the chemistry and those of the automation platform.

Three key chemistry issues became apparent during this development phase. The first related to the quality of the triphenylphosphine resin used. It was found that resin from different suppliers had different ratios of supported phosphine to phosphine oxide, sufficient to require modifications to the stoichiometries employed in the reaction. Importantly, it was determined that the oxide impurity arose from aerial oxidation[19] and that resins supplied by different companies demonstrated different degrees of oxygen sensitivity.[20] For the purposes of this work, we fixed on one supplier that provided resin with consistent high loading of phosphine with little or no related oxide, as determined by elemental analysis and ^{31}P NMR.[21] It was also helpful to open bottles of this reagent just prior to the synthesis setup. Consistent with these observations was the need to carefully exclude oxygen from the reaction in order to optimize yields.

Other key development issues related to the observation that secondary alcohols were, not unsurprisingly, consistently less reactive than primary alcohols. However, it was found that performing a double addition of DBAD and the secondary alcohol precursor in the presence of a 2-fold excess of the supported phosphine reagent compensated for the reduced reactivity and resulted in significantly improved reaction performance.[18] Also, during this phase of the protocol development, we explored the use of both DCM and THF as reaction solvent and noted only minor differences in the yields of products obtained. Interestingly, we also determined that the introduction of up to 40% DMA as a cosolvent did not significantly impact the efficiency of the reaction. This was important because it greatly increased the range of compounds that could be solubilized for derivatization by this process. The optimized conditions identified from these studies are described in Scheme 1.

Table 2. Comparison of Manual and Automation Runs for Aliphatic Monomers

	Phenol Core	Alcohol Precursors			
		—OH A1	OH A14	OH A37	OH A46
Manual Method	OH Cl Ph	61%	71%	89%	84%
Automation Run	OH Cl Ph	60%	73%	85%	45%

Subsequently, these conditions were employed on our automation platform using the same reaction partners shown above. After significant optimization of the various pipetting and transfer processes involved in the automated synthesis, a high degree of correlation between the bench and automated processes was achieved, as shown by the data in Table 2. The newly developed automated protocol was then adapted to run 48 reactions using the phenol **I** in combination with the set of the precursors listed in Figure 1.

As was commented above, this set of alcohols was chosen to investigate hydrophobic interactions in lead optimization exercises and was not designed specifically for the Mitsunobu protocol. Not unsurprisingly therefore, several failed to react.

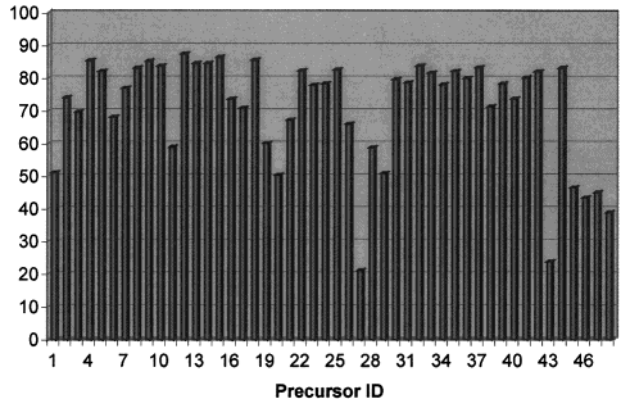


Figure 7. Aliphatic alcohol precursors yields: average = 71%; SD = 17%.

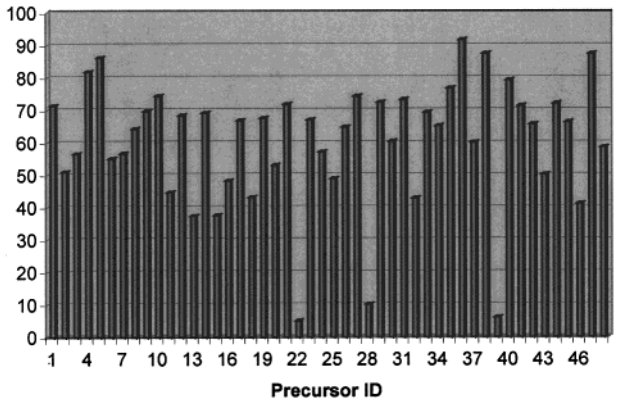


Figure 8. Phenolic precursor yields: average = 60%; SD = 19%.

Most obvious were precursors **A8**, **A13**, and **A38**, all of which contained a 3° alcohol functionality.[17] Similarly, compounds **A42**, **A45**, and **A47** contain constrained 2° alcohol groups, which would not be expected to invert readily under the normal S_N2 conditions of the Mitsunobu reaction. In addition, precursors **A29**, **A30**, and **A31** could be anticipated to be prone to a competing β-elimination reaction involving the activated oxyphosphonium intermediate,[22] while the acidic alcohols **A19** and **A20** could be expected to be inductively deactivated and therefore unreactive under the conditions explored. It was also supposed that the neopentyl system **A15** would be prone to rearrangement,[23] while the adamantyl alcohol precursor **A48** was determined to be too hindered to react under the conditions investigated.

These unreactive precursors where then replaced with others more compatible with the conditions of the Mitsunobu reaction. The substitutions were designed to retain as much of the character of the original set as possible. This involved replacement of terminal acetylenes with internal variants, tertiary alcohols were replaced with sterically less hindered but highly α-branched secondary analogues, and compounds susceptible to β-elimination were replaced with others containing substituents in positions not prone to such reactions.

In addition to making replacements, it was helpful to change the physical order of the precursors within the set such that the less reactive 2° alcohols were grouped together. This greatly facilitated the execution of the double addition of reagents by the synthesizer, allowing the single addition of DBAD and less reactive precursor first and allowing them to react while the synthesizer was setting up the remaining 30 reactions using primary alcohols. On completion of the initial pipetting operations, a suitable time delay had ensued prior to the second addition of reagents to the subset of 2° alcohols. Figure 9 shows the final order and content of the optimized set of precursors, and the yields observed using this reagent set are reported in Figure 7.

With these modifications, we achieved a reaction success rate of 100% and the reaction yields across the set were relatively uniform (SD = 15%) and averaged 68%. It was estimated that this represents a near-quantitative chemical conversion, since we typically see peak-to-peak transformation of starting material to product by LC−MS, and in independent experiments we have determined that we can loose up to 25% of the product masses during the postsynthesis sample manipulations required for analysis and purification.

An exercise essentially identical to that outlined above was then repeated using alcohol **II** shown in Scheme 2, in combination with four phenolic probes representative of the range of chemical reactivity of the set under investigation. These reagents are shown in Table 3, with the optimal reaction conditions being depicted at the bottom of Scheme 2. Attempts to vary the order of addition of reagents whereby the phenolic reagents were introduced last resulted in the formation of significant amounts of alkylated hydrazine derivatives.[24] Thus, for both protocols, an identical order of addition of reagents was observed. The optimized protocol was then transferred to our automation platform and used to run reactions employing the previously selected set of 64 phenols. The results for the highest yielding 48 reactions are shown in Figure 8, with the specific phenols associated with these reactions shown in Figure 2. Their position within the set and their original cluster assignment are indicated by the letters P and C, respectively, and the distribution of this set within the clusters of the original ACD phenols is shown graphically as the smaller columns in Figure 6.

In comparison with the aliphatic alcohol run, the average yield was lower (60%) and the individual yields were slightly more variable (SD = 19%), as might be expected with a diversity-based experiment covering a wider range of reactants. However, these differences are less than might have been expected, and the overall reaction performance is obvious and gives an excellent indication of the generality of the procedure.

Concluding Remarks

Given these results, it is apparent that the use of optimized precursor sets significantly improves the performance of automated chemical procedures, in terms of both the reaction success rates and the overall yields of the syntheses. This enhanced efficiency is significant in that it greatly increases the applicability of this methodology to lead optimization where larger sets of compounds can now be reliably prepared from relatively small amounts of valuable starting materials. We have also established that the co-optimization of precursor sets in terms of experimental design and chemical compliance is a realistic goal that does not require undue

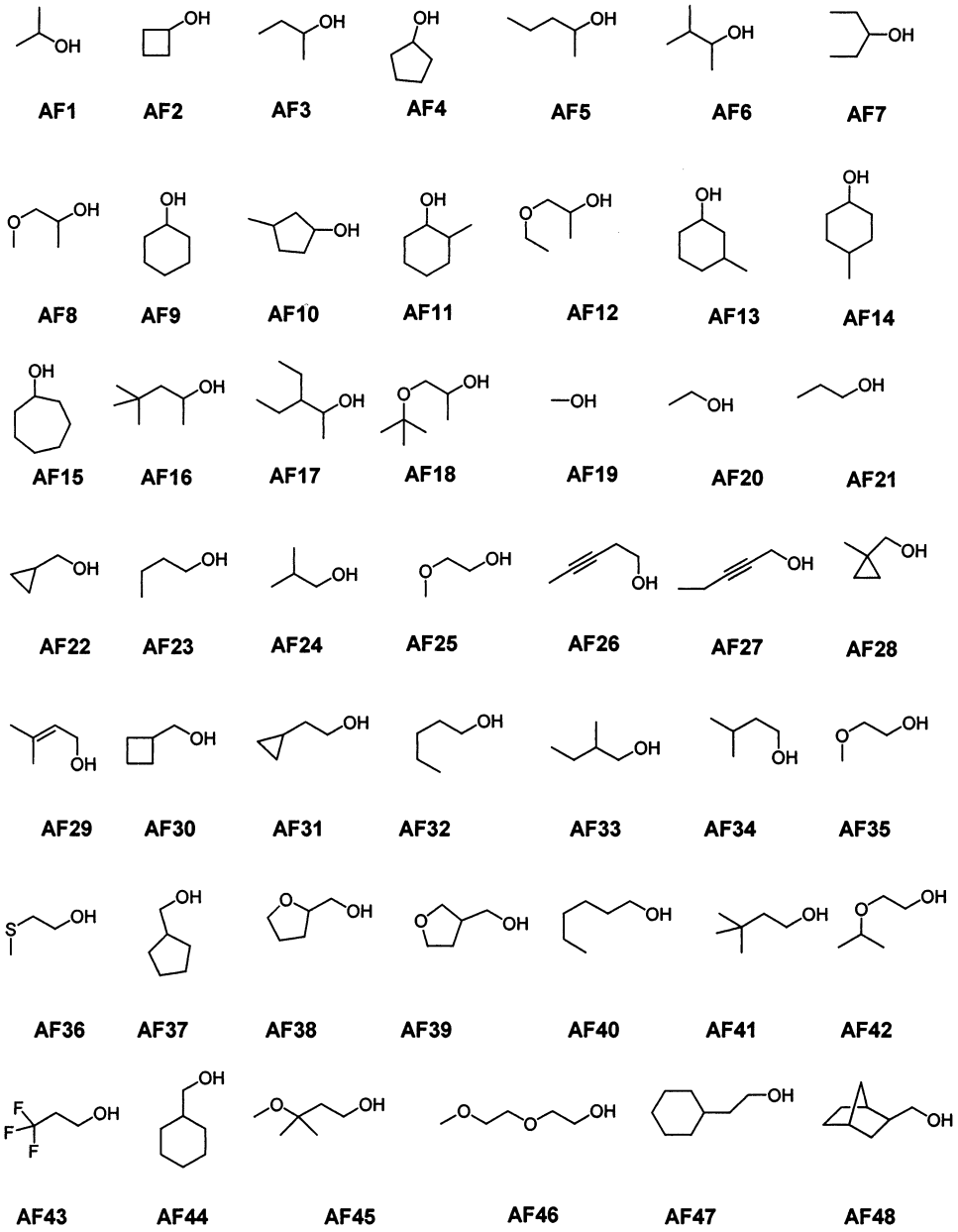
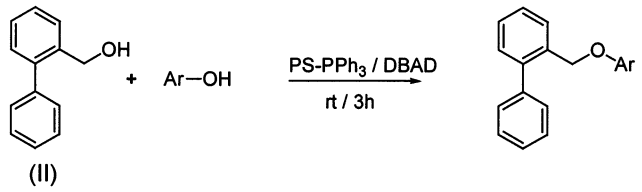


Figure 9. Optimized set of aliphatic alcohols for the Mitsunobu reaction.

Scheme 2



(II)

Ar-OH = P9-C9, P18-C20, P37-C47 and P40-C60

1. PS-PPh_3	2.2 eq.
2. Phenol	1.5 eq.
3. DBAD	1.6 eq.
4. Biphenyl-2-yl-methanol	1.0 eq.

compromises to be made to the fundamental medicinal chemistry objectives. As regards the generality of the chemical protocols, it should be noted that the phenols used in the above experiments cover a wide range of structural classes and related reactivities and therefore give a good indication of the scope of this procedure. It is also apparent that such optimized precursor sets have widespread application in a number of problems in lead optimization, and in our laboratories, they are the preferred method for performing initial analogue exercises, particularly in the absence of compelling structural information or extensive SAR data. We will shortly report on the application of this strategy to other reactions and alternative experimental designs.

Experimental Section

General. Starting materials, reagents, and solvents were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise stated and were used as supplied without further purification. DBAD was purchased from Lancaster Synthesis Inc., Windham, NH. In the case of PS−PPh_3, only newly opened bottles were used for all of the reactions

Table 3. Comparison of Manual and Automation Runs for Phenolic Monomers

	Alcohol Core	Phenolic Precursors			
		 P9-C9	 P18-C20	 P37-C47	 P40-C60
Manual Method		83%	45%	78%	87%
Automation Run		70%	43%	60%	79%

described below. All ^{1}H NMR spectra were recorded on a Varian Unity 500 plus NMR spectrometer, and chemical shifts (δ) are reported in ppm relative to TMS as internal standard. All samples were dissolved in $CDCl_3$ unless otherwise specified. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; br, broad. Coupling constants (*J* values) where noted are quoted in hertz. Low-resolution mass spectra were recorded using a Finnigan DCI/MS SSQ7000 single-quadruple mass spectrometer. LC−MS analyses were performed using a Hewlett-Packard HP1100 instrument fitted with photodiode array and ELSD (SEDEX 55) detectors and employing the following methods: solvent A of 0.1% TFA; solvent B of acetonitrile (ACN); 4 min gradient of 10−95% B; column, YMC ODS-AQ 2.0 mm × 50 mm cartridge; APCI positive ionization to identify the mass ion. All parallel syntheses were performed using a PE Biosystems (Applied Biosystems) Solaris 530 organic synthesizer configured as supplied by the manufacturer with the exception of precursor racks, which were customized to accommodate a 6 × 4 array of 4 mL precursor vials configured in a 96-well footprint format. All precursors used in the automated synthesis were supplied as either oils or solids in capped 4 mL Kimble vials (Kimble 60881A-1545, convenience pack) with each vial containing 0.6 mmol of material supplied directly from Aldrich Chemical Co. The synthesis scripts used to execute the automated protocol are provided in the Supporting Information and are annotated to facilitate an understanding of the logic of the programming. All samples after synthesis were purified using preparative reverse-phase HPLC employing a Waters Nova-Pak HR C18 column (25 mm × 100 mm, 6 μm particle size) using a gradient of 10−100% ACN, 0.1% aqueous TFA over 8 min (10 min run time) at a flow rate of 40 mL/min.

General Bench Protocol for the Synthesis of Aryl Alkyl Ethers Using Aliphatic Alcohols as Precursors. PS−PPh_3 resin (54 mg, 2.2 equiv for 1° alcohols; 108 mg, 4.4 equiv for 2° alcohols) was added to a dried 20 mL scintillation vial that was then capped and flushed with nitrogen. The resin was suspended in 1 mL of anhydrous THF. After a period of 2 min, the phenolic core **I** (15 mg, 0.073 mmol) dissolved in 0.5 mL of anhydrous THF was added in a single portion. The resultant suspension was mixed briefly, after which a solution of DBAD (27 mg, 1.6 equiv) in 0.5 mL of anhydrous THF was added in a single portion. This mixture was then agitated on an orbital shaker for 3 min, after which a solution of the alcohol precursor (1.25 equiv) in 1.0 mL of anhydrous THF was added in a single portion. The reaction mixture was then agitated for a period of 3 h. Then, for 2° alcohols, additions of DBAD (27 mg in 0.5 mL of anhydrous THF) and monomer (1.25 equiv in 0.5 mL of anhydrous THF) were repeated. The stirring was maintained for an additional 6 h. The resultant suspension was filtered, and the resin was washed with THF (3 × 3 mL). The filtrate and washings were combined and evaporated in vacuo, and the weight of the crude reaction mixture was determined. LC−MS analysis was performed on this mixture prior to dissolving the residue in 1.5 mL of a 1:1 mixture of DMSO/MeOH and to submitting to purification by preparative reverse-phase HPLC. Homogeneous fractions were combined and evaporated in vacuo, and the residue's weight was determined to calculate the yield of the reaction. Products were typically obtained as amorphous solids or oils, and their NMR and MS data were consistent with the desired structures.

General Bench Protocol for the Synthesis of Aryl Alkyl Ethers Using Phenols as Precursors. PS−PPh_3 resin (60 mg, 2.2 equiv) was added to a dried 20 mL scintillation vial that was then capped and flushed with nitrogen. The resin was suspended in 1 mL of anhydrous THF. After a period of 2 min, the phenolic precursor (1.5 equiv) dissolved in 0.5 mL of anhydrous THF was added in a single portion. The resultant suspension was mixed briefly, after which a solution of DBAD (30 mg, 1.6 equiv) in 0.5 mL of anhydrous THF was added in a single portion. This mixture was then agitated on an orbital shaker for 3 min, after which a solution of the alcohol core **II** (15 mg, 0.081 mmol) in 1.0 mL of anhydrous THF was added in a single portion. The reaction mixture was then agitated for a period of 9 h. The resultant suspension was filtered, and the resin was washed with THF (3 × 3 mL). The filtrate and washings were combined and evaporated in vacuo, and the weight of the crude reaction mixture was determined. LC−MS analysis was performed on this mixture prior to dissolving the residue in 1.5 mL of a 1:1 mixture of DMSO/MeOH and to submitting to purification by preparative reverse-phase HPLC. Homogeneous fractions were combined and evaporated in vacuo, and the residue's weight was determined to calculate the yield of the reaction. Products were typically obtained as amorphous solids or oils, and their NMR and MS data were consistent with the desired structures.

HCl Digest. The crude material obtained from evaporation of solvents after the synthesis was treated with 4.0 mL of 4 M HCl in dioxane at room temperature for 4 h. The resulting solution was evaporated in vacuo, and the workup was continued as described above. The HCl digest was performed to decompose the hydrazine byproduct formed from reduction of DBAD and was applied to crude materials from automated runs employing the phenolic precursors **P33-C39** and **P39-C55**, for which there was a possibility of a coelution

of the byproduct and the resulting ether during HPLC purification.

Automated Protocol for the Synthesis of Aryl Alkyl Ethers Using the Aliphatic Alcohols as Precursors. For 2° Alcohols. A reaction vessel of the Solaris 530 synthesizer was charged with PS−PPh_3 resin (108 mg, 4.4 equiv) and was purged by passing a stream of N_2 for 45 s. A solution of the phenolic core **I** (1.000 mL, 15 mg/mL) was added to the vessel, and the resultant suspension was shaken for 15 min. A solution of DBAD (0.600 mL, 54 mg/mL) in anhydrous THF was then added, the contents of the flask were shaken for 10 min, and a solution of the alcohol precursor (0.345 mL, 0.3 mM) was added. The resultant suspension was shaken at room temperature for 3 h. The addition of DBAD and monomer was then repeated, and the agitation was maintained for an additional 6 h. The solution was drained and transferred to a destination vial. The resin was washed with 3.0, 3.5, and 3.5 mL of THF. The washes were combined with the filtrate, and resultant solution was processed as described before in the corresponding bench protocol.

For 1° Alcohols. A reaction vessel of the Solaris 530 synthesizer was charged with PS−PPh_3 resin (54 mg, 2.2 equiv) and was purged by passing a stream of N_2 for 45 s. A solution of the phenolic core **I** (1.000 mL, 15 mg/mL) was added to the vessel, and the resultant suspension was shaken for 15 min. A solution of DBAD (0.600 mL, 54 mg/mL) in anhydrous THF was then added, and the contents of the flask were shaken for 10 min prior to the addition of a solution of the alcohol precursor (0.345 mL, 0.3 mM). The resultant suspension was shaken at room temperature for 9 h. The solution was drained and transferred to a destination vial. The resin was then washed with 2.5, 3.5, and 3.5 mL of THF. The washes were combined with the filtrate, and the resultant solution was processed as described before in the corresponding bench protocol.

Automated Protocol for the Synthesis of Aryl Alkyl Ethers Using the Phenols as Precursors. A reaction vessel of the Solaris 530 synthesizer was charged with PS−PPh_3 resin (60 mg, 2.2 equiv) and was purged by passing a stream of N_2 for 45 s. A solution of a phenolic precursor (0.410 mL, 0.3 mM solution) was added to the vessel, and the resultant suspension was shaken for 15 min. A solution of DBAD (0.600 mL, 60 mg/mL) in anhydrous THF was then added, and the contents of the flask were shaken for 10 min prior to the addition of a solution of the alcohol core **II** (1.000 mL, 15 mg/mL). The resultant suspension was shaken at room temperature for 9 h. The solution was drained and transferred to a destination vial. The resin was then washed with 2.5, 3.5, and 3.5 mL of THF. The washes were combined with the filtrate, and the resultant solution was processed as described before in the corresponding bench protocol.

For each synthesized compound, the following data are provided: yield from the automated run, ^{1}H NMR data, MS data, and retention time R_T (min) for purified sample on the analytical HPLC.

3-Chloro-4-isopropoxybiphenyl (derived from I and AF1): 8.8 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.59 (m, 1H), 1.41 (d, J = 5.9 Hz, 6H); MS (DCI/NH_3) m/z 264 $[M + NH_4]^+$; R_T = 2.40.

3-Chloro-4-cyclobutyloxybiphenyl (derived from I and AF2): 13.4 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.52 (m, 1H), 7.40 (m, 2H), 7.31 (m, 3H), 6.85 (m, 1H), 6.84 (d, J = 8.7 Hz, 1H), 4.72 (m, 1H), 2.50 (m, 2H), 2.28 (m, 2H), 1.90 (m, 1H), 1.71 (m, 1H); MS (DCI/NH_3) m/z 276 $[M + NH_4]^+$; R_T = 2.48.

4-*sec*-Butoxy-3-chlorobiphenyl (derived from I and AF3): 12.7 mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.52 (m, 1H), 7.41 (m, 2H), 7.32 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 4.37 (m, 1H), 1.82 (m, 1H), 1.70 (m, 1H), 1.36 (d, J = 5.9 Hz, 1H), 1.03 (t, J = 7.3 Hz, 1H); MS (DCI/NH_3) m/z 278 $[M + NH_4]^+$; R_T = 2.53.

3-Chloro-4-cyclopentyloxybiphenyl (derived from I and AF4): 16.3 mg (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (d, J = 2.2 Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.85 (m, 1H), 1.80−2.02 (m, 6H), 1.65 (m, 2H); MS (DCI/NH_3) m/z 290 $[M + NH_4]^+$; R_T = 2.60.

3-Chloro-4-(1-methylbutoxy)biphenyl (derived from I and AF5): 15.8 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.41 (m, 1H), 1.83 (m, 1H), 1.40−1.70 (m, 3H), 1.36 (d, J = 6.2 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; R_T = 2.65.

3-Chloro-4-(1,2-dimethylpropoxy)biphenyl (derived from I and AF6): 13.1 mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.5 Hz, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.22 (m, 1H), 2.01 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; R_T = 2.66.

3-Chloro-4-(1-ethylpropoxy)biphenyl (derived from I and AF7): 14.8 mg (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), (4.21 (m, 1H), 1.76 (m, 4H), 1.01 (t, J = 7.5 Hz, 6H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; R_T = 2.64.

3-Chloro-4-(2-methoxy-1-methylethoxy)biphenyl (derived from I and AF8): 16.1 mg (83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.5 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.33 (m, 1H), 7.08 (d, J = 8.7 Hz, 1H), 4.56 (m, 1H), 3.67 (dd, J = 10.3, 5.9 Hz, 1H), 3.55 (dd, J = 10.3, 4.7 Hz, 1H), 3.44 (s, 3H), 1.38 (d, J = 6.2 Hz, 3H); MS (DCI/NH_3) m/z 294 $[M + NH_4]^+$; R_T = 2.25.

3-Chloro-4-cyclohexyloxybiphenyl (derived from I and AF9): 17.1 mg (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.33 (m, 1H), 1.98 (m, 2H), 1.84 (m, 2H), 1.68 (m, 2H), 1.56 (m, 1H), 1.38 (m, 3H); MS (DCI/NH_3) m/z 304 $[M + NH_4]^+$; R_T = 2.70.

3-Chloro-4-(3-methylcyclopentyloxy)biphenyl [mixture of cis/trans ~1:2; not assigned] (derived from I and AF10): 16.8 mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm

7.61 (m, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.95 (m, 1H), 4.85 (m, 1H), 2.34 (m, 1H), 1.77−2.24 (m, 4H), 1.42 (m, 1H), 1.23 (m, 1H), 1.12 (d, J = 6.9 Hz, 1H), 1.04 (d, J = 6.9 Hz, 2H); MS (DCI/NH_3) m/z 304 $[M + NH_4]^+$; R_T = 2.72.

3-Chloro-4-(2-methylcyclohexyloxy)biphenyl [mixture of cis/trans ∼1:2; not assigned] (derived from I and AF11): 12.4 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (m, 1H), 7.52 (m, 2H), 7.40 (m, 3H), 7.32 (m, 1H), 6.99 (m, 1H), 4.44 (m, 1H), 3.83 (m, 0.5H), 2.15 (m, 0.5H), 2.03 (m, 1H), 1.84 (m, 2H), 1.69 (m, 2H), 1.26−1.50 (m, 3H), 1.09 (d, J = 6.2 Hz, 1H), 1.06 (d, J = 6.9 Hz, 2H); MS (DCI/NH_3) m/z 318 $[M + NH_4]^+$; R_T = 2.83.

3-Chloro-4-(2-ethoxy-1-methylethoxy)biphenyl (derived from I and AF12): 17.8 mg (87%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.60, 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 4.57 (m, 1H), 3.71 (dd, J = 10.3, 5.9 Hz, 1H), 3.57 (dd, J = 10.5, 4.8 Hz, 1H), 1.39 (d, J = 6.2 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H); MS (DCI/NH_3) m/z 308 $[M + NH_4]^+$; R_T = 2.37.

3-Chloro-4-(3-methylcyclohexyloxy)biphenyl [mixture of cis/trans ∼1:1; not assigned] (derived from I and AF13): 17.8 mg (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.31 (m, 1H), 7.01 (m, 1H), 4.69 (m, 0.5H), 4.21 (m, 0.5H), 2.18 (m, 1H), 2.01 (m, 1H), 1.62−1.90 (m, 2H), 1.15−1.60 (m, 5H), 0.97 (d, J = 6.6 Hz, 1.5H), 0.91 (d, J = 6.6 Hz, 1.5H); MS (DCI/NH_3) m/z 318 $[M + NH_4]^+$; R_T = 2.80.

3-Chloro-4-(4-methylcyclohexyloxy)biphenyl [mixture of cis/trans ∼1:2; not assigned] (derived from I and AF14): 17.8 mg (85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 7.01 (m, 1H), 4.60 (m, 0.6H), 4.19 (m, 0.3H), 2.18 (m, 1H), 2.06 (m, 1H), 1.81 (m, 1H), 1.42−1.64 (m, 6H), 0.94 (m, 3H); MS (DCI/NH_3) m/z 318 $[M + NH_4]^+$; R_T = 2.82.

3-Chloro-4-cycloheptyloxybiphenyl (derived from I and AF15): 18.2 mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.50 (m, 1H), 2.04 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H), 1.63 (m, 4H), 1.48 (m, 2H); MS (DCI/NH_3) m/z 318 $[M + NH_4]^+$; R_T = 2.80.

3-Chloro-4-(1,3,3-trimethylbutoxy)biphenyl (derived from I and AF16): 15.6 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.5 Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, J = 8.7 Hz, 1H), 4.58 (m, 1H), 1.93 (dd, J = 14.7, 8.1 Hz, 1H), 1.47 (dd, J = 14.7, 2.8 Hz, 1H), 1.34 (d, J = 6.2 Hz, 1H), 0.98 (s, 9H); MS (DCI/NH_3) m/z 320 $[M + NH_4]^+$; R_T = 2.81.

3-Chloro-4-(2-ethyl-1-methylbutoxy)biphenyl (derived from I and AF17): 15.0 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.5 Hz, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), 4.48 (m, 1H), 1.65 (m, 1H), 1.53 (m, 3H), 1.36 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H), 0.96 (m, 6H); MS (DCI/NH_3) m/z 320 $[M + NH_4]^+$; R_T = 2.85.

4-(2-*tert*-Butoxy-1-methylethoxy)-3-chlorobiphenyl (derived from I and AF18): 19.1 mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 7.11 (d, J = 8.7 Hz, 1H), 4.50 (m, 1H), 3.66 (dd, J = 9.4, 5.6 Hz, 1H), 3.44 (dd, J = 9.4, 5.6 Hz, 1H), 1.39 (d, J = 6.2 Hz, 3H), 1.21 (m, 9H); MS (DCI/NH_3) m/z 336 $[M + NH_4]^+$; R_T = 2.59.

3-Chloro-4-methoxybiphenyl (derived from I and AF19): 9.2 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, J = 2.5 Hz, 1H), 7.53 (m, 2H), 7.44 (m, 3H), 7.32 (m, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H); MS (DCI/NH_3) m/z 218 $[M + H]^+$; R_T = 2.15.

3-Chloro-4-ethoxybiphenyl (derived from I and AF20): 8.2 mg (50%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.5 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 3H), 7.33 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 1H), 1.49 (t, J = 7.0 Hz, 3H); MS (DCI/NH_3) m/z 232 $[M + H]^+$; R_T = 2.30.

3-Chloro-4-propoxybiphenyl (derived from I and AF21): 11.6 mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.5 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), 4.04 (t, J = 6.4 Hz, 2H), 1.89 (m, 2H), 1.09 (t, J = 7.5 Hz, 1H); MS (DCI/NH_3) m/z 264 $[M + NH_4]^+$; R_T = 2.45.

3-Chloro-4-cylcopropylmethoxybiphenyl (derived from I and AF22): 14.9 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.7 Hz, 1H), 3.93 (d, J = 6.6 Hz, 2H), 1.33 (m, 1H), 0.67 (m, 2H), 0.41 (m, 2H); MS (DCI/NH_3) m/z 276 $[M + NH_4]^+$; R_T = 2.40.

4-Butoxy-3-chlorobiphenyl (derived from I and AF23): 14.2 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 1.85 (m, 2H), 1.55 (m, 2H), 1.00 (t, J = 7.5 Hz, 1H); MS (DCI/NH_3) m/z 278 $[M + NH_4]^+$; R_T = 2.58.

3-Chloro-4-isobutoxybiphenyl (derived from I and AF24): 14.3 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 3H), 7.33 (m, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 6.6 Hz, 2H), 2.17 (m, 1H), 1.08 (d, J = 6.9 Hz, 6H); MS (DCI/NH_3) m/z 278 $[M + NH_4]^+$; R_T = 2.60.

3-Chloro-4-(2-methoxyethoxy)biphenyl (derived from phenol I and AF25): 15.2 mg (83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 3H), 7.33 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.22 (m, 2H), 3.83 (m, 2H), 3.50 (s, 3H); MS (DCI/NH_3) m/z 280 $[M + NH_4]^+$; R_T = 2.11.

3-Chloro-4-pent-3-ynyloxybiphenyl (derived from I and AF26): 12.5 mg (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.33 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.16 (t, J = 7.3 Hz, 2H), 2.70 (m, 2H), 1.81 (t, J = 2.5 Hz, 3H); MS (DCI/NH_3) m/z 288 $[M + NH_4]^+$; R_T = 2.38.

3-Chloro-4-pent-2-ynyloxybiphenyl (derived from I and AF27): 4.0 mg (21%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, J = 2.2 Hz, 1H), 7.53 (m, 2H), 7.43 (m, 3H), 7.33 (m, 1H), 7.16 (d, J = 8.7 Hz, 1H), 4.79 (t, J = 2.0 Hz, 2H), 2.24 (m, 2H), 1.14 (t, J = 7.6 Hz, 3H); MS (DCI/NH_3) m/z 288 $[M + NH_4]^+$; R_T = 1.85.

3-Chloro-4-(1-methylcyclopropylmethoxy)biphenyl (derived from I and AF28): 11.2 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, J = 2.5 Hz, 1H), 7.52 (m,

2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 3.94 (d, $J = 6.9$ Hz, 2H), 1.10 (d, $J = 5.9$ Hz, 3H), 1.03 (m, 1H), 0.82 (m, 1H), 0.56 (dt, $J = 8.5$, 4.8 Hz, 1H), 0.41 (dt, $J = 8.1$, 5.0 Hz, 1H); MS (DCI/NH_3) m/z 290 $[M + NH_4]^+$; $R_T = 2.54$.

3-Chloro-4-(3-methylbut-2-enyloxy)biphenyl (derived from I and AF29): 9.7 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, $J = 8.7$ Hz, 1H), 5.53 (m, 1H), 4.64 (d, $J = 6.6$ Hz, 2H), 1.79 (d, $J = 19.7$ Hz, 6H); MS (DCI/NH_3) m/z 290 $[M + NH_4]^+$; $R_T = 2.52$.

3-Chloro-4-cyclobutylmethoxybiphenyl (derived from I and AF30): 15.2 mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 4.03 (d, $J = 6.6$ Hz, 2H), 2.84 (m, 1H), 2.17 (m, 2H), 1.97 (m, 4H); MS (DCI/NH_3) m/z 290 $[M + NH_4]^+$; $R_T = 2.64$.

3-Chloro-4-(2-cyclopropylethoxy)biphenyl (derived from I and AF31): 15.0 mg (79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, $J = 2.5$ Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 4.15 (t, $J = 6.6$ Hz, 2H), 1.76 (dd, $J = 13.4$, 6.9 Hz, 2H), 0.91 (m, 1H), 0.51 (m, 2H), 0.16 (m, 2H); MS (DCI/NH_3) m/z 290 $[M + NH_4]^+$; $R_T = 2.58$.

3-Chloro-4-pentyloxybiphenyl (derived from I and AF32): 16.1 mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 4.07 (t, $J = 6.6$ Hz, 2H), 1.87 (m, 2H), 1.44 (m, 4H), 0.95 (t, $J = 7.3$ Hz, 3H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; $R_T = 2.71$.

3-Chloro-4-(2-methylbutoxy)biphenyl (derived from I and AF33): 15.7 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 3.93 (dd, $J = 9.0$, 5.9 Hz, 1H), 3.84 (dd, $J = 9.0$, 6.6 Hz, 1H), 1.96 (m, 1H), 1.63 (m, 1H), 1.33 (m, 1H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; $R_T = 2.71$.

3-Chloro-4-(3-methylbutoxy)biphenyl (derived from I and AF34): 15.0 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 4.10 (t, $J = 6.6$ Hz, 2H), 1.91 (m, 1H), 1.76 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 6H); MS (DCI/NH_3) m/z 292 $[M + NH_4]^+$; $R_T = 2.69$.

3-Chloro-4-(2-methoxyethoxy)biphenyl (derived from I and AF35): 15.9 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.33 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.23 (t, $J = 5.1$ Hz, 2H), 3.86 (t, $J = 5.1$ Hz, 2H), 3.66 (dd, $J = 14.0$, 7.2 Hz, 2H), 1.25 (t, $J = 7.0$ Hz, 3H); MS (DCI/NH_3) m/z 294 $[M + NH_4]^+$; $R_T = 2.23$.

3-Chloro-4-(2-methylsulfanylethoxy)biphenyl (derived from phenol I and AF36): 15.6 mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 4H), 7.33 (m, 1H), 7.00 (d, $J = 8.4$ Hz, 1H), 4.27 (t, $J = 6.7$ Hz, 2H), 2.96 (t, $J = 6.7$ Hz, 2H), 2.28 (s, 3H); MS (DCI/NH_3) m/z 296 $[M + NH_4]^+$; $R_T = 2.34$.

3-Chloro-4-cyclopentylmethoxybiphenyl (derived from I and AF37): 16.7 mg (83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 3.95 (d, $J = 6.9$ Hz, 2H), 2.45 (m, 1H), 1.89 (m, 2H), 1.64 (m, 4H), 1.44 (m, 2H); MS (DCI/NH_3) m/z 304 $[M + NH_4]^+$; $R_T = 2.75$.

2-(3-Chlorobiphenyl-4-yloxymethyl)tetrahydrofuran (derived from I and AF38): 14.4 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 4.35 (m, 1H), 4.08 (m, 2H), 3.98 (m, 1H), 3.85 (m, 1H), 1.89−2.16 (m, 4H); MS (DCI/NH_3) m/z 306 $[M + NH_4]^+$; $R_T = 2.22$.

3-(3-Chlorobiphenyl-4-yloxymethyl)tetrahydrofuran (derived from I and AF39): 15.8 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.33 (m, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 3.98 (m, 4H), 3.80 (m, 2H), 2.82 (m, 1H), 2.15 (m, 1H), 1.81 (m, 1H); MS (DCI/NH_3) m/z 306 $[M + NH_4]^+$; $R_T = 2.19$.

3-Chloro-4-hexyloxybiphenyl (derived from I and AF40): 14.9 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 4.07 (t, $J = 6.6$ Hz, 2H), 1.86 (m, 2H), 1.52 (m, 2H), 1.37 (m, 4H), 0.92 (t, $J = 7.0$ Hz, 3H); MS (DCI/NH_3) m/z 306 $[M + NH_4]^+$; $R_T = 2.83$.

3-Chloro-4-(3,3-dimethylbutoxy)biphenyl (derived from I and AF41): 16.2 mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (d, $J = 2.2$ Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.99 (d, $J = 8.7$ Hz, 1H), 4.13 (t, $J = 7.2$ Hz, 2H), 1.82 (t, $J = 7.2$ Hz, 2H), 1.03 (s, 9H); MS (DCI/NH_3) m/z 306 $[M + NH_4]^+$; $R_T = 2.76$.

3-Chloro-4-(2-isopropoxyethoxy)biphenyl (derived from I and AF42): 16.7 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 4.21 (t, $J = 5.3$ Hz, 2H), 3.85 (t, $J = 5.3$ Hz, 2H), 3.75 (m, 1H), 1.21 (d, $J = 5.9$ Hz, 6H); MS (DCI/NH_3) m/z 308 $[M + NH_4]^+$; $R_T = 2.35$.

3-Chloro-4-(3,3,3-trifluoropropoxy)biphenyl (derived from I and AF43): 5.0 mg (24%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.43 (m, 3H), 7.34 (m, 1H), 6.99 (d, $J = 8.4$ Hz, 1H), 4.30 (t, $J = 6.7$ Hz, 2H), 2.72 (m, 2H); MS (DCI/NH_3) m/z 300 $[M + H]^+$; $R_T = 1.84$.

3-Chloro-4-cyclohexylmethoxybiphenyl (derived from I and AF44): 17.5 mg (83%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.5$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 3.86 (d, $J = 6.2$ Hz, 2H), 1.68−1.96 (m, 6H), 1.06−1.38 (m, 5H); MS (DCI/NH_3) m/z 318 $[M + NH_4]^+$; $R_T = 2.87$.

3-Chloro-4-(3-methoxy-3-methylbutoxy)biphenyl (derived from I and AF45): 9.9 mg (46%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.53 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 4.18 (t, $J = 7.0$ Hz, 2H), 3.24 (s, 3H), 2.09 (t, $J = 7.0$ Hz, 2H), 1.27 (s, 6H); MS (DCI/NH_3) m/z 305 $[M + H]^+$; $R_T = 2.41$.

3-Chloro-4-[2-(2-methoxyethoxy)ethoxy]biphenyl (derived from I and AF46): 9.3 mg (43%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m,

2H), 7.42 (m, 3H), 7.32 (m, 1H), 7.01 (d, $J = 8.7$ Hz, 1H), 4.25 (t, $J = 5.0$ Hz, 2H), 3.94 (t, $J = 5.0$ Hz, 2H), 3.79 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H); MS (DCI/NH_3) *m/z* 324 $[M + NH_4]^+$; $R_T = 2.07$.

3-Chloro-4-(2-cyclohexylethoxy)biphenyl (derived from I and AF47): 9.9 mg (45%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.42 (m, 3H), 7.32 (m, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 4.10 (t, $J = 6.9$ Hz, 2H), 1.54−1.84 (m, 8H), 1.13−1.34 (m, 3H), 1.01 (m, 2H); MS (DCI/NH_3) *m/z* 332 $[M + NH_4]^+$; $R_T = 2.94$.

4-(Bicyclo[2.2.1]hept-2-ylmethoxy)-3-chlorobiphenyl [mixture of exo and endo] (derived from I and AF48): 8.5 mg (39%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (d, $J = 2.2$ Hz, 1H), 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (m, 1H), 6.99 (m, 1H), 3.76−4.10 (m, 2H), 2.21−2.49 (m, 3H), 1.77−2.08 (m, 1H), 1.08−1.64 (m, 6H), 0.81 (m, 1H); MS (DCI/NH_3) *m/z* 330 $[M + NH_4]^+$; $R_T = 2.85$.

3-(Biphenyl-2-ylmethoxy)benzoic acid methyl ester (derived from II and P1-C1): 18.4 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 2H), 7.51 (m, 1H), 7.38 (m, 8H), 7.30 (dd, $J = 8.0$, 8.0 Hz, 1H), 7.06 (m, 1H), 4.97 (s, 2H), 3.89 (s, 3H); MS (DCI/NH_3) *m/z* 319 $[M + H]^+$, 336 $[M + NH_4]^+$; $R_T = 2.99$.

2-(3,4,5-Trimethylphenoxymethyl)biphenyl (derived from II and P2-C2): 12.5 mg (51%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.55 (m, 1H), 7.30 (m, 8H), 6.47 (s, 2H), 4.82 (s, 2H), 2.14 (s, 6H), 2.01 (s, 3H); MS (DCI/NH_3) *m/z* 303 $[M + H]^+$, 320 $[M + NH_4]^+$; $R_T = 3.36$.

(*S*)-2-Amino-3-[4-(biphenyl-2-ylmethoxy)phenyl]propionic acid methyl ester, TFA salt (derived from II and P3−C3): 21.8 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.51 (m, 1H), 7.29 (m, 8H), 6.98 (d, $J = 8.6$ Hz, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 4.81 (s, 2H), 4.08 (dd, $J = 6.1$, 6.1 Hz, 1H), 3.62 (s, 3H), 3.10 (m, 2H); MS (DCI/NH_3) *m/z* 362 $[M + H]^+$, 379 $[M + NH_4]^+$; $R_T = 2.13$.

2-(Biphenyl-2-ylmethoxy)naphthalene (derived from II and P4-C4): 20.6 mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.67 (d, $J = 8.4$ Hz, 1H), 7.65 (d, $J = 9.0$ Hz, 1H), 7.60 (m, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.30 (m, 10H), 7.10 (dd, $J = 9.0$, 2.5 Hz, 1H), 6.95 (d, $J = 2.5$ Hz, 1H), 4.98 (s, 2H); MS (DCI/NH_3) *m/z* 311 $[M + H]^+$, 328 $[M + NH_4]^+$; $R_T = 3.28$.

1-[4-(Biphenyl-2-ylmethoxy)-3-methylphenyl]ethanone (derived from II and P5-C5): 22.1 mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.71 (m, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.32 (m, 8H), 6.60 (d, $J = 8.7$ Hz, 1H), 4.96 (s, 2H), 2.45 (s, 3H), 2.20 (s, 3H); MS (DCI/NH_3) *m/z* 317 $[M + H]^+$, 334 $[M + NH_4]^+$; $R_T = 2.96$.

2-(4-Propylphenoxymethyl)biphenyl (derived from II and P6-C6): 13.5 mg (55%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.56 (m, 1H), 7.30 (m, 8H), 6.97 (d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 8.7$ Hz, 2H), 4.84 (s, 2H), 2.43 (t, $J = 7.6$ Hz, 2H), 1.52 (m, 2H), 0.84 (t, $J = 7.3$ Hz, 3H); MS (DCI/NH_3) *m/z* 302 $[M]^+$, 320 $[M + NH_4]^+$; $R_T = 3.42$.

2-(3-Isopropylphenoxymethyl)biphenyl (derived from II and P7-C7): 13.9 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.56 (m, 1H), 7.30 (m, 8H), 7.08 (t, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 7.5$ Hz, 1H), 6.69 (m, 1H), 6.60 (m, 1H), 4.86 (s, 2H), 2.77 (hept, $J = 6.9$ Hz, 1H), 1.14 (d, $J = 6.9$ Hz, 6H); MS (DCI/NH_3) *m/z* 303 $[M + H]^+$, 320 $[M + NH_4]^+$; $R_T = 3.36$.

2-(4-Chloro-3-fluorophenoxymethyl)biphenyl (derived from II and P8-C8): 16.3 mg (64%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.50 (m, 1H), 7.32 (m, 8H), 7.13 (dd, $J = 8.6$, 8.6 Hz, 1H), 6.55 (dd, $J = 10.6$, 2.8 Hz, 1H), 6.51 (m, 1H), 4.83 (s, 2H); MS (DCI/NH_3) *m/z* 312 $[M + H]^+$, 330 $[M + NH_4]^+$; $R_T = 3.23$.

2-(Biphenyl-2-ylmethoxy)benzonitrile (derived from II and P9-C9): 16.1 mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (m, 1H), 7.47 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.33 (m, 8H), 7.25 (m, 1H), 6.89 (td, $J = 7.6$, 0.7 Hz, 1H), 6.67 (d, $J = 8.4$ Hz, 1H), 5.00 (s, 2H); MS (DCI/NH_3) *m/z* 286 $[M + H]^+$, 303 $[M + NH_4]^+$; $R_T = 2.81$.

2-(2-Chloro-4-methylphenoxymethyl)biphenyl (derived from II and P10-C10): 18.6 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (m, 1H), 7.32 (m, 7H), 7.25 (m, 1H), 7.10 (d, $J = 1.9$ Hz, 1H), 6.82 (m, 1H), 6.56 (d, $J = 8.4$ Hz, 1H), 4.90 (s, 2H), 2.17 (s, 3H); MS (DCI/NH_3) *m/z* 308 $[M]^+$, 326 $[M + NH_4]^+$; $R_T = 3.27$.

4-(Biphenyl-2-ylmethoxy)-2-nitrophenylamine (derived from II and P11-C11): 11.6 mg (45%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.50 (m, 1H), 7.37 (d, $J = 3.1$ Hz, 1H), 7.30 (m, 8H), 6.96 (dd, $J = 9.0$, 3.1 Hz, 1H), 6.64 (d, $J = 9.0$ Hz, 1H), 4.83 (s, 2H); MS (DCI/NH_3) *m/z* 321 $[M + H]^+$, 338 $[M + NH_4]^+$; $R_T = 2.79$.

2-(2-Benzyloxyphenoxymethyl)biphenyl (derived from II and P12-C12): 20.3 mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.62 (m, 1H), 7.29 (m, 13H), 6.85 (m, 1H), 6.77 (m, 2H), 6.69 (m, 1H), 5.04 (s, 2H), 4.96 (s, 2H); MS (DCI/NH_3) *m/z* 366 $[M]^+$, 384 $[M + NH_4]^+$; $R_T = 3.24$.

2-(Biphenyl-2-ylmethoxy)benzamide (derived from II and P13-C13): 9.2 mg (37%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.08 (d, $J = 7.8$ Hz, 1H), 7.68 (br s, 1H, *NH*), 7.46 (d, $J = 7.2$ Hz, 1H), 7.29 (m, 9H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.28 (br s, 1H, *NH*), 5.01 (s, 2H); MS (DCI/NH_3) *m/z* 304 $[M + H]^+$, 321 $[M + NH_4]^+$; $R_T = 2.43$.

2-(2-Methyl-5 nitrophenoxymethyl)biphenyl (derived from II and P14-C14): 17.9 mg (69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.72 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.60 (m, 1H), 7.48 (d, $J = 2.2$ Hz, 1H), 7.39 (m, 8H), 7.23 (m, 1H), 5.05 (s, 2H), 2.29 (s, 3H); MS (DCI/NH_3) *m/z* 337 $[M + NH_4]^+$; $R_T = 3.11$.

5-(Biphenyl-2-ylmethoxy)naphthalen-1-ylamine, TFA salt (derived from II and P15-C15): 13.4 mg (38%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.82 (d, $J = 8.4$ Hz, 1H), 7.75 (m, 1H), 7.40 (m, 10H), 7.28 (m, 1H), 6.84 (dd, $J = 7.2$, 0.9 Hz, 1H), 6.69 (d, $J = 7.5$ Hz, 1H), 5.11 (s, 2H); MS (DCI/NH_3) *m/z* 326 $[M + H]^+$; $R_T = 2.37$.

[3-(Biphenyl-2-ylmethoxy)phenyl]phenylamine, TFA salt (derived from II and P16-C17): 18.2 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.36 (m, 8H), 7.24 (m, 2H), 7.10 (t, $J = 8.1$ Hz, 1H), 7.02 (m, 2H), 6.93 (m, 1H), 6.62 (m, 1H), 6.58 (m, 1H), 6.43 (m, 1H), 4.91 (s, 2H); MS (DCI/NH_3) *m/z* 352 $[M + H]^+$; $R_T = 3.20$.

2-(2-Chloro-4-methoxyphenoxymethyl)biphenyl (derived from II and P17-C18): 17.6 mg (67%); ^{1}H NMR (500

MHz, $CDCl_3$) δ ppm 7.69 (m, 1H), 7.39 (m, 7H), 7.32 (m, 1H), 6.93 (d, $J = 2.8$ Hz, 1H), 6.64 (dd, $J = 9.0$, 2.8 Hz, 1H), 6.63 (d, $J = 2.8$ Hz, 1H), 4.94 (s, 2H), 3.73 (s, 3H); MS (DCI/NH_3) *m/z* 324 $[M]^+$, 342 $[M + NH_4]^+$; $R_T = 3.12$.

1-(Biphenyl-2-ylmethoxy)-4-methoxynaphthalene (derived from II and P18-C20): 11.9 mg (43%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.24 (m, 2H), 7.75 (m, 1H), 7.49 (m, 2H), 7.43 (m, 4H), 7.36 (m, 4H), 6.60 (dd, $J = 16.2$, 8.4 Hz, 2H), 5.07 (s, 2H), 3.93 (s, 3H); MS (DCI/NH_3) *m/z* 341 $[M + H]^+$, 358 $[M + NH_4]^+$; $R_T = 3.35$.

[4-(Biphenyl-2-ylmethoxy)phenyl]acetic acid methyl ester (derived from II and P19-C22): 18.2 mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.38 (m, 8H), 7.15 (m, 2H), 6.82 (m, 2H), 4.92 (s, 2H), 3.67 (s, 3H), 3.54 (s, 2H); MS (DCI/NH_3) *m/z* 332 $[M]^+$, 350 $[M + NH_4]^+$; $R_T = 2.92$.

2-(Biphenyl-2-ylmethoxy)-5-methylbenzoic acid ethyl ester (derived from II and P20-C23): 14.9 mg (53%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (m, 1H), 7.58 (d, $J = 2.2$ Hz, 1H), 7.39 (m, 7H), 7.30 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.13 (ddd, $J = 8.4$, 2.5, 0.6 Hz, 1H), 6.66 (d, $J = 8.4$ Hz, 1H), 5.00 (s, 2H), 4.34 (dd, $J = 14.4$, 7.2 Hz, 2H), 2.28 (s, 3H), 1.31 (t, $J = 7.0$ Hz, 3H); MS (DCI/NH_3) *m/z* 347 $[M + H]^+$, 364 $[M + NH_4]^+$; $R_T = 3.13$.

2-(4-Bromo-2-fluorophenoxymethyl)biphenyl (derived from II and P21-C25): 20.8 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.37 (m, 8H), 7.21 (dd, $J = 10.5$, 2.3 Hz, 1H), 7.08 (m, 1H), 6.64 (dd, $J = 8.7$, 8.7 Hz, 1H), 4.97 (s, 2H); MS (DCI/NH_3) *m/z* 374/376 $[M + NH_4]^+$; $R_T = 3.22$.

2-[4-(Biphenyl-2-ylmethoxy)phenyl]ethylamine, TFA salt (derived from II and P22-C26): 3.5 mg (5%); 1:1 mixture with alcohol **II**; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.56 (m, 1H), 7.36 (m, 8H), 7.02 (d, $J = 8.7$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 4.88 (s, 2H), 3.08 (t, $J = 7.6$ Hz, 2H), 2.85 (t, $J = 7.6$ Hz, 2H); MS (DCI/NH_3) *m/z* 304 $[M + H]^+$; $R_T = 2.11$.

[3-(Biphenyl-2-ylmethoxy)phenyl]urea (derived from II and P23-C27): 17.3 mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.58 (m, 1H), 7.36 (m, 7H), 7.13 (dd, $J = 8.1$, 8.1 Hz, 1H), 6.83 (m, 3H), 6.58 (dd, $J = 8.3$, 2.0 Hz, 1H), 4.90 (s, 2H); MS (DCI/NH_3) *m/z* 319 $[M + H]^+$, 336 $[M + NH_4]^+$; $R_T = 2.40$.

4-[4-(Biphenyl-2-ylmethoxy)phenyl]butan-2-one (derived from II and P24−C29): 15.3 mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, 1H), 7.39 (m, 7H), 7.34 (m, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 4.91 (s, 2H), 2.81 (t, $J = 7.5$ Hz, 2H), 2.70 (t, $J = 7.5$ Hz, 2H), 2.11 (s, 3H); MS (DCI/NH_3) *m/z* 330 $[M]^+$, 348 $[M + NH_4]^+$; $R_T = 2.93$.

2-(Biphenyl-2-ylmethoxy)benzoic acid ethyl ester (derived from II and P25-C30): 13.2 mg (49%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (m, 2H), 7.36 (m, 9H), 6.95 (td, $J = 7.5$, 0.9 Hz, 1H), 6.77 (dd, $J = 8.4$, 0.6 Hz, 1H), 5.03 (s, 2H), 4.35 (q, $J = 7.2$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H); MS (DCI/NH_3) *m/z* 333 $[M + H]^+$, 350 $[M + NH_4]^+$; $R_T = 3.01$.

***trans*-2-[2-Ethoxy-5-(1-propenyl)phenoxymethyl]biphenyl (derived from II and P26-C31):** 18.2 mg (65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.69 (m, 1H), 7.40 (m, 7H), 7.31 (m, 1H), 6.81 (m, 2H), 6.71 (d, $J = 2.0$ Hz, 1H), 6.23 (m, 1H), 5.96 (m, 1H), 5.02 (s, 2H), 4.05 (dd, $J = 13.9$, 7.1 Hz, 2H), 1.82 (dd, $J = 6.4$, 1.7 Hz, 3H), 1.40 (t, $J = 7.0$ Hz, 3H); MS (DCI/NH_3) *m/z* 345 $[M + H]^+$, 362 $[M + NH_4]^+$; $R_T = 3.07$.

2-(Biphenyl-2-ylmethoxy)-5-methoxybenzoic acid methyl ester (derived from II and P27-C32): 21.0 mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (d, $J = 7.5$ Hz, 1H), 7.40 (m, 7H), 7.32 (d, $J = 3.1$ Hz, 1H), 7.30 (dd, $J = 7.5$, 1.2 Hz, 1H), 6.90 (dd, $J = 9.0$, 3.4 Hz, 1H), 6.71 (d, $J = 9.0$ Hz, 1H), 4.98 (s, 2H), 3.88 (s, 3H), 3.77 (s, 3H); MS (DCI/NH_3) *m/z* 349 $[M + H]^+$, 366 $[M + NH_4]^+$; $R_T = 2.89$.

4-(Biphenyl-2-ylmethoxy)-3-chlorophenylamine (derived from II and P28-C33): 3.5 mg (10%); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.64 (m, 1H), 7.43 (m, 7H), 7.33 (m, 1H), 7.02 (d, $J = 2.5$ Hz, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 6.81 (dd, $J = 8.7$, 2.5 Hz, 1H), 4.93 (s, 2H); MS (DCI/NH_3) *m/z* 310 $[M + H]^+$, 327 $[M + NH_4]^+$; $R_T = 2.14$.

2-(2-Isopropoxyphenoxymethyl)biphenyl (derived from II and P29-C34): 18.7 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.70 (m, 1H), 7.40 (m, 7H), 7.31 (m, 1H), 6.91 (dd, $J = 8.0$, 1.7 Hz, 1H), 6.87 (td, $J = 7.5$, 1.6 Hz, 1H), 6.82 (m, 1H), 6.76 (dd, $J = 8.1$, 1.6 Hz, 1H), 4.99 (s, 2H), 4.48 (m, 1H), 1.31 (d, $J = 6.2$ Hz, 6H); MS (DCI/NH_3) *m/z* 336 $[M + NH_4]^+$; $R_T = 3.15$.

2-(4-Allyl-2-methoxyphenoxymethyl)biphenyl (derived from II and P30-C35): 16.2 mg (61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.67 (m, 1H), 7.37 (m, 7H), 7.30 (m, 1H), 6.70 (d, $J = 1.6$ Hz, 1H), 6.61 (m, 2H), 5.93 (m, 1H), 5.05 (m, 2H), 4.99 (s, 2H), 3.83 (s, 3H), 3.30 (d, $J = 6.9$ Hz, 2H); MS (DCI/NH_3) *m/z* 348 $[M + NH_4]^+$; $R_T = 3.17$.

1-[4-(Biphenyl-2-ylmethoxy)phenyl]propan-1-one (derived from II and P31-C36): 18.8 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.90 (m, 2H), 7.60 (m, 1H), 7.38 (m, 8H), 6.87 (m, 2H), 5.00 (s, 2H), 2.92 (q, $J = 7.3$ Hz, 2H), 1.20 (t, $J = 7.3$ Hz, 3H); MS (DCI/NH_3) *m/z* 317 $[M + H]^+$, 334 $[M + NH_4]^+$; $R_T = 3.00$.

[3-(Biphenyl-2-ylmethoxy)phenyl]diethylamine, TFA salt (derived from II and P32-C38): 15.5 mg (43%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (m, 1H), 7.38 (m, 9H), 7.06 (dd, $J = 8.1$, 1.6 Hz, 1H), 6.93 (t, $J = 2.2$ Hz, 1H), 6.85 (dd, $J = 8.3$, 2.0 Hz, 1H), 5.01 (s, 2H), 3.46 (m, 4H), 1.09 (t, $J = 7.2$ Hz, 6H); MS (DCI/NH_3) *m/z* 332 $[M + H]^+$; $R_T = 2.16$.

5-(Biphenyl-2-ylmethoxy)isoquinoline, TFA salt (derived from II and P33-C39): 23.9 mg (69%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.63 (s, 1H), 8.50 (d, $J = 6.4$ Hz, 1H), 8.45 (d, $J = 6.4$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.74 (t, $J = 8.1$ Hz, 1H), 7.64 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.48 (m, 2H), 7.40 (m, 1H), 7.34 (m, 5H), 7.20 (d, $J = 7.8$ Hz, 1H), 5.26 (s, 2H); MS (DCI/NH_3) *m/z* 312 $[M + H]^+$; $R_T = 2.07$.

2-(3-Biphenyloxymethyl)biphenyl (derived from II and P34-C41): 17.8 mg (65%); mixture containing 20% of isomeric 2-(4-biphenyloxymethyl)biphenyl; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 (m, 1H), 7.53 (m, 2H), 7.41 (m, 9H), 7.35 (m, 2H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.16 (m, 1H), 7.08 (dd, $J = 2.0$, 2.0 Hz, 1H), 6.84 (m, 1H), 5.00 (s, 2H); ^{1}H NMR, isomer, δ ppm 7.65 (m, 1H), 7.53 (m, 2H), 7.47

(d, $J = 8.7$ Hz, 1H), 7.41 (m, 9H), 7.35 (m, 2H), 6.93 (d, $J = 8.7$ Hz, 1H), 4.98 (s, 2H); MS (DCI/NH_3) m/z 337 $[M + H]^+$, 354 $[M + NH_4]^+$; $R_T = 3.36$.

2-(2-Fluoro-5-methylphenoxymethyl)biphenyl (derived from II and P35-C42): 18.2 mg (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 (m, 1H), 7.39 (m, 7H), 7.33 (m, 1H), 6.92 (dd, $J = 11.2$, 8.1 Hz, 1H), 6.65 (m, 1H), 6.59 (dd, $J = 8.1$, 1.9 Hz, 1H), 4.98 (s, 2H), 2.21 (s, 3H); MS (DCI/NH_3) m/z 310 $[M + NH_4]^+$; $R_T = 3.11$.

2-(Biphenyl-2-ylmethoxy)-4-methoxybenzoic acid methyl ester (derived from II and P36-C46): 25.9 mg (92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (m, 2H), 7.40 (m, 7H), 7.31 (m, 1H), 6.47 (dd, $J = 8.7$, 2.5 Hz, 1H), 6.27 (d, $J = 2.5$ Hz, 1H), 5.03 (s, 2H), 3.86 (s, 3H), 3.74 (s, 3H); MS (DCI/NH_3) m/z 349 $[M + H]^+$, 366 $[M + NH_4]^+$; $R_T = 2.88$.

2-(2-Benzylphenoxymethyl)biphenyl (derived from II and P37-C47): 17.1 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.36 (m, 1H), 7.29 (m, 5H), 7.23 (m, 3H), 7.16 (m, 2H), 7.08 (m, 3H), 7.02 (m, 2H), 6.78 (t, $J = 7.3$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 4.84 (s, 2H), 3.91 (s, 2H); MS (DCI/NH_3) m/z 368 $[M + H]^+$; $R_T = 3.42$.

6-(Biphenyl-2-ylmethoxy)-3,4-dihydro-2*H*-naphthalen-1-one (derived from II and P38-C50): 23.3 mg (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.85 (d, $J = 8.7$ Hz, 1H), 7.49 (m, 1H), 7.28 (m, 8H), 6.66 (dd, $J = 8.7$, 2.2 Hz, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 4.89 (s, 2H), 2.76 (t, $J = 6.1$ Hz, 2H), 2.49 (t, $J = 6.6$ Hz, 2H), 1.98 (m, 2H); MS (DCI/NH_3) m/z 329 $[M + H]^+$, 346 $[M + NH_4]^+$; $R_T = 2.92$.

8-(Biphenyl-2-ylmethoxy)-2-methylquinoline, TFA salt (derived from II and P39-C55): 2.2 mg (6%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.34 (d, $J = 8.4$ Hz, 1H), 7.76 (m, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 7.40 (m, 9H), 7.31 (m, 1H), 6.78 (dd, $J = 7.3$, 1.4 Hz, 1H), 5.37 (s, 2H), 3.01 (s, 3H); MS (DCI/NH_3) m/z 326 $[M + H]^+$; $R_T = 1.99$.

2-(2-Fluoro-4-nitrophenoxymethyl)biphenyl (derived from II and P40-C60): 20.8 mg (79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.96 (dd, $J = 10.5$, 2.7 Hz, 1H), 7.93 (m, 1H), 7.60 (m, 1H), 7.40 (m, 8H), 6.80 (t, $J = 8.4$ Hz, 1H), 5.11 (s, 2H); MS (DCI/NH_3) m/z 341 $[M + NH_4]^+$; $R_T = 2.99$.

5-Acetyl-2-(biphenyl-2-ylmethoxy)benzamide (derived from II and P41-C61): 20.0 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.78 (d, $J = 2.5$ Hz, 1H), 8.04 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.57 (dd, $J = 7.5$, 1.2 Hz, 1H), 7.30−7.55 (m, 8H), 6.91 (d, $J = 8.7$ Hz, 1H), 5.20 (s, 2H), 2.60 (s, 3H); MS (DCI/NH_3) m/z 345 $[M + H]^+$, 363 $[M + NH_4]^+$; $R_T = 2.31$.

2-(Indan-5-ylmethoxyl)biphenyl (derived from II and P42-C67): 16.0 mg (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.51 (m, 1H), 7.25 (m, 8H), 6.94 (d, $J = 8.1$ Hz, 1H), 6.63 (d, $J = 1.2$ Hz, 1H), 6.54 (dd, $J = 8.1$, 2.2 Hz, 1H), 4.78 (s, 2H), 2.71 (m, 4H), 1.93 (m, 2H); MS (DCI/NH_3) m/z 301 $[M + H]^+$, 318 $[M + NH_4]^+$; $R_T = 3.34$.

1-[4-Biphenyl-2-ylmethoxy)phenyl]-1*H*-imidazole (derived from II and P43-C72): 13.3 mg (50%); ^{1}H NMR (500 MHz, CDCL3) δ ppm 7.82 (br s, 1H), 7.62 (m, 1H), 7.39 (m, 8H), 7.25 (m, 2H), 7.20 (m, 2H), 6.93 (m, 2H), 4.98 (s, 2H); MS (DCI/NH_3) m/z 327 $[M + H]^+$; $R_T = 2.09$.

2-(Biphenyl-2-ylmethoxy)dibenzofuran (derived from II and P44-C73): 20.5 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (d, $J = 7.5$ Hz, 1H), 7.68 (m, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.43 (m, 8H), 7.36 (m, 2H), 7.30 (m, 2H), 7.02 (dd, $J = 9.0$, 2.5 Hz, 1H), 5.04 (s, 2H); MS (DCI/NH_3) m/z 351 $[M + H]^+$, 368 $[M + NH_4]^+$; $R_T = 3.40$.

7-(Biphenyl-2-ylmethoxy)-2,2-dimethyl-2,3-dihydrobenzofuran (derived from II and P45-C83): 17.8 mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (m, 1H), 7.24 (m, 7H), 7.16 (m, 1H), 6.60 (dd, $J = 7.2$, 0.6 Hz, 1H), 6.51 (t, $J = 7.6$ Hz, 1H), 6.41 (d, $J = 8.1$ Hz, 1H), 4.92 (s, 2H), 2.87 (s, 2H), 1.36 (s, 6H); MS (DCI/NH_3) m/z 330 $[M]^+$, 348 $[M + NH_4]^+$; $R_T = 3.16$.

5-(Biphenyl-2-ylmethoxy)-2-methylbenzothiazole, TFA salt (derived from II and P46-C88): 14.9 mg (41%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.64 (m, 2H), 7.41 (m, 7H), 7.34 (m, 2H), 7.02 (dd, $J = 8.7$, 2.5 Hz, 1H), 5.01 (s, 2H), 2.84 (s, 3H); MS (DCI/NH_3) m/z 332 $[M + H]^+$; $R_T = 2.94$.

5-[2-(Biphenyl-2-ylmethoxy)phenyl]isoxazole (derived from II and P47-C90): 23.2 mg (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.22 (s, 1H), 8.00 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.2$ Hz, 1H), 7.44 (m, 2H), 7.34 (m, 7H), 7.06 (t, $J = 7.6$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.66 (s, 1H), 5.09 (s, 2H); MS (DCI/NH_3) m/z 328 $[M + H]^+$, 345 $[M + NH_4]^+$; $R_T = 3.00$.

6-(Biphenyl-2-ylmethoxy)benzo[1,3]oxathiol-2-one (derived from II and P48-C99): 15.9 mg (59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.49 (m, 1H), 7.32 (m, 4H), 7.26 (m, 4H), 7.10 (d, $J = 9.4$ Hz, 1H), 6.68 (m, 2H), 4.85 (s, 2H); MS (DCI/NH_3) m/z 334 $[M]^+$, 352 $[M + NH_4]^+$; $R_T = 3.04$.

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Supporting Information Available. Automated protocol for syntheses and NMR spectra of various compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) It was observed that the amount of polymer-supported phosphine oxide as determined by ^{31}P NMR increased on exposure to air, as evidenced by an increase the resonance observed at 29.4 ppm.[21]
(20) Aldrich PS−PPh_3 {lot number 15608HI, loading 3 mmol/g}: the percentage of phosphine oxide increased from 4% to 9% over 7 days, atmospheric exposure. Argonaut PS−PPh_3 {lot number 113-81, loading 1.24 mmol/g}: the percentage of phosphine oxide increased from 23% to 36% over 7 days, atmospheric exposure.
(21) ^{31}P NMR experiments were performed as gel-phase MAS, with samples suspended in $CDCl_3$ using 85% aqueous H_3PO_4 as an external standard. The pulse delay employed was 15 s, and chemical shifts are quoted in ppm. Under these conditions, the phosphine resonance was observed at −6.25 ppm, with the oxide being observed at 29.40 ppm.
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