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Article

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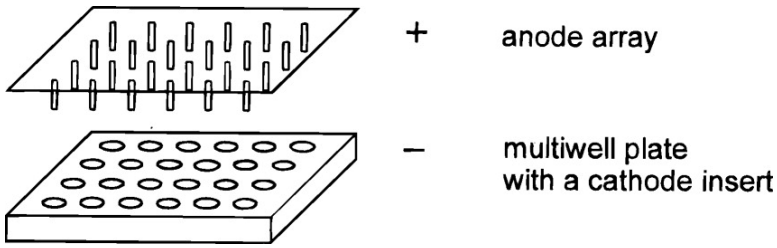
J. Comb. Chem., **2000**, 2 (5), 545-549• DOI: 10.1021/cc000035v • Publication Date (Web): 03 August 2000



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Parallel Electrosynthesis of α-Alkoxycarbamates, α-Alkoxyamides, and α-Alkoxysulfonamides Using the Spatially Addressable Electrolysis Platform (SAEP)

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Received May 1, 2000

The spatially addressable electrolysis platform (SAEP) has been designed and constructed. It is demonstrated that the advantages of electrochemistry can be readily adapted to combinatorial chemistry and parallel synthesis formats. Parallel electrosynthesis of α-alkoxycarbamates, α-alkoxyamides, and α-alkoxysulfonamides via anodic oxidation of carbamates, amides, and sulfonamides, respectively, highlights the main features of the SAEP.

The demand for diverse compound libraries for screening in the drug discovery programs has been the major driving force behind development of new methodologies for high-throughput synthesis.[1−5] Much emphasis has been placed on solid-phase techniques due to facilitated separation of excess reagents and byproducts from the resin-bound compounds. The solution-phase approach, on the other hand, has the advantages of shorter reaction times and easier scale-up. Among solution-phase techniques applied to parallel synthesis and combinatorial chemistry, electrosynthesis remains an area of tremendous, albeit underutilized, potential.[6] Considerable advances in creating molecular diversity not available by other means, and/or running known processes under mild conditions, would be possible if electrosynthesis was carried out in a high-throughput fashion. To the best of our knowledge, no electrochemical reactions have been used to generate libraries of organic compounds. One of the likely reasons for this is the lack of methodology for running parallel electrosynthesis. In this regard, one of the goals of our research has been to adapt electrosynthetic methodologies to combinatorial chemistry and high-throughput synthesis formats. Our first target was to develop instrumentation for running parallel electrosynthetic reactions. This contribution describes the development and application of the spatially addressable electrolysis platform (SAEP) which allows one to carry out solution-phase electrosynthesis in a multiwell format.

Electrochemistry is at the interface of solution- and solid-phase chemistry as the electron transfer steps take place in the Helmholtz double layer at the electrode surface. Highly reactive intermediates such as radical-ions, radicals, carbanions, and carbocations can be generated under very mild reaction conditions in that region. Thus, many well-established electrosynthetic reactions proceed with little or no byproducts. In addition, these processes often lead to compounds that are not readily accessible using traditional methodologies. Selected examples include Kolbe electrolysis and electrohydrodimerization (EHD), which give carbon−carbon bond formation in a manner difficult to match by other routes.[7] Another advantage of electrosynthesis over conventional chemical methods is selective transformation of functional groups by controlling the applied potential. For example, nitroalkanes can be selectively reduced to hydroxylamines *or* amines.[8]

Electrochemical methods were introduced in the field of combinatorial chemistry only recently by Smotkin and Mallouk in parallel screening of electrocatalysts.[9] In their study, a 645-member electrode array containing five elements and their binary, ternary, and quaternary combinations, was screened in order to identify the most active alloy catalyst compositions for the electrooxidation of methanol. Protons generated at the anode were detected by a fluorescent acid−base indicator which was then correlated with catalytic activity. In the area of synthetic applications, a handful of electrochemically generated solid supports and solid-phase electrochemical reactions appeared. For instance, the feasibility of running Merrifield chemistry on amino-derivatized polypyrrole support, prepared electrochemically, was demonstrated by Pickett et al.[10] Pilard and co-workers[11] showed that the sulfonamide N−S linkage can be cleaved electrochemically with high selectivity on the surface of functionalized polythiophenes. The combination of electrosynthesis and parallel synthesis of small organic molecules has not been exploited yet.

To prove the feasibility of parallel electrosynthesis, we constructed a 16-well electrolysis platform with two types of electrolysis cells, i.e., a Teflon block with 16 wells (Figure 1a,b) and a set of 16 glass vials (Figure 1c). As illustrated in Figure 1a−c, the 16 Teflon or cylindrical glass cells were arranged in a 4 by 4 array, each equipped with a tubular stainless steel cathode and a graphite rod anode. The stainless steel cathodes were welded into a stainless steel plate, which acted as a common terminal for the connection to the current source. The graphite anodes served as working electrodes

10.1021/cc000035v CCC: $19.00
Published on Web 08/03/2000

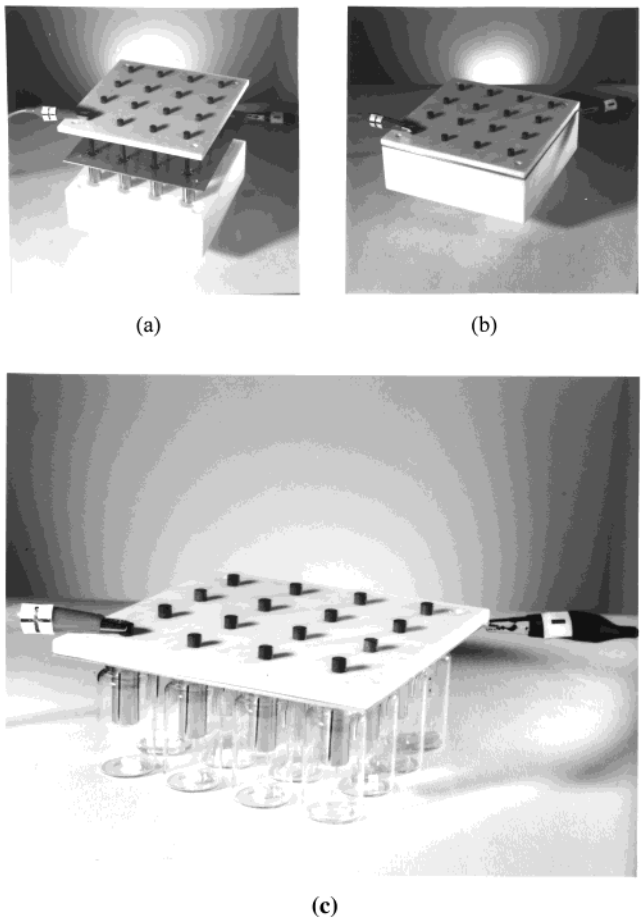


Figure 1. Experimental SAEP setup with Teflon reactor plate: (a) before electrode assembly; (b) after electrode assembly. (c) Experimental SAEP setup with glass reactors after electrode assembly.

and were insulated from each other and cathodes by planting through a Teflon plate. Parallel connection of the 16 cells was achieved using this setup. This design was intended for running electrochemical reactions under galvanostatic (constant current) conditions. In theory, potentiostatic (constant potential) methods can be realized, but they would require extra reference electrodes for each cell. By incorporating more sophisticated circuits, the parameter of each individual electrolysis cell can also be controlled, allowing one to optimize the reaction conditions.

A DC power supply was used to run electrolyses under galvanostatic condition, and the total charge passed was determined by a digital coulometer. When the parameters (solvent, supporting electrolyte, surface area of electrode, and temperature) are identical for each cell, the current must be distributed evenly among the 16 cells and the individual cell current I_i can be calculated from the total current I_t according to eq 1.

$$I_i = I_t/16, \quad i = 1, 2, ..., 16 \tag{1}$$

The α-alkoxylation of carbamates and sulfonamides[12,13] (Table 1) was chosen to test the idea of parallel electrosynthesis. This process constitutes a direct and convenient method for generation and trapping of *N*-acyliminium cations. An alternative way of making the derivatized

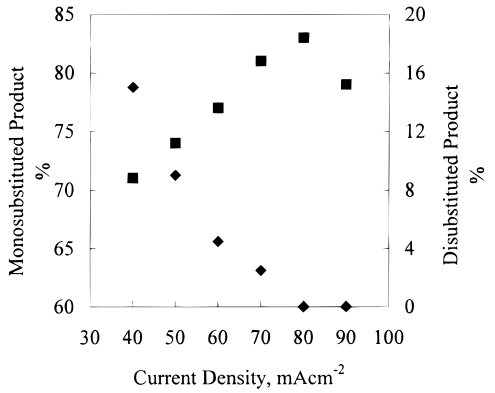


Figure 2. Current density effect on reaction between **3** and methanol. ■: monosubstituted product; ◆: disubstituted product.

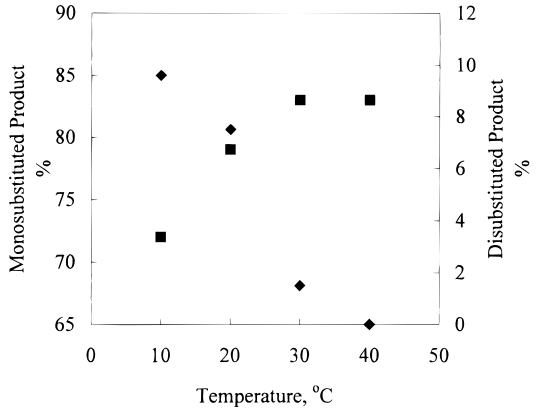
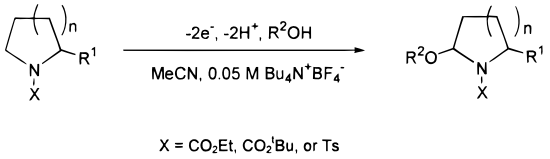


Figure 3. Temperature effect on reaction between **3** and methanol. ■: monosubstituted product; ◆: disubstituted product.

α-alkoxycarbamates is through the reduction of *N*-alkoxycarbonylactams.[14] The latter method, however, requires cooling of the reaction mixture (−6 °C) and relatively long reaction time (4−5 h). The electrochemical method can essentially be performed at room temperature, and typical reaction time is only 10 min for a reaction on a 1 mmol scale. The corresponding α-alkoxycarbamates are versatile synthetic intermediates and can be further elaborated into valuable products.[15]

At the beginning, 16 reactions between carbamate **3** and *n*-propanol were conducted. The same GC yield of the alkoxylation product was obtained for each cell, indicating that each one of them was operating under identical conditions. The individual cell current was calculated using eq 1. We then used a series of primary alcohols with acetonitrile as a cosolvent, in a series of reactions with carbamates and sulfonamides according to eq 2.



(2)

To find optimal electrolysis reaction conditions, the reaction between **3** and methanol was chosen. A current density of 80 mA/cm^2 and a temperature of 30 °C were found to afford the highest yield and selectivity. Acetonitrile content was also optimized, and a 50:50 (by volume) acetonitrile/

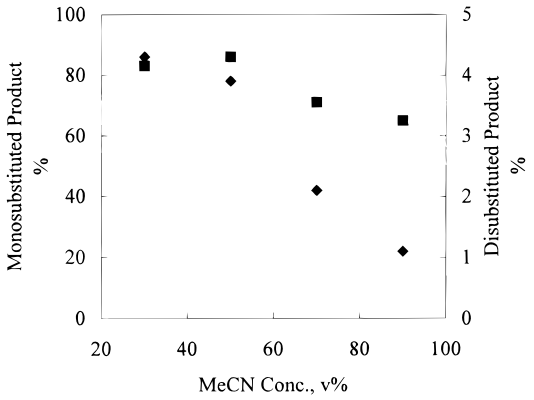


Figure 4. Acetonitrile content effect on reaction between **3** and methanol. ■: monosubstituted product; ◆: disubstituted product.

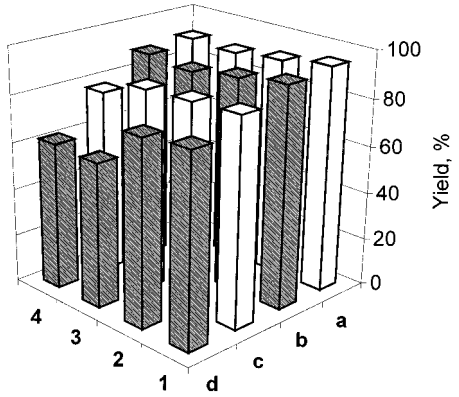


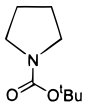
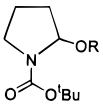
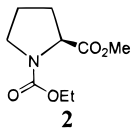
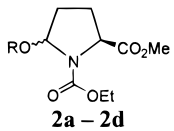
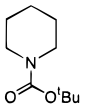
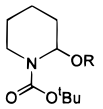
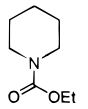
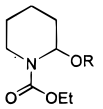
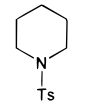
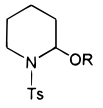
Figure 5. Parallel electrolysis of substrates **1**−**4** in alcohols **a**−**d**.

alcohol mixture was found to give the highest conversion. The optimization results are shown in Figures 2−4. The supporting electrolyte was removed before GC analysis by passing the reaction mixture through a short plug of silica gel, which was eluted with ethyl acetate/hexanes (1:1). The solid-phase extraction (SPE) technique was also applied at the product isolation stage (see Experimental Section).

Parallel electrosynthesis results for the substrates **1**−**4** and four alcohols are shown in Figure 5. In the cases of methanol and ethanol, all four substrates gave high yields, while small amounts of disubstituted byproducts (up to 5%) were detected for substrates **1**, **3**, and **4**. No such byproducts were found in the cases of *n*-propanol and *n*-butanol, which gave only moderate yields. We infer that the increase of chain length in alcohols is unfavorable for attacking the intermediate *N*-acyliminium cation for steric reasons. The substrate **2** gave equal amounts of two diastereomeric products. The alkoxylation of sulfonamide **5** and intramolecular cyclization of substrates **6**−**11**, which led to the isolation of a series of hetero-bicyclic compounds, have also been conducted, and the yields are given in Tables 1 and 2, respectively.

In summary, we have, for the first time, applied electrosynthesis in a parallel format on a preparative scale. This study illustrates that combinatorial chemistry and parallel synthesis can benefit from the power and simplicity intrinsic to electrochemical approaches. The documented SAEP design features can now be readily expanded to 96-well microtiter and other formats, and a wide range of previously unavailable electrochemical reactions can be introduced.

Table 1. α-Alkoxylation of Carbamates **1**−**4** and Sulfonamide **5**

Substrate	Product	R	Yield, %
 **1**	 **1a** – **1d**	**a**: Me	95[a]
		b: Et	93[a]
		c: ^{n}Pr	87[a] (75[b])
		d: ^{n}Bu	80[a] (70[b])
 **2**	 **2a** – **2d**	**a**: Me	92[a] (88[b])
		b: Et	90[a] (88[b])
		c: ^{n}Pr	86[a] (79[b])
		d: ^{n}Bu	78[a] (72[b])
 **3**	 **3a** – **3e**	**a**: Me	90[a]
		b: Et	87[a]
		c: ^{n}Pr	78[a]
		d: ^{n}Bu	61[a] (60[b])
		e: ^{i}Pr	63[a]
 **4**	 **4a** – **4d**	**a**: Me	91[a]
		b: Et	89[a]
		c: ^{n}Pr	85[a] (81[b])
		d: ^{n}Bu	62[a]
 **5**	 **5a** – **5d**	**a**: Me	90[b]
		b: Et	85[b]
		c: ^{n}Pr	78[b]
		d: ^{n}Bu	60[b]

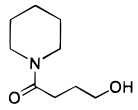
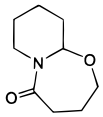
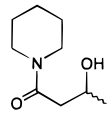
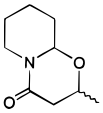
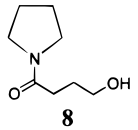
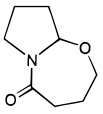
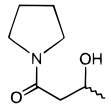
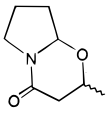
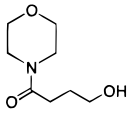
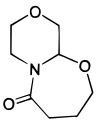
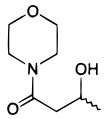
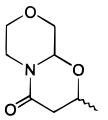
[a] GC yield. [b] Isolated yield.

Experimental Section

The parallel electrosynthesis was conducted using the spatially addressable electrolysis platform (SAEP) described in the text. Laboratory DC power supply was used (GW, model GPR-3060D). The electrolyte solution in each cell contained the substrate (0.5 M), tetrabutylammonium tetrafluoroborate ($Bu_4N^+BF_4^-$) as supporting electrolyte (0.05 M), tetralin as a GC internal standard, and 1:1 acetonitrile/alcohol as cosolvent in the case of substrate **1**−**5** or just acetonitrile in the case of substrate **6**−**11**. The SAEP was submerged in a water bath to maintain temperature at 30 °C. Electrolysis proceeded at constant current until theoretical charge (2.0 F) had been passed through each cell. After electrolysis, approximately 0.2 mL of each solution was loaded onto a short plug of silica gel (0.5 cm i.d. × 5 cm) and eluted with ca. 5 mL of ethyl acetate/hexanes (1:1). The eluted solution was analyzed by GC (HP-5 capillary column, H_2 carrier gas, 2.0 mL/min constant flow rate, temperature gradient 50−250 (C, FID detector). In the case of sulfonamides **4**, the solvent was evaporated and the residue was flash chromatographed on silica gel column with 1:4 ethyl acetate/hexanes as eluent.

A solid-phase extraction (SPE) procedure was tested on purification of product **10a** by the following steps: (1) conditioning an SPE column (*ISOLUTE* C18, 0.5 g of sorbent) with 5 mL of MeOH (0.1 mL/s); (2) loading 0.2 mL of the reaction mixture (containing ca. 25 mg of product and supporting electrolyte) onto the column; (3) column wash with 10 mL of H_2O (0.1 mL/s); (4) elution column with 5 mL of MeOH (0.1 mL/s) and eluent collection into a receiving test tube for GC analysis.

Table 2. Intramolecular Cyclization of Amides **6**−**11**

Substrate	Product	GC Yield, %
 **6**	 **6a**	80
 **7**	 **7a**	93
 **8**	 **8a**	94
 **9**	 **9a**	92
 **10**	 **10a**	95
 **11**	 **11a**	91

The NMR spectra were taken on Gemini 200 (200 MHz) with $CDCl_3$ as solvent.

2-Methoxypyrrolidine-1-carboxylic acid *tert*-butyl ester 1a: ^{1}H δ 1.48 (s, 9H), 1.70−2.05 (m, 4H), 3.20−3.45 (m, 5H), 5.00−5.20 (m, 1H).

2-Ethoxypyrrolidine-1-carboxylic acid *tert*-butyl ester 1b: ^{1}H δ 1.05 (t, J = 7.0 Hz, 3H), 1.35 (s, 9H), 1.60−2.00 (m, 4H), 3.10−3.55 (m, 4H), 5.00−5.20 (m, 1H).

2-Propoxypyrrolidine-1-carboxylic acid *tert*-butyl ester 1c: ^{1}H δ 0.92 (t, J = 7.2 Hz, 3H), 1.20−1.90 (m, 15H), 2.80−3.00 (m, 1H), 3.28 (t, J = 5.8 Hz, 2H), 3.80−4.00 (m, 1H), 5.25−5.50 (m, 1H).

2-Butoxypyrrolidine-1-carboxylic acid *tert*-butyl ester 1d: ^{1}H δ 0.88 (t, J = 7.2 Hz, 3H), 1.32 (q, J = 8.1 Hz, 2H), 1.45−2.10 (m, 15H), 3.15−3.65 (m, 4H), 5.10−5.25 (m, 1H).

5-Methoxy-1-ethoxycarbonyl-L-proline methyl ester 2a: ^{1}H δ 1.10−1.40 (m, 3H), 1.70−2.50 (m, 4H), 3.30−3.50 (m, 3H), 3.70−3.80 (m, 3H), 4.00−4.25 (m, 2H), 4.30−4.45 (m, 1H), 5.15−5.40 (m, 1H).

5-Ethoxy-1-ethoxycarbonyl-L-proline methyl ester 2b: ^{1}H δ 1.15 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.3 Hz, 3H), 1.80−2.50 (m, 4H), 3.50−3.80 (m, 5H), 4.00−4.25 (m, 2H), 4.30−4.45 (m, 1H), 5.25−5.50 (m, 1H).

5-Propoxy-1-ethoxycarbonyl-L-proline methyl ester 2c: ^{1}H δ 0.89 (t, J = 7.2 Hz, 3H), 1.15−1.30 (m, 3H), 1.45−1.65 (m, 2H), 1.80−2.50 (m, 4H), 3.30−3.70 (m, 5H), 4.00−4.45 (m, 3H), 5.25−5.50 (m, 1H).

5-Butoxy-1-ethoxycarbonyl-L-proline methyl ester 2d: ^{1}H δ 0.90 (t, J = 7.2 Hz, 3H), 1.10−1.60 (m, 7H), 1.70−2.50 (m, 4H), 3.30−3.70 (m, 5H), 4.00−4.45 (m, 3H), 5.25−5.50 (m, 1H).

2-Methoxypiperidine-1-carboxylic acid *tert*-butyl ester 3a: ^{1}H δ 1.30−1.70 (m, 15H), 2.80−3.00 (m, 1H), 3.22 (s, 3H), 3.80−4.00 (m, 1H), 5.25−5.50 (m, 1H).

2-Ethoxypiperidine-1-carboxylic acid *tert*-butyl ester 3b: ^{1}H δ 1.19 (t, J = 7.1 Hz, 3H), 1.30−1.90 (m, 15H), 2.80−3.05 (m, 1H), 3.30−3.50 (m, 2H), 3.70−4.00 (m, 1H), 5.30−5.50 (m, 1H).

2-Propoxypiperidine-1-carboxylic acid *tert*-butyl ester 3c: ^{1}H δ 0.91 (t, J = 7.4 Hz, 3H), 1.20−1.90 (m, 17H), 2.80−3.00 (m, 1H), 3.28 (m, 2H), 3.80−4.00 (m, 1H), 5.25−5.50 (m, 1H).

2-Butoxypiperidine-1-carboxylic acid *tert*-butyl ester 3d: ^{1}H δ 0.89 (t, J = 7.1 Hz, 3H), 1.10−1.90 (m, 19H), 2.80−3.00 (m, 1H), 3.20−3.60 (m, 2H), 3.80−3.95 (m, 1H), 5.25−5.50 (m, 1H).

2-Isopropoxypiperidine-1-carboxylic acid *tert*-butyl ester 3e: ^{1}H δ 1.12 (d, J = 6.8 Hz, 6H), 1.30−1.80 (m, 15H), 2.80−3.00 (m, 1H), 3.20−3.35 (m, 1H), 3.80−4.00 (m, 1H), 5.25−5.50 (m, 1H).

2-Methoxypiperidine-1-carboxylic acid ethyl ester 4a: ^{1}H δ 1.21 (t, J = 7.0 Hz, 3H), 1.40−1.85 (m, 6H), 2.80−3.00 (m, 1H), 3.18 (s, 3H), 3.80−3.95 (b, 1H), 4.00−4.20 (m, 2H), 5.20−5.40 (m, 1H).

2-Ethoxypiperidine-1-carboxylic acid ethyl ester 4b: ^{1}H δ 1.01 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 6.9 Hz, 3H), 1.30−1.80 (m, 6H), 2.80−3.00 (m, 1H), 3.28 (t, J = 5.8 Hz, 2H), 3.80−4.00 (b, 1H), 4.05−4.20 (m, 2H), 5.25−5.50 (m, 1H).

2-Propoxypiperidine-1-carboxylic acid ethyl ester 4c: ^{1}H δ 0.89 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.35−1.90 (m, 8H), 2.92 (t, J = 12.8 Hz, 1H). 3.28 (t, J = 5.7 Hz, 2H), 3.80−4.00 (b, 1H), 4.05−4.20 (m, 2H), 5.30−5.50 (b, 1H).

2-Butoxypiperidine-1-carboxylic acid ethyl ester 4d: ^{1}H δ 0.91 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.35−1.65 (m, 8H), 1.70−1.90 (m, 2H), 2.95 (t, J = 13.0 Hz, 1H), 3.30−3.45 (m, 2H), 3.80−4.00 (b, 1H), 4.05−4.20 (m, 2H), 5.35−5.50 (b, 1H).

2-Methoxy-1-(toluene-4-sulfonyl)-piperidine 5a: ^{1}H δ 1.40−1.95 (m, 6H), 2.43 (s, 3H), 2.90−3.10 (m, 2H), 3.38 (s, 3H), 5.10−5.20 (b, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H).

2-Ethoxy-1-(toluene-4-sulfonyl)-piperidine 5b: ^{1}H δ 1.23 (t, J = 6.0 Hz, 3H), 1.35−1.80 (m, 6H), 2.43 (s, 3H), 2.94 (t, J = 6.8 Hz, 2H), 3.35−3.45 (m, 2H), 5.05−5.25 (m, 1H), 7.20−7.35 (m, 2H), 7.55−7.70 (m, 2H).

2-Propoxy-1-(toluene-4-sulfony)-piperidine 5c: ^{1}H δ 0.89 (t, J = 6.8 Hz, 3H), 1.30−1.80 (m, 8H), 2.41 (s, 3H), 2.90−3.10 (m, 2H), 3.30−3.50 (m, 2H), 5.10−5.25 (m, 1H), 7.25−7.35 (m, 2H), 7.55−7.70 (m, 2H).

2-Butoxy-1-(toluene-4-sulfony)-piperidine 5d: ^{1}H δ 0.89 (t, J = 6.8 Hz, 3H), 1.20−1.90 (m, 10H), 2.42 (s, 3H), 2.95−3.10 (m, 2H), 3.30−3.50 (m, 2H), 5.10−5.25 (m, 1H), 7.25−7.35 (m, 2H), 7.55−7.70 (m, 2H).

1-Aza-6-oxabicyclo[5.4.0]undecan-2-one 6a: ^{1}H δ 1.40−2.00 (m, 8H), 2.61 (ddd, J_1 = 14.3 Hz, J_2 = 6.2 Hz, J_3 =

2.9 Hz, 1H), 2.87 (ddd, $J_1 = 14.6$ Hz, $J_2 = 11.6$ Hz, $J_3 = 3.6$ Hz, 1H), 3.19 (qd, $J_1 = 13.5$ Hz, $J_2 = 4.7$ Hz, 1H), 3.74 (qd, $J_1 = 11.7$ Hz, $J_2 = 3.1$ Hz, 1H), 3.91 (dq, $J_1 = 13.6$ Hz, $J_2 = 5.0$ Hz, 1H), 4.06 (dq, $J_1 = 12.2$ Hz, $J_2 = 3.8$ Hz, 1H), 5.03 (q, $J = 7.8$ Hz, 1H); ^{13}C δ 17.38, 22.73, 25.90, 29.79, 36.27, 38.53, 71.75, 85.45, 176.30. HRMS: 169.1104 (calcd mass 169.1103, $C_9H_{15}NO_2$).

1-Aza-4-methyl-5-oxabicyclo[4.4.0]decan-2-one 7a: ^{1}H δ 1.28 (d, $J = 6.4$ Hz, 3H), 1.35−2.00 (m, 6H), 2.15−2.55 (m, 3H), 3.76−3.92 and 4.12−4.28 (two sets of multiplet, 1H), 4.52−4.78 (m, 2H); ^{13}C (20.21, 21.47, 23.09, 23.89, 25.06, 25.26, 32.46, 33.32, 39.63, 40.30, 40.61, 41.63, 66.29, 70.01, 84.37, 86.74, 165.64, 166.78. HRMS: 169.1099 (Calcd mass 169.1103, $C_9H_{15}NO_2$).

1-Aza-6-oxabicyclo[5.3.0]decan-2-one 8a: ^{1}H δ 1.60−2.20 (m, 6H), 2.60−2.75 (m, 2H), 3.30−3.50 (m, 1H), 3.65 (td, $J_1 = 12.1$ Hz, $J_2 = 2.3$ Hz, 2H), 4.12 (dt, $J_1 = 12.3$ Hz, $J_2 = 2.7$ Hz, 1H), 5.09 (dd, $J_1 = 5.8$ Hz, $J_2 = 2.5$ Hz, 1H); ^{13}C δ 22.44, 25.74, 34.45, 37.24, 73.11, 90.49, 175.01. HRMS: 155.0953 (calcd mass 155.0946, $C_8H_{13}NO_2$).

1-Aza-4-methyl-5-oxa-bicyclo[4.3.0]nonan-2-one 9a: ^{1}H δ 1.10−1.30 (m, 5H), 2.95 (ddd, $J_1 = 18.8$ Hz, $J_2 = 17.6$ Hz, $J_3 = 8.9$ Hz, 2H), 3.20−3.40 (m, 2H), 3.80−4.00 (m, 1H), 4.05−4.25 (m, 2H), 4.87 + 5.06 (two sets of triplet, $J = 5.7$ Hz, 1H); ^{13}C δ 17.76, 19.98, 22.02, 23.10, 32.45, 34.15, 45.86, 45.94, 64.63, 64.80, 69.06, 72.55, 83.81, 89.27, 174.24, 176.16. HRMS: 155.0950 (calcd mass 155.0946, $C_8H_{13}NO_2$).

1-Aza-6,9-dioxabicyclo[5.4.0]undecan-2-one 10a: ^{1}H δ 1.60−2.20 (m, 2H), 2.58 (ddd, $J_1 = 14.4$ Hz, $J_2 = 6.0$ Hz, $J_3 = 2.6$ Hz, 1H), 2.75−2.90 (m, 1H), 3.20−3.40 (m, 1H), 3.56 (td, $J_1 = 11.4$ Hz, $J_2 = 4.3$ Hz, 1H), 3.65−4.10 (m, 5H), 4.08 (dt, $J_1 = 12.1$ Hz, $J_2 = 4.0$ Hz, 1H), 4.87 (t, $J = 3.6$ Hz, 1H); ^{13}C δ 25.55, 35.68, 38.80, 65.93, 68.44, 72.22, 83.02, 176.39. HRMS: 171.0888 (calcd mass 171.0895, $C_8H_{13}NO_3$).

1-Aza-4-methyl-5,8-dioxabicyclo[4.4.0]decan-2-one 11a: ^{1}H δ 1.29 (d, $J = 6.2$ Hz, 3H), 2.84 (td, $J_1 = 13.3$ Hz, $J_2 = 3.4$ Hz, 1H), 3.18 (dd, $J_1 = 11.1$ Hz, $J_2 = 9.2$ Hz, 1H), 3.35−3.50 (m, 2H), 3.85−4.05 (m, 4H), 4.46 (dd, $J_1 = 14.0$ Hz, $J_2 = 2.0$ Hz, 1H), 4.77 (dd, $J_1 = 9.2$ Hz, $J_2 = 3.7$ Hz, 1H); ^{13}C δ 21.39, 39.74, 40.32, 67.24, 70.09, 70.47, 82.91, 166.11. HRMS: 171.0892 (calcd mass 171.0895, $C_8H_{13}NO_3$).

Acknowledgment. This work was supported by the Research Corporation, the National Science and Engineering Research Council (NSERC), Canada Foundation for Innovation (CFI), the Connaught Fund, and the University of Toronto. Postdoctoral support of Dr. Wei Li was provided by NRC, NSERC, and MRC grants to Professor Aled Edwards.

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