Published in final edited form as:

J Am Chem Soc. 2018 April 11; 140(14): 4877–4883. doi:10.1021/jacs.8b00590.

A Case for Lithium Tetramethylpiperidide-Mediated Ortholithiations: Reactivity and Mechanisms

Kyle A. Mack and David B. Collum*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853–1301, dbc6@cornell.edu

Abstract

Rate and mechanistic studies of ortholithiations by lithium 2,2,6,6-tetramethylpiperidide focus on four arenes: 1,4-bis(trifluoromethyl)benzene, 1,3-bis(trifluoromethyl)benzene, 1,3-dimethoxybenzene, and 4,4-dimethyl-2-phenyl-2-oxazoline. Metalations occur via substrate-dependent combinations of monosolvated monomer, disolvated monomer, and tetrasolvated dimer (triple ions). Density functional theory computational studies augment the experimental data. We discuss the challenges presented by shifting dimer–monomer proportions in determining the observable reaction orders and our mathematical treatment of such shifting in reactant structure.

TOC Graphic

Introduction

Few transformations are more important than functionalizations of C–H bonds on aromatic and heteroaromatic rings.¹ Traditional electrophilic aromatic substitutions are limited to electron-rich arenes, have marginal regioselectivities, and can generate noxious waste streams when used on scale.² Emergent efforts to achieve catalytic transition-metal-mediated C–H activations are making great strides but remain in the early to mid-developmental stages.³ Ortholithiations with subsequent trapping by electrophiles are not without limitations but generally offer high reactivities of organolithium bases and exceptional regiocontrol.^{4,5}

The choice of base for orthometalations has chemical, economic, and safety consequences. Lithium diisopropylamide (LDA) is ideal for relatively acidic, multi-functional arenes.⁵ Less

*David B. Collum, dbc6@cornell.edu.

Supporting Information: Spectroscopic, kinetic, and computational data and authors for reference 19. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interests.

reactive arenes are most often metalated using *n*- or *sec*-butyllithium facilitated by a variety of accelerants such as tetrahydrofuran (THF) or *N,N,N',N'*-tetramethylethylenediamine. There are, however, some large disparities separating LDA and alkyllithiums: the high basicity and reactivity offered by alkyllithiums is offset by functional group incompatibilities. Note that casual mentions of basicity and reactivity can connote kinetic or thermodynamic effects depending on context. Does a base observably metalate (thermodynamic) and, if so, how fast (kinetic)?

Nestled between LDA and alkyllithiums lies lithium 2,2,6,6-tetramethylpiperidide (LiTMP).⁶ This base *has* been used for many ortholithiations, of course, but we sense that many practitioners are unaware of its advantages. *LiTMP is not simply a more expensive equivalent of LDA.* LiTMP-mediated metalations have a greater driving force^{7,8} and disproportionately higher metalation rates, both of which may stem from high steric demands that inhibit stabilizing aggregation—a form of ground-state destabilization. The high steric demands also amplify sterically dictated regiocontrol, and the hindered 2,2,6,6-tetramethylpiperidine (TMPH) byproduct precludes regiochemical equilibrations that are readily mediated by *i*-Pr₂NH.^{9–11} The higher cost of TMPH is also a red herring. TMPH is significantly more expensive than *i*-Pr₂NH, but current prices are markedly lower in bulk and should be susceptible to further downward pressure given that TMPH is prepared from acetone, ammonia, hydrazine, and KOH.¹²

This paper describes our progress beyond the above analysis through the probing of a combination of selectivities and mechanisms of LiTMP-mediated ortholithiations. Although the selectivities are largely founded in prior art,¹³ only one detailed rate and mechanistic study of an LiTMP-mediated reaction—an epoxide elimination—has been reported.^{14,15} We surveyed more than 40 arene metalations and selected arenes **1–4** (Scheme 1) for detailed study.

Results

Spectroscopic studies have shown that LiTMP is a 10:1 mixture of dimer **5** and monomer **6** in neat THF and >99:1 dimer at <1.3 M THF–hexane (eq 1).¹⁶ The dimer–monomer solvation states were first studied with semi-empirical calculations¹⁷ that were later augmented with density functional theory (DFT) computations.^{18,19} To simplify the presentation, we use the following shorthand: A = LiTMP subunit; S = THF; ArH = arene; ArLi = aryllithium. For example, A₂S₂ is a disolvated dimer and [A₂S₂(ArH)][‡] is the corresponding disolvated-dimer-based transition structure.

Kinetics: General Protocol.²⁰

LiTMP was held in excess at standard concentrations (0.025–0.25 M). THF was also used in high but variable concentrations (2.6–12.2 M) with hexane as a cosolvent. Arenes were the limiting reagents (0.0025–0.010 M). Metalation rates were monitored using in situ IR spectroscopy by following the loss of strong arene absorbances in the range of 1323–1655 cm^{-1} . The time-dependent decays fit the first-order function $f(x) = ae^{-bx}$ such that b corresponds to the pseudo-first-order rate constant, k_{obsd} . Values of k_{obsd} were shown to be independent of initial arene concentration as required for a first-order dependence. On occasion, initial rates were used if the LiTMP/ArH proportions deviated from pseudo-first order. All metalations displayed large isotope effects ($k_{\text{obsd(H)}}/k_{\text{obsd(D)}} = 23\text{--}40$), which confirmed rate-limiting proton transfers. Large isotope effects in orthometalations, which can be evidence of contributions from tunneling, are common.^{20a} A standard control experiment excluded the intervention of autocatalysis.^{20b} After a first-order decay, the baseline was reestablished, and a second aliquot of arene was injected; the two rate constants were indistinguishable.

The orders in THF were determined by monitoring k_{obsd} versus THF concentration using hexane as the cosolvent. Similarly, plots of k_{obsd} versus LiTMP concentration afforded orders in LiTMP. The LiTMP dimer–monomer equilibrium in eq 1 presents added mathematical complexity to attaining rigorous fitting of THF and LiTMP concentration dependencies. We routinely cite orders stemming from fits to a simple power function ($y = ax^n$). The fits shown graphically, by contrast, are more rigorous and complex, as described below.

To account for the shift in ground state from dimer (A_2S_2) to monomer (AS_2), we must solve for the monomer and dimer concentration dependencies as a function of the equilibrium constant (K_{eq}), total base concentration ($[\text{A}_{\text{total}}]$), and total solvent concentration ($[\text{S}]$). Solving the system of two equations (eq 2 and 3) provides two sets of roots. We chose the sets corresponding to real, positive concentrations.

$$K_{\text{eq}} = \frac{[\text{AS}_2]^2}{[\text{A}_2\text{S}_2][\text{S}]^2} \quad (2)$$

$$[\text{A}_{\text{total}}] = 2[\text{A}_2\text{S}_2] + [\text{AS}_2] \quad (3)$$

$$[\text{A}_2\text{S}_2] = \frac{1}{8} \left(4[\text{A}_{\text{total}}] + K_{\text{eq}}[\text{S}]^2 - \sqrt{K_{\text{eq}}[\text{S}]} \sqrt{8[\text{A}_{\text{total}}] + K_{\text{eq}}[\text{S}]^2} \right) \quad (4)$$

The choice of species (A_2S_2 versus AS_2) for writing rate expressions is arbitrary: A_2S_2 was chosen because of its dominance across the accessible THF concentration range (*vide infra*).

Eq 4 describes the concentration of A_2S_2 . In the discussion, we return to the challenges posed by two or more observable reactants with concentrations that vary with reaction conditions.

1,4-*bis*-(trifluoromethyl)benzene (**1**).

A plot of k_{obsd} versus THF concentration (Figure 1) for the metalation of **1** to form **1-Li** shows a clean second-order dependence, $n = 2.02 \pm 0.07$ when fit to a simple power function, although a rigorous fit is more complex (*vide infra*). A plot of k_{obsd} versus LiTMP concentration at a 6.0 M THF concentration (Figure 2) shows an approximate first-order dependence. (Origins of the slight downward curvature are discussed in detail below.) When these results are taken together, the idealized rate law²¹ in eq 5 is consistent with the generic mechanism shown in eq 6.

$$d[\text{ArLi}] / dt = k[\text{ArH}]^1[\text{S}]^2[\text{A}_2\text{S}_2]^1 \quad (5)$$

Owing to the severe steric hindrance of an A_2S_4 cyclic dimer^{15–18} as a reactant or a transition structure, the rate data implicate triple ions.²² Such LiTMP-derived triple ions have been structurally characterized²³ and studied computationally.¹⁷

1,3-*bis*-(trifluoromethyl)benzene (**2**).

The metalation of **2** at -78°C affords exclusively the 4-lithiated product **2-Li** as shown by deuteration. Fitting the THF dependence to a simple power function shows an intermediate order of 1.50 ± 0.04 (Figure 3), which suggests at least two mechanisms at play. Similarly, the measured LiTMP order fit to a power function is 0.76 ± 0.04 (Figure 4), which attests to competing monomer- and dimer-based metalations. The fits in Figures 3 and 4 are consistent with the idealized rate law in eq 7 and the mechanisms shown in eqs 8 and 9.²⁴

$$d[\text{ArLi}] / dt = k_1[\text{ArH}]^1[\text{S}]^1[\text{A}_2\text{S}_2]^1 / 2 + k_2[\text{ArH}]^1[\text{S}]^2[\text{A}_2\text{S}_2]^1 \quad (7)$$

1,3-bis-(methoxy)benzene (3).

The metalation of **3** at -40°C to form **3-Li** shows a clean first-order THF dependence (Figure 5) and half-order LiTMP dependence (Figure 6) when fit to a simple power function. The results are consistent with exclusively disolvated-monomer-based metalation (eqs 10 and 11).

$$\frac{d[\text{ArLi}]}{dt} = k[\text{ArH}]^1[\text{S}]^1[\text{A}_2\text{S}_2]^{1/2} \quad (10)$$

4,4-Dimethyl-2-phenyl-2-oxazoline (4).

The metalation of **4** to form **4-Li** at -40°C shows a zeroth-order THF dependence (Figure 7). The slight downward drift is too small to be relevant, particularly given subtle secondary-shell effects of similar magnitude;²⁰ however, there is a subtle and pedagogical reason why it *should* be observable. The THF dependence in conjunction with a half-order LiTMP dependence (Figure 8) are consistent with the monosolvated-monomer-based mechanism (eqs 12 and 13).

$$\frac{d[\text{ArLi}]}{dt} = k[\text{ArH}]^1[\text{S}]^0[\text{A}_2\text{S}_2]^{1/2} \quad (12)$$

Discussion

Qualitative Observations.

The work described herein focuses on rate studies of four LiTMP-mediated orthometalations. It is instructive, however, to qualitatively compare LiTMP with LDA as well as with sodium diisopropylamide (NaDA) based on a survey of approximately 40 arene metalations carried out to choose appropriate substrates for study. Thermochemically

recalcitrant metalations such as arene **3** metalate incompletely *at equilibrium* using excess LDA or NaDA, whereas metalations by LiTMP are generally quantitative.^{25,26} However, stoichiometric LiTMP also affords an incomplete metalation of **3** at equilibrium, putting the relative thermochemical boost by LiTMP in the vicinity of an order of magnitude (a single pK_A unit), consistent with the results of Fraser and co-workers.⁷ Comparing and contrasting the metalation rates shows that reactions with LiTMP are 5–500 times faster than those with LDA under comparable conditions for the few substrates slow enough to be monitored. By contrast, metalation rates for LiTMP and NaDA tend to be comparable.²⁶

The regioselectivities of LiTMP are distinct from those of either LDA or NaDA. The hindered TMP fragment has two effects: (1) LiTMP metalates less acidic but sterically more accessible sites,⁴ such as the 4 position of **2** to give **2-Li**; and (2) the product TMPH does not mediate regiochemical equilibration to the more acidic sites.¹⁰ Previous studies of arene metalations using LDA showed facile equilibration from kinetic to thermodynamic products in the presence of free diisopropylamine: the metalations are reversible.¹² We submit that many reported regioselectivities lack sufficient controls with which to ascertain whether the regioselectivity is the result of kinetic or thermodynamic control.

Contrary to our earlier report,²⁷ the metalation of **8** lacking the protective gem-dimethyl moiety of **4** by LDA results in decomposition consistent with the formation of **9** rather than the reported orthometalated product **10** (eq 14).²⁶ Similar decomposition is obtained with NaDA.²⁶ By contrast, the LiTMP-mediated ortholithiation of **8** affords **10**, as shown by deuterium quenching, along with limited (15%) decomposition.

Mechanism of Ortholithiation.

Orthometalation of the four substrates reveals a substrate-dependent mix of mechanisms. Arene **1**,^{13a} which has para-disposed CF_3 moieties, proceeds via a transition structure of stoichiometry $[A_2S_4(ArH)]^\ddagger$. The high solvation numbers are incompatible with any form of cyclic- or open-dimer-based metalation and instead implicates triple ion **11** analogous to those invoked in a number of previous investigations.^{20,22,23} DFT computations suggest a weak dipolar interaction between a fluorine and the lithium cation owing to minor distortion that does not rise to the level of a discrete contact.

Notably, 1,3-bis(trifluoromethyl)benzene (**2**)^{13b} metalates at the external C-4 position with no tendency to equilibrate to the C-2 position. Adding diisopropylamine causes complete equilibration to the 2-lithiated isomer, which confirms that the regioselectivity is under kinetic control. Rate studies reveal a composite of an $[\text{A}_2\text{S}_4(\text{ArH})]^\ddagger$ dimer-based metalation along with $[\text{AS}_2(\text{ArH})]^\ddagger$ monomer-based metalation consistent with computed transition structures **12** and **13**, respectively. DFT computations indicate that metalation at C-2 via **14** is a barrier +2.0 kcal/mol higher barrier than that via **13**, consistent with experiment.

1,3-Dimethoxybenzene (**3**) metalates exclusively at the internal (doubly ortho) C-2 position.^{13c} Rate studies showed only an $[\text{AS}_2(\text{ArH})]^\ddagger$ monomer-based pathway. DFT computations revealed a 2.1 Å $\text{MeO}-\text{Li}$ interaction (**15**) and affiliated near-tetrahedral lithium coordination sphere (Figure 9). Compared with those of **15**, computations of the AS_2 -mediated external metalation (**16**) also manifested a $\text{MeO}-\text{Li}$ interaction and a +2.6 kcal/mol higher energy consistent with experiment.

Lithiation of oxazoline **4** proceeds via an $[\text{AS}(\text{ArH})]^\ddagger$ monosolvated monomer (**17**).^{13d} Previous studies have all supported an N–Li versus O–Li interaction at the transition structure.²⁸ Indeed, N-bound transition structure **17** is 4.4 kcal/mol more stable than the O-bound isomer **18**. On first inspection, the computed preference along with a seemingly modest threefold reduction in metalation rate compared with that of **8** (eq 14) may seem odd given the apparent steric demands of the methyl moieties. However, the methyl moieties in transition structure **17** seem to add no significant congestion.

Consequence of a Shifting Ground State.

Organolithium mechanistic studies often present the complexity of either mixtures of reactants or multiple competing pathways (rate-limiting transition structures.) The latter is a relatively simple kinetic problem of deconvoluting the contributions of a multi-term rate law.^{20a} Condition-dependent changes in reactants, by contrast, are far more challenging, historically prompting us to simply avoid them. Only recently did we begin to address the challenges of the influence of multiple reactants on observable rate behavior.²⁹

At the outset of the present study, we surmised that a shift in the observable form of LiTMP from purely disolvated dimer (2.0–9.0 M THF/hexane) to a 90/10 mixture of disolvated dimer and disolvated monomer in neat THF (eq 1) would have a significant ($\approx 10\%$) impact on the measured reaction order in LiTMP. That hypothesis proved only partly correct. Consider the simplest depiction of a monomer-based metalation (devoid of solvents) in eq 15. In the limit that dimer “A₂” is the sole observable form, a fit to the simple power function $y = a[A_{\text{total}}]^n$ would show a clean half-order dependence ($n = 0.50$). Conversely, exclusively observable monomer “A” would afford a first-order LiTMP dependence ($n = 1.0$). We posed this question: what is the effect of a dimer-monomer mixture on the measured LiTMP order? A plot of measured order ascertained from the simple power function versus percent observable monomer is shown in Figure 10. We hasten to add that we use *normality* rather than molarity (50% monomer would be a 1:1 integration in the ⁶Li NMR spectrum).

The blue box in Figure 10 shows the dimer–monomer concentration range observed for LiTMP from nearly neat hexane to neat THF. The presence of 10% monomer has an insignificant effect on the measured order ($n = 0.53$). We confess to being a bit surprised. By contrast, owing to the nonlinearity, the perturbation of the measured order when observable monomer is contaminated by 10% dimer is more significant ($n = 0.82$).

This point in the discussion seems to be an opportune time to mention another misunderstood concept about how deaggregation influences reactivity. First, the notion that monomers are more reactive than dimers is by no means a foregone conclusion; this anachronistic thinking derives from rate studies of polymerizations during the 1960s and 1970s.³⁰ Aggregates often react preferentially.^{13c,14,20,23a,31} Second, even if a monomer is the preferred reactive form, changes in solvent or solvent concentration that force monomer formation will *not* necessarily increase the reaction rate (eq 16). If, for example, “AS” is the reactive form, driving the reactant to AS₂ by using a high solvent concentration will inhibit the metalation.²⁹

Conclusions

LiTMP offers advantages over alkyllithiums by being less nucleophilic—more functional-group-compatible—and advantages over LDA with respect to both the metalation rate and steric-based regiocontrol. The absence of amine-mediated equilibration ensures kinetic control of the regioselectivity except when ArH–ArLi direct exchanges are possible.¹¹ Cost, the primary limitation, appears to be artificial, especially on scales at which competitive pricing should be available. The functional-group-dependent mechanisms— $[A_2S_4(ArH)]^\ddagger$, $[AS_2(ArH)]^\ddagger$, and $[AS(ArH)]^\ddagger$ —determined from a survey of only four substrates representing only two functionalities (MeO and CF₃) suggest that careful control of conditions, particularly coordinating solvent and solvent concentration,^{20a} offers the potential for often overlooked regiocontrol. For the more mechanistically minded, the progress made in addressing mechanisms in which multiple species are observable reactants is notable and remains one of the more serious challenges for exploring complex ensembles.

Experimental

Reagents and Solvents.

THF and *n*-hexane were distilled from solutions containing sodium benzophenone ketyl. LiTMP, [⁶Li]LiTMP, and [⁶Li, ¹⁵N]LiTMP were prepared as described previously.^{16a} Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques. The arenes were purchased from Sigma Aldrich.

NMR Spectroscopy.

All NMR samples for reaction monitoring and structure elucidation were prepared using stock solutions and sealed under partial vacuum as described in detail previously.^{9k,20b} Standard ¹H, ⁶Li, ¹³C, and ¹⁵N NMR spectra were recorded at 500, 73.57, 125.79, and 36.14 MHz, respectively.

IR Spectroscopy.

IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm⁻¹. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped with a septum for injections and a nitrogen line. After evacuation under full vacuum, heating, and flushing with nitrogen, the flask was charged with LiTMP (73.6 mg, 0.50 mmol) in THF/hexane (4.9 mL total volume) and cooled to –78 °C with a dry ice/acetone bath. After a background spectrum was recorded, arene **1** was added (0.050 mmol in 0.10 mL) with stirring. The absorbance at 1323 cm⁻¹ was monitored over the course of the reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

We thank the National Institutes of Health (GM39764) for support.

References and Footnotes

1. Murakami K; Yamada S; Kaneda T; Itami K *Chem. Rev* 2017, 117, 9302. [PubMed: 28445033]
- 2 (a). Sartori G; Maggi R *Chem. Rev* 2011, 111, PR181. [PubMed: 21488695] (b)Smith K; El-Hiti GA *Green Chem* 2011, 13, 1579.
- 3 (a). Yang Y; Lan J; You J *Chem. Rev* 2017, 117, 8787. [PubMed: 28085272] (b)Shang R, Ilies L, Nakamura E *Chem. Rev* 2017, 117, 908.(c)Yang L; Huang H *Chem. Rev* 2015, 115, 3468. [PubMed: 25749375] (d)Lorion MM; Maindan K; Kapdi AR; Ackermann L *Chem. Sov. Rev* 2017, 46, 7399
- 4 (a). Mongin F; Quéguiner G *Tetrahedron* 2001, 57, 5897.(b)Mongin F; Quéguiner G *Tetrahedron* 2001, 57, 4059.(c)Clayden J In *The Chemistry of Organolithium Compounds*; Rappoport Z; Marek I, Eds.; Wiley: New York, 2004; Vol. 1, p 495.(d)Caubere P *Chem. Rev* 1993, 93, 2317. (e)Schlosser M; Mongin F *Chem. Soc. Rev* 2007, 36, 1161. [PubMed: 17576483] (f)Hartung CG; Snieckus V In *Modern Arene Chemistry*; Astruc D (Ed.), Wiley-VCH: Weinheim, 2002; Chapter 10.(g)Snieckus V *Chem. Rev* 1990, 90, 879.
- 5 (a). Bakker WII; Wong PL; Snieckus V *Lithium Diisopropylamide*. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Paquette LA, Ed.; John Wiley: New York, 2001.(b)Eames J *Product Subclass 6: Lithium Amides In Science of Synthesis*; Snieckus V, Ed.; Thieme: New York, 2006; Vol. 8a, p 173.
- 6 (a). Campbell M; Snieckus V; Baxter EW In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Paquette LA, Ed.; John Wiley & Sons: Chichester; New York, 2008; Vol. 5.(b)Mulvey RE; Robertson SD *Angew. Chem., Int. Ed* 2013, 52, 11470.
7. Fraser RR; Mansour TS *J. Org. Chem* 1984, 49, 3442.
8. Owing to loose usage, we emphasize that driving force connotes exergonicity (thermodynamics).
- 9 (a). Cottet F; Schlosser M *Eur. J. Org. Chem* 2004, 3793.(b)Trecourt F; Mallet M; Marsais F; Quéguiner G *J. Org. Chem* 1988, 53, 1367.(c)Comins DL; LaMunyon DH *Tetrahedron Lett* 1988, 29, 773.(d)Eaton PE; Cunkle GT; Marchioro G; Martin RM *J. Am. Chem. Soc* 1987, 109, 948.(e)Bridges AJ; Patt WC; Stickney TM *J. Org. Chem* 1990, 55, 773.(f)Trécourt F; Marsais F; Güngör T; Quéguiner G *J. Chem. Soc., Perkin Trans. 1* 1990, 2409.(g)Gros PC; Fort Y *Eur. J. Org. Chem* 2009, 4199.(h)Cottet F; Marull M; Lefebvre O; Schlosser M *Eur. J. Org. Chem* 2003, 1559.(i)Güngör T; Marsais F; Queguiner G *J. Organomet. Chem* 1981, 215, 139.(j)Viciu MS; Gupta L; Collum DB *J. Am. Chem. Soc* 2010, 132, 6361. [PubMed: 20397635] (k)Hoepker; Gupta L; Ma Y; Faggin MF; Collum DB *J. Am. Chem. Soc* 2011, 133, 7135. [PubMed: 21500823] (l)Fukuda T; Ohta T; Sudo E; Iwao M *Org. Lett* 2010, 12, 2734. [PubMed: 20486653]
- 10 (a). Groenendaal L; Van Loo ME; Vekemans JAJM; Meijer EW *Synth. Commun* 1995, 25, 1589. (b)Plé N; Turck A; Martin P; Barbey S; Quéguiner G *Tetrahedron Lett* 1993, 34, 1605.
11. (a)For discussions of possible slow regiochemical equilibration during an LiTMP-mediated orthometalation, see: Mongin F; Desponds O; Schlosser M *Tetrahedron Lett* 1996, 37, 2767. (b)Schlosser M; Marull M *Eur. J. Org. Chem* 2003, 8, 1569.(c)Also, see reference 9l.
12. Cantatore G; Cassandrini P *Process for Preparing 2,2,6,6-Tetramethyl-4-Piperdone*. U.S. Patent 4,536,581, 8 20, 1985.
13. (a)Previous orthometalations of substrates **1–4**: **1**: Capel VL; Dillon KB; Goeta AE; Howard JAK; Monks PK; Probert MR; Shepherd HJ; Zorina NV *Dalton Trans* 2011, 40, 1808. [PubMed: 21249260] **1–41**(b)**2**: Wang L; Wang Y; Guo F; Zheng Y; Bhadury PS; Sun Z *Tetrahedron Lett* 2013, 54, 6053.(c)**3**: Chadwick ST; Rennels RA; Rutherford JL; Collum DB *J. Am. Chem. Soc* 2000, 122, 8640.(d)**4**: Bellamy E; Bayh O; Hoarau C; Trécourt F; Quéguiner G; Marsais F *Chem. Commun* 2010, 46, 7043.**4**
14. Wiedemann SH; Ramírez A; Collum DB *J. Am. Chem. Soc* 2003, 125, 15893. [PubMed: 14677981]

15. Computations and crystal structures of various MTMP derivatives: Armstrong DR; Graham DV; Kennedy AR; Mulvey RE; O'Hara CT *Chemistry* 2008, 14, 8025. [PubMed: 18645993]
- 16 (a). Hall PL; Gilchrist JH; Harrison AT; Fuller DJ; Collum DB *J. Am. Chem. Soc* 1991, 113, 9575. (b) Renaud P; Fox MA *J. Am. Chem. Soc* 1988, 110, 5702.
17. Romesberg FE; Collum DB *J. Am. Chem. Soc* 1992, 114, 2112.
- 18 (a). Pratt LM; Newman A; Cyr JS; Johnson H; Miles B; Lattier A; Austin E; Henderson S; Hershey B; Lin M; Balamraju Y; Sammonds L; Cheramie J; Karnes J; Hymel E; Woodford B; Carter CJ. *Org. Chem* 2003, 68, 6387. [PubMed: 12895075] (b) Balamraju Y; Sharp CD; Gammill W; Manuel N; Pratt LM *Tetrahedron* 1998, 54, 7357.
19. Frisch MJ; Trucks GW; Schlegel HB; Scuseria GE; Robb MA; Cheeseman JR; Zakrzewski VG; Montgomery JA, Jr.; Stratmann RE; Burant JC; Dapprich S; Millam JM; Daniels AD; Kudin KN; Strain MC; Farkas O; Tomasi J; Barone V; Cossi M; Cammi R; Mennucci B; Pomelli C; Adamo C; Clifford S; Ochterski J; Petersson GA; Ayala PY; Cui Q; Morokuma K; Malick DK; Rabuck AD; Raghavachari K; Foresman JB; Cioslowski J; Ortiz JV; Baboul AG; Stefanov BB; Liu G; Liashenko A; Piskorz P; Komaromi I; Gomperts R; Martin RL; Fox DJ; Keith T; Al-Laham MA; Peng CY; Gill A; Nanayakkara C; Gonzalez M; Challacombe PMW; Johnson B; Chen W; Wong MW; Andres JL; Gonzalez C; Head-Gordon M; Replogle ES; Pople JA *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, 2009.
- 20 (a). Collum DB; McNeil AJ; Ramírez A *Angew. Chem., Int. Ed* 2007, 46, 3002. (b) Algera RF; Gupta L; Hoepker AC; Liang J; Ma Y; Singh KJ; Collum DB *J. Org. Chem* 2017, 82, 4513. [PubMed: 28368117]
21. We define the idealized rate law as that obtained by rounding the observed reaction orders to the nearest rational order.
22. Gilchrist JH; Harrison AT; Fuller DJ; Collum DB *J. Am. Chem. Soc* 1991, 113, 5751.
- 23 (a). For attempted compilation of a comprehensive bibliography of triple ions of lithium salts, see: Ma Y; Ramírez A; Singh KJ; Keresztes I; Collum DB *J. Am. Chem. Soc* 2006, 128, 15399. [PubMed: 17132006] (b) Also, see: Reich HJ *Chem. Rev* 2013, 113, 7130. [PubMed: 23941648]
24. One cannot rigorously exclude a combination of $[A_2S_3(ArH)]^{\ddagger}$ and $[AS_3(ArH)]^{\ddagger}$, but both suffer from steric demands associated with the high per-lithium solvation number.^{23†3†}
- 25 (a). Liang J; Hoepker AC; Bruneau AM; Ma Y; Gupta L; Collum DB *J. Org. Chem* 2014, 79, 11885. [PubMed: 25000303] (b) Liang J; Hoepker AC; Algera RF; Ma Y; Collum DB *J. Am. Chem. Soc* 2015, 137, 6292. [PubMed: 25900574]
26. Algera RF; Ma Y; Collum DB *J. Am. Chem. Soc* 2017, 139, 15197. [PubMed: 28946744]
27. Gupta L; Hoepker AC; Singh KJ; Collum DB *J. Org. Chem* 2009, 74, 2231. [PubMed: 19191711]
- 28 (a). Sammakia T; Latham HA *J. Org. Chem* 1996, 61, 1629. [PubMed: 11667028] (b) Stol M; Snelders DJM; de Pater JJM; van Klink GPM; Kooijman H; Spek AL; van Koten F *Organometallics* 2005, 24, 743. (c) Jayasuriya K; Alster J; Politzer P J. *Org. Chem* 1988, 53, 677. (d) Chadwick ST; Ramírez A; Gupta L; Collum DB *J. Am. Chem. Soc* 2007, 129, 2259. [PubMed: 17269777]
29. Reyes-Rodríguez GJ; Algera RF; Collum DB *J. Am. Chem. Soc* 2017, 139, 1233. [PubMed: 28080036]
- 30 (a). Hsieh HL; Quirk RP *Anionic Polymerization: Principles and Practical Applications*; Marcel Dekker: New York, 1996. (b) *Ions and Ion Pairs in Organic Reactions*; Szwarc M, Ed.; Wiley: New York, 1972; Vol. 1 and 2.
- 31 (a). Bartlett PD; Goebel CV; Weber WP *J. Am. Chem. Soc* 1969, 91, 7425. (b) Al-Aseer MA; Smith SG *J. Org. Chem* 1984, 49, 2608 and references cited therein. (c) McGarrity JF; Ogle CA *J. Am. Chem. Soc* 1985, 107, 1810. (d) Jones AC; Sanders AW; Bevan MJ; Reich HJ *J. Am. Chem. Soc* 2007, 129, 3492. [PubMed: 17341084] (e) Jones AC; Sanders AW; Sikorski WH; Jansen KL; Reich HJ *J. Am. Chem. Soc* 2008, 130, 6060. [PubMed: 18419118]

Figure 1.

Plot of k_{obsd} vs tetrahydrofuran (THF) concentration for the metalation of **1** (0.010 M) at $-78\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1323 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 5 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 0.10 \pm 0.02$, $n = 2.02 \pm 0.07$.

Figure 2.

Plot of initial rate vs lithium 2,2,6,6-tetramethylpiperidide (LiTMP) concentration for the metalation of **1** (0.010 M) in 6.0 M THF/hexane at $-78\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1323 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 5 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 33.07 \pm 2.19$, $n = 0.97 \pm 0.04$.

Figure 3.

Plot of k_{obsd} vs THF concentration for the metalation of **2** (0.0025 M) at -78°C measured with IR spectroscopy (1356 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 7 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 0.018 \pm 0.002$, $n = 1.50 \pm 0.04$.

Figure 4.

Plot of k_{obsd} vs LiTMP concentration for the metalation of **2** (0.0025 M) in 6.0 M THF/hexane at $-78\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1356 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 7 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 1.9 \pm 0.1$, $n = 0.76 \pm 0.04$.

Figure 5.

Plot of k_{obsd} vs free THF concentration for the metalation of **3** (0.0025 M) at $-40\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1496 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 10 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 0.065 \pm 0.005$, $n = 0.98 \pm 0.03$.

Figure 6.

Plot of k_{obsd} vs LiTMP concentration for the metalation of **3** (0.0025 M) in 6.0 M THF/hexane at -40°C measured with IR spectroscopy (1496 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 10 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 1.39 \pm 0.05$, $n = 0.57 \pm 0.02$.

Figure 7.

Plot of initial rate vs free THF concentration in hexane for the metalation of **4** (0.010 M) at $-40\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1655 cm^{-1}). The curve depicts an unweighted least-squares fit to $y = ax + b$ ($a = 0.91 \pm 0.02$, $b = -0.017 \pm 0.002$).

Figure 8.

Plot of initial rate vs LiTMP concentration in hexane for the metalation of **4** (0.010 M) at $-40\text{ }^{\circ}\text{C}$ measured with IR spectroscopy (1655 cm^{-1}). The curve depicts an unweighted least-squares fit to eq 12 that accounts for the shifting dimer–monomer mixtures described by eq 4. A simple fit to $y = ax^n$ affords $a = 2.7 \pm 0.1$, $n = 0.57 \pm 0.02$.

Figure 9.
Ball-and-stick representation of transition structures **15** and **17**.

Figure 10.

Simulated plot of LiTMP order as a function of percent monomer (measured using normality, N). The blue box represents the range accessible to 0.10 N LiTMP in THF/hexane mixtures at -78°C (eq 1).

Scheme 1.

Lithium 2,2,6,6-tetramethylpiperidide-mediated metalations of arenes.