Experimental Characterization and Computational Study of Unique C,N-Chelated Lithium Dianions

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Part I: Experimental Methods

Part II: NMR Spectroscopic Studies

Part III: DFT Computational Studies

Part I: Experimental Methods

1. Reagents and Solvents.

[^{6}Li]*n*-BuLi was prepared and recrystallized in *n*-pentane as described previously.[1] An aliquot was removed and the pentane was evaporated and replaced with freshly distilled cyclopentane. *n*-BuLi was then titrated using diphenylacetic acid to determine the precise molarity. THF-d_8 was distilled from a solution containing sodium benzophenone ketyl. Cyclopentane was distilled from a blue solution containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques.

2. Sample Preparation.

A stock solution of **8** was prepared at room temperature. After flame drying the NMR tube under vacuum and flushing with argon, the tube was placed in a -78 °C dry ice/acetone bath. The appropriate amount of the amine and THF-d_8 was added via syringe, followed by dropwise addition *n*-BuLi. All samples had a total volume of 0.60 mL. The tube was sealed under partial vacuum and immediately vortexed for approximately 5 seconds before being replaced into a -78 °C bath. The samples were stored in a -94 °C freezer.

3. Spectroscopic Analysis.

NMR spectra were recorded at -90 °C or -100 °C on a 500 or 600 MHz spectrometer with a delay between scans set to >5 x T1 to ensure accurate integrations. ^{6}Li chemical shifts are reported relative to a 0.30 M ^{6}LiCl/MeOH standard (0.0 ppm) and ^{15}N chemical shifts are reported relative to a neat *N*,*N*-dimethylethylamine (DMEA) standard (25.6 ppm).

Part II: NMR Spectroscopic Studies

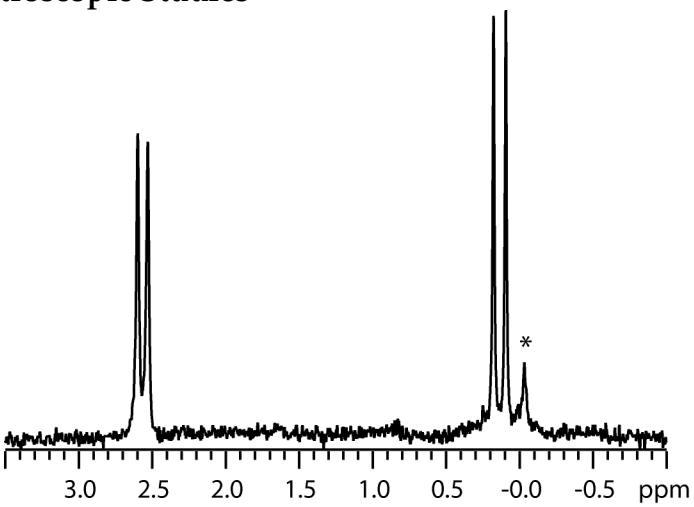


Figure 1a. ^{6}Li NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C. * Denotes an impurity from [^{6}Li]*n*-BuLi.

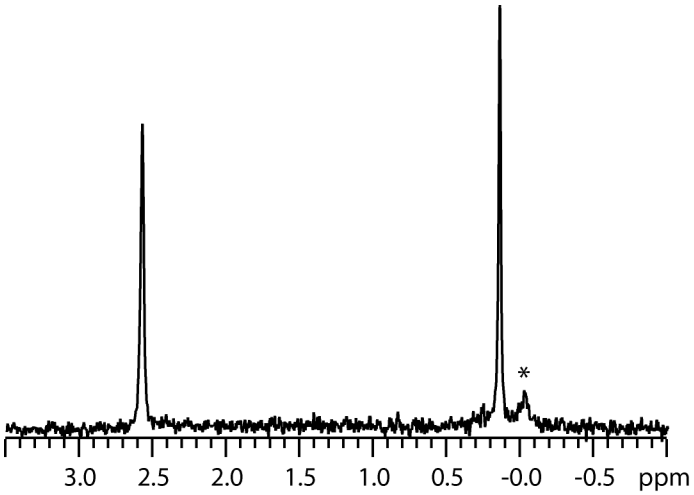


Figure 1b. {^{15}N}^{6}Li NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C. * Denotes an impurity from [^{6}Li]*n*-BuLi.

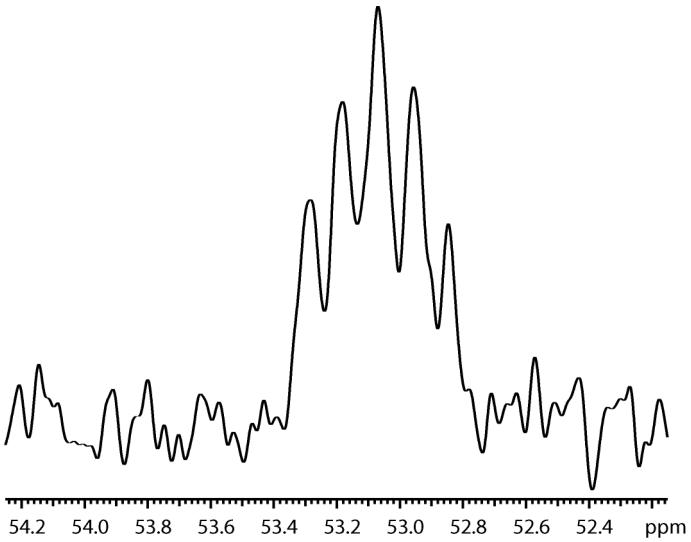


Figure 2. ^{15}N NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -90 °C.

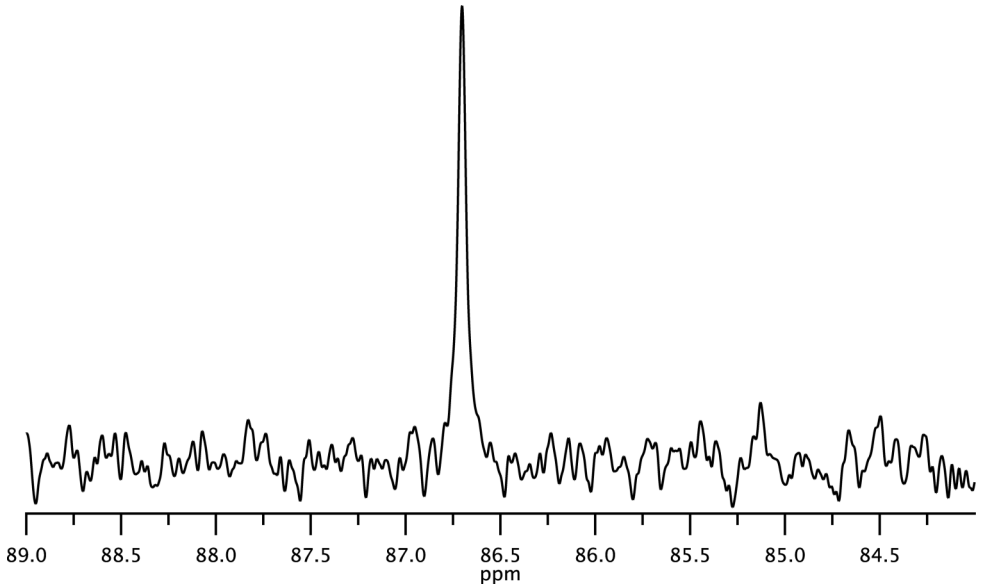
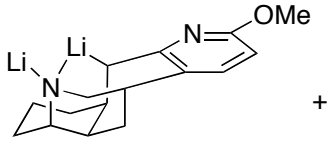
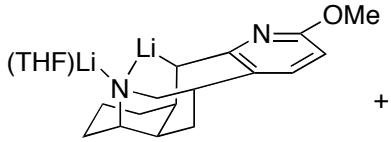
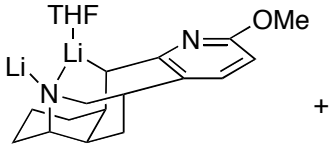
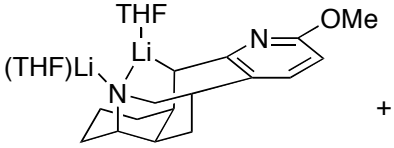
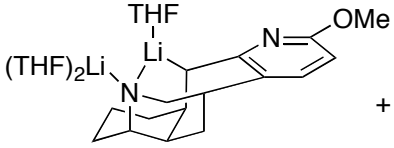
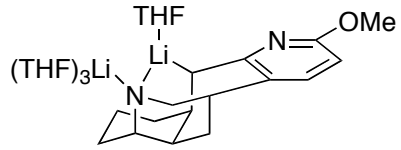
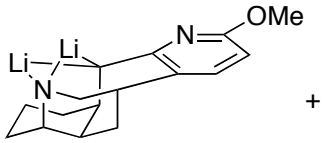
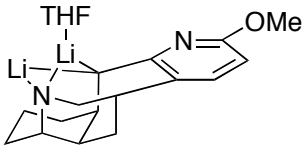
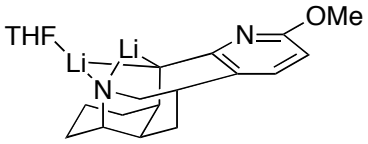
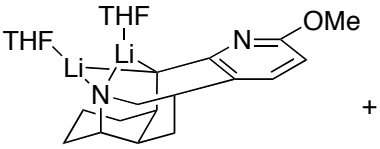
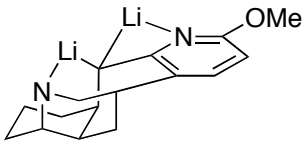
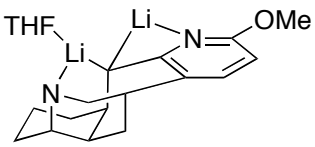


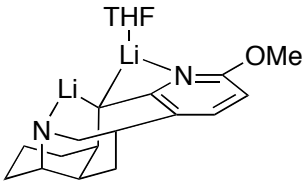
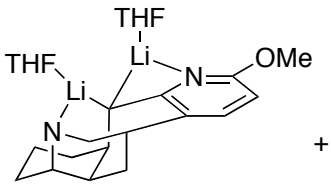
Figure 3. ^{13}C NMR spectrum of 0.025 M [^{14}N]**8** and 2.0 equiv [^{6}Li]*n*-BuLi in THF-d_8 at -100 °C expanded around the benzylic carbon resonance. 2-D NMR techniques (COSY, HMBC, and HSQC) were used to identify the chemical shift of the benzylic carbon.

Part III: DFT Computational Studies

Table 1. Relative free energies (ΔG, kcal/mol) of **9**, **10**, and **11** at -78 °C calculated using B3LYP level of theory with 6-31G(d) basis set.

Structure	Free Energy (ΔG, kcal/mol)
	0.0
	-19.9
	-19.5
	-32.0
	-38.9 (see Fig. 4)

	-38.3
 + 4 THF	+4.2
 + 3 THF	-13.7
 + 3 THF	-13.8
 + 2 THF	-33.7 (see Fig. 4)
 + 4 THF	-3.2
 + 3 THF	-20.1

 + 3 THF	-21.7
 + 2 THF	-34.2 (see Fig. 4)

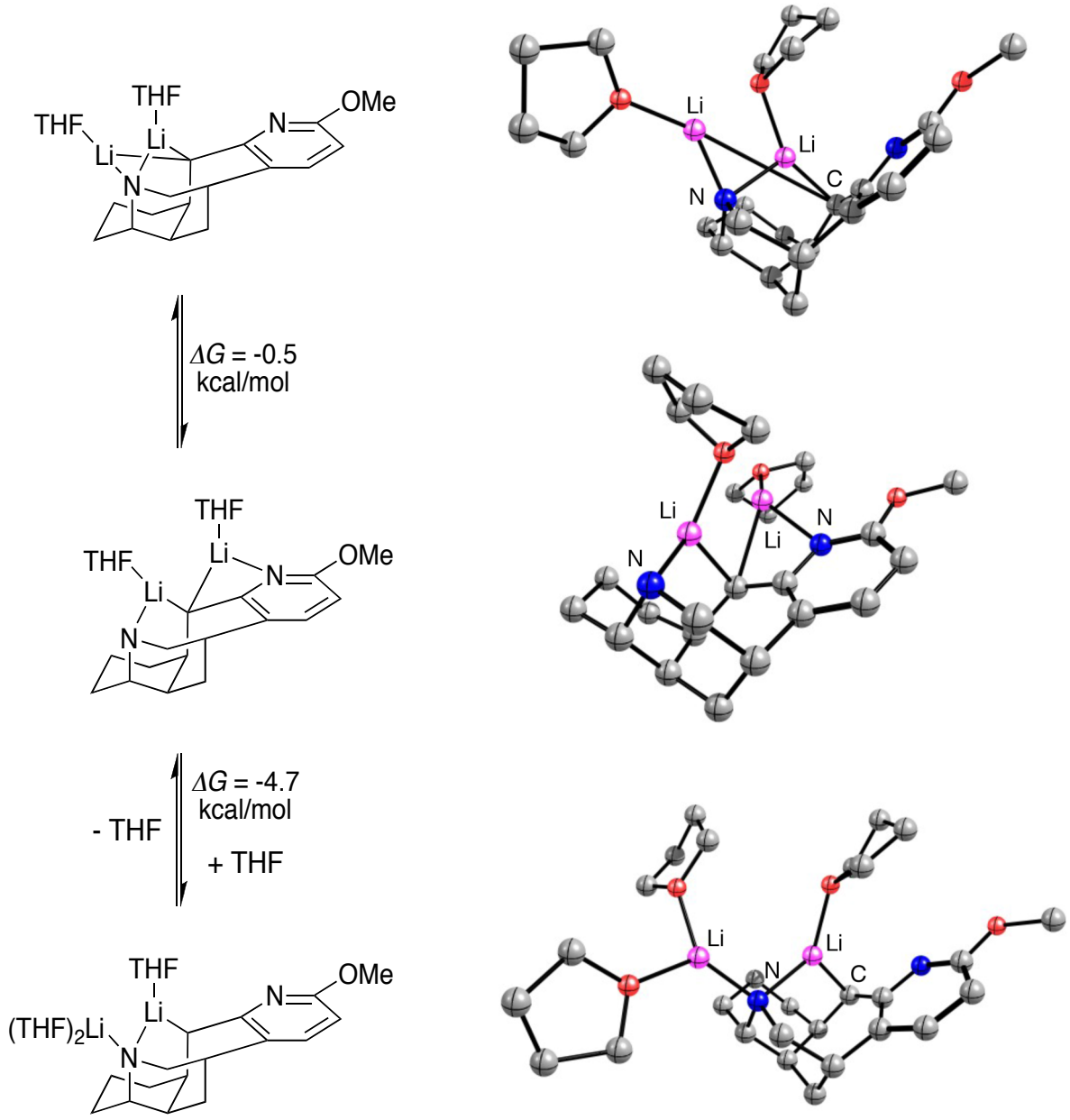
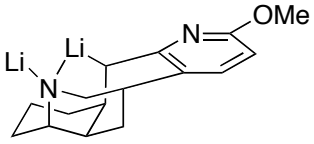


Figure 4. The relative energies of the three most stable solvates of **9**, **10**, and **11**.

Table 2. Optimized geometries at B3LYP level of theory with 6-31G(d) basis set for the serial solvation of open dimer **9** at -78 °C with free energies (Hartrees), and Cartesian coordinates (X,Y,Z).

G = -232.349373

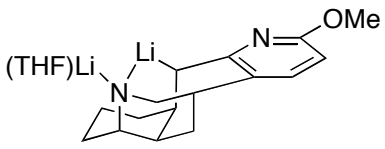
Atom	X	Y	Z
C	-0.73320	0.75864	-0.22699
C	-1.16581	-0.66851	0.13194
O	-0.00087	-1.49011	-0.00008
C	1.16504	-0.66980	-0.13184
C	0.73406	0.75792	0.22693
H	-1.94955	-1.06099	-0.52668
H	-1.53562	-0.72079	1.16790
H	1.94831	-1.06314	0.52684
H	1.53490	-0.72246	-1.16775
H	0.79733	0.91645	1.31025
H	1.34480	1.52213	-0.26387
H	-1.34309	1.52360	0.26368
H	-0.79630	0.91704	-1.31034



G = -821.216489

Atom	X	Y	Z
C	1.97800	0.16056	-1.07595
C	1.08536	1.27946	-1.63224
C	0.06500	1.80926	-0.60906
C	0.82403	2.17404	0.70033
N	1.56463	1.04524	1.28409
Li	0.07796	-0.24644	1.35783
C	-1.16941	-0.53398	-0.33765
C	-1.15770	0.92251	-0.37087
C	-2.37975	1.57434	-0.18801
C	-3.57699	0.90717	0.05562
C	-3.48012	-0.49681	0.11532
N	-2.36783	-1.17142	-0.06179
O	-4.56014	-1.30534	0.36818

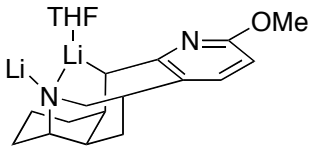
C	-5.82550	-0.69476	0.53221
C	-0.03579	-1.39625	-0.35170
C	1.29217	-1.22905	-1.07691
C	2.31111	-2.27048	-0.54857
C	2.83793	-1.92082	0.85109
C	3.48114	-0.52575	0.84944
C	2.57229	0.59600	0.29494
Li	2.54569	0.93106	2.82224
H	-6.13322	-0.13966	-0.36469
H	-6.53202	-1.50979	0.70642
H	-5.84589	-0.01291	1.39417
H	-4.50565	1.44819	0.18038
H	-2.39512	2.66278	-0.24873
H	-0.34480	-2.44062	-0.30360
H	1.15068	-1.46174	-2.15099
H	1.85128	-3.26593	-0.53059
H	3.16450	-2.32860	-1.24167
H	3.57247	-2.66651	1.18307
H	2.00297	-1.96319	1.56476
H	4.39248	-0.55789	0.23730
H	3.86727	-0.28042	1.87035
H	3.23669	1.45699	0.06100
H	0.10385	2.55703	1.43713
H	1.51212	3.01390	0.46069
H	-0.32116	2.75893	-1.00724
H	1.72729	2.12244	-1.92843
H	0.57489	0.93560	-2.54074
H	2.83930	0.06285	-1.75710



G = -1053.597570

Atom	X	Y	Z
C	-0.81251	2.61978	0.72957
C	-1.59588	2.07544	1.93227
C	-1.60155	0.53835	2.00677
C	-0.12942	0.04090	1.89639
N	0.55216	0.46565	0.66373
Li	-0.73130	-0.14367	-0.68249
C	-2.81619	0.21535	-0.33777
C	-2.54256	-0.17664	1.03936
C	-3.19573	-1.31131	1.52109

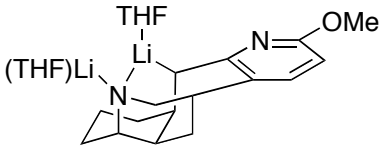
C	-4.04773	-2.09741	0.74661
C	-4.19679	-1.67814	-0.58876
N	-3.62716	-0.61231	-1.10113
O	-4.96644	-2.36188	-1.50070
C	-5.66155	-3.50849	-1.05378
C	-2.19301	1.26037	-1.07108
C	-1.62740	2.58818	-0.58922
C	-0.75854	3.21833	-1.70765
C	0.58957	2.50249	-1.87444
C	1.37470	2.49875	-0.55407
C	0.58732	1.94273	0.65065
Li	2.25446	-0.19297	0.28248
O	3.85554	-1.12731	-0.03982
C	4.36164	-2.21186	0.79214
C	5.80102	-2.43174	0.33157
C	5.72099	-2.07731	-1.16171
C	4.75409	-0.89393	-1.16415
H	-6.37458	-3.27104	-0.25201
H	-6.21227	-3.88401	-1.91988
H	-4.97870	-4.29276	-0.69655
H	-4.54705	-2.96291	1.16204
H	-3.03364	-1.59249	2.56208
H	-2.60353	1.32848	-2.07893
H	-2.46116	3.29703	-0.41390
H	-1.30732	3.20487	-2.65763
H	-0.56864	4.27572	-1.46659
H	1.18636	2.98747	-2.65915
H	0.40738	1.47364	-2.21722
H	2.32924	1.94733	-0.67538
H	1.66893	3.53239	-0.32277
H	1.12329	2.28616	1.56479
H	5.30498	-2.91418	-1.73367
H	6.69018	-1.81675	-1.59539
H	5.27014	0.05841	-0.99680
H	4.14986	-0.81884	-2.07253
H	6.47928	-1.74811	0.85447
H	6.13978	-3.45512	0.51399
H	3.73690	-3.09644	0.62158
H	4.27113	-1.90523	1.83773
H	-0.12417	-1.05806	1.95901
H	0.40926	0.41492	2.79740
H	-1.93907	0.26772	3.01839
H	-1.12388	2.44878	2.85359
H	-2.62247	2.46426	1.92211
H	-0.61795	3.68738	0.92532



G = -1053.596858

Atom	X	Y	Z
C	2.94948	-1.21605	0.20671
C	2.36883	-2.40472	-0.57313
C	1.07866	-2.05675	-1.33681
C	1.35510	-0.76866	-2.17061
N	1.75790	0.38141	-1.35363
C	3.02957	0.04968	-0.70303
C	3.61424	1.23527	0.08715
C	2.95822	1.46475	1.45695
C	2.95148	0.17788	2.29455
C	2.24028	-0.99282	1.56789
C	0.73869	-0.75715	1.58250
Li	0.33474	0.55909	0.02708
C	-0.30023	-1.30161	0.80356
N	-1.58342	-1.01801	1.27723
C	-2.65291	-1.48730	0.67462
C	-2.63634	-2.25433	-0.50113
C	-1.36882	-2.42042	-1.07565
C	-0.19550	-1.93426	-0.50977
O	-3.82356	-1.09504	1.29416
C	-5.04179	-1.60764	0.78852
Li	0.93187	1.93302	-1.89819
O	-0.73145	2.15005	-0.83572
C	-2.01317	1.58912	-1.31806
C	-3.04811	2.04363	-0.29726
C	-2.51208	3.41890	0.13168
C	-1.00207	3.19470	0.16721
H	-2.19907	2.00563	-2.31541
H	-1.89639	0.50444	-1.38136
H	-3.07761	1.34505	0.54486
H	-4.04842	2.09921	-0.73637
H	-2.89356	3.73988	1.10474
H	-2.76944	4.18712	-0.60697
H	-0.66556	2.81382	1.13682
H	-0.41283	4.07679	-0.10012
H	-5.06777	-2.70491	0.82011
H	-5.82799	-1.21329	1.43710
H	-5.23108	-1.28169	-0.24463
H	-3.52323	-2.66671	-0.96356
H	-1.29714	-2.95324	-2.02412
H	0.37397	-0.38713	2.54172

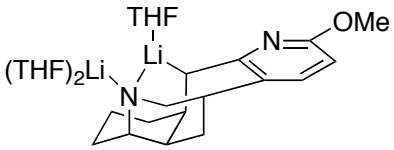
H	2.46876	-1.90369	2.15519
H	2.47381	0.36206	3.26558
H	3.99294	-0.10880	2.50487
H	3.48513	2.26665	1.99226
H	1.92114	1.81818	1.33540
H	4.68417	1.04309	0.25198
H	3.55854	2.14496	-0.53327
H	3.77142	-0.20226	-1.49089
H	0.44083	-0.52403	-2.74158
H	2.13408	-1.01764	-2.92365
H	0.90139	-2.86594	-2.06109
H	3.11111	-2.73067	-1.31695
H	2.20274	-3.25601	0.10057
H	3.99046	-1.47357	0.46193



G = -1285.966188

Atom	X	Y	Z
C	-1.94928	0.30529	0.97763
C	-1.04147	1.45296	1.43264
C	-0.04467	1.89226	0.34764
C	-0.84906	2.11093	-0.98902
N	-1.59576	0.93906	-1.43191
Li	0.27675	0.33016	-1.66575
C	1.17796	0.97062	0.21094
C	1.14263	-0.47499	0.08524
C	-0.06834	-1.27731	-0.05542
C	-1.25098	-1.08056	0.93675
C	-2.35868	-2.14540	0.72134
C	-3.20520	-1.92784	-0.55352
Li	-1.53203	-0.93384	-1.61062
C	-3.64017	-0.44481	-0.75709
C	-2.60348	0.66025	-0.38875
N	2.31362	-1.16053	-0.08929
C	3.47768	-0.53848	-0.11368
C	3.62221	0.85310	0.03068
C	2.44305	1.57355	0.18873
O	4.53038	-1.38709	-0.29037
C	5.83918	-0.84148	-0.30303
H	6.08141	-0.34255	0.64461
H	6.51326	-1.68861	-0.44430

H	5.97733	-0.13016	-1.12850
H	4.58307	1.35133	0.03002
H	2.50430	2.65429	0.30813
H	0.23044	-2.32952	-0.05668
H	-0.86798	-1.25464	1.95765
H	-1.92468	-3.15290	0.70537
H	-3.03602	-2.10827	1.58525
H	-4.10704	-2.54880	-0.51259
H	-2.68225	-2.35298	-1.43589
H	-4.50249	-0.28414	-0.10029
H	-3.99713	-0.28259	-1.78416
H	-3.21175	1.57381	-0.23363
H	-0.14667	2.43680	-1.78252
H	-1.50924	2.98895	-0.82703
H	0.35380	2.87519	0.63637
H	-1.67808	2.31724	1.67293
H	-0.51066	1.18331	2.35552
H	-2.75396	0.21841	1.72658

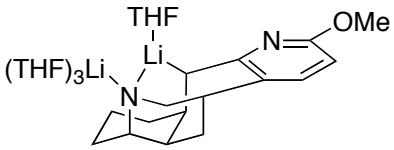


G = -1518.326520

Atom	X	Y	Z
C	-0.14256	-2.84415	1.75587
C	-0.69798	-3.69209	0.60475
C	-1.01575	-2.86277	-0.65290
C	0.23532	-1.99347	-0.98694
N	0.68035	-1.10768	0.09055
C	1.02303	-1.94678	1.24523
C	1.59952	-1.13164	2.42060
C	0.53931	-0.37493	3.23387
C	-0.56930	-1.32553	3.70803
C	-1.24354	-2.07923	2.53362
C	-2.15655	-1.12917	1.77466
Li	-0.91724	0.00494	0.45899
C	-2.78741	-1.28306	0.52132
N	-3.91530	-0.48834	0.33418
C	-4.59414	-0.52358	-0.79064
C	-4.26936	-1.31599	-1.90020
C	-3.09225	-2.06580	-1.76302
C	-2.31232	-2.06619	-0.61476
O	-5.67375	0.34542	-0.78697

C	-6.57585	0.27406	-1.87440
O	-1.45892	1.80457	-0.14748
C	-2.36207	2.47232	0.78171
C	-3.01751	3.56554	-0.05373
C	-3.22775	2.84030	-1.39364
C	-1.99604	1.92534	-1.49719
Li	2.11940	0.07233	-0.41532
O	3.68236	-0.55649	-1.38824
C	3.92552	-1.97622	-1.56693
C	5.41395	-2.07979	-1.88635
C	5.64430	-0.80604	-2.71544
C	4.73538	0.21313	-2.01763
O	2.57677	1.95635	-0.03258
C	1.70593	3.08966	-0.32250
C	2.01961	4.15686	0.74135
C	2.71843	3.35315	1.85111
C	3.47513	2.30540	1.04158
H	-1.20265	2.35751	-2.11957
H	-2.24672	0.92886	-1.87162
H	-4.13898	2.23855	-1.34437
H	-3.30306	3.52374	-2.24529
H	-3.95450	3.91788	0.38742
H	-2.34324	4.42404	-0.16827
H	-3.09394	1.74055	1.14019
H	-1.75182	2.84016	1.61163
H	-6.99672	-0.73383	-1.98882
H	-7.38249	0.97558	-1.64588
H	-6.10536	0.56795	-2.82393
H	-4.86004	-1.35628	-2.80597
H	-2.77067	-2.68197	-2.60316
H	-2.76602	-0.52802	2.45216
H	-1.85990	-2.87531	2.99829
H	-1.32562	-0.76823	4.27602
H	-0.12964	-2.05808	4.40262
H	1.01192	0.11855	4.09543
H	0.09385	0.42625	2.62648
H	2.37106	-0.43500	2.05012
H	2.12086	-1.82521	3.09687
H	1.82362	-2.66861	0.94451
H	1.98453	2.86245	2.49975
H	3.37840	3.96367	2.47431
H	0.67467	2.73058	-0.26860
H	1.91800	3.43759	-1.33964
H	2.69804	4.91785	0.33973
H	1.11576	4.66483	1.08893
H	4.40701	2.71270	0.62299
H	3.70419	1.39113	1.59534
H	0.01376	-1.39860	-1.88765
H	1.03826	-2.71566	-1.27676

H	-1.12086	-3.57307	-1.48720
H	0.06251	-4.43769	0.32591
H	-1.58368	-4.25216	0.93383
H	0.30236	-3.54045	2.48707
H	6.68911	-0.48289	-2.73543
H	5.31955	-0.96420	-3.75017
H	6.00658	-2.05416	-0.96418
H	5.66267	-2.99730	-2.42724
H	3.30496	-2.34136	-2.39421
H	3.61726	-2.48231	-0.64974
H	4.28095	0.93176	-2.70673
H	5.26736	0.76776	-1.23567

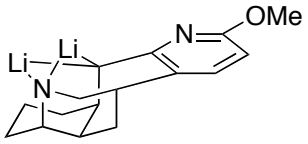


G = -1750.675050

Atom	X	Y	Z
C	0.27008	-3.49201	-0.53640
C	0.84109	-3.79257	0.85397
C	1.20335	-2.51858	1.63560
C	-0.02202	-1.55477	1.58299
N	-0.47221	-1.18152	0.24411
C	-0.85881	-2.42177	-0.43850
C	-1.45124	-2.17987	-1.83977
C	-0.40102	-1.87491	-2.91740
C	0.67621	-2.96876	-2.95786
C	1.36401	-3.16958	-1.58381
C	2.31918	-2.01689	-1.31548
Li	1.13445	-0.37266	-0.60520
C	2.97808	-1.64330	-0.12488
N	4.13449	-0.88961	-0.31041
C	4.84367	-0.46757	0.71236
C	4.52439	-0.69089	2.05847
C	3.32333	-1.38464	2.27065
C	2.51394	-1.85013	1.24409
O	5.95496	0.26423	0.32226
C	6.88198	0.63245	1.32510
O	1.81939	1.46662	-0.94108
C	2.66034	1.52356	-2.12961
C	3.42449	2.83427	-1.98793
C	3.72821	2.84621	-0.48038
C	2.47881	2.19231	0.13397
Li	-1.82108	0.28609	0.24311

O	-1.72346	1.66736	1.79272
C	-0.59612	2.07535	2.58234
C	-1.02909	1.83521	4.03507
C	-2.57383	1.99948	3.98566
C	-2.88120	2.16536	2.48198
O	-3.77815	-0.29864	0.54241
C	-3.97732	-1.42112	1.43859
C	-4.97736	-2.33093	0.72985
C	-5.86318	-1.31200	-0.00425
C	-4.84567	-0.24920	-0.43286
O	-2.02437	1.69576	-1.28718
C	-2.40167	1.50670	-2.67002
C	-1.63725	2.56798	-3.46126
C	-1.56062	3.72032	-2.44933
C	-1.34970	2.97226	-1.13121
H	1.76132	2.93336	0.50771
H	2.72911	1.49225	0.93657
H	4.60962	2.23218	-0.27777
H	3.90057	3.85216	-0.08434

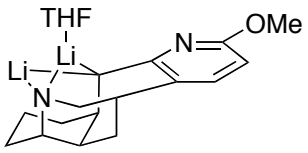
Table 3. Optimized geometries at B3LYP level of theory with 6-31G(d) basis set for the serial solvation of closed dimer **10** at -78 °C with free energies (Hartrees), and Cartesian coordinates (X,Y,Z).



G = -821.209733

Atom	X	Y	Z
C	-1.94928	0.30529	0.97763
C	-1.04147	1.45296	1.43264
C	-0.04467	1.89226	0.34764
C	-0.84906	2.11093	-0.98902
N	-1.59576	0.93906	-1.43191
Li	0.27675	0.33016	-1.66575
C	1.17796	0.97062	0.21094
C	1.14263	-0.47499	0.08524
C	-0.06834	-1.27731	-0.05542
C	-1.25098	-1.08056	0.93675
C	-2.35868	-2.14540	0.72134
C	-3.20520	-1.92784	-0.55352

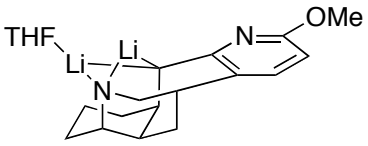
Li	-1.53203	-0.93384	-1.61062
C	-3.64017	-0.44481	-0.75709
C	-2.60348	0.66025	-0.38875
N	2.31362	-1.16053	-0.08929
C	3.47768	-0.53848	-0.11368
C	3.62221	0.85310	0.03068
C	2.44305	1.57355	0.18873
O	4.53038	-1.38709	-0.29037
C	5.83918	-0.84148	-0.30303
H	6.08141	-0.34255	0.64461
H	6.51326	-1.68861	-0.44430
H	5.97733	-0.13016	-1.12850
H	4.58307	1.35133	0.03002
H	2.50430	2.65429	0.30813
H	0.23044	-2.32952	-0.05668
H	-0.86798	-1.25464	1.95765
H	-1.92468	-3.15290	0.70537
H	-3.03602	-2.10827	1.58525
H	-4.10704	-2.54880	-0.51259
H	-2.68225	-2.35298	-1.43589
H	-4.50249	-0.28414	-0.10029
H	-3.99713	-0.28259	-1.78416
H	-3.21175	1.57381	-0.23363
H	-0.14667	2.43680	-1.78252
H	-1.50924	2.98895	-0.82703
H	0.35380	2.87519	0.63637
H	-1.67808	2.31724	1.67293
H	-0.51066	1.18331	2.35552
H	-2.75396	0.21841	1.72658



G = -1053.587758

Atom	X	Y	Z
C	0.38485	-0.68113	1.52926
C	-0.68069	-1.21976	0.77151
N	-1.94052	-0.77359	1.16320
C	-3.04079	-1.17524	0.56429
C	-3.07511	-2.05765	-0.53007
C	-1.81989	-2.47296	-0.98979
C	-0.61064	-2.08225	-0.41195
Li	-0.49997	-0.07445	-1.40411

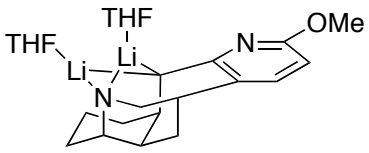
C	1.12040	-1.37369	-2.11410
C	0.66697	-2.50583	-1.13841
C	1.87350	-2.86536	-0.25880
C	2.54809	-1.63949	0.37333
C	2.74430	-0.50892	-0.68627
N	1.50522	-0.15889	-1.40561
Li	0.81908	0.83629	0.12451
O	-0.78709	1.77581	-0.75727
C	-0.39255	2.90261	-1.58887
C	-0.48431	4.13338	-0.66569
C	-1.36675	3.65939	0.52607
C	-1.85798	2.27282	0.10474
C	3.46256	0.69738	-0.03307
C	2.93295	1.14616	1.34774
C	2.69574	-0.04234	2.29783
C	1.82882	-1.15710	1.65796
O	-4.17053	-0.60740	1.10078
C	-5.42744	-1.01958	0.59300
H	2.23407	0.31117	3.22898
H	3.67335	-0.46499	2.57078
H	3.65082	1.84739	1.79258
H	2.01101	1.75770	1.27607
H	4.51082	0.40558	0.11477
H	3.46986	1.53715	-0.74188
H	3.47090	-0.90744	-1.42475
H	-1.09767	2.97275	-2.42697
H	0.60322	2.67310	-1.97358
H	-0.92678	4.98130	-1.19609
H	0.50654	4.44416	-0.32158
H	-2.20106	4.33714	0.72672
H	-0.77227	3.58653	1.44226
H	-1.99013	1.53555	0.89961
H	-2.77379	2.33006	-0.49777
H	0.29290	-1.17368	-2.83463
H	1.93583	-1.75970	-2.76065
H	-1.78037	-3.14270	-1.84912
H	-3.98782	-2.40677	-0.99384
H	-5.58024	-2.10010	0.71279
H	-6.17810	-0.48518	1.17973
H	-5.54887	-0.75950	-0.46792
H	0.41338	-3.39416	-1.73679
H	2.60543	-3.37246	-0.90478
H	1.58843	-3.58609	0.51982
H	3.55351	-1.95528	0.69783
H	1.87060	-2.01505	2.35695
H	0.01821	-0.20473	2.44125



G = -1053.587786

Atom	X	Y	Z
C	0.38604	-0.68139	1.52950
C	-0.67918	-1.22069	0.77177
N	-1.93932	-0.77565	1.16375
C	-3.03930	-1.17778	0.56468
C	-3.07306	-2.05975	-0.53008
C	-1.81758	-2.47399	-0.99003
C	-0.60857	-2.08272	-0.41205
Li	-0.49939	-0.07510	-1.40252
C	1.12147	-1.37149	-2.11423
C	0.66927	-2.50469	-1.13905
C	1.87623	-2.86371	-0.25989
C	2.54990	-1.63762	0.37275
C	2.74512	-0.50645	-0.68635
N	1.50560	-0.15678	-1.40518
Li	0.81862	0.83765	0.12544
O	-0.78864	1.77493	-0.75551
C	-0.39727	2.90152	-1.58870
C	-0.48769	4.13218	-0.66559
C	-1.37342	3.65994	0.52453
C	-1.86039	2.27076	0.10617
C	3.46290	0.69991	-0.03286
C	2.93331	1.14775	1.34820
C	2.69670	-0.04118	2.29786
C	1.83045	-1.15628	1.65770
O	-4.16942	-0.61100	1.10146
C	-5.42604	-1.02334	0.59314
H	2.23485	0.31175	3.22914
H	3.67456	-0.46334	2.57067
H	3.65096	1.84905	1.79332
H	2.01127	1.75899	1.27675
H	4.51138	0.40868	0.11450
H	3.46946	1.54001	-0.74129
H	3.47167	-0.90420	-1.42529
H	-1.10485	2.97086	-2.42484
H	0.59769	2.67279	-1.97598
H	-0.92657	4.98163	-1.19649
H	0.50344	4.43980	-0.31944
H	-2.21016	4.33633	0.71966
H	-0.78225	3.59191	1.44318
H	-1.98999	1.53472	0.90258

H	-2.77671	2.32377	-0.49591
H	0.29350	-1.17172	-2.83430
H	1.93690	-1.75647	-2.76138
H	-1.77761	-3.14327	-1.84970
H	-3.98555	-2.40929	-0.99395
H	-5.57857	-2.10395	0.71240
H	-6.17704	-0.48942	1.17987
H	-5.54724	-0.76284	-0.46771
H	0.41634	-3.39284	-1.73798
H	2.60849	-3.36984	-0.90625
H	1.59187	-3.58509	0.51839
H	3.55560	-1.95280	0.69699
H	1.87302	-2.01449	2.35633
H	0.01920	-0.20580	2.44184

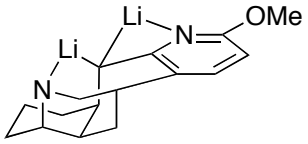


G = -1285.968944

Atom	X	Y	Z
C	2.09242	1.88821	0.65619
C	2.42116	0.93273	-0.32537
Li	0.56999	0.46714	0.66269
N	-1.00095	1.19399	-0.26824
C	-0.74153	0.97299	-1.69081
C	0.62296	1.54880	-2.18029
C	0.62236	3.06060	-1.89069
C	0.22288	3.40060	-0.44765
C	-1.07993	2.63835	-0.04779
C	-1.47861	2.99415	1.39635
C	-0.33205	2.87415	2.41130
C	0.89973	3.67027	1.95641
C	1.39676	3.23679	0.55337
C	1.80426	0.75291	-1.63920
C	2.30688	-0.26213	-2.44432
C	3.30717	-1.15571	-2.03663
C	3.73837	-0.99032	-0.71069
N	3.32347	-0.04344	0.09983
O	4.62627	-1.85693	-0.10149
C	5.22027	-2.86105	-0.90067
Li	-1.77091	-0.36869	0.44408
O	-0.11954	-1.34861	1.27767
C	0.55914	-2.41938	0.53044

C	1.57930	-2.99394	1.50544
C	0.85211	-2.86490	2.85367
C	0.11715	-1.53098	2.71599
O	-3.44532	-1.23476	0.13850
C	-4.42535	-0.35853	-0.49264
C	-4.99055	-1.17793	-1.64783
C	-4.99253	-2.59837	-1.05940
C	-3.70806	-2.61659	-0.22202
H	1.71051	3.56447	2.68908
H	0.63629	4.73867	1.93042
H	-0.66920	3.22202	3.39772
H	-0.04798	1.81842	2.54720
H	-1.83488	4.03465	1.40858
H	-2.33460	2.36988	1.69811
H	-1.87522	3.05726	-0.70612
H	-3.89736	0.55120	-0.78808
H	-5.19636	-0.11072	0.24744
H	-4.32656	-1.11793	-2.51764
H	-5.98468	-0.83836	-1.95189
H	-4.99764	-3.38253	-1.82159
H	-5.86934	-2.74394	-0.41834
H	-3.79737	-3.20501	0.69616
H	-2.85065	-2.98568	-0.79791
H	-0.85178	-1.50265	3.22322
H	0.72814	-0.68888	3.05751
H	0.13714	-3.68493	2.99085
H	1.53471	-2.86287	3.70791
H	2.49470	-2.39426	1.48422
H	1.83664	-4.02884	1.26111
H	1.00076	-1.97253	-0.36342
H	-0.20057	-3.15762	0.24277
H	-0.75384	-0.11007	-1.91439
H	-1.53701	1.43100	-2.32549
H	1.89475	-0.37038	-3.44802
H	3.68683	-1.91923	-2.70270
H	5.77821	-2.43472	-1.74516
H	5.91481	-3.39623	-0.24808
H	4.47854	-3.57160	-1.29423
H	0.64257	1.42773	-3.27416
H	-0.10687	3.52425	-2.57211
H	1.60024	3.50067	-2.12864
H	-0.02906	4.47391	-0.42575
H	2.13809	3.99921	0.24197
H	2.75073	1.81627	1.52325

Table 4. Optimized geometries at B3LYP level of theory with 6-31G(d) basis set for the serial solvation of open dimer **11** at -78 °C with free energies (Hartrees), and Cartesian coordinates (X,Y,Z).



G = -821.221522

Atom	X	Y	Z
C	-0.04831	-1.28687	0.36150
C	1.09130	-0.36630	0.27578
N	2.28548	-1.04204	0.09818
Li	1.35915	-2.50059	-0.67832
Li	-0.78124	-0.75706	-1.61410
N	-1.60479	0.85167	-1.45276
C	-0.85716	2.03225	-1.11054
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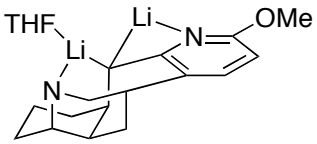

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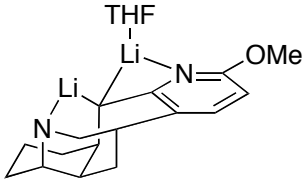

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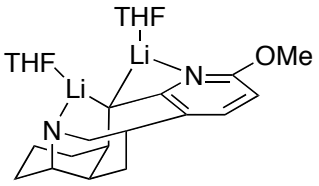

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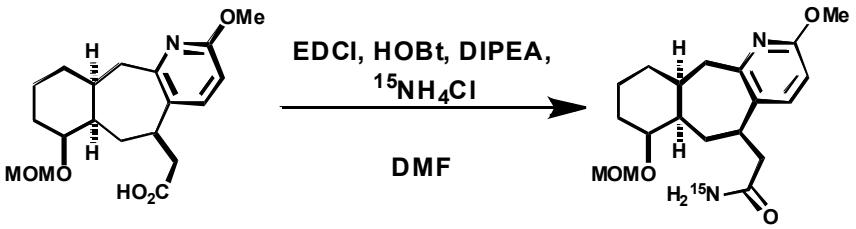
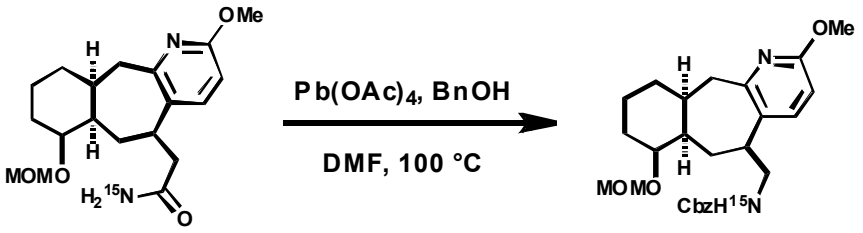
Part IV: Synthesis of [^{15}N] Tetracycle
Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride. N,N-Diisopropylethylamine (DIPEA) was distilled over calcium hydride prior to use. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde stain. SiliCycle Silia-P silica gel (particle size 40-63 μm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 125, 125 and 150 MHz, respectively. ^{15}N NMR spectra were recorded on Bruker AVB-400 with ^{15}N operating frequency of 40 MHz. Chemical shifts (δ) are reported in ppm. ^{15}N NMR spectra are reported relative to $^{15}NH_4Cl$ in D_2O (δ = 20.0 ppm). Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley.

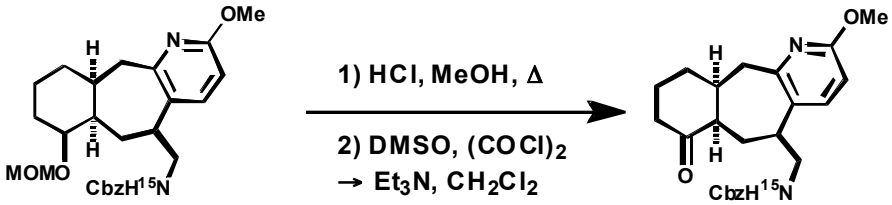


Amide (6): To a solution of acid **5** (500 mg, 1.43 mmol) in N,N-dimethylformamide (DMF, 14 mL) was added ^{15}N-labeled ammonium chloride ($^{15}NH_4Cl$, 156 mg, 2.86 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI, 412 mg, 2.15 mmol), and 1-hydroxybenzotriazole (HOBt, 291 mg, 2.15 mmol) followed by N,N-diisopropylethylamine (DIPEA, 0.996 mL, 5.72 mmol). The reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with CH_2Cl_2/Et_2O (1:3, 50 mL) and poured on H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2/Et_2O (1:3, 25 mL). The combined organic layers were washed with water (3 x 25 mL), saturated NH_4Cl (2 x 25 mL), saturated NaCl (25 mL), dried over $MgSO_4$ and concentrated under vacuum to afford amide **6** (456 mg) in 91% yield. This material was >95% pure and was taken on to the next step without purification. $\mathbf{R_f}$ 0.10 (9:1 CH_2Cl_2/MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) 7.26 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 5.72 (d, $J(^{15}N,H)$ = 88.4 Hz, 1H), 5.61 (d, $J(^{15}N,H)$ = 88.6 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.62 (d, J = 6.70 Hz, 1H), 3.87 (s, 3H), 3.61-3.55 (m, 1H), 3.37 (s, 3H), 3.35-3.29 (m, 1H), 3.25-3.19 (m, 1H), 2.90 (dd, J = 13.7, 7.0 Hz, 1H), 2.69 (dd, J = 14.8, 6.2 Hz, 1H), 2.52 (dd, J = 14.8, 8.8 Hz, 1H), 2.40-2.32 (m, 1H), 1.92-1.81 (m, 2H), 1.67-1.54 (m, 2H), 1.35-1.18 (m, 4H), 0.66-0.54 (m, 1H); **^{13}C NMR** (125

MHz, $CDCl_3$) 173.76 (d, $J(C,^{15}N)$ = 13.8 Hz), 161.56, 157.03, 134.73, 131.05, 106.53, 94.42, 78.07, 55.33, 53.34, 45.18, 42.54, 41.08, 36.30, 35.89, 27.13, 25.11, 24.22, **^{15}N NMR** (40 MHz, $CDCl_3$) 105.5; **IR** (film) υ_{max} 2929, 1673, 1595, 1477, 1299, 1150, 1102, 1010, 915, 825 cm^{-1}; **HRMS** (ESI) m/z 350.2104 [$(M+H)^+$; calculated for $[C_{19}H_{29}{}^{15}NNO_4]^+$: 350.2092].

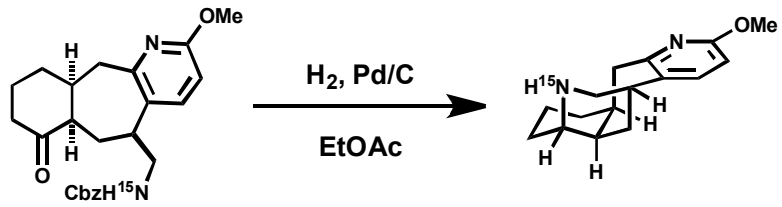


Cbz-amine (7): To a solution of amide **6** (320 mg, 0.92 mmol) in N,N-dimethylformamide (DMF, 14 mL) was added lead (IV) tetraacetate (2.45 g, 5.5 mmol) and benzyl alcohol (574 L, 5.5 mmol). The reaction vial was sealed and heated at 100 °C for 48 h. The reaction was allowed to cool to rt, poured on saturated $NaHCO_3$ (30 mL), and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), water (2 x 25 mL), and saturated NaCl (25 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (8:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to provide Cbz-amine **7** (193 mg) in 46% yield. $\mathbf{R_f}$ 0.35 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.21 (m, 6H), 6.50 (d, J = 8.4 Hz, 1H), 5.11-5.04 (m, 2H), 4.95-4.77 (dt, $J(^{15}N,H)$ = 90.8 Hz, $J(H,H)$ = 5.6 Hz, 1H), 4.67-4.61 (m, 2H), 3.86 (s, 3H), 3.65-3.43 (m, 3H), 3.39-3.29 (m, 3H), 3.13-2.98 (m, 1H), 2.96-2.78 (m, 2H), 2.32-2.15 (m, 1H), 1.92-1.80 (m, 1H), 1.67-1.51 (m, 2H), 1.40-1.14 (m, 5H), 0.68-0.53 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) 161.71, 157.23, 156.30 (d, $J(C,^{15}N)$ = 26.9 Hz), 136.46, 129.30, 128.49, 128.10, 128.09, 128.06, 106.84, 94.88, 78.69, 66.72, 55.30, 53.30, 44.75 (d, $J(C,^{15}N)$ = 12.0 Hz), 42.37, 40.22, 34.63, 27.09, 24.75, 24.14, 23.51; **^{15}N NMR** (40 MHz, $CDCl_3$) 80.9; **IR** (film) υ_{max} 3336, 2937, 2146, 1701, 1594, 1533, 1474, 1299, 1254, 1032, 915, 823 cm^{-1}; **HRMS** (ESI) m/z 456.2530 [$(M+H)^+$; calculated for $[C_{26}H_{35}{}^{15}NNO_5]^+$: 456.2511].



Ketone (S1): Cbz-protected amine **7** (100 mg, 0.22 mmol) was dissolved in MeOH (4 mL). To this solution was added concentrated HCl (0.2 mL) and the resultant reaction mixture was heated at reflux for 6 h. The reaction mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The residue was neutralized with saturated aq. $NaHCO_3$ (10 mL) which was extracted with CH_2Cl_2 (3 X 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to afford the intermediate alcohol as a colorless oil. This material was used in the next step without further purification.

A flame-dried round-bottom flask was charged with DMSO (62 μL, 0.88 mmol), CH_2Cl_2 (3 mL) and cooled to -78 °C. To this solution, oxalyl chloride (38 μL, 0.44 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise *via* syringe over 2 min. After stirring for 20 min at -78 °C, the crude intermediate alcohol in CH_2Cl_2 (1.5 mL) was added dropwise to the reaction mixture over 2 min and stirred at -78 °C for 2.5 h. Triethylamine (245 μL, 1.8 mmol) was added to the reaction mixture dropwise and it was slowly allowed to warm to rt. After stirring at rt for 1.5 h, the reaction mixture was diluted with CH_2Cl_2, poured into a separatory funnel and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 X 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to afford 72 mg (80% yield) of **S1** as a white foam. $\mathbf{R_f}$ 0.70 (1:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$, major rotamer) δ 7.38-7.25 (m, 6H), 6.53 (d, J = 8.3 Hz, 1H), 5.08 (br s, 2H), 3.88 (s, 3H), 3.61-3.28 (m, 2H), 3.11-2.96 (m, 2H), 2.96-2.87 (m, 1H), 2.73-2.58 (m, 1H), 2.33-2.15 (m, 3H), 2.00-1.87 (m, 1H), 1.76-1.54 (m, 4H), 1.26-1.12 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, major rotamer) 213.53, 161.97, 156.46, 156.28, 140.44, 136.40, 128.42, 128.04, 128.01, 127.99, 107.37, 66.69, 53.28, 52.72, 44.36 (d, J(C,^{15}N) = 10.7 Hz), 41.22, 38.66, 37.27, 30.56, 28.92, 24.59, 19.03; **^{15}N NMR** (40 MHz, $CDCl_3$) 80.4; **IR** (film) υ_{max} 3335, 2937, 1709, 1595, 1477, 1301, 1255, 1032, 734, 698 cm^{-1}; **HRMS** (ESI) m/z 410.2102 [$(M+H)^+$; calculated for $[C_{24}H_{29}{}^{15}NNO_4]^+$: 410.2092].



Tetracyclic amine (8): Amino ketone **S1** (72 mg, 0.18 mmol) was dissolved in EtOAc (5 mL) and sparged with nitrogen for 5 min. 10% Pd on activated carbon (18 mg) was added and the mixture was sparged with hydrogen and placed under a hydrogen atmosphere (1 atm. balloon). The reaction mixture was stirred at rt for 24 h then sparged with nitrogen. The reaction mixture was filtered through a pad of celite, washed with EtOAc (15 mL), and concentrated under vacuum to provide 43 mg of **8** (92% yield, >95% pure) as a white foam. $\mathbf{R_f}$ 0.15 (10% MeOH in CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 4.66 (m, 1H), 3.89 (s, 3H), 3.27-3.15 (m, 2H), 3.02 (br s, 1H), 2.74 (dd, J =15.5, 4.5 Hz, 1H), 2.66 (m, 1H), 2.13-2.06 (m, 1H), 2.00 (m, 1H), 1.95-1.79 (m, 3H), 1.79-1.54 (m, 4H), 1.43-1.33 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.36, 158.96, 141.21, 134.32, 106.19, 56.50 (d, J(C,^{15}N) = 3.0 Hz), 54.25(d, J(C,^{15}N) = 3.3 Hz), 53.12, 45.54 (d, J(C,^{15}N) = 2.2 Hz), 38.84, 37.73, 35.58, 34.12, 33.75, 33.37, 16.01; **^{15}N NMR** (40 MHz, $CDCl_3$) 48.1; **IR** (film) υ_{max} 2928, 2865, 1596, 1478, 1425, 1307, 1283, 1034, cm^{-1}; **HRMS** (ESI) m/z 260.1774 [$(M+H)^+$; calculated for $[C_{16}H_{23}{}^{15}NNO]^+$: 260.1775].

Part IV. References

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