Application of ^{6}Li diffusion-ordered NMR spectroscopy (DOSY) to confirming the solution structure of *n*-butyllithium

Weibin Li,[†] Gerald Kagan,[†] Russell Hopson, and Paul G. Williard*

Department of Chemistry, Brown University, 324 Brook Street, Providence, Rhode Island 02912, USA
E-mail: pgw@brown.edu

Dedicated to Dr. William F. Bailey on the occasion of his 65th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.515

Abstract

The utility of recently introduced ^{6}Li diffusion-ordered NMR spectroscopy (DOSY) is demonstrated. ^{6}Li DOSY results can be correlated to ^{1}H data through 2-D ^{6}Li{^{1}H} heteronuclear Overhauser effect NMR spectroscopy (HOESY) experiments. ^{6}Li DOSY quickly confirms ^{1}H DOSY results and allows unambiguous assignment of resonances to specific aggregates. Well known aggregates of lithium-6 *n*-butyllithium (*n*-Bu^{6}Li) are examined in deuterated tetrahydrofuran (THF-d_8) solution as an example, and to reaffirm the previous literature conclusions about these complexes.

Keywords: Structure analysis, DOSY, NMR, lithium, solution state, diffusion

Introduction

The organolithium compound *n*-BuLi has long been known as an exceptionally strong base and alkylating agent, and has been studied in detail since the 1920s.[1] In the 1990s, the crystal structures of *n*-BuLi with various solvents were solved. It was shown that *n*-BuLi could be crystallized with tetrahydrofuran (THF) from hexane as a tetrasolvated tetramer (Figure 1a).[2]

Following this work, the solution structure of *n*-BuLi in a variety of solvents was investigated by several groups with various solvation.[3] These include several ethers and diamine solvents.

With the advent of diffusion-ordered NMR spectroscopy (DOSY) in the 1990s, the investigation of aggregates in solution became much more accessible. This method enables the resolution of NMR spectra along a diffusion axis, thereby arraying resonances of aggregates by weight, as heavier complexes diffuse more slowly than lighter complexes.[4] Solutions of *n*-BuLi

were studied with this method by our group, and both dimeric and tetrameric tetrasolvated aggregates were found to exist in THF (Figure 1b).[5]

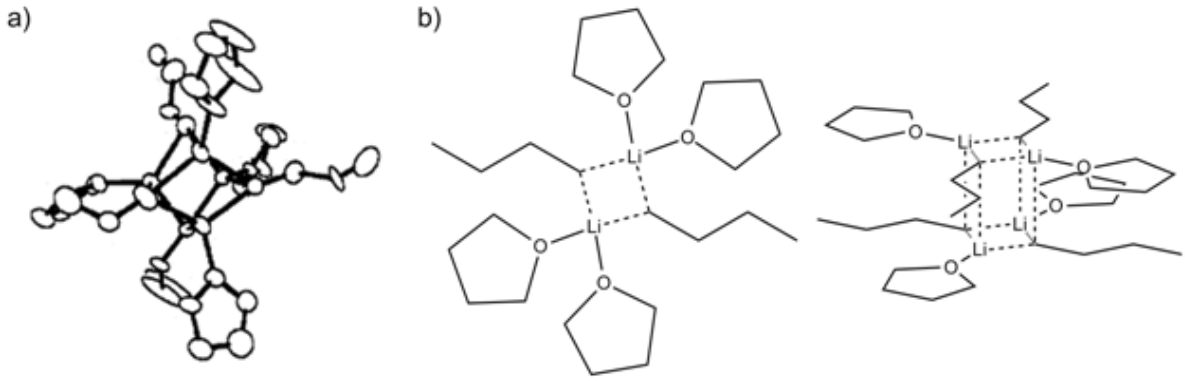

Figure 1. (a) Computer-generated plot for a crystal of *n*-BuLi solvated by THF crystallized from hexane. Hydrogen atoms omitted for clarity. Ellipsoids are shown with 30% probability. Adapted from reference 2; (b) Line drawings of possible dimeric and tetrameric tetrasolvated aggregates of *n*-BuLi.

Recently, our group has pioneered DOSY diffusion coefficient-formula weight (D-fw) analysis, in which formula weights are derived from correlation of the diffusion coefficients and formula weights of references in solution and interpolation or extrapolation of diffusion data of analytes, as well as application of D-fw to several nuclei including ^{1}H, ^{13}C, and ^{31}P.[6] Additionally, we have established the use of ^{6}Li DOSY NMR for the examination of organometallic species.[7] Here, we report confirmation of the aggregates formed by *n*-BuLi in THF solution by ^{6}Li DOSY and ^{6}Li{^{1}H} HOESY experiments.

Results and Discussion

The *n*-Bu^{6}Li used in these experiments was synthesized from ^{6}Li metal and 1-chlorobutane. Initial NMR in THF-d_8 at -80 °C clearly showed the two characteristic peaks in the 1-D proton spectrum at -1.22 and -1.31 ppm resulting from the protons geminal to the lithium. One-dimensional ^{6}Li NMR also showed two characteristic peaks, corresponding to (*n*-BuLi)$_2$●(THF)$_4$ and (*n*-BuLi)$_4$●(THF)$_4$ (Figures 2 and 3).

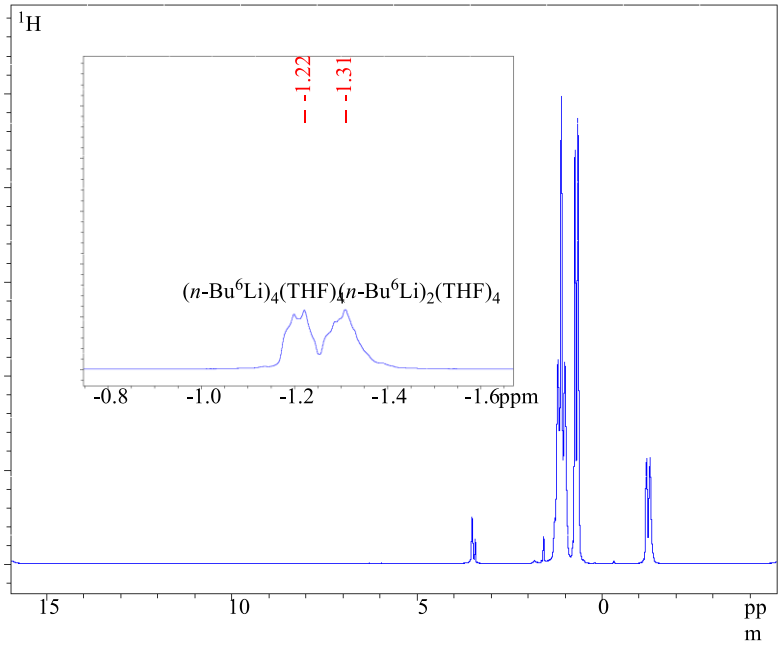

Figure 2. ^{1}H NMR of *n*-Bu^{6}Li at -80 °C in THF-*d*$_8$. Inset shows the detail of the two peaks from *n*-Bu^{6}Li.

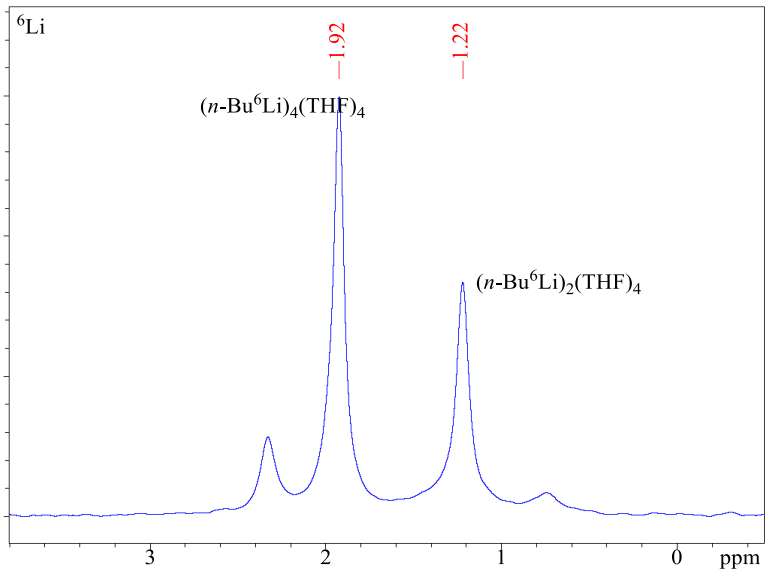

Figure 3. ^{6}Li NMR of *n*-Bu^{6}Li at -80 °C in THF-*d*$_8$.

While it is clear from 1-D experiments that there are indeed two distinct aggregates of *n*-Bu^{6}Li in THF solution, their assignment cannot be made on this 1-D data alone. DOSY NMR provides a direct observation of which of the two aggregates diffuses more quickly, and therefore a fast determination of which resonance is that of the dimer and which is the tetramer.

References inert to *n*-Bu^{6}Li were added for D-fw analysis. These were benzene (78.11 g mol^{-1}), cyclooctene (110.2 g mol^{-1}), and squalene (410.72 g mol^{-1}). The ^{1}H DOSY spectrum clearly separates the resonances based on their weights along the diffusion axis. The largest diffusion coefficient (lightest compound) belongs to benzene, followed by cyclooctene, then one *n*-Bu^{6}Li resonance (δ -1.31), squalene, and the second *n*-Bu^{6}Li resonance (δ -1.22) (Figure 4).

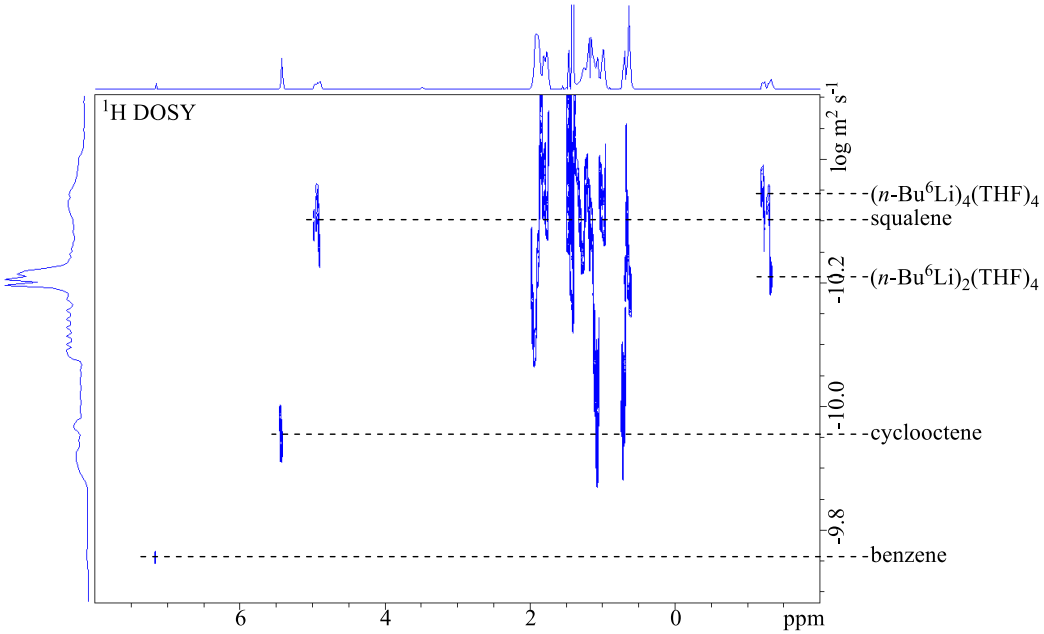

Figure 4. ^{1}H DOSY NMR of nBu^{6}Li at -80 °C in THF-d_8.

Thus, the assignment was made that the more upfield *n*-Bu^{6}Li resonance is that of the relatively faster diffusing tetrasolvated dimer, and the further downfield *n*-Bu^{6}Li peak belongs to the slower diffusing tetrasolvated tetramer.

Following this assignment, confirmation was sought by ^{6}Li DOSY NMR. The ^{6}Li DOSY experiment shows the two major resonances present in the 1-D ^{6}Li spectrum, with the further upfield peak having a larger diffusion coefficient than that of the downfield peak (Figure 5).

The assignment was made that the upfield *n*-Bu^{6}Li resonance is the tetrasolvated dimer, and the downfield peak belongs to the tetrasolvated tetramer.

In order to correlate the ^{6}Li DOSY results to the ^{1}H DOSY data, 2-D ^{6}Li{^{1}H} heteronuclear Overhauser effect NMR spectroscopy (^{6}Li{^{1}H} HOESY) experiments were performed. This directly correlates peaks from the 1-D ^{1}H and 1-D ^{6}Li experiments, allowing comparison of the ^{1}H and ^{6}Li DOSY data. The ^{6}Li{^{1}H} HOESY experiment shows crosspeaks from the upfield *n*-Bu^{6}Li peak in the 1-D ^{1}H NMR to the upfield *n*-Bu^{6}Li peak in the 1-D ^{6}Li NMR, and from the downfield *n*-Bu^{6}Li peak in the 1-D ^{1}H NMR to the downfield *n*-Bu^{6}Li peak in the 1-D ^{6}Li NMR (Figure 6). Therefore, it can be seen that the ^{1}H and ^{6}Li DOSY data and the 1-D peak assignments are fully consistent.

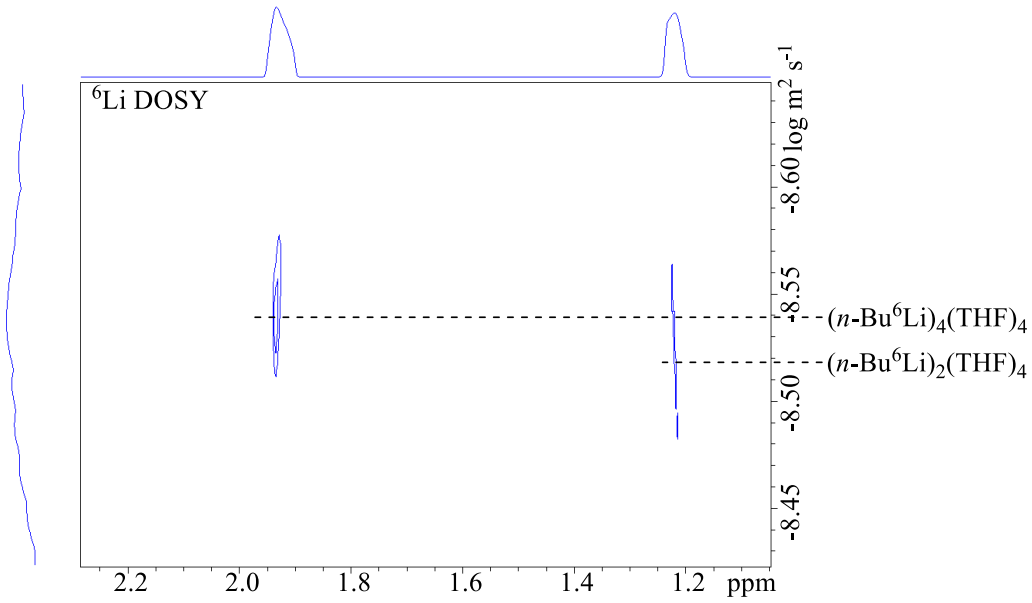

Figure 5. ^{6}Li DOSY NMR of *n*-Bu^{6}Li at -80 °C in THF-d_8.

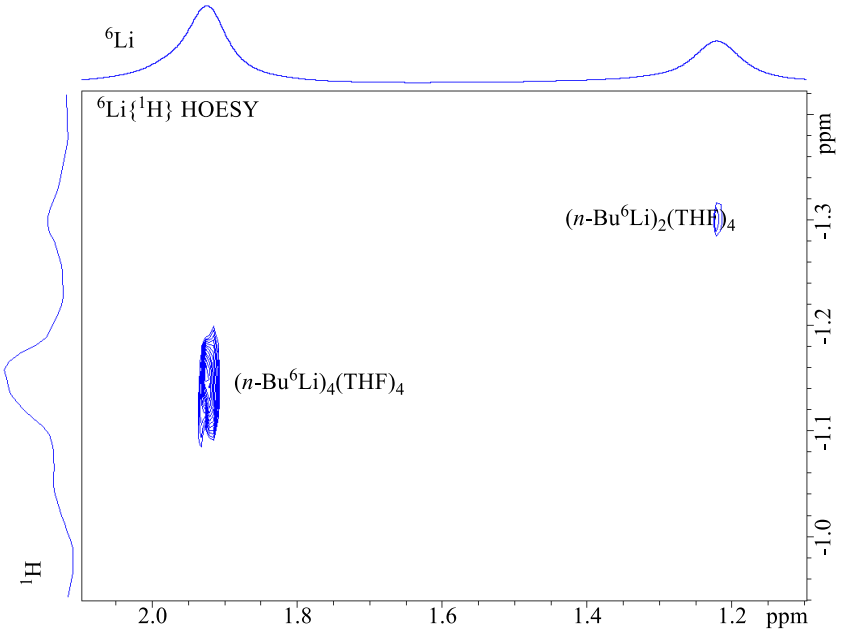

Figure 6. ^{6}Li{^{1}H} HOESY NMR of *n*-Bu^{6}Li at -80 °C in THF-d_8.

In addition to the application of ^{6}Li DOSY, we attempted D-fw analysis on the ^{1}H DOSY data. Plotting the diffusion data and formula weights of the references gave a reasonably good correlation (r^2 = 0.99). Predicted formula weights (fw*) of the two *n*-Bu^{6}Li aggregates were both slightly heavier than expected, but consistent with a tetrasolvated dimer and tetramer. Two peaks were observed for THF, apparently one for ^{6}Li bound THF and another for free THF. The

predicted formula weight of one THF resonance is much heavier than that of free THF, indicating it is bound in a complex. The fw* of the second THF resonance is very close to that of free THF (Figure 7, Table 1).

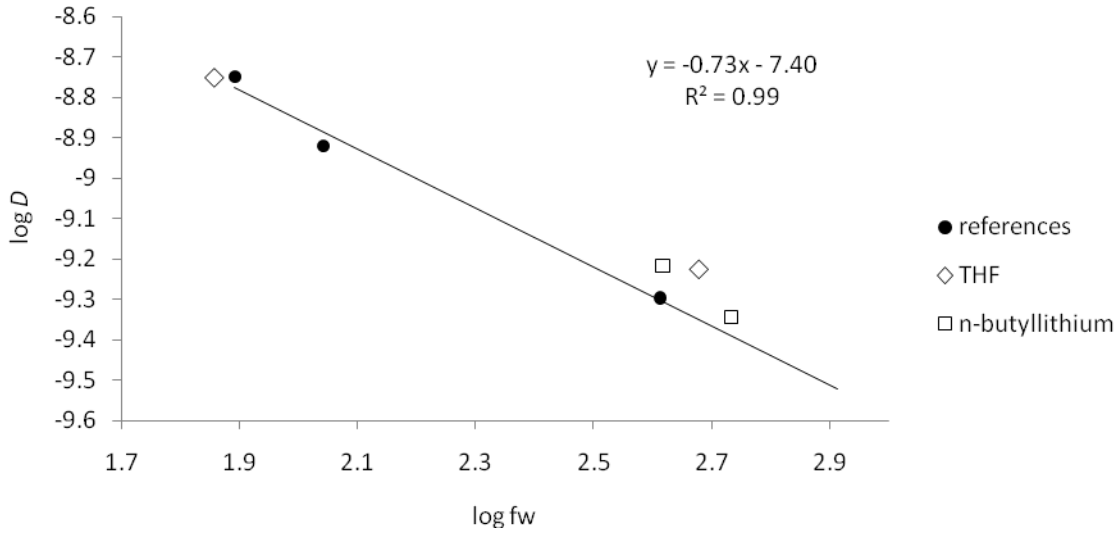

Figure 7. D-fw results of the ^{1}H DOSY experiment at -80 °C. References benzene, cyclooctene, and squalene are shown as black circles. Two peaks of THF are shown as open diamonds. Two peaks of nBu^{6}Li are shown as open squares. The fw* errors of the THF resonances are based on an average of 1:1 nBu^{6}Li dimer to tetramer formation and free THF.

Table 1. D-fw results of the ^{1}H DOSY experiment at -80 °C showing fw* of analytes

Compound	fw (g mol^{-1})	D x 10^{-10} (m^{2} s^{-1})	fw*(g mol^{-1})	% Difference
benzene	78.11	17.810	72	8.3
cyclooctene	110.2	12.000	123	-11.6
squalene	410.72	5.0600	402	2.2
(*n*-BuLi)$_4$●(THF)$_4$	540.94	4.5340	467	13.7
(*n*-BuLi)$_2$●(THF)$_4$	414.68	6.0720	313	24.6
bound THF	414.68-540.94	5.9470	322	32.6
free THF	72.11	17.670	72	-0.4

Conclusions

We have applied a variety of modern NMR techniques to confirm the identification of two solution state aggregates of *n*-BuLi. These aggregates appear to exist in THF solution as a tetrasolvated dimer and a tetrasolvated tetramer. These conclusions are consistent with

previously reported data.[2] NMR techniques include ^{6}Li DOSY, an important tool for the study of organolithium complex aggregation. ^{6}Li DOSY is especially useful when correlated to more traditional ^{1}H DOSY and 1-D experiments through 2-D correlation experiments such as ^{6}Li{^{1}H} HOESY. These methods have wide applicability to the study of organometallic compounds important for organic synthesis beyond *n*-BuLi, such as lithium amide bases.

Experimental Section

Procedures for NMR Experiments. NMR samples were prepared in tubes sealed with serum septa and Parafilm®. Five millimeter NMR tubes were evacuated *in vacuo*, flame dried, and filled with argon. Samples were prepared in about 600 μL tetrahydrofuran-d_8. NMR experiments were performed at -80 °C using a liquid nitrogen heat exchanger and nitrogen cooling gas. ^{1}H chemical shifts were referenced internally or externally to benzene at 7.16 ppm. ^{6}Li chemical shifts were calibrated to saturated LiBr in D_2O as an external reference at 0 ppm. DOSY experiments were performed on a Bruker DRX400 spectrometer (^{1}H 400.13 MHz, ^{6}Li 58.88 MHz) equipped with an Accustar *z*-axis gradient amplifier and an ATMA BBO probe with a z-axis gradient coil. Spectral widths for ^{1}H experiments were 3188.78 Hz, and for ^{6}Li were 366.78 Hz. Maximum gradient strength was 0.214 T/m. ^{1}H DOSY experiments were performed using the Bruker pulse program stegp1s, using stimulated echo and 1 spoil gradient. Diffusion time was 200 ms and rectangular gradient pulse duration was 2500 μs. Gradient recovery delays were 200 μs. A program for ^{6}Li DOSY was adapted from the standard Bruker dstebpgp3s program, using double stimulated echo and longitudinal eddy current delay with bipolar gradient pulses and 3 spoil gradients. Diffusion time was 50 ms and rectangular gradient pulse duration was 2000 μs. Gradient recovery delays were 200 μs. Individual rows of the quasi 2-D diffusion databases were phased and baseline corrected.

Synthesis of *n*-Bu^{6}Li. About 1.0 g (166 mmol) of finely cut ^{6}Li metal (Oak Ridge National Labs) was placed into a flame dried flask flushed with argon. The flask was fitted with a serum septum and sealed with Parafilm®. The metal was washed with dry pentane by adding 10 mL of pentane to the flask via syringe. The flask was then placed in ultrasound for 5 minutes. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (3 times). Dry heptane (15 mL) was added to the flask, followed by 9.6 g (10.9 mL, 104 mmol) of 1-chlorobutane (Sigma-Aldrich), dropwise. This mixture was kept under ultrasound overnight at room temperature, after which a purple slurry was obtained. The suspension was transferred via syringe to a clean, flame dried vial flushed with argon and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This *n*-Bu^{6}Li solution in heptane was titrated using 2,2-diphenylacetic

acid in tetrahydrofuran and found to be 1.04 M. Diagnostic NMR resonances: $(n\text{-Bu}^6\text{Li})_2(\text{THF})_4$ ^{1}H NMR δ -1.31; ^{6}Li NMR δ 1.22; $(n\text{-Bu}^6\text{Li})_4(\text{THF})_4$ ^{1}H NMR δ -1.22; ^{6}Li NMR δ 1.92.

Acknowledgements

This research was supported through NSF Grant No. 0718275.

References

† These authors contributed equally to this research.

1. (a) Ziegler, K.; Colonius, H. German Patent 512882, 1929; (b) Ziegler, K.; Colonius, H. *Justus Liebigs Ann. Chem.* **1930**, *479*, 135.
2. Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1993,** *115*, 1568.
3. (a) Waldmueller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997,** *119*, 5479-5480; (b) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2006,** *128*, 9355.
4. (a) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1992,** *114*, 3139; (b) Wu, D.; Chen, A.; Johnson, C. S., Jr. *Bull. Magn. Reson.* **1995,** *17*, 21-6; (c) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005,** *44*, 520.
5. Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000,** *122*, 10228.
6. (a) Li, D.; Kagan, G.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2009,** *131*, 5627; (b) Li, D.; Hopson, R.; Li, W.; Liu, J.; Williard, P. G. *Org. Lett.* **2008,** *10*, 909; (c) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2009,** *11*, 4818.
7. Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2010,** *12*, 520.

