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n-Butyllithium/*N,N,N′,N′*-Tetramethylethylenediamine-Mediated Ortholithiations of Aryl Oxazolines: Substrate-Dependent Mechanisms

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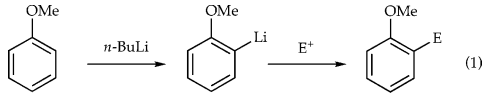
Abstract: *n*-Butyllithium/*N,N,N′,N′*-tetramethylethylenediamine-mediated ortholithiations of aryloxazolines are described. Methyl substituents on the aryloxazoline and substituents at the meta position of the arenes (methoxy, oxazolinyl, and fluoro) influence the rates and the mechanisms. Monomer- and dimer-based reactions are implicated. Density functional calculations probe details of the mechanism and suggest the origins of cooperative effects in meta-substituted aryl oxazolines.

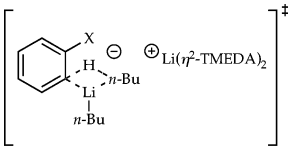
Introduction

Ortholithiations were first described by Wittig and Gilman in the 1930s.[1] Using a protocol that was remarkably selective for the era, they treated anisole with *n*-butyllithium (*n*-BuLi) to generate an aryllithium that could be functionalized with electrophiles (eq 1). They suggested that the selective and facile metalation was caused by the increased acidity of the ortho protons. Of course, as the applications of ortholithiations expanded, an understanding of the underlying organolithium chemistry also evolved.[2] Solvent-dependent regioselectivities[3,4] suggested mechanistic complexity. Despite a paucity of detailed mechanistic studies of ortholithiations,[5] the seemingly simple notions of Wittig and Gilman have given way to more ornate models. It is now widely accepted that ortholithiations involve coordination of the ortho substituents to the lithium cation during the rate-limiting proton transfer.[6]



(1)

Although many ortholithiations may be directed by metal-substituent interactions at the rate-limiting transition structure, summary dismissal of Wittig's and Gilman's original hypothesis may have been hasty. Extensive studies by Schlosser and co-workers reveal that ortholithiation rates do indeed correlate with acidities in some substrate classes.[7] Lithiations of benzene, anisole, and several alkoxy-substituted aromatics by *n*-BuLi/TMEDA mixtures (*N,N,N′,N′*-tetramethylethylenediamine) are congruent with Schlosser's results.[8] Relative rate constants (k_{rel}) span a range of 60 000, eliciting a considerable number of mechanistic hypotheses.[1−11] Nonetheless, benzene and several alkoxy-substituted aromatics metalate via transition structures $[(n\text{-BuLi})_2(\text{TMEDA})_2(\text{ArH})]^{‡}$, which were suggested to be based on triple ions exemplified by **1**.[8,12] Electronic effects appear to dominate, whereas the importance of coordination by alkoxy groups is less clear. Mechanistic studies of *n*-BuLi/TMEDA-mediated ortholithiations have been thoroughly summarized by Saá.[11b]

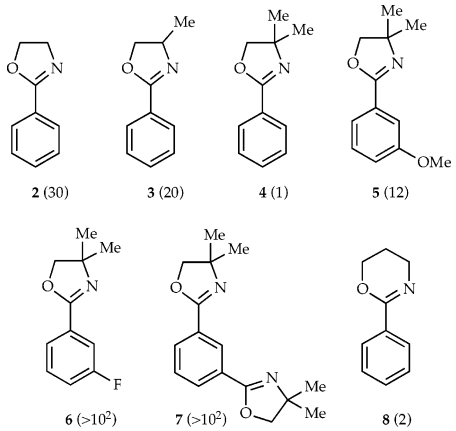


1; X = H, OMe, OR

We report herein rate studies of the *n*-BuLi/TMEDA-mediated ortholithiations of arenes **2**−**8** (Chart 1, eq 2). Ortholithiations of aryl oxazolines, first investigated by Gschwend and Hamdan[4] and Meyers and Mihelich,[13] are very rapid compared with those of anisoles bearing weakly directing methoxy moieties.[2,14−16] The regioselectivity of a constrained oxazoline reported by

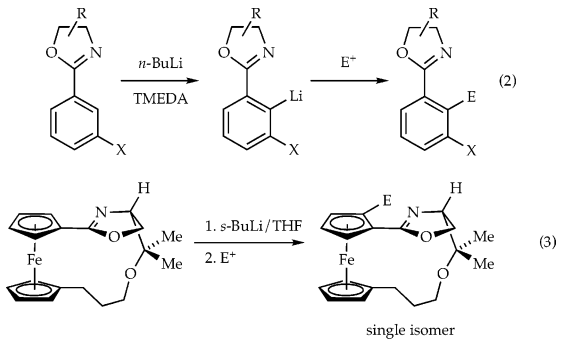
(1) (a) Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71*, 1903. (b) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
(2) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry, Vol. 23; Pergamon: Oxford, 2002.
(3) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.
(4) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.
(5) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.
(6) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 330−367. (c) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(7) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (b) Maggi, R.; Schlosser, M. *Tetrahedron Lett.* **1999**, *40*, 8797. (c) Schlosser, M.; Mongin, F.; Porwisiak, J.; Dmowski, W.; Büker, H. H.; Nibbering, N. M. M. *Chem. Eur. J.* **1998**, *4*, 1281. (d) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1497.
(8) (a) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640. (b) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421.

Chart 1[a]



[a] Relative rate constants adjusted to −40 °C are shown in parentheses.

Sammakia and Latham implicates an N-directed rather than an O-directed metalation (eq 3).[17]



We find that the substrate-dependent ortholithiation rates (listed in parentheses in Chart 1) derive from monomer- and dimer-based mechanisms. Density functional theory (DFT) computations underscore the importance of N−Li and O−Li interactions and offer insights into the substrate dependencies. Of potential greatest interest to synthetic chemists, we examine how meta-disposed directing substituents function *cooperatively*. Nonspecialists will find a summary of the results at the start of the discussion section.

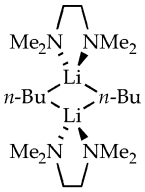
Results

A. Rate Studies.[18] *n*-BuLi was twice recrystallized from concentrated pentane solutions at −90 °C.[19] TMEDA was purified via recrystallization of the HCl salt.[8a,20] TMEDA concentrations (0.50−5.0 M) were adjusted using pentane as the cosolvent.[21] *n*-BuLi concentrations (0.050−1.0 M) were maintained high relative to arenes (≤0.02) to ensure pseudo-first-order conditions.[22] (Precipitations of the aryllithiums occur at substrate concentrations greater than 0.05 M). *n*-BuLi/TMEDA forms disolvated dimer **9** at all *n*-BuLi and TMEDA concentrations studied.[23] In situ IR spectroscopy reveals absorbances of arenes **2**−**8** at 1655 cm^{-1} and their corresponding lithiated forms at 1635 cm^{-1}. Arene−BuLi complexes, evidenced by a 10 to 30 cm^{-1} shift of the C═N stretch to lower frequencies,[24] were not observable in the presence of TMEDA.

Table 1. Summary of Rate Studies for the *n*-BuLi/TMEDA-Mediated Ortholithiation of Arenes **3**−**5** and **8**[a]

ArH	temp	*n*-BuLi order	k_H/k_D
3	−78 °C	0.94 ± 0.03	27 ± 4
4	−40 °C	0.69 ± 0.04	20 ± 3
5	−78 °C	1.00 ± 0.04	32 ± 5
8	−40 °C	0.60 ± 0.02	22 ± 3

[a] Chart 1.



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In all cases, loss of starting material follows clean first-order decay to five half-lives. The rate constants are invariant (±10%) over 10-fold arene concentrations, confirming the first-order dependence on arene. Substantial kinetic isotope effects (Table 1), determined by comparing metalations of **3**−**5** and **8** with

(9) For a report describing a 200:1 preference for the *n*-BuLi/TMEDA-mediated lithiation of anisole relative to benzene, see: Broaddus, C. D. *J. Org. Chem.* **1970**, *35*, 10.
(10) (a) Nguyen, T.-H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765. (b) Anderson, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553. (c) Slocum, D. W.; Dietzel, P. *Tetrahedron Lett.* **1999**, *40*, 1823. (d) Saà, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194. (e) Slocum, D. W.; Thompson, J.; Friesen, C. *Tetrahedron Lett.* **1995**, *36*, 8171. (f) Slocum, D. W.; Moon, R.; Thompson, J.; Coffey, D. S.; Li, J. D.; Slocum, M. G.; Siegel, A.; Gayton-Garcia, R. *Tetrahedron Lett.* **1994**, *35*, 385. (g) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903. (h) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. (i) Saà, J. M.; Deyà, P. M.; Suñer, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093. (j) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (k) Kminek, I.; Kaspar, M.; Trekoval, J. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1124. (l) Rausch, M. D.; Ciapenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127. (m) Screttas, C. G.; Eastham, J. F. *J. Am. Chem. Soc.* **1965**, *87*, 3276. (n) Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, *29*, 2928. (o) Stratakis, M. *J. Org. Chem.* **1997**, *62*, 3024. (p) Fagley, T. F.; Klein, E. *J. Am. Chem. Soc.* **1955**, *77*, 786.
(11) (a) Saá, J. M.; Deya, P. M.; Suñer, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093. (b) Saá, J. M. *Helv. Chim. Acta* **2002**, *85*, 814.
(12) For an attempted compilation of a comprehensive bibliography of triple ions of lithium salts, see: Ma, Y.; Ramirez, A.; Singh, K. J.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 15399.
(13) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158.
(14) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44,* 4463. (b) Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464.
(15) For a quantitative determination of pKa values of monosubstituted benzenes in THF, see: Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.
(16) (a) Catalan, J.; Yañez, M. *J. Am. Chem. Soc.* **1979**, *101*, 3490. (b) Lau, Y. K.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 7452.
(17) (a) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629. For related studies showing lithiated oxazolines that display N−Li rather than O−Li contacts, see: (b) Stol, M.; Snelders, D. J. M.; de Pater, J. J. M.; van Klink, G. P. M.; Kooijman, H.; Spek, A. L.; van Koten, F. *Organometallics* **2005**, *24*, 743. (c) Jayasuriya, K.; Alster, J.; Politzer, P. *J. Org. Chem.* **1988**, *53*, 677. (d) Jantzi, K. L.; Guzei, I. A.; Reich, H. J. *Organometallics* **2006**, *25*, 5390.
(18) (a) For a tutorial on solution kinetics of organolithium reactions, see: Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *45*, in press. (b) For earlier summaries of organolithium mechanism, see: Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 1, Chapter 2. *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1972; Vols. I,II.
(19) (a) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810. (b) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.
(20) Freund, M.; Michaels, H. *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1374.
(21) [*n*-BuLi] refers to the concentration of the monomer subunit (normality). [TMEDA] refers to the molarity of the excess (uncoordinated) TMEDA.
(22) The low arene concentrations preclude the formation of substantial concentrations of ArLi mixed aggregates. For studies of *n*-BuLi/ArLi heteroaggregates formed during ortholithiations, see: Kronenburg, C. M. P.; Rijnberg, E.; Jastrzebski, J. T. B. H.; Kooijman, H.; Lutz, M.; Spek, A. L.; Gossage, R. A.; van Koten, G. *Chem.—Eur. J.* **2005**, *11*, 253. Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem., Int. Ed.* **2006**, *44*, 1448.
(23) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810 and references cited therein.

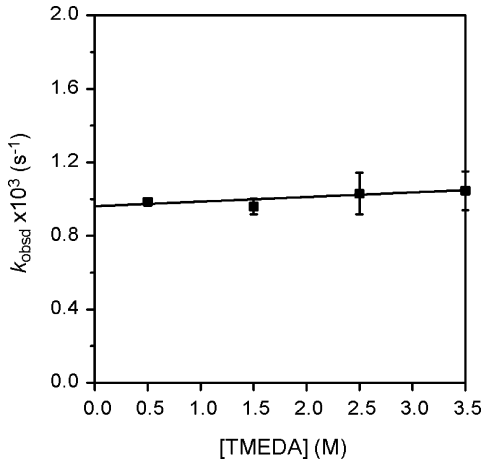


Figure 1. Plot of k_{obsd} vs [TMEDA] in pentane cosolvent for the ortholithiation of 4-methyl-2-phenyl-4,5-dihydrooxazole (**3**, 0.02 M) by *n*-BuLi (0.50 M) at −78 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k$[TMEDA] + k' ($k = (2 \pm 1) \times 10^{-5}$, $k' = (9.5 \pm 0.3) \times 10^{-4}$).

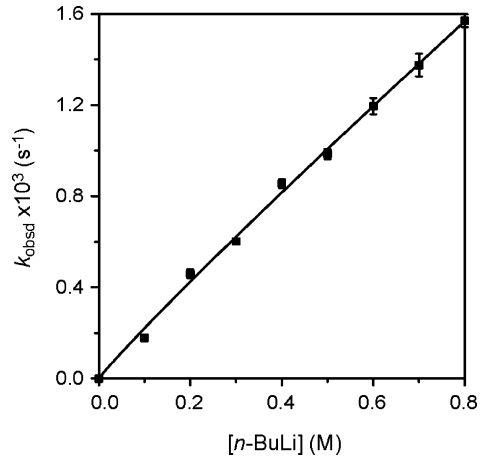


Figure 2. Plot of k_{obsd} vs [*n*-BuLi] in TMEDA (0.50 M) and pentane cosolvent for the ortholithiation of 4-methyl-2-phenyl-4,5-dihydrooxazole (**3**, 0.02 M) at −78 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k$[*n*-BuLi]^n ($k = (1.93 \pm 0.01) \times 10^{-3}$, $n = 0.94 \pm 0.03$).

those of their deuterated analogues,[25] confirm a rate-limiting proton abstraction. Zeroing the IR baseline and monitoring the reaction of a second aliquot of substrate affords no significant change in the rate constant, showing that autocatalysis, autoinhibition, and other conversion-dependent effects are unimportant under these conditions.[26] The results of the rate studies are summarized in Table 1. Representative rate data are depicted in Figures 1−3; additional data are included in Supporting Information.

Relative Rate Constants. The ortholithiation rates of aryl oxazolines are structure dependent as shown by the numbers in parentheses in Chart 1. The relative rate constants are normalized to oxazoline **4**. The analogous temperature-corrected values of k_{rel} for the ortholithiation of benzene, anisole, and resorcinol dimethyl ether of 10^{-5}, 10^{-2}, and 1.0, respectively, serve as benchmarks.[8a]

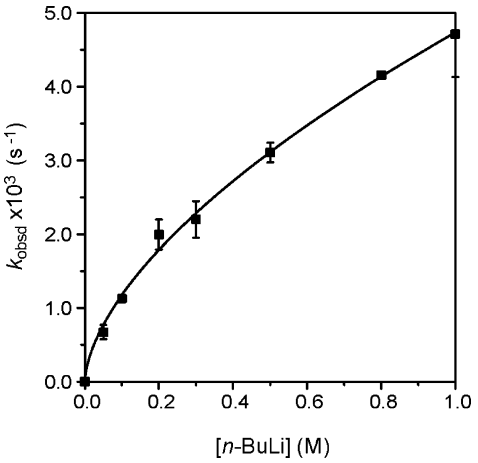


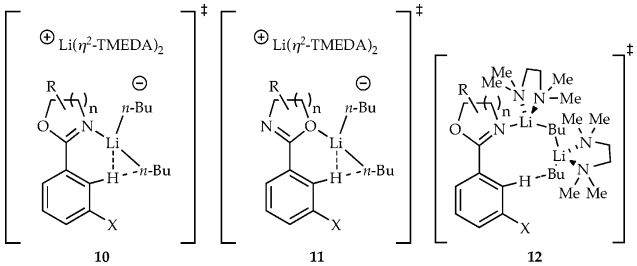
Figure 3. Plot of k_{obsd} vs [*n*-BuLi] in TMEDA (0.50 M) and pentane cosolvent for the ortholithiation of 2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (**8**, 0.02 M) at −40 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = k$[*n*-BuLi]^n affording $k = (3.8 \pm 0.1) \times 10^{-3}$, $n = 0.60 \pm 0.02$. Alternatively, a fit to $k_{obsd} = k$[*n*-BuLi]$^{1/2} + k'$[*n*-BuLi] affords $k = (2.7 \pm 0.2) \times 10^{-3}$, $k' = (1.1 \pm 0.2) \times 10^{-3}$.

Rate Laws. The ortholithiations of arenes **3**−**5** and **8** were investigated in detail and shown to be independent of TMEDA concentrations (Figure 1), consistent with a mechanism requiring no net change in the per-lithium solvation number on progression from **9** to the rate-limiting transition structures. Limited positive or negative deviations fall well within the generalized medium effects noted previously.[8,27]

The influence of *n*-BuLi concentration on rates shows significant substrate dependence. The ortholithiations of arenes **3** and **5** are linearly dependent on *n*-BuLi concentration (Table 1; Figure 2). The idealized[28] rate law (eq 4) implicates the general lithiation mechanism described by eq 5.

$$\mathrm{d[ArH]/d}t = k'[\mathrm{ArH}]^1[\mathrm{TMEDA}]^0[(n\text{-BuLi})_2(\mathrm{TMEDA})_2]^1 \quad (4)$$

$$(n\text{-BuLi})_2(\mathrm{TMEDA})_2 + \mathrm{ArH} \rightarrow \underset{(\mathbf{9})}{} [(n\text{-BuLi})_2(\mathrm{TMEDA})_2(\mathrm{ArH})]^{\ddagger} \quad (5)$$



The $[(n\text{-BuLi})_2(\mathrm{TMEDA})_2(\mathrm{ArH})]^{\ddagger}$ stoichiometry is analogous to that observed in benzene and anisole metalations[8] and

(24) Arene-*n*-BuLi complexes were detected in the absence of coordinating TMEDA. For leading references to analogous frequency shifts resulting from oxazoline-metal complexation, see: (a) Braunstein, P.; Fryzuk, M. D.; Le Dall, M.; Naud, F.; Rettig, S. J.; Speiser, F. *Dalton Trans.* **2000**, 1067. (b) Bonnardel, P. A.; Parish, R. V.; Pritchard, R. G. *Dalton Trans.* **1996**, 3185.

(25) (a) Arenes **3**-d_5, **4**-d_5, and **8**-d_5 were prepared from benzoyl-d_5 chloride and the corresponding amino alcohol following reported procedures (see also ref 2c): Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. (b) Arene **5**-d_1: Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, *21*, 3335. (c) See also ref 3.

(26) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78−139.

(27) (a) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (b) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: New York, 1988; Chapter 5. (c) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.

(28) We define the idealized rate law as that obtained by rounding the observed reaction orders to the nearest rational order.

consistent with generic triple ion-based transition structures **10** and **11**, which are discussed in the context of the computational studies. More conventional open dimers (**12**) are also evaluated computationally.

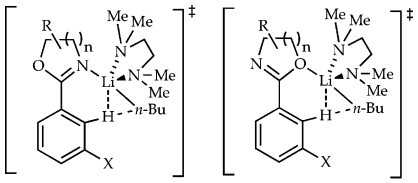
Ortholithiations of arenes **4** and **8** appear to be mechanistically complex. In both cases, plots of k_{obsd} versus *n*-BuLi concentration furnish *n*-BuLi orders between 0.5 and 1.0 (Figure 3), which, in conjunction with zeroth-order dependencies on the TMEDA concentration, implicate the idealized rate law described by eq 6 and the affiliated dimer- and monomer-based mechanisms depicted in eqs 7 and 8, respectively.

$$d[ArH]/dt = k'[ArH]^1[TMEDA]^0[(n\text{-BuLi})_2(TMEDA)_2]^1 + k''[ArH]^1[TMEDA]^0[(n\text{-BuLi})_2(TMEDA)_2]^{1/2} \quad (6)$$

$$(n\text{-BuLi})_2(TMEDA)_2 + ArH \rightarrow \underset{(\mathbf{9})}{} [(n\text{-BuLi})_2(TMEDA)_2(ArH)]^{\ddagger} \quad (7)$$

$$1/2(n\text{-BuLi})_2(TMEDA)_2 + ArH \rightarrow \underset{(\mathbf{9})}{} [(n\text{-BuLi})(TMEDA)(ArH)]^{\ddagger} \quad (8)$$

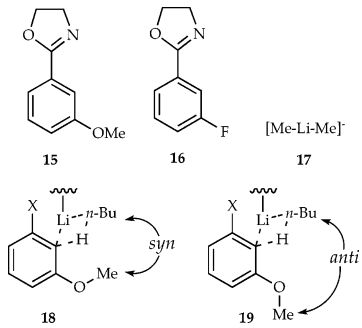
We discuss triple ion-based transition structures **10** and **11** and monomer-based transition structures **13** and **14**[29] below in the context of computational studies.



13 **14**

B. Density Functional Theory Calculations. Rate studies implicate contributions from monomer- and dimer-based transition structures $[(n\text{-BuLi})(TMEDA)(ArH)]^{\ddagger}$ and $[(n\text{-BuLi})_2(TMEDA)_2(ArH)]^{\ddagger}$, respectively. We investigated the reaction coordinate computationally to examine specific issues, including (1) N- versus O-directed lithiation, (2) the possible role of triple ions, $[(n\text{-Bu})_2Li^-(ArH)//^+Li(TMEDA)_2]^{\ddagger}$,[8] and (3) the origins of substrate-dependent rates and mechanisms.

General. DFT calculations were performed with the Gaussian 03 package at the B3LYP/6-31G(d) level.[30] MeLi was used as a model for *n*-BuLi. Fully optimized structures were obtained for arenes **2**−**4** and **8**. Arene **5** was modeled using oxazoline **15**. Although the ortholithiation of arene **16** was not investigated experimentally, we examined it computationally for comparison. Naked triple ion fragment, **17**, was optimized and confirmed[31] to be linear.[32] We sampled initial geometries for reactants and transition structures, and we established saddle points by the existence of a single imaginary frequency. The relative Gibbs free energies of activation ($\Delta G^{\ddagger}$, kcal/mol) at 298.15 K and 1.0 atm are shown under the structures. Selected geometric characteristics of the calculated transition structures are archived in Supporting Information. Isomeric structures displaying N- or O-coordinated lithiums were calculated. The methoxy-substituted derivatives afforded transition structures and activation energies for both syn and anti forms **18** and **19**, respectively.



15 **16** **17** **18** **19**

Caveats. In the following discussion, references to "stabilities" or "stabilization" risk sounding linguistically and scientifically imprecise, but they simply refer to the relative free energies of metalation described for monomers (eq 9, $\Delta G_m^{\ddagger}$), dimers (eq 10, $\Delta G_d^{\ddagger}$), and triple ions (eq 15, $\Delta G_{ti}^{\ddagger}$). Also, eq 15 represents a fundamentally different transformation than those described by eqs 9 and 10. In principle, the free energies reported in eq 15 can be adjusted by including the free energy of ionization (eq 13) to allow for a direct comparison. In practice, the calculated ionization energy in eq 13 is of no quantitative value because of huge distortions imparted by DFT on ionizations.[33] Although we discuss the structural details that influence the monomer-, dimer-, and triple ion-based metalations, triple ions and the other two classes are not compared directly.

Monomer-Based Ortholithiations. The rate studies provide evidence that monomer-based metalations become competitive for substrates that display relatively low reactivity (although low reactivity may not be the key variable). The calculations are only partially successful at mirroring experiment. The relative free energies of monomer-based metalations described generically by eq 9 are included under each transition structure. The transition structure for the monomer-based ortholithiation of benzene (**20**) serves as a benchmark. The planes crudely defined by the TMEDA-lithium chelate, the aryl ring, and the C_2HLi fragment in **20** are nearly orthogonal. H−Li agostic interactions are conspicuous.[34]

$$1/2(MeLi)_2(TMEDA)_2 + ArH \xrightarrow{\Delta G_m^{\ddagger}} [(MeLi)(TMEDA)(ArH)]^{\ddagger} \quad (9)$$

The monomer-based metalations display a high preference for N- versus O-directed metalation[35] and a high sensitivity to steric effects. Thus, the transition structure for N-directed ortholithiation of unsubstituted aryl oxazoline **2** displays

(29) For a discussion on triple ion versus monomer reactivity, see: Reich, H. J.; Sikorski, W. H.; Gudmundsson, B. Ö.; Dykstra, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4035.

(30) Frisch, M. J.; et al. *Gaussian 03*, revision B.04; Gaussian, Inc.: Wallingford, CT, 2004.

(31) A relaxed potential energy surface scan along the C−Li−C angle at the B3LYP/6-31G(d) level of theory shows an exponential increase in energy as the angle slightly deviates from linearity (see Supporting Information).

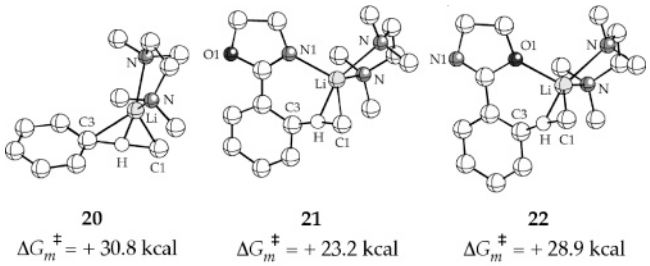
(32) (a) Hill, M. S.; Hitchcock, P. B. *Organometallics* **2002**, *21*, 220. (b) Bildmann, U. J.; Müller, G. *Organometallics* **2001**, *20*, 1689. (c) Bock, H.; Beck, R.; Havlas, Z.; Schödel, H. *Inorg. Chem.* **1998**, *37*, 5046. (d) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187.

(33) Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15376.

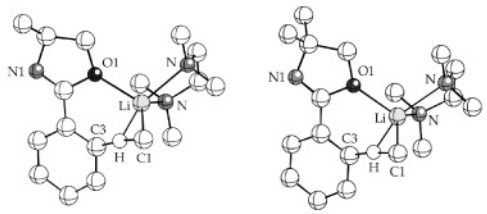
(34) Scherer, W.; McGrady, G. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1782 and references cited therein.

(35) For other examples of lithium azaphilicity, see: (a) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217. (b) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573. (c) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081. (d) Ramirez, A.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 11114.

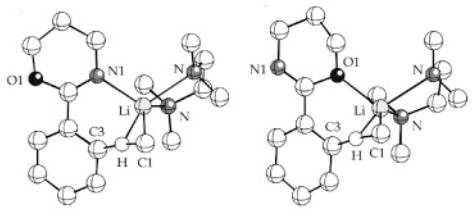
significant stabilization relative to the ortholithiation of benzene (cf., **20** and **21**). By contrast, the O-directed ortholithiation of **2** shows a surprisingly limited stabilization (cf., **20** and **22**). This pronounced N-selectivity is eliminated by methyl substituents proximate to the nitrogen; transition structures **23** and **24** corresponding to O-directed lithiations can be found, whereas the corresponding N-bound transition structures cannot. We presume this difference results from steric interactions of the oxazoline substituents with the chelated TMEDA ligand. The difference also presents a significant conflict with experiment as discussed below, however. The oxazines also display a pronounced N versus O selectivity (cf., **25** and **26**), but are inferior to oxazolines at directing lithiation.



20 $\Delta G_m^{\ddagger} = +30.8$ kcal **21** $\Delta G_m^{\ddagger} = +23.2$ kcal **22** $\Delta G_m^{\ddagger} = +28.9$ kcal



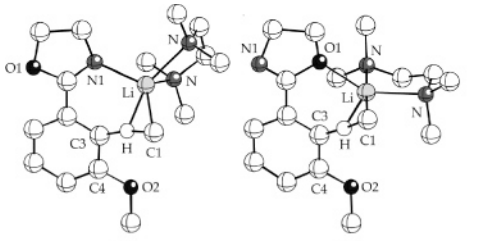
23 $\Delta G_m^{\ddagger} = +29.0$ kcal **24** $\Delta G_m^{\ddagger} = +29.3$ kcal



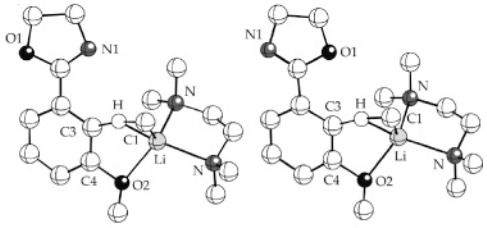
25 $\Delta G_m^{\ddagger} = +25.7$ kcal **26** $\Delta G_m^{\ddagger} = +31.0$ kcal

It is unclear (to us, at least) how the well-documented cooperative directing effects of meta substituents[2] could derive from *concurrent* interactions of both moieties with lithium in all but exceptional cases; the geometries appear to be unreasonable. By inference, the cooperativity arises from induction by an ancillary (non-coordinated) substituent. The roles of meta substituents on the ortholithiations of aryl oxazolines were probed as follows.

Monomer-based ortholithiations are very sensitive to the orientation of ancillary methoxy moieties. Syn-oriented methoxy substituents appear to *destabilize* the monomer-based transitions structures; none could be located, presumably because of severe steric effects. (This relationship is not the same for triple ions; see later). Conversely, anti-oriented methoxy groups allow for either oxazoline- or methoxy-directed metalations (**27**−**30**). The most stable form (**27**) displays an N−Li interaction. Interestingly, the methoxy moiety of **27** adds little stability when compared with unsubstituted analogue **21**, suggesting that an ancillary methoxy substituent does not facilitate monomer-based metalations.

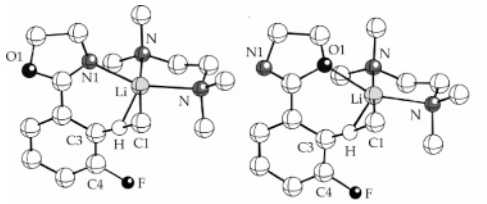


27 $\Delta G_m^{\ddagger} = +23.0$ kcal **28** $\Delta G_m^{\ddagger} = +30.2$ kcal

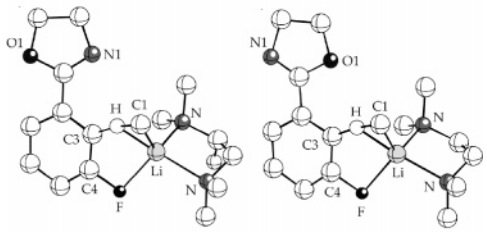


29 $\Delta G_m^{\ddagger} = +27.2$ kcal **30** $\Delta G_m^{\ddagger} = +27.7$ kcal

Although we have no experimental data on the cooperative effects of oxazolines and fluoro substituents because the metalations are too fast, we thought it would be instructive to probe the role of meta fluoro substituents computationally. Comparing **21** with **31** as well as **22** with **32** suggests that the monomer-based metalations are relatively insensitive to inductive effects. In fact, the fluoro-directed metalations without coordination by the oxazolinyl group appear to be equally facile (cf., **33** and **31**).



31 $\Delta G_m^{\ddagger} = +22.7$ kcal **32** $\Delta G_m^{\ddagger} = +26.8$ kcal

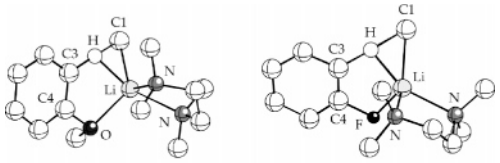


33 $\Delta G_m^{\ddagger} = +22.4$ kcal **34** $\Delta G_m^{\ddagger} = +22.0$ kcal

Having examined the inductive effects of fluoro and methoxy moieties on oxazoline-directed ortholithiations, we posed the question in reverse: Does the oxazoline function inductively as an ancillary activating group for methoxy- and fluoro-directed ortholithiations by monomers? Comparison of transition structure **29** with the most favorable anisole-derived analogue, **35**, indicates that the addition of a non-coordinating oxazoline meta

to the methoxy group *does not* grant any stabilization. Similarly, an ancillary oxazoline does not facilitate a fluoro-directed ortholithiation (cf., **34** and **36**).

Open Dimer- and Broken Dimer-Based Ortholithiations. There is mounting evidence that dimer-based organolithium chemistry may involve partial dimer scission or so-called open dimers.[11,36] Nonetheless, it is unclear how congestion in a transition structure of stoichiometry $[(n\text{-BuLi})_2(\text{TMEDA})_2\,(\text{ArH})]^{\ddagger}$

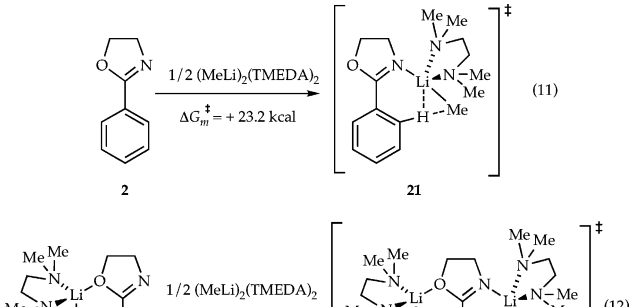


35 $\Delta G_m^{\ddagger} = +26.9$ kcal **36** $\Delta G_m^{\ddagger} = +21.7$ kcal

could be tolerated in the open dimer motif (which was our motivation for turning to triple ions in previous studies).[8a] Still, we considered a number of transition structures, **37**−**39**, summarized in Chart 2. The free energies are described by eq 10.

$$(\text{MeLi})_2(\text{TMEDA})_2 + \text{ArH} \xrightarrow{\Delta G_d^{\ddagger}} [(\text{MeLi})_2(\text{TMEDA})_2(\text{ArH})]^{\ddagger} \quad (10)$$

Transition structure **37** preserves the connectivities of the $(\text{MeLi})_2(\text{TMEDA})_2$ cyclic dimer, whereas structures **38** and **39** represent isomeric open dimers. Attempting to find transition structures corresponding to **37**−**39**, however, invariably led to highly distorted structures **40** and **41**, which manifested an extraordinarily long (>2.3 Å) Me−Li bond. Indeed, fully fragmented dimers−broken dimers−described as **42** and **43** were found to be 4−5 kcal/mol more stable than **40** and **41**.



The free energies of activation of stretched and broken dimers **40**−**43** are >40 kcal/mol, which, by comparison with monomer-based metalations, are enormous. These results did, however, present an interesting question: Could complexation of a monomer (or, more generally, a Lewis acid) at the remote heteroatom of an oxazoline facilitate metalation directed by the second heteroatom? The calculations suggest the answer is no. By comparing the metalation of the simple oxazoline (eq 11) with that of a monomer-complexed oxazoline (eq 12), we found the ancillary monomer fragment to be highly deactivating even in the best-case scenario in which the cost of complexing the monomer fragment is discounted. The deactivation by a pre-complexed monomer could be due, in part, to the reduced Lewis basicity of the directing heteroatom, which is key in monomer-based metalations. Most important, simple dimer-based metalations appear to be uncompetitive with monomer-based cases. For these reasons, we turned to triple ions.

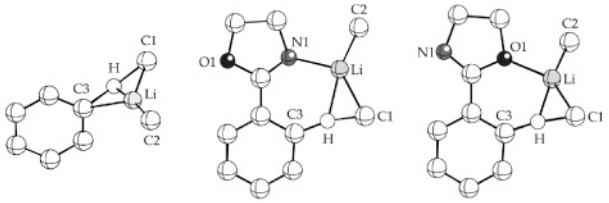
Triple Ion-Based Ortholithiations. Triple ion-based metalations (see **44** and **45**) are described by eqs 13−15. Unfortunately, DFT calculations grossly exaggerate energies affiliated with such ionizations and are not particularly well suited for ascertaining the ion pairing energies.[33,37] However, because the pairing energies of Me_2Li^- (**17**) and $[(\text{Me}_2\text{Li})(\text{ArH})^-]^{\ddagger}$ fragments with $^+\text{Li}(\text{TMEDA})_2$ (eq 14) should largely cancel[37b] the *relative* arene-dependent activation energies can be evaluated by omitting the $^+\text{Li}(\text{TMEDA})_2$ altogether (eq 15).

$$(\text{MeLi})_2(\text{TMEDA})_2 \xrightarrow{\Delta G^{\circ}} (\text{Me}_2\text{Li})^- + {}^+\text{Li}(\text{TMEDA})_2 \quad (13)$$

$$(\text{Me}_2\text{Li})^- + {}^+\text{Li}(\text{TMEDA})_2 + \text{ArH} \rightarrow [(\text{Me}_2\text{Li})(\text{ArH})^-]^{\ddagger} + {}^+\text{Li}(\text{TMEDA})_2 \quad (14)$$

$$(\text{Me}_2\text{Li})^- + \text{ArH} \xrightarrow{\Delta G_{ti}^{\ddagger}} [(\text{Me}_2\text{Li})(\text{ArH})^-]^{\ddagger} \quad (15)$$

The triple ion-based transition structures derived from aryl oxazolines are compared with the analogous transition structure for the ortholithiation of benzene (**46**) as a benchmark. We reiterate that the free energies for monomer-based metalations (eq 9, $\Delta G_m^{\ddagger}$) and triple-ion-based metalations (eq 15, $\Delta G_{ti}^{\ddagger}$) *cannot* be compared.[38]



46 $\Delta G_{ti}^{\ddagger} = +21.5$ kcal **47** $\Delta G_{ti}^{\ddagger} = +16.6$ kcal **48** $\Delta G_{ti}^{\ddagger} = +17.9$ kcal

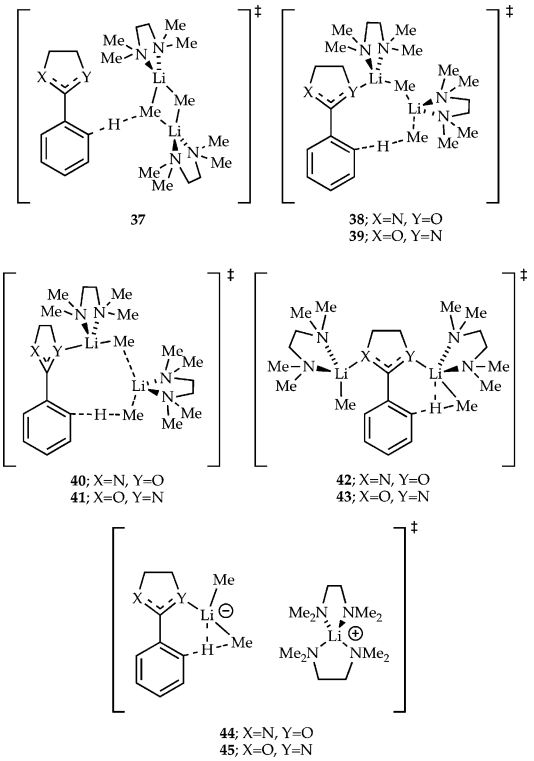
All triple ion-based transition structures display H−Li agostic interactions.[34] The existence of an X−Li interaction (X═N or O) correlates with the orientation of the plane defined by the CH_3−Li−CH_3 triple ion fragment involved in the deprotonation relative to the plane defined by the arene ring: Transition structure **46** for the lithiation of benzene shows planes that are

(36) For discussions of open dimer-based mechanisms for reactions of alkyllithiums, see: (a) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Nakamura, E.; Nakamura, M.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016. (c) Pratt, L. M.; et al. *J. Org. Chem.* **2003**, *68*, 6387 and references cited therein. (d) For additional leading references to spectroscopic, crystallographic, and kinetic evidence of open dimers, see: Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411.

(37) (a) B3LYP/6-31G(d) computations give a free energy of ionization (eq 13) of $\Delta G^{\circ} = 28.9$ kcal/mol. (b) Cioslowski, J.; Piskorz, P.; Schirneczek, M.; Boche, G. *J. Am. Chem. Soc.* **1998**, *120*, 2612.

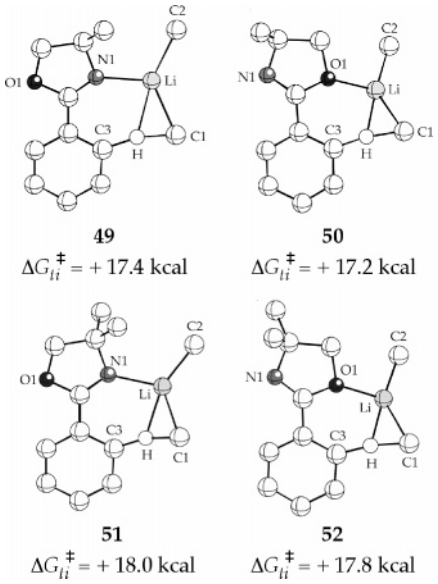
(38) Other computational studies considering monomer-based ortholithiations: (a) Balle, T.; Begtrup, M.; Jaroszewski, J. W.; Liljefors, T.; Norrby, P.-O. *Org. Biomol. Chem.* **2006**, *7*, 1261. (b) Nguyen, T.-H.; Chau, N.-T.-T.; Castanet, A.-S.; Nguyen, K.-P.-P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445. (c) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903. (d) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755 and references cited therein. (e) See ref 11b.

Chart 2. Possible Dimer-Based Mechanisms



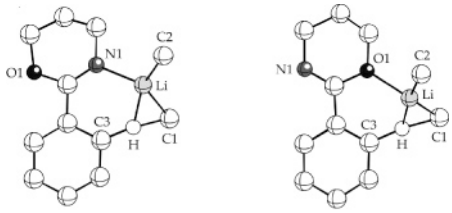
37; **38**; X=N, Y=O; **39**; X=O, Y=N; **40**; X=N, Y=O; **41**; X=O, Y=N; **42**; X=N, Y=O; **43**; X=O, Y=N; **44**; X=N, Y=O; **45**; X=O, Y=N

nearly orthogonal, whereas the two planes in transition structures **47**, **48**, and all subsequent cases studied are nearly coincident. The oxazoline group reduces $\Delta G_{ti}^{\ddagger}$ by 5 kcal/mol when compared with the analogous $\Delta G_{ti}^{\ddagger}$ derived from benzene (cf., **46** and **47**). The N−Li interaction is preferred to the O−Li contact by 1.3 kcal/mol (cf., **47** and **48**). This difference is smaller than we expected given the results from monomer-based metalations.



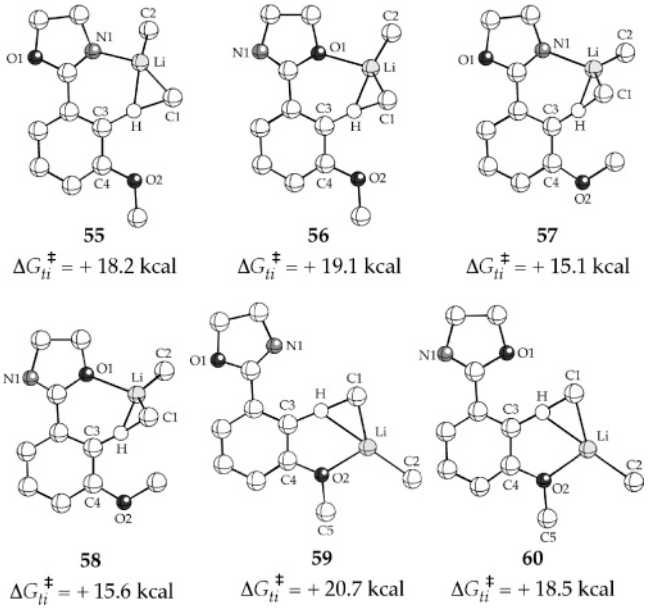
49 $\Delta G_{ti}^{\ddagger} = +17.4$ kcal; **50** $\Delta G_{ti}^{\ddagger} = +17.2$ kcal; **51** $\Delta G_{ti}^{\ddagger} = +18.0$ kcal; **52** $\Delta G_{ti}^{\ddagger} = +17.8$ kcal

A methyl group on the carbon α to the oxazoline nitrogen in arene **3** retards the N-directed ortholithiations when compared with the N-directed ortholithiations of unsubstituted aryl oxazoline **2** (cf., **49** and **47**). A distinct twisting of the plane defined by the $CH_3-Li-CH_3$ fragment and reduction of the $CH_3-Li-CH_3$ angle in **49** suggests that steric interactions between the oxazoline methyl substituent and the ancillary (nonmetalating) methyl group are important.[31,32,39] The absence of such an interaction in **50** makes N− and O-directed ortholithiations comparable. A second methyl group has an attenuated effect (cf., **51** and **52**). By contrast, relative rate constants in Chart 1 reveal little effect of the first methyl group but a 20-fold deceleration by the second (cf., **2**, **3** and **4**; Chart 1). We hasten to add that substituent effects on O- versus N-directed lithiations are likely to be underestimated by the MeLi model system.



53 $\Delta G_{ti}^{\ddagger} = +18.8$ kcal; **54** $\Delta G_{ti}^{\ddagger} = +18.9$ kcal

The ortholithiation of oxazine **8** affords activation energies that are higher than those calculated for oxazoline **2** (cf., **47** and **53** as well as **48** and **54**), consistent with experiment (Chart 1). The rotation of the $CH_3-Li-CH_3$ plane in **53** suggests



55 $\Delta G_{ti}^{\ddagger} = +18.2$ kcal; **56** $\Delta G_{ti}^{\ddagger} = +19.1$ kcal; **57** $\Delta G_{ti}^{\ddagger} = +15.1$ kcal; **58** $\Delta G_{ti}^{\ddagger} = +15.6$ kcal; **59** $\Delta G_{ti}^{\ddagger} = +20.7$ kcal; **60** $\Delta G_{ti}^{\ddagger} = +18.5$ kcal

that the destabilization in **53** may derive from steric interactions between the methylene group α to the heteroatom and the triple ion. The Lewis basicity of the nitrogen and oxygen also might be sensitive to ring size.[40]

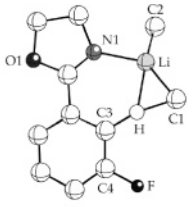
Isomeric transition structures **55**−**60** were located for the triple ion-based ortholithiation of methoxy-substituted oxazoline **15**. The results support previous assertions[8a] that only syn-oriented methoxy groups (see **18**) are stabilizing in the triple ion-based transition structures. The small stabilization of **57** and **58** relative to **47** and **48** (respectively) is in accord with experi-

(39) (a) Tahara, N.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2002**, *43*, 9069. (b) Wehman, E.; van Koten, G.; Erkamp, C. J. M.; Knotter, D. M.; Jastrzebski, J. T. B. H.; Stam, C. H. *Organometallics* **1989**, *8*, 94.

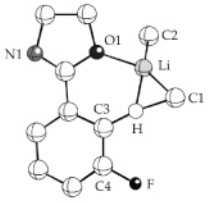
(40) (a) Rozeboom, M. D.; Houk, K. N.; Searles, S.; Seyedrezail, S. E. *J. Am. Chem. Soc.* **1982**, *104*, 3448. (b) Arnett, E. M.; Wu, C. Y. *J. Am. Chem. Soc.* **1962**, *84*, 1684. (c) Cook, A. G.; Absi, M. L.; Bowden, V. K. *J. Org. Chem.* **1995**, *60*, 3169 and references cited therein.

ment (Chart 1). Importantly, the oxygen atom of a syn-oriented methoxy group cannot interact with lithium. Some activation by syn-oriented methoxy groups occurs despite potentially destabilizing steric interactions, and it likely stems from induction.[41] Transition structures **55** and **56**, with anti-oriented methoxy groups, are significantly *destabilized* compared to their unsubstituted counterparts. We previously posited that electron repulsion between the lone pairs of the oxygen of the anti-oriented methoxy group and the electron rich triple ion may be destabilizing.[8a] The markedly different influences of methoxy moieties on monomer- and triple ion-based metalations are discussed later.

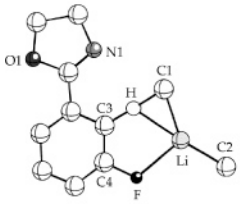
We examined cooperative effects in meta fluoro-substituted aryloxazolines and located four transition structures. Transition structures **61** and **62** display oxazoline−Li coordination, whereas **63** and **64** display F−Li interactions. Although F−Li interactions are stabilizing relative to their MeO−Li counterparts by >4 kcal/mol (cf., **59** and **63** as well as **60** and **64**),[42] coordination to the oxazoline group is still preferred. Interestingly, introduction of a non-coordinating fluoro substituent reduces $\Delta G_{ti}^{\ddagger}$ by >4 kcal/mol (cf., **47** and **61**).



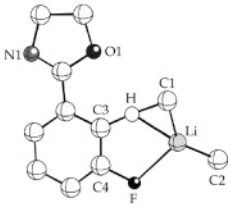
61
$\Delta G_{ti}^{\ddagger}$ = + 12.3 kcal



62
$\Delta G_{ti}^{\ddagger}$ = + 12.8 kcal

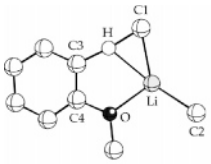


63
$\Delta G_{ti}^{\ddagger}$ = + 16.2 kcal

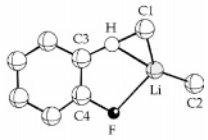


64
$\Delta G_{ti}^{\ddagger}$ = + 14.6 kcal

One can gain insight into the inductive influence of the oxazoline ring on ortholithiation by comparing methoxy- and fluorine-directed ortholithiations bearing uncoordinated oxazolines with metalations of anisole and fluorobenzene (cf., **60** and **65** as well as **64** and **66**). The non-coordinating oxazoline affords <0.4 kcal/mol of stabilization, suggesting that induction is minimal. By inference, the ~3.0 kcal/mol of stabilization by a coordinated oxazoline group (cf., **57** and **65** as well as **61** and **66**) largely derives from the N−Li interaction. The relative rate constants for **4** and **7** (Chart 1) show that a second oxazoline moiety is highly activating. The failure of the calculations to mimic a large inductive effect by the oxazoline suggests a discrepancy between theory and experiment. We wonder whether a fundamentally different mechanism is intervening (vide infra).



65
$\Delta G_{ti}^{\ddagger}$ = + 18.2 kcal



66
$\Delta G_{ti}^{\ddagger}$ = +14.9 kcal

Discussion

Oxazolines are one of the prominent directing groups in the vast literature of ortholithiation.[43] Substituents on the oxazoline often influence the rate of metalation, preclude side reactions, and control selectivities.[17,44] *n*-BuLi/TMEDA-mediated ortholithiations of aryl oxazolines described herein show that the substituent-dependent rates are affiliated with changes in mechanism. There are, however, many factors contributing to the rates and mechanisms.

Summary of Rate Studies. Relative rate constants in Chart 1 confirm that substituents on strongly ortho-directing oxazoline and arene rings markedly influence the rates. Detailed rate studies of **3**, **4**, **5**, and **8** reveal substrate-dependent mechanisms (Table 1). By example, aryl oxazolines **3** and **5**, bearing sterically demanding substituents, ortholithiate via exclusively dimer-based mechanisms described generically by eqs 4 and 5. Dimer-based metalations were the only detectable mechanisms observed from analogous lithiations of benzene, anisole, and related alkoxy-substituted arenes.[8] Conversely, ortholithiation of arenes **4** and **8**, the most unreactive substrates, appear to proceed by both dimer- and monomer-based mechanisms (eqs 7 and 8).

Mechanisms. The rate data define the stoichiometries of the rate-limiting transition structures and, with the aid of kinetic isotope effects, confirm that the rate-limiting steps involve proton transfers. There are, however, many subtle issues presented by the ortholithiations of oxazolines that cannot be addressed experimentally. Computational studies allowed us to probe underlying steric and electronic influences of substituents. The detailed comparisons delineated in the Results section are not repeated. Readers also may note the absence of direct numerical comparisons of monomer-, dimer-, and triple ion-based ortholithiations for reasons explicitly noted above. We do, however, find that the influences of the ortholithiation mechanisms in isolation offer considerable insights into how the structure of the substrate influences the rates and mechanisms of ortholithiation.

Monomer-based metalations exemplified by generic transition structures **13** and **14** are viable and relatively straightforward. By contrast, dimer-based metalations pose a conundrum in that

(41) For a discussion on *anti*-MeO-Li interactions, see: Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

(42) F−Li interactions are stabilizing: (a) Leharie, M.-L.; Scopelliti, R.; Severin, K. *Inorg. Chem.* **2002**, *41*, 5466. (b) Wiberg, K. B.; Sklenak, S.; Bailey, W. F. *J. Org. Chem.* **2000**, *65*, 2014. (c) Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345. (d) Streitwieser, A.; Abu-Hasanyan, F.; Neuhaus, A.; Brown, F. *J. Org. Chem.* **1996**, *61*, 3151. (e) Stalke, D.; Klingebiel, U.; Sheldrick, G. M. *Chem. Ber.* **1988**, *121*, 1457.

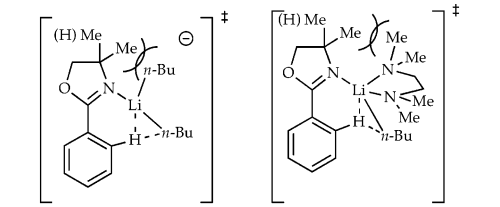
(43) (a) Govindasamy, M.; Singh, H. B. *Acc. Chem. Res.* **2002**, *35*, 226. (b) Overman, L. E.; Owen, C. E.; Zipp, G. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3884. (c) Iwamoto, K.; Chatani, N.; Murai, S. *J. Org. Chem.* **2000**, *65*, 7944. (d) Arnoldi, A.; Bassoli, A.; Borgonovo, G.; Merlini, L.; Morini, G. *J. Agric. Food Chem.* **1997**, *45*, 2047. (e) Evans, P. A.; Nelson, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298. (f) Misra, R. N.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Kocy, O.; Harris, D. N.; Goldenberg, H. J.; Michel, I. M.; Schumacher, W. A.; Webb, M. L.; Monshizadegan, H.; Ogletree, M. L. *J. Med. Chem.* **1993**, *36*, 1401. (g) Sibi, M. P.; Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737. (h) Ellefson, C. R. *J. Org. Chem.* **1979**, *44*, 1533.

(44) (a) Geisler, F. M.; Helmchen, G. *J. Org. Chem.* **2006**, *71*, 2486. (b) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.

juxtaposition of two *n*-BuLi fragments, two TMEDA ligands, and the substrate is not easy to imagine within the dimer motif. Dimer-like mechanisms examined are summarized in Chart 2. We considered cyclic and open dimer-based transition structures (**37**−**39**), and found that they invariably stretched the C−Li bond (**40** and **41**) akin to related transition structures calculated by Saá.[11b] We subsequently discovered more stable "broken dimers"−transition structures in which complete scission of the dimer is tantamount to reaction requiring two monomers (**42** and **43**). Although the stretched and broken dimers are provocative, computational evidence suggests that the ancillary monomer appended on the oxazoline ring is highly counterproductive. Accordingly, we turned to triple ion-based transition structures (**44** and **45**). Triple ions have been studied spectroscopically, crystallographically, and computationally but have been slow to gain the attention of nonspecialists.[12] The remaining issues are discussed in the context of these general classes of mechanism.

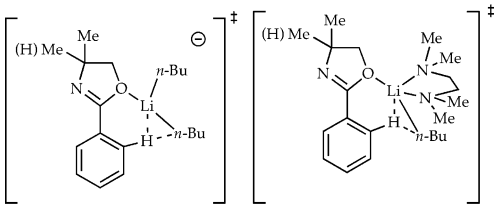
N- versus O-Directed Ortholithiation. Sammakia and Latham used a constrained substrate (eq 3) to show that *sec*-BuLi/THF-mediated metalations of aryl oxazolines proceed via N- rather than an O-directed mechanism.[17] Their conclusion seems reasonable in light of the $^{\delta+}O-C{=}N^{\delta-}$ polarization of the imino moiety.[45] Computational studies suggest that the balance between N- and O-directed lithiation may be more subtle.

Triple ion-based metalation of the parent oxazoline **2** favors N−Li versus O−Li interactions, but the difference is small. By contrast, the preference for N-directed ortholithiation is much more dramatic in the monomer-based metalations. Interestingly, monomeric lithium amides also display an inordinate azaphilicity compared to their dimeric counterparts.[35] Overall, the azaphilicities versus the oxaphilicities of the two ortholithiation mechanisms are quite different. The devil is in the details, however, in that the inherent nitrogen versus oxygen selectivity is superseded by substituents on the oxazolinyl ring.



67

68



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Effects of Oxazoline Substituents. The computational studies show that substituents on the oxazoline ring retard the ortholithiations in several ways. These substituents clash with the ancillary (nonreacting) alkyllithium fragment in triple ion **67** and with the TMEDA ligand on monomer-based transition structure **68**. The transition structures all show distortions consistent with steric relief and manifest moderately elevated activation energies compared with those of the non-methylated cases. The monomer-based metalations are predicted to be substantially more sensitive than the triple ion-based cases to the steric demands of the oxazoline substituents. This observation represents the first of two significant disagreements of theory and experiment. According to theory, attenuated rates should correlate with a disproportionate suppression of the sterically sensitive monomer-based metalation. Conversely, monomer-based metalations were detected experimentally for oxazolines **4** and **8**. Although it might be tempting to invoke O-directed transition structures **69** or **70**, calculations also suggest that such monomer-based, O-directed lithiations are problematic. Of course, MeLi may be a poor model for *n*-BuLi, but that seems dismissive.

Cooperative Directing Effects. We find cooperative directing effects by meta-disposed directing groups to be vexing. The cooperativity is not in doubt, as evidenced by high regioselectivities[46,47] and high metalation rates;[2,44,48] *how* two groups cooperate is less clear. Some have suggested, for example, that two meta-disposed groups coordinate lithium concurrently in the transition structure.[49] We find such models unconvincing and lacking support (although we revisit this model for one case below). Two groups that acidify the ortho protons inductively certainly could function cooperatively, and the influences may even be quantitatively additive. Schlosser has contributed significantly to understanding such inductive effects.[7] The most interesting form of cooperation, however, may arise when one group displays a penchant for interaction with lithium whereas the second group−what we call the *ancillary* or uncoordinated group−acidifies the ortho proton inductively. *The two directing substituents play fundamentally different roles*. Oxazolines appear to strongly coordinate lithium, and computations suggest oxazolinyl moieties have no tendency to activate inductively (vide infra). Thus, cooperativity in aryl oxazoline metalations requires an inductive ancillary group at the meta position. Of course, substituents on the oxazoline ring (Me versus H), the choice of directing group (O versus N), and the mechanistic pathway (monomer versus triple ion) all influence cooperativity.

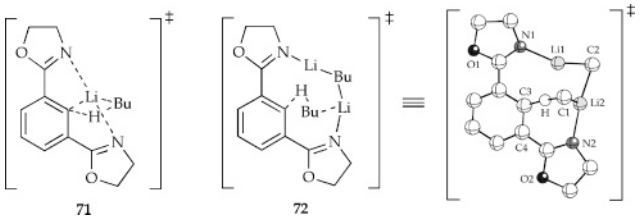
(45) Durig, J. R.; Riethmiller, S.; Li, Y. S. *J. Chem. Phys.* **1974**, *60*, 253.
(46) Examples of regioselective lithiation at position 2 in 1,3-orthodirecting disubtituted arenes include the following. (i) Low selectivity: (a) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805. (ii) High selectivity: (b) Harder, S.; Meijboom, R.; Moss, J. R. *J. Organomet. Chem.* **2004**, *689*, 1095. (c) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455. (d) Kostas, I. D.; Gruter, G.-J. M.; Akkerman, O. S.; Bickelhaupt, F.; Kooijman, H.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1996**, *15*, 4450. (e) Pfeffer, M.; Urriolabeitia, E. P.; de Cian, A.; Fischer, J. *J. Organomet. Chem.* **1995**, *494*, 187. (f) Cho, I. S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288. (g) Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 1696. (h) Kress, T. H.; Leanna, M. R. *Synthesis* **1988**, 803. (i) Guillaumet, G.; Hretani, M.; Coudert, G. *Tetrahedron Lett.* **1988**, *29*, 475. (j) Becker, A. M.; Irvine, R. W.; McCormick, A. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.* **1986**, *27*, 3431. (k) Terheijden, J.; van Koten, G.; van Beek, J. A. M.; Vriesema, B. K.; Kellogg, R. M.; Zoutberg, M. C.; Stam, C. H. *Organometallics* **1987**, *6*, 89. (l) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805. (m) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1984**, *25*, 2941. (n) Edgar, K. J.; Bradsher, C. K. *J. Org. Chem.* **1982**, *47*, 1585. (o) Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739. (p) De Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, *51*, 5099. (q) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.
(47) For example, if the ortho selectivity of the metalation of resorcinol dimethyl ether arises exclusively from a formal delivery-based mechanism via a single MeO−Li interaction, the lithiation should afford a statistical 1:1 mixture of 2,6-dimethoxy- and 2,4-dimethoxyphenyllithiums.
(48) (a) Paquette, L. A.; Schulze, M. M. *Tetrahedron Lett.* **1993**, *34*, 3235. (b) Thornton, T. J.; Jarman, M. *Synthesis* **1990**, 295. (c) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
(49) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (b) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923. (c) Christensen, H. *Synth. Commun.* **1975**, *5*, 65. (d) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209. (e) See also ref 11.

We briefly consider ancillary methoxy, fluoro, and oxazolinyl substituents as follows.

In previous studies we concluded that methoxy moieties of anisoles do not necessarily coordinate to lithium during ortholithiation even when it is geometrically possible. The results described herein are in agreement in that we find no evidence that lithiations are directed by MeO−Li interactions. An interesting question resurfaced: Does an uncoordinated methoxy orient syn or anti (cf., **21** and **22**) to the proton being abstracted? Computations suggest that only a syn orientation is stabilizing despite potentially problematic steric effects. We suspect the lone pairs on the anti form are destabilizing but have no direct support. There appears to be a pronounced mechanism dependence on the orientation of the methoxy moiety. Triple ion-based transition structures benefit from syn-oriented methoxy groups, whereas monomer-based analogues do not. Indeed, oxazoline **5** shows a modest acceleration in comparison with **4** (Chart 1), and the rate studies show no evidence of a monomer-based pathway intervening.

Although fluoro-substituted oxazolines are too reactive to study, the pronounced activation by fluorine is still fascinating. Computational studies suggest that fluorine is a versatile directing group, facilitating ortholithiations via either a distinct F−Li interaction or simple induction. The two roles show a distinct dependence on mechanism. The capacity of fluorine to direct ortholithiations through an F−Li interaction is calculated to be particularly important in the sterically sensitive monomer-based metalations, presumably because of the low steric demands of a F−Li interaction. The capacity of fluorine to inductively facilitate the metalation as an ancillary group is more pronounced in triple ion-based pathways, which appear to be pK_a sensitive.

We finish this discussion by considering cooperative effects imparted by an ancillary oxazoline ligand and confront the second significant disagreement between theory and experiment. The experimental data are unequivocal: bisoxazoline **7** ortholithiates ≥100 times faster than its monooxazoline counterpart **4**. Computations, however, reveal no evidence that an uncoordinated oxazoline promotes ortholithiation. Although one could blame the MeLi model or computational failure, it seems possible that the high reactivity observed for **7** stems from a fundamental change in mechanism. A bis-chelated, monomer-based transition structure such as **71** is appealing on first inspection, but computations show that the distances are unreasonable given the small radius of lithium. Interestingly, the MeLi analogue of ansa-bridged dimer **72** can be found computationally, and displays a reasonable geometry, but attempts to include coordinated TMEDA ligands cause reversion to stretched dimers noted above.



Summary and Conclusions

The rate and computational studies of the ortholithiation of aryloxazolines described herein underscore a seemingly straightforward question: How are ortholithiations directed? The rate studies demanded that we focus on monomer- and dimer-based mechanisms. The issue is not binary, however. A number of dimer-based mechanisms were considered, of which triple ions captivated the bulk of our attention. Both monomer- and triple ion-based mechanisms displayed sensitivities to substituents on the oxazoline and arene rings. The issue of N- versus O-directed lithiation could not be put to rest as readily as we anticipated; both appeared to be competitive depending on the choice of substrate and mechanism.

Possibly, the question that most demands an answer pertains to polyfunctional substrates: How do meta-disposed substituents direct ortholithiation cooperatively? This issue is enormously important given the prevalence of ortholithiation in the synthesis of complex arenes and heteroarenes. [2,5,6,43] Substrate-, base-, and solvent-dependent regioselectivities[3] observed in ortholithiations likely derive from mechanism-dependent cooperative effects. Directed arene lithiation is often presented simplistically, but it is not simple. We conclude that the two groups most often serve different roles—one as a formal directing group via a distinct substrate−lithium interaction and the other as a non-coordinating ancillary group activating the metalation inductively.

In closing, we wish to underscore the synergies offered by experimental and computational methods: The rate data focus the calculations by defining the stoichiometries of the rate-limiting transition structures, whereas the calculations offer details that are unavailable from experiment. It is a tribute to computational chemistry that the computational methods can play the dominant role in shaping mechanistic hypotheses.

Experimental Section

Reagents and Solvents. Substrates were prepared using literature procedures described in the Supporting Information. Pentane was distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. The diphenylacetic acid used to determine *n*-BuLi solution titers was recrystallized from methanol and sublimed at 120 °C under full vacuum.[50] Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques.

Kinetics. The rate studies were carried out as briefly described in the text and in detail previously.[8,51]

Acknowledgment. We thank the National Science Foundation for direct support of this work as well as DuPont Pharmaceuticals, Merck Research Laboratories, Pfizer, Sanofi-Aventis, R. W. Johnson, Boehringer-Ingelheim, and Schering-Plough for indirect support.

Supporting Information Available: Experimental procedures, rate data, tabular and graphical presentation of computational results, and complete refs 30 and 36c. This material is available free of charge via the Internet at http://pubs.acs.org.

JA068057U

(50) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
(51) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.