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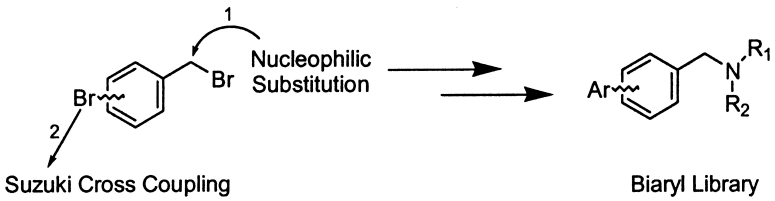

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Solution-Phase Synthesis of an Aminomethyl-Substituted Biaryl Library via Sequential Amine N-Alkylation and Suzuki Cross-Coupling

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Described herein is the semiautomated preparation of a 20-member aminomethyl-substituted biaryl library. The two-step solution-phase synthesis was achieved via sequential N-alkylation of various amines with either 3- or 4-bromobenzyl bromide and Suzuki cross-coupling of the resultant aryl bromides with various boronic acids.

Introduction

We have demonstrated previously the use of polyfunctionalized olefins as templates for metal-catalyzed, multistep reaction sequences to provide polysubstituted olefin targets.[1] Further, we have utilized this strategy to prepare molecular libraries of allylic amines[2] and β-amino alcohols.[3] A similar strategy with a functionalized aromatic template would produce biaryls. 3-Bromobenzyl bromide and 4-bromobenzyl bromide would serve as such a scaffold, thus allowing the introduction of diversity by sequential nucleophilic substitution with various amines at the benzylic position and metal-catalyzed cross-coupling at the aryl bromide site to give compounds with the general structure shown in Figure 1. This general aminomethyl biaryl motif appears in many biologically active compounds and known drugs, including the angiotensin II receptor antagonist Losartan (Figure 2) for the treatment of hypertension,[4] as well as ACAT inhibitors[5] and dopamine receptor ligands.[6] Thus, we had considerable interest in designing a synthetic method to prepare an aminomethyl-substituted biaryl library.

Biaryl bond construction using the Suzuki reaction is attractive because both solution-phase[7] and solid-phase[8] reaction conditions are documented. Relative to other coupling procedures, the Suzuki coupling has proven to be particularly effective for preparing sterically congested biaryls.[9,10] Additionally, the boric acid byproducts of this process are essentially nontoxic. This is of particular importance in library synthesis, where frequently only rudimentary purification techniques are employed. The use of ion exchange chromatography for the expedited purification of libraries of small molecules has been demonstrated effectively by a number of groups, and it was believed that this technique would remove readily the remaining boron-derived impurities from the Suzuki reaction.[2,3,11] In this study we demonstrate the use of catch and release purification with strong cation exchange (SCX) resin to clean up the Suzuki reaction products, taking advantage of the protonateable amine handle installed in the nucleophilic substitution reaction in the first step.

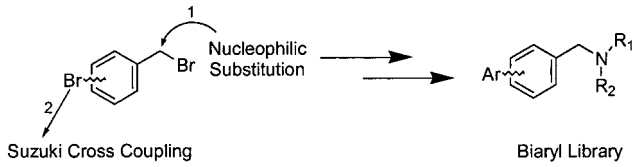

Figure 1. Possible functionalization of the bromobenzyl bromide scaffold.

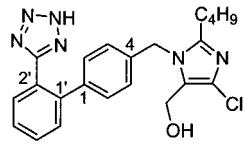

Figure 2. Structure of Losartan, an angiotensin II receptor antagonist.

Results and Discussion

Preparation of the Arylbromide Sublibrary. Before library construction could begin, the efficacy of the proposed two-step synthetic sequence had to be established (Scheme 1). We recently described the synthesis of such arylamine intermediates **3** and **4** from the reaction of 4- or 3-bromobenzyl bromide **1** or **2** with secondary amines[12] in the presence of polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD resin) as the base.[13] While this system produced suitable results, the expense of PTBD resin made its use in large-scale library production less desirable. Thus, we chose to investigate the use of potassium carbonate in aqueous DMF as a suitable replacement for the PTBD resin system. To expedite the substitution reactions, the process was conducted in a parallel synthesis format using a Radley's 12-place PTFE carousel. Secondary amines (1.0 equiv) reacted with excess **1** or **2** (1.2 equiv) in the presence of potassium carbonate (1.0 equiv) in aqueous DMF, giving rise to arylamines **3** or **4**, respectively, in excellent yield (Table 1). Intermediates **3** and **4** were purified quickly by passage through an SCX column, providing essentially clean material. No signals from the secondary amine could be detected in the proton NMR spectra of the products, which were used without further purification in the next step.

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Scheme 1

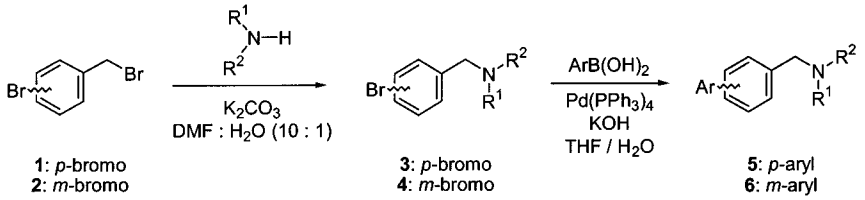


Table 1. Yields[a] for the Nucleophilic Substitution of Secondary Amines onto 3- and 4-Bromobenzyl Bromide

Amine	(1)	(2)
	3a, 85%	4a, 95%
	3b, 98%	4b, 98%
	3c, 98%	4c, 97%
	3d, 97%	4d, 97%
	3e, 99%	4e, 98%

[a] Yields are based on mass recovery and ^{1}H NMR spectra of the crude products.

Suzuki Reaction To Establish the Biaryl Bond. The reaction conditions for the Suzuki cross-coupling were established by preparing 20 amino-substituted biaryl compounds in a 96-well Robbins FlexChem reactor block. 4-Bromobenzylamines **3a**−**e** were reacted with either 4-fluorophenyl- or 4-acetylphenylboronic acid, and 3-bromobenzylamines **4a**−**e** were reacted with either phenyl- or 4-methoxyphenylboronic acid. The cross-couplings proceeded smoothly in good to excellent yield and purity (Table 2). The only problem encountered in the procedure was the insolubility of some arylamines in THF (the worst case being arylamine **4a**), which affected the yield considerably. On the basis of these observations, larger-scale library preparation would be conducted in DMF as solvent in order to avoid any problems originating from poor solubility.

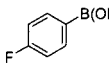
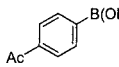
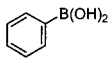
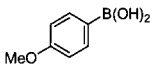
In summary, an effective two-step benzylic amination/cross-coupling sequence has been devised to prepare large libraries of aminomethyl biaryl compounds using solution-phase techniques. In these preliminary studies, the procedure provided good to excellent yields for the desired biaryls and suitable purity for biological screening purposes. This method is now being applied to the preparation of a larger proprietary molecular library.

Experimental Section

All reagents were purchased from Aldrich Chemical Co. and were used without further purification. Tetrakis(triphenylphosphine)palladium(0) was prepared by reduction of $PdCl_2(PPh_3)_2$ with hydrazine.[15] ChemElut[16] and SCX Bond-Elut prepacked cartridges were purchased from Varian. Mass spectra were obtained using a PE SCIEX API 2000 triple quadrupole mass spectrometer with turbo-ion-spray ionization (full scan: 100−700 amu). Chromatograms were obtained using a Shimadzu liquid chromatograph possessing a dual LC-8A pump system in conjunction with a SPD10VP UV detector (λ = 254 and 280 nm) and a Gilson 215 autosampler. The UV detector and mass spectrometer were used in parallel with a near 50:50 split of the mobile-phase post column. Separations were achieved using a Zorbax C_{18} (75 mm × 4.6 mm, 5 μm) analytical column and a linear gradient (from 80% **A** to 10% **A**, where **A** = H_2O + 1% AcOH and **B** = MeOH + 1% AcOH). Proton NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer. Chemical shifts are quoted in ppm and referenced to the residual solvent peak (7.27 ppm for $CDCl_3$).

General Procedure for the Alkylation of Benzyl Bromides 1 or 2 with Amines (Preparation of 3 and 4). Alkylation of amines was carried out using the Radleys 12-place PTFE carousel in conjuction with an IKALabortechnik magnetic stirring plate. To a solution of either 4- or 3-bromobenzyl bromide **1** or **2** (0.75 g, 3.0 mmol, 1.2 equiv) in DMF/H_2O (10 mL:1 mL) in a Radleys' reaction tube was added K_2CO_3 (0.35 g, 2.5 mmol, 1 equiv) and a secondary amine (2.5 mmol, 1 equiv). The reaction mixture was heated to 50 °C and stirred vigorously for 16 h. When the mixture was cooled to room temperature, a total of 7 mL of AcOH

Table 2. Yields[a] and Purities[b] for the Cross-Coupling Reaction

Aryl amine			Aryl amine		
3a	5i, 67% (94%)	5vi, 71% (83%)	**4a**	6i, 17% (91%)	6vi, 43% (95%)
3b	5ii, 65% (>80%)[c]	5vii, 73% (61%)	**4b**	6ii, 58% (93%)	6vii, 97% (91%)
3c	5iii, 63% (96%)	5viii, 78% (88%)	**4c**	6iii, 44% (73%)	6viii, 56% (83%)
3d	5iv, 46% (93%)	5ix, 51% (86%)	**4d**	6iv, 41% (69%)	6ix, 81% (79%)
3e	5v, 58% (91%)	5x, 79% (88%)	**4e**	6v, 59% (93%)	6x, 98% (94%)

[a] Yields are reported following SCX[14] chromatography. [b] The percent purity (in parentheses) was measured by HPLC analysis (see Experimental Section for full details). [c] The percent purity was estimated from the proton NMR spectrum.

was added to adjust the pH from 10 to 3. The mixture was diluted with a 25 mL solution of MeOH/CH_2Cl_2 (4:1) and loaded on an SCX column (BondElut, 5 g, 0.82 mequiv/g). The resin was then washed thoroughly with MeOH followed by CH_2Cl_2 until the eluent became colorless (to remove impurities). Elution with a 2 M NH_3/MeOH solution (3 × 5 mL) followed by solvent removal in vacuo afforded either 4- or 3-bromobenzylamines **3** or **4** that were used in the Suzuki coupling without further purification.

General Procedure for the Suzuki Coupling of Aryl Bromides 3 or 4 in a 96-Well Robbins FlexChem Reactor Block (1.8 mL Capacity). (Preparation of 5 and 6). The following procedure was repeated for each of the 20 wells of the reactor block. To a solution of bromobenzylamine **3** or **4** (100 μmol) and boronic acid (200 μmol, 2 equiv) in THF (300 μL) was added a 1 M aqueous solution of KOH (300 μL, 300 μmol, 3 equiv) and a 0.05 M solution of Pd-$(PPh_3)_4$ (200 μL, 10 μmol, 0.01 equiv) in THF. The plate was agitated at 55−60 °C overnight in a rotisserie oven. Upon cooling to room temperature, the mixture was pipetted out of the well and the well was rinsed with CH_2Cl_2 (800 μL × 3). The pooled organic phase (X 20) was then filtered through ChemElut, and the resin was rinsed with CH_2Cl_2. After solvent removal in vacuo, the residue was dissolved in a 10% AcOH solution in MeOH and loaded on an SCX cartridge (Whatman, 500 mg). After being rinsed with MeOH (3 × 2.5 mL), the product was eluted with a 2 M NH_3 solution in MeOH (3 × 2.5 mL), which afforded the desired biaryl compounds **5** and **6** after solvent removal in vacuo.

Representative Data and Spectra for the Final Biaryl Library. 1-[(4′-Fluoro-1,1′-biphen-4-yl)methyl]-4-methylpiperazine (5i). Yield, 67%; *m/z* $[M + H]^+$ 285; 94% pure (HPLC); ^{1}H NMR δ 7.55 (dd, J = 8.5, 3.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 8.5, 8.5 Hz, 2H), 3.56 (s, 2H), 2.56 (bs, 8H), 2.35 (s, 3H).

1-[(4′-Fluoro-1,1′-biphen-4-yl)methyl]-4-phenylpiperazine (5ii). Yield, 65%; *m/z* $[M + H]^+$ 347; >80% pure (estimated from proton NMR spectrum); ^{1}H NMR δ 7.58−6.85 (m, 13H), 3.64 (s, 2H), 3.24 (t, J = 5.0 Hz, 4H), 2.66 (bs, 4H).

4-[(4′-Fluoro-1,1′-biphen-4-yl)methyl]morpholine (5iii). Yield, 63%; *m/z* $[M + H]^+$ 272; 96% pure (HPLC); ^{1}H NMR δ 7.55 (dd, J = 8.5, 6.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 8.5, 8.5 Hz, 2H), 3.74 (t, J = 4.5 Hz, 4H), 3.55 (s, 2H), 2.50 (bs, 4H).

***N*-[(4′-Fluoro-1,1′-biphen-4-yl)methyl]-*N*-cyclohexyl-*N*-methylamine (5iv).** Yield, 46%; *m/z* $[M + H]^+$ 298; 93% pure (HPLC); ^{1}H NMR δ 7.55 (dd, J = 8.5, 5.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.12 (dd, J = 8.5, 8.5 Hz, 2H), 3.63 (s, 2H), 2.49 (m, 1H), 2.25 (s, 3H), 1.92 (d, J = 12.5 Hz, 2H), 1.83 (d, J = 12.5 Hz, 2H), 1.65 (d, J = 12.5 Hz, 1H), 1.38−1.12 (m, 5H).

***N*-[(4′-Fluoro-1,1′-biphen-4-yl)methyl]-*N*-benzyl-*N*-methylamine (5v).** Yield, 58%; *m/z* $[M + H]^+$ 308; 91% pure (HPLC); ^{1}H NMR δ 7.57−7.25 (m, 11H), 7.13 (dd, J = 8.5, 8.5 Hz, 2H), 3.60 (s, 4 H), 2.25 (s, 3H).

1-{4′-[(4-Methylpiperazin-1-yl)methyl]-1,1′-biphen-4-yl}ethanone (5vi). Yield, 71%; *m/z* $[M + H]^+$ 309; 83% pure (HPLC); ^{1}H NMR δ 8.02 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7. 42 (d, J = 8.0 Hz, 2H), 3.57 (s, 2H), 2.64 (s, 3H), 2.54 (bs, 8H), 2.33 (s, 3H).

1-{4′-[(4-Phenylpiperazin-1-yl)methyl]-1,1′-biphen-4-yl}ethanone (5vii). Yield, 73%; *m/z* $[M + H]^+$ 371; 61% pure (HPLC); ^{1}H NMR δ 8.04 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 8.0 Hz, 1H), 3.65 (s, 2H), 3.25 (t, J = 4.5 Hz, 4H), 2.68 (t, J = 4.5 Hz, 4H), 2.65 (s, 3H).

1-[4′-(Morpholin-4-ylmethyl)-1,1′-biphen-4-yl]ethanone (5viii). Yield, 78%; *m/z* $[M + H]^+$ 296; 88% pure (HPLC); ^{1}H NMR δ 8.03 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 3.74 (t, J = 4.5 Hz, 4H), 3.56 (s, 2H), 2.64 (s, 3H), 2.50 (bs, 4H).

1-{4′-[(*N*,*N*-cyclohexylmethylamino)methyl]-1,1′-biphen-4-yl}ethanone (5ix). Yield, 51%; *m/z* $[M + H]^+$ 322; 86% pure (HPLC); ^{1}H NMR δ 8.02 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.44 (d, J 8.0 Hz, 2H), 3.64 (s, 2H), 2.64 (s, 3H), 2.50 (m, 1H), 2.24 (s, 3H), 1.92 (d, J = 11.5 Hz, 2H), 1.83 (d, J = 11.5 Hz, 2H), 1.63 (d, J = 11.0 Hz, 1H), 1.35−1.24 (m, 5H).

1-{4′-[(*N*,*N*-benzylmethylamino)methyl]-1,1′-biphen-4-yl}ethanone (5x). Yield, 79%; *m/z* $[M + H]^+$ 330; 88% pure (HPLC); ^{1}H NMR δ 8.03 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.58 (s, 2H), 2.64 (s, 3H), 2.24 (s, 3H).

1-(1,1′-Biphen-3-ylmethyl)-4-methylpiperazine (6i). Yield, 17%; *m/z* $[M + H]^+$ 267; 91% pure (HPLC); ^{1}H NMR δ 7.60 (d, J = 7.5 Hz, 2H), 7.55 (s, 1H), 7.30−7.50 (m, 6H), 3.60 (s, 2H), 2.56 (bs, 8H), 2.34 (s, 3H).

1-(1,1′-Biphen-3-ylmethyl)-4-phenylpiperazine (6ii). Yield, 58%; *m/z* $[M + H]^+$ 329; 93% pure (HPLC); ^{1}H NMR δ 7.69−7.26 (m, 11H), 6.94 (d, J = 7.0 Hz, 2H), 6.87 (t, J = 7.0 Hz, 1H), 3.67 (s, 2H), 3.25 (t, J = 4.5 Hz, 4H), 2.69 (t, J = 4.5 Hz, 4H).

4-(1,1′-Biphen-3-ylmethyl)morpholine (6iii). Yield, 44%; *m/z* $[M + H]^+$ 254; 73% pure (HPLC); ^{1}H NMR δ 7.62−7.33 (m, 9H), 3.75 (t, J = 4.5 Hz, 4H), 3.60 (s, 2H), 2.51 (s, 4H).

***N*-(1,1′-Biphen-3-ylmethyl)-*N*-cyclohexyl-*N*-methylamine (6iv).** Yield, 41%; *m/z* $[M + H]^+$ 280; 69% pure (HPLC); ^{1}H NMR δ 7.62 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 7.49−7.33 (m, 6H), 3.66 (s, 2H), 2.50 (m, 1H), 2.26 (s, 3H), 1.93 (d, J = 11.5 Hz, 2H), 1.83 (d, J = 11.5 Hz, 2H), 1.64 (d, J = 12 Hz, 1H), 1.39−1.12 (m, 5H).

***N*-(1,1′-Biphen-3-ylmethyl)-*N*-benzyl-*N*-methylamine (6v).** Yield, 59%; *m/z* $[M + H]^+$ 288; 93% pure (HPLC); ^{1}H NMR δ 7.62 (d, J = 7.0 Hz, 2H), 7.57−7.29 (m, 12H), 3.64 (s, 2H), 3.50 (s, 2H), 2.25 (s, 3H).

1-[(4′-Methoxy-1,1′-biphen-3-yl)methyl]-4-methylpiperazine (6vi). Yield, 43%; *m/z* $[M + H]^+$ 297; 95% pure (HPLC); ^{1}H NMR δ 7.54 (d, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.47 (d, J = 7. 5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 3.82 (s, 3H), 3.58 (s, 2H), 2.52 (bs, 8H), 2.27 (s, 3H).

1-[(4′-Methoxy-1,1′-biphen-3yl)methyl]-4-phenylpiperazine (6vii). Yield, 97%; *m*/*z* $[M + H]^+$ 359; 91% pure (HPLC); ^{1}H NMR δ 7.57 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.32 (d, $J = 7.5$ Hz, 1H), 7.27 (t, $J = 8.0$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 6.93 (d, $J = 8.0$ Hz, 2H), 6.86 (t, $J = 8.0$ Hz, 1H), 3.86 (s, 3H), 3.66 (s, 2H), 3.24 (m, 4H), 2.69 (m, 4H).

1-[(4′-Methoxybiphen-3-yl)methyl]morpholine (6viii). Yield, 56%; *m*/*z* $[M + H]^+$ 284; 83% pure (HPLC); ^{1}H NMR δ 7.54 (s, 1H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 2H), 3.81 (s, 3H), 3.69 (t, $J = 4.5$ Hz, 4H), 3.56 (s, 2H), 2.45 (bs, 4H).

***N*-(4′-Methoxy-1,1′-biphen-3-yl)-*N*-cyclohexyl-*N*-methylamine (6ix).** Yield, 81%; *m*/*z* $[M + H]^+$ 310; 79% pure (HPLC); ^{1}H NMR δ 7.55 (d, $J = 9.0$ Hz, 2H), 7.53 (s, 1H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 9.0$ Hz, 2H), 3.86 (s, 3H), 3.64 (s, 2H), 2.50 (m, 1H), 2.25 (s, 3H), 1.92 (d, $J = 11.5$ Hz, 2H), 1.83 (d, $J = 11.5$ Hz, 2H), 1.67 (d, $J = 11.5$ Hz, 1H), 1.35−1.24 (m, 5H).

***N*-(4′-Methoxy-1,1′-biphen-3-yl)-*N*-benzyl-*N*-methylamine (6x).** Yield, 98%; *m*/*z* $[M + H]^+$ 318; 94% pure (HPLC); ^{1}H NMR δ 7.58 (s, 1H), 7.56 (d, $J = 9.0$ Hz, 2H), 7.47−7.27 (m, 8H), 6.99 (d, $J = 8.5$ Hz, 2H), 3.87 (s, 3H), 3.63 (s, 2H), 3.61 (s, 2H), 2.25 (s, 3H).

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Supporting Information Available. ^{1}H NMR spectra and HPLC/TIC MS data for all 20 compounds prepared in the biaryl library, where spectra for compounds **5vii**, **5x**, and **6ii** were acquired on a 400 MHz Bruker Avance spectrometer in $CDCL_3$ solvent and all other NMR spectra were acquired using a stop-flow probe (Bruker BEST system) on a Bruker 600 MHz NMR Avance spectrometer equipped with AUTODROP software for the rapid processing of libraries using a Gilson 215 autosampler, with the samples dissolved in CH_3-OH and run with solvent suppression. This material is available free of charge via the Internet at http://pubs.acs.org.

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