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Sodium Diisopropylamide in Tetrahydrofuran: Selectivities, Rates, and Mechanisms of Arene Metalations

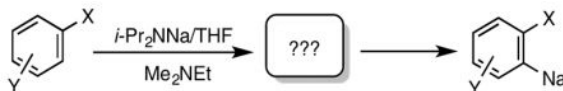
Russell F. Algera, Yun Ma, and David B. Collum*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853–1301

Abstract

Sodium diisopropylamide (NaDA)-mediated metalations of arenes in tetrahydrofuran (THF)/hexane or THF/Me₂NEt solutions are described. A survey of >40 benzenoid- and pyridine-based arenes with a range of substituents demonstrates the efficacy and regioselectivity of metalation. Metalations of activated disubstituted arenes and selected monosubstituted arenes are rapid at –78 °C. Rate studies of 1,3-dimethoxybenzene and related methoxylated arenes show exclusively monomer-based orthometalations with two or three coordinated THF ligands. Rate studies of the isotopic exchange of benzene and monosubstituted arenes with weakly activating groups reveal analogous di- and trisolvated monomer-based metalations. Cooperative inductive, mesomeric, steric, and chelate effects are discussed.

Graphical abstract



Introduction

In 1908, Schorigin reported that ethylsodium metalates benzene, constituting the first example of an organosodium-mediated arene metalation.¹ Progress accelerated with seminal studies by Gilman in the 1930s and Morton in the 1940s that explored highly reactive aryl- and alkylsodiums.^{2–4} Renewed activity in organosodium chemistry appeared with the emergence of mixed-alkali-metal super bases⁵ and, most recently, the structural studies of Mulvey and coworkers.⁶

Of course, a number of sodium-based reagents are used routinely. Sodium hexamethyldisilazide is illustrative and, despite a relatively low basicity, is commonly used.⁷ By comparison to organolithium chemistry, however, organosodium chemistry has been in a

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

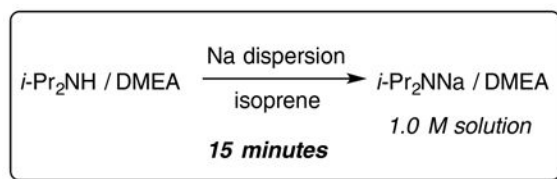
Notes

The authors declare no competing financial interests.

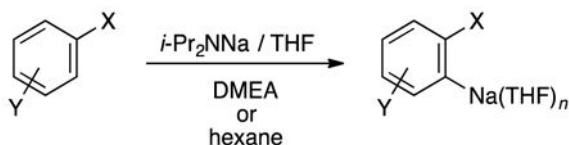
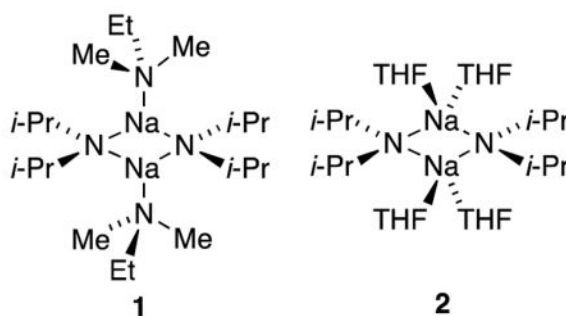
Supporting Information: Spectroscopic, kinetic, and computational data and authors for reference 38. This material is available free of charge via the Internet at <http://pubs.acs.org>.

protracted period of latency. Sodium diisopropylamide (NaDA) is an excellent case in point. Although lithium diisopropylamide (LDA) is used hundreds if not thousands of times *daily*, only a dozen reports on NaDA have appeared in the literature during the intervening six decades since the first report by Levine and co-workers in 1959.^{8,9} It is difficult to explain with confidence this dearth of publications, but a recent statement online probably captures the essence of the problem by referring to organosodium reagents as “limited in part due to competition from organolithium compounds” and “poorly soluble.”

We have begun a program to examine the synthetic, structural, and mechanistic organosodium chemistry that centers on the chemistry of NaDA.¹⁰ In the first of a series of papers, we showed that 1.0 M solutions of NaDA in *N,N*-dimethylethylamine (DMEA) can be prepared in minutes using technical-grade reagents (eq 1).^{10a} Subsequent studies probed the stability and solubility of NaDA in a range of solvents—dimers **1** and **2** are germane to the work described below^{10b}—as well as the reactivity of NaDA toward alkenes and dienes.^{10c} Metalation of substituted arenes by NaDA must have been examined and possibly even reported, but our failure to find a literature example underscores a glaring omission (eq 2).¹¹ In this paper, we describe NaDA-mediated arene sodiation from a synthetic organic and mechanistic perspective.¹²



(1)



(2)

Results

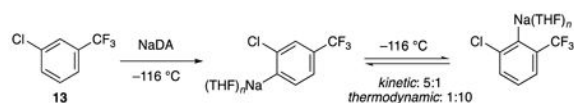
Methods

NaDA was prepared and purified with a modified literature procedure.^{9a,10a} It can be handled as a pyrophoric white solid or as a 1.0 M solution in DMEA, both of which are stable for weeks at 25 °C and for months at –20 °C.^{10a,b} Control experiments showed that NaDA/tetrahydrofuran (THF)/DMEA and NaDA/THF/hexane are operationally indistinguishable, consistent with the weak donicity of trialkylamines and exergonic substitution by THF.^{13,14} We use the two cosolvents interchangeably but favor NaDA/THF/hexane because of our specific interest in structural and mechanistic studies. The typical practitioner is likely to find NaDA/DMEA stock solutions convenient. Rate studies of NaDA-mediated THF decomposition at 25 °C were carried out previously;^{10b} the decomposition is not a problem under the conditions described herein.

Arene metalations were monitored using ¹H, ²H, and ¹⁹F NMR or in situ IR spectroscopies.^{15,16} By habit and protocols tied to rate studies, we routinely carry out metalations with 0.10 M NaDA, although metalations of 0.50–1.0 M arene occur without detectable precipitation of the arylsodiums in most instances.¹⁷ Arenes can be cataloged as those that metalate instantaneously at –78 °C (Chart 1), slowly enough to monitor at –78 °C (Chart 2), detectably only through isotopic exchange (Chart 3), and destructively (Chart 4). Metalations of the substrates in Charts 1–4 using other bases have been reported.¹² We have not observed any evidence of polymetalation.

Regioselectivity and Reversible Metalation

The regioselectivities for the substrates in Charts 1 and 3 are implicitly ortho or doubly ortho. Arrows denote selectivities that are ambiguous or less obvious. Whether the selectivities are kinetically or thermodynamically controlled *cannot* be ascertained unless an equilibration is explicitly detected. A rare example is the ~5:1 selectivity for the metalation of **13** at –116 °C that reverses to a 1:10 selectivity on standing at –116 °C (eq 3 and Chart 1). Such an isomerization would be undetectable at –78 °C.

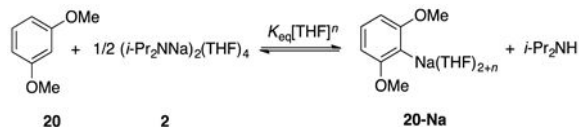


(3)

Kinetics and Mechanism of Arene Metalation.¹⁸

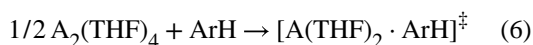
The muted reactivity of arenes in Chart 2 allowed us to monitor rates under pseudo-first-order conditions in which the substrate was the limiting reagent (0.010 M). The metalation of 1,3-dimethoxybenzene (**20**, eq 4) at –78 °C by NaDA in THF/hexane follows a clean decay to partial conversion at equilibrium (Figure 1). A plot of initial rate versus THF concentration (Figure 2) shows a linear dependence with a substantial non-zero intercept. The rates monitored versus NaDA concentration (Figure 3) afford an approximate half-order

dependence. The idealized rate law¹⁹ (eq 5) and assignment of NaDA as tetrasolvated dimer **2**^{10b} are consistent with the dominant disolvated-monomer-based metalation depicted generically in eq 6.²⁰ The collective data on THF dependencies (below) suggest that the first-order dependence is likely to be a primary shell solvation step consistent with low levels of an intervening trisolvated-monomer-based metalation (eq 7).



(4)

$$-d[\text{ArH}]/dt = (k[\text{THF}]^0 + k'[\text{THF}]^1)[\text{A}_2\text{S}_4]^{1/2}[\text{ArH}]^1 \quad (5)$$



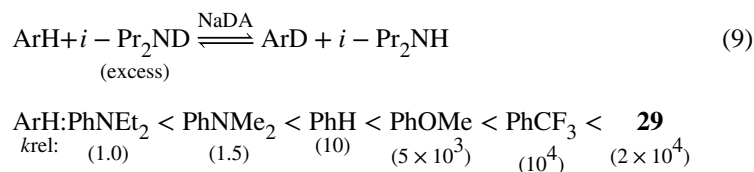
Rate studies using 1,2,4-trimethoxybenzene (**21**) show that metalation occurs threefold faster than **20** via an otherwise analogous mechanism and incomplete conversion at equilibrium (Supporting Information). Unlike the metalation of **20**, however, metalation of high concentrations of **21** reveals autocatalysis in the form of a sigmoidal decay (Figure 4). Decays at lower arene concentrations are nearly exponential (see Figure 4, inset). An approximate²² first-order dependence of initial rates on ArNa is consistent with the intermediacy of a fleeting NaDA/ArNa mixed aggregate (eq 8).²³ Curiously, arylsodium **21-Na** also catalyzes the metalation of **20**, whereas **20-Na** does *not* catalyze the metalation of **21**.



Kinetics and Mechanism of Isotopic Exchange

The influence of arene substituents on the rates, mechanisms, and selectivities of metalation was examined by monitoring deuterium exchange (eq 9) for substrates that metalate only transiently (see Chart 3).²⁴ Monitoring initial rates by ²H NMR spectroscopy precludes multiple exchanges and minimizes the slower but detectable exchange with α protons in

THF.^{10b} The regiochemistries (arrows in Chart 3) attest to competitive steric, chelation, inductive, and π effects (discussed below).



Rate studies show approximate half-order NaDA dependencies in all cases, which signify monomer-based metalations. Plots of rate versus THF concentration show substrate-dependent contributions of zeroth- and first-order dependencies attributed to the reactions of di- and trisolvated-monomer-based metalations (Figures 5–8). PhNEt₂ markedly attenuates ortho metalation rates relative to PhNMe₂ while leaving meta metalation unchanged. PhCF₃ shows evidence of exchange into the para position but only at elevated temperature (–20 °C). The Supporting Information has full details.

Discussion

We examined NaDA-mediated metalations of >40 arenes grouped by those that metalate instantaneously at –78 °C (see Chart 1), at tractable rates (see Chart 2), via fleeting arylsodiums (see Chart 3), and destructively (see Chart 4). Collectively, these metalations allow us to confront issues and questions recognizable to those versed in base-mediated arene functionalization.¹⁰

The Case for Sodium

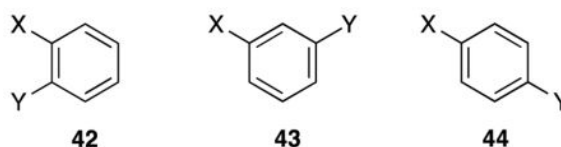
NaDA is easy to prepare as stable 1.0 M solutions in trialkylamines (DMEA) and is readily isolated as a white solid.^{10a,b} The steric demands of trialkylamines^{13,14} allow for exergonic substitution by standard ethereal ligands either before or after metalation. Adding >3 equiv THF to NaDA/DMEA quantitatively converts DMEA-solvated dimer **1** to THF-solvated dimer **2**.^{10b} Rates of arene metalations using NaDA/THF are often so rapid that they cannot be studied mechanistically. The lack of previously cited NaDA-mediated arene metalations underscores the degree to which the community may have overlooked organosodium chemistry. That said, the full advantages of NaDA will take time to emerge.

Regioselectivities

The selectivities in Charts 1–3 are singly or doubly ortho unless otherwise indicated by arrows. This story is not so simple, however. The issue of regiochemical equilibration in ortholithiations has surfaced previously,²⁶ been studied mechanistically,²⁷ and emerges again here. Explicit kinetic versus thermodynamic control was documented for arene **13** (eq 3). However, we cannot rule out the possibility that many arylsodiums equilibrate rapidly; kinetic versus thermodynamic preferences remain unresolved. This ambiguity is more pervasive than researchers may realize in many studies of regioselectivity. From reviewing

limited data, we suspect—it is more of a hunch than an observation—that isomerization may be more prevalent with NaDA than LDA.

Over the decades, practitioners of orthometalations have surveyed relative directing effects of arene substituents largely through internal competitions of ortho-, meta-, and para-disubstituted arenes **42**, **43**, and **44**, respectively.¹² Empirically observed fast versus slow metalations add to the story.



These experiments are well suited to researchers who want orthometalations to be predictable. However, there are latent approximations in using such disubstituted arenes because *inductive, resonance, steric, and chelation effects are not always restricted to the ortho position*. How do meta and para substituents influence the rates of ortho metalations? In short, the effects are additive and underdetermined in such seemingly simple regiochemical competitions. It is in this context that we have become enamored with the isotopic exchange studies of the transiently metalated substrates in Chart 3.^{24,25} Monosubstituted arenes present no such additivities, and observable meta and para exchanges reveal long-range effects that cannot be ignored. We should add that entirely regioselective orthometalations of arenes **27** and **29** tell us *nothing* about these long range effects and show only that the influence at the ortho position is large by comparison (dominant); the rate of benzene exchange provides a benchmark for the rates of meta and para metalation.

We discerned separate contributions at play: (1) PhCF₃ (**28**) shows a distribution suggesting that CF₃ exerts a dominantly inductive influence, as noted by Mulvey using *n*BuNa¹¹; (2) a comparison of the relative rates of benzene (**24**) and PhNMe₂ (**25**) reactions shows that anilines are *deactivated* toward metalation (even accounting for statistics), with the most marked inhibition occurring at the para position suggesting a destabilizing resonance effect; and (3) a comparison of PhNMe₂ (**25**) and PhNEt₂ (**26**) confirms that steric effects retard orthometalation, tacitly promoting meta substitution. The conclusions that should surprise few are as follows: resonance effects inhibit ortho and para metalation; inductive effects promote ortho, meta, and para metalation in that order; steric effects inhibit only orthometalation; and chelation (substituent coordination to sodium) promotes only orthometalation.

Decompositions

There were, of course, a few failures (see Chart 4). Benzyne formation poses a problem in some cases (unless it is the targeted outcome).²⁸ The stabilized ortho-halo arylsodiums derived from most substrates in Chart 1 illustrate that elimination to form benzyne is not a chronic problem. In several cases, we saw limited darkening of the solutions that seemed to accompany decomposition, but the NMR spectra of the arylsodiums and successful deuterations revealed no major problems.

Although the failures in Chart 4 could stem from benzyne formation, we cannot exclude $[\text{Ar}-\text{Br}-\text{NR}_2]^-$ adducts,²⁹ electron-transfer-based reductions,³⁰ or migration (halogen dancing).³¹ One cannot help but notice bromoarenes appear to be problematic. Arenes **38–40** share a 3-halopyridine motif that may present special problems in contrast to the successful 2-halo arene metalations in Chart 1; enhanced electrophilicity may be the cause. Nucleophilic addition to pyridines, particularly self-condensation,³² is a problem we hoped to avoid.

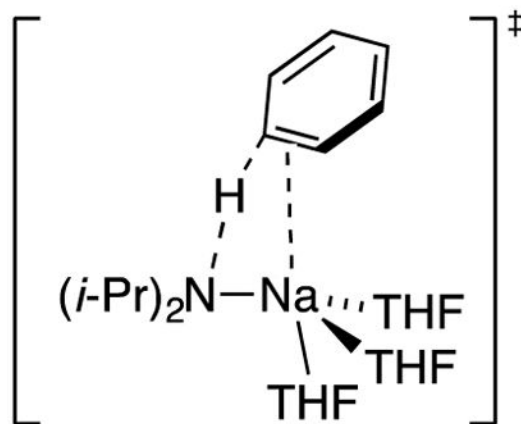
The CF_3 substituent seems particularly sensitive to destruction,³³ possibly owing to the formation of benzocyclopropane as reported by Billups.^{33b} Interestingly, PhCF_3 should be highly sensitive to decomposition, but NaDA-mediated isotopic exchange was readily achieved. Several doubly activated forms including **14** and **16** showed darkening but no direct evidence of destruction.

Oxazoline **41** appears to undergo facile elimination of the saturated heterocycle backbone, which often elicits the use of 4,4-dimethylated analog **29**. We are the only group to report the LDA-mediated orthometalation of **41**.³⁴ Suspecting that this result might be erroneous, we repeated the metalation and confirmed our mistake (one likely caused by inadequate supervision).³⁴ Nonetheless, alkylolithiums and lithium 2,2,6,6-tetramethylpiperidide orthometalate **41** without competing decomposition.^{35,36}

Mechanisms

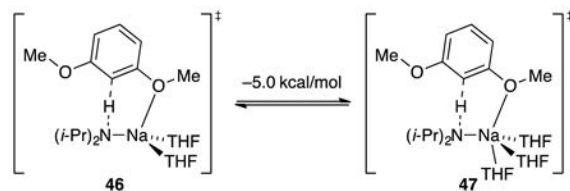
All rate studies of observable metalations of **20** and **21** as well as of isotopic exchange via fleeting anions derived from **24–30** show approximately half-order dependencies on NaDA consistent with monomer-based metalations. Plots of rate versus THF concentration showing non-zero intercepts and linear dependencies on THF concentration are consistent with di- and trisolvated monomers, respectively.¹⁸ Minor THF dependencies could be ascribed to medium effects, but the absence of dependence in some cases (see Figure 8) and striking dependence in others (see Figures 5 and 7) argue strongly for primary shell solvation. We add that secondary-shell effects are generally small when using *lithium* bases.^{18,37} We can glean some insights about substituent dependencies by noting the relative contributions of the two solvation states.

The metalation of benzene, a cornerstone of any discussion of arene metalation, occurs via the trisolvated-monomer-based mechanism shown by density functional theory (DFT) computations³⁸ to be **45**. The slight upward curvature in the plot in Figure 5 suggests a contributing tetrasolvate. Although DFT data are unsupportive, we are reluctant to dismiss such a mechanism because we have found transition states based on five- and even six-coordinate sodiums to be computationally viable in other instances.^{10c}

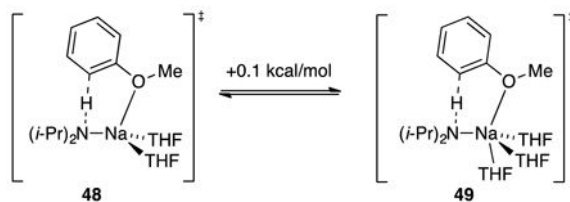


45

Metallations of **20** and **21** with meta-disposed methoxy moieties yield a mixture of di- and trisolvates consistent with encroaching steric demand. DFT computations show discrete MeO–Na interactions in both **46** and **47** and predict a distinct preference for trisolvation (eq 10) that is *not* borne out experimentally (see Figure 2). Analogous studies of *n*-butyllithium/*N,N,N,N*-tetramethylethylenediamine-mediated metallations showed no experimental or computational evidence of methoxy-lithium contacts. Anisole, a less congested variant of **20** and **21**, shows MeO–Na contacts and no significant preference for the di- vs. trisolvate experimentally or computationally (eq 11). The somewhat baffling quantitative difference in eqs 10 and 11 was explored extensively, but no obvious explanation was found.

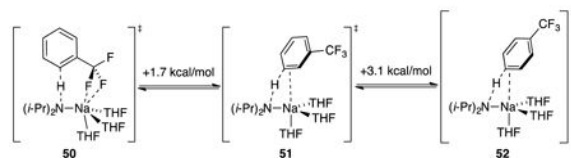


(10)



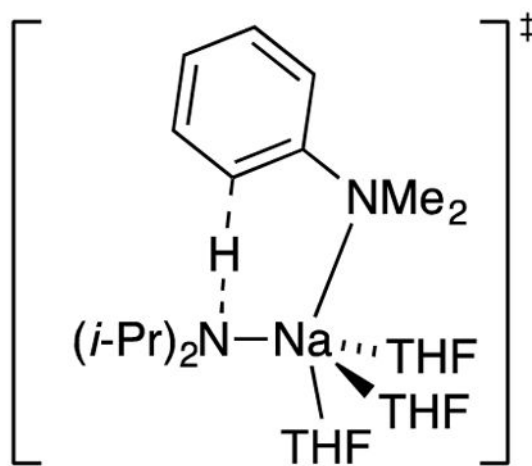
(11)

PhCF₃ behaves as an inductively activated benzene, facilitating metalations at all positions. Orthometalation represents a potential battle of steric inhibition versus activation through induction and Na–F interaction (chelation). DFT computations support such an interaction (**50**), but the resulting regioselectivity suggests that it cannot be highly stabilizing (eq 12).



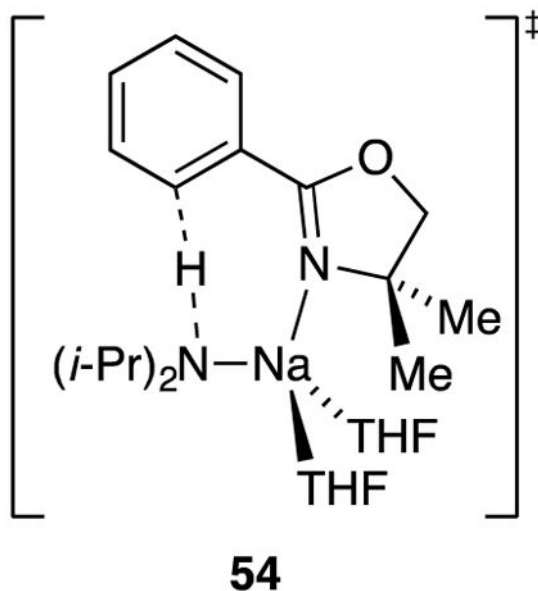
(12)

Metalations of anilines **25** and **26** are especially interesting. Anilines are notoriously poor directing groups, a fact readily ascribed to both prominent steric effects and the weak Lewis basicity of the dimethylamino moiety.¹² Although early studies using alkylsodiums suggest that anilines are acidic relative to benzene,² we found that both **25** and **26** metalate more slowly than benzene. DFT computations of orthometalation (**53**) show evidence of an N–Na contact, but it could merely reflect the minimization of steric effects. The de facto preference for meta metalation results from inhibited ortho and para metalation. Isotopic exchange of the benzene-like meta position occurs by di- and trisolvated monomers in contrast to the absence of disolvated-monomer-based metalation of benzene and gives us pause.

**53**

Oxazoline **29** appears to be a prime candidate for a chelation-directed orthometalation, which is implicated by high rates and a dominant disolvated-monomer-based pathway. Previous studies of the lithium analog suggest that the N–Li contact is preferred relative to the O–Li contact.^{39,40} Indeed, DFT computations show a >6 kcal/mol preference for the N–Na interaction shown in **54** despite the steric demands imparted by the methyl moieties. The proton transfer in transition structure **54** displays significant distortion, with the arene C–H

bond deviating 17° degrees out of the benzene plane accompanied by 19° rotation of the oxazoline moiety relative to the benzene fragment. This potentially strong directing group appears to be laboring to achieve optimal alignment.



Conclusion

NaDA-mediated metalations of arenes are much faster than those with LDA. However, time will tell whether investigators facing specific challenges will find such accelerations advantageous. That NaDA is trivial to prepare and handle ought to bolster its synthetic appeal. We also suspect that reactions of the resulting arylsodiums are ripe for development. Metathesis with other metal salts such as copper chloride or zinc chloride for subsequent couplings will occur under “salt-free” conditions given the insolubility of NaCl.^{41,42} In anticipation of such interest, we began studying the solution structures of the arylsodiums generated herein. Thinking that the task would be easy, we discovered it is a research project in its own right. For now, we can say that NaDA-mediated metalations of arenes generally work well and are mechanistically tractable.

Experimental

IR spectroscopic analyses

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 NaDA (60.4 mg, 0.49 mmol) in THF/hexane (4.9 mL) and cooled in a dry ice–acetone bath prepared with fresh acetone. After recording a background spectrum, a stock

solution of arene **20** (100 μ L, 0.049 mmol) was added with stirring. For the most rapid reactions, IR spectra were recorded every 6 s with monitoring of the absorbance at 1493 cm^{-1} over the course of the reaction.

NMR Spectroscopy

NMR samples for reaction monitoring were routinely prepared using stock solutions of NaDA and flame-sealed under partial vacuum. DMEA-free solutions of NaDA with added ligands used DMEA-free crystallized NaDA. Standard ^1H , ^2H , and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer at 500, 76.7, and 125.7 MHz, respectively. The ^1H , ^2H , and ^{13}C resonances were referenced to the $\text{C}\text{H}_2\text{O}$ resonance (3.58 ppm), $\text{C}\text{D}(\text{H})\text{O}$ resonance (3.58 ppm), and CH_2O resonance (67.57 ppm) of THF at -80°C , respectively.

DFT Computations

DFT calculations were carried out at the B3LYP/6–31G(d) level with single-point calculations at the MP2 level of theory.³⁸ Transition structures each had a single negative frequency.

Arene Metalations: Method A

A representative reaction was carried out as follows: Sodium dispersion in toluene (3.0 mL, 35 mmol) in a 15 mL pear-shaped flask was washed three times with DMEA (2.0 mL each) using a syringe to remove of the supernatants. A final aliquot of DMEA was added (3.6 mL) followed by diisopropylamine (1.05 mL, 7.5 mmol). After cooling to 0°C , isoprene (380 μ L, 3.75 mmol) was added. The solution was allowed to warm to rt over the course of 20 minutes, after which the stirring was halted and insoluble materials were allowed to settle providing a yellow supernatant. A dried vial was charged with this stock solution (2.9 mL, 4.4 mmol), to which THF (5.0 mL) was added and cooled to -78°C . Neat 1,2-dichlorobenzene (382 μ L, 3.4 mmol) was added with stirring for 30 sec and subsequently quenched with 1.00 mL MeOD. After warming to rt, the reaction mixture was diluted with water and pentane. The organic layer was washed with water (4×5 mL), dried over sodium sulfate, and concentrated. The crude product was chromatographed in neat pentane ($R_f = 0.7$) to provide 1,2-dichlorobenzene (270 mg, 55% mass recovery) with 80% deuteration at the ortho position. The extent and regiochemistry of proton loss was taken to represent the metalation event.

Arene Metalations: Method B

A representative reaction was carried out as follows: A dried vial flushed with argon was sequentially charged with solid NaDA (49 mg, 0.400 mmol) and THF (1.00 mL) and cooled to -78°C . Neat 1,2-dichlorobenzene (42 μ L, 0.38 mmol) was added with stirring for 10 s and subsequently quenched with 500 μ L MeOD. Neat cyclohexene (100 μ L) was added to the flask as an internal standard. After the sample was warmed to rt, a portion was transferred to an NMR tube for analysis as noted above.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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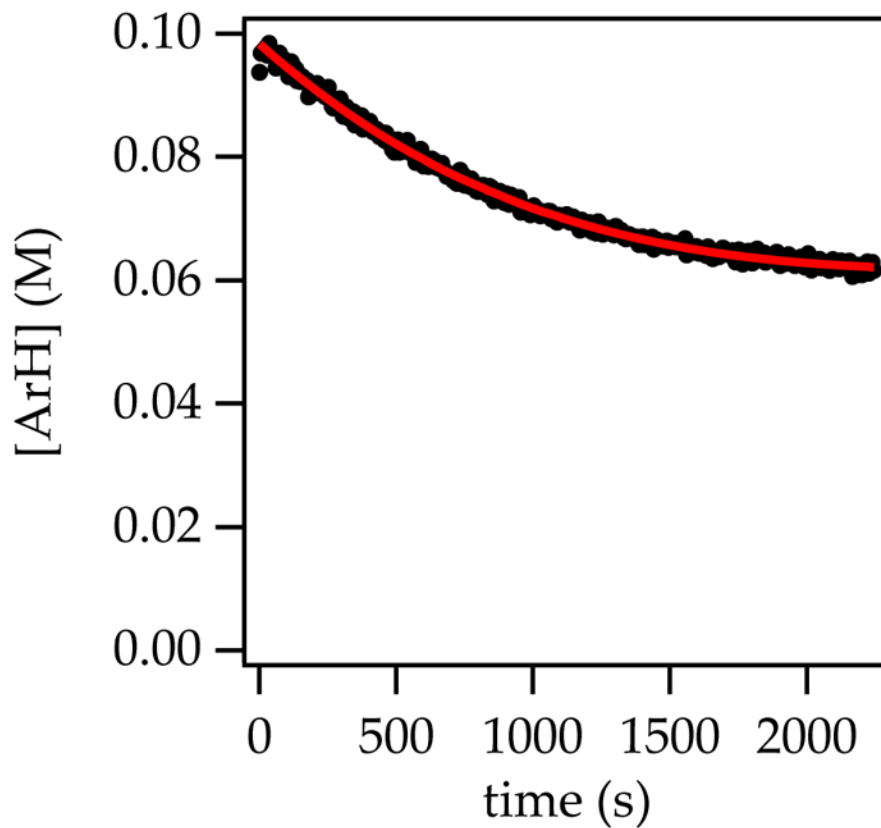


Figure 1.

Plot of 1,3-dimethoxybenzene (**20**, ArH) concentration versus time for stoichiometric orthometalation with 0.10 M NaDA in 5.83 M THF/hexane at -78 °C. The curve depicts an unweighted least-squares fit to the function^{18,21} $[\text{ArH}] = \{[\text{ArH}]_s^{1-n} + k(n-1)t\}^{1/(1-n)} + [\text{ArH}]_\infty$; $[\text{ArH}]_s = 0.0368 \pm 0.0004$; $n = 0.71 \pm 0.03$; $k = (4.1 \pm 0.4) \times 10^{-4}$; $[\text{ArH}]_\infty = 0.0616 \pm 0.0003$. The deviation from 1.5-order behavior (first order in arene and one-half order in NaDA) is likely due to mild autocatalysis.

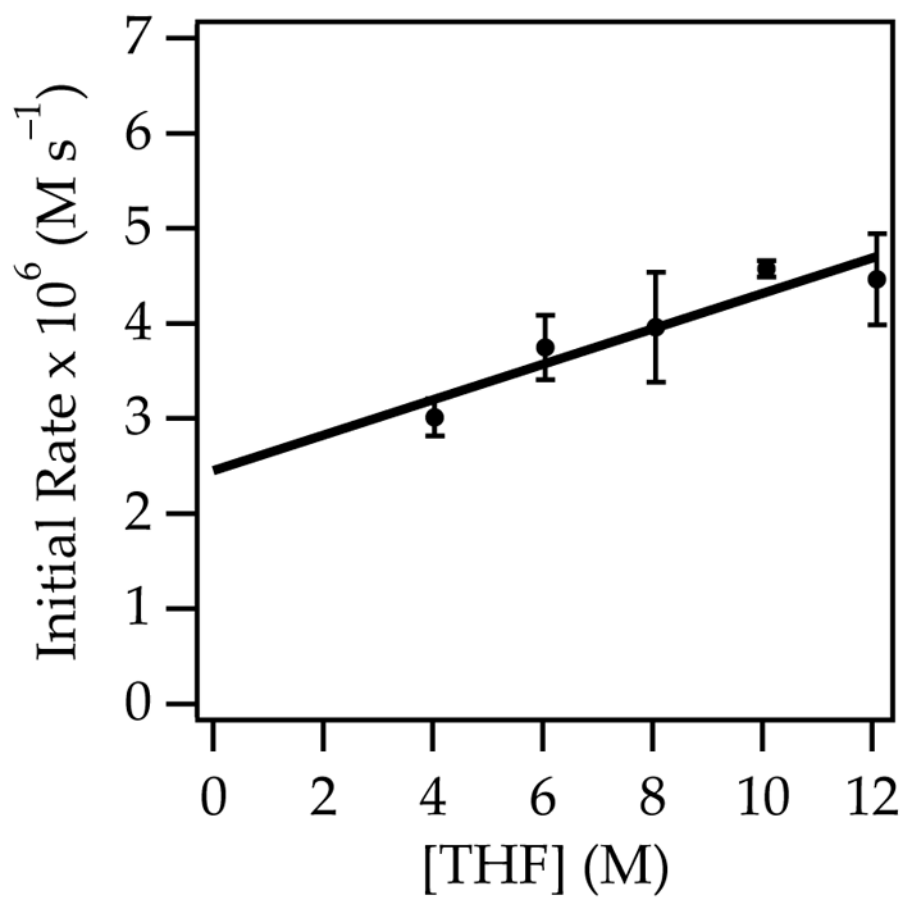


Figure 2. Plot of initial rate versus THF concentration for the orthometalation of 0.010 M 1,3-dimethoxybenzene (**20**) with 0.10 M NaDA at -78 °C. The curve depicts an unweighted least-squares fit to the function $f(x) = ax + b$: $a = 0.19 \pm 0.04$; $b = 2.5 \pm 0.03$.

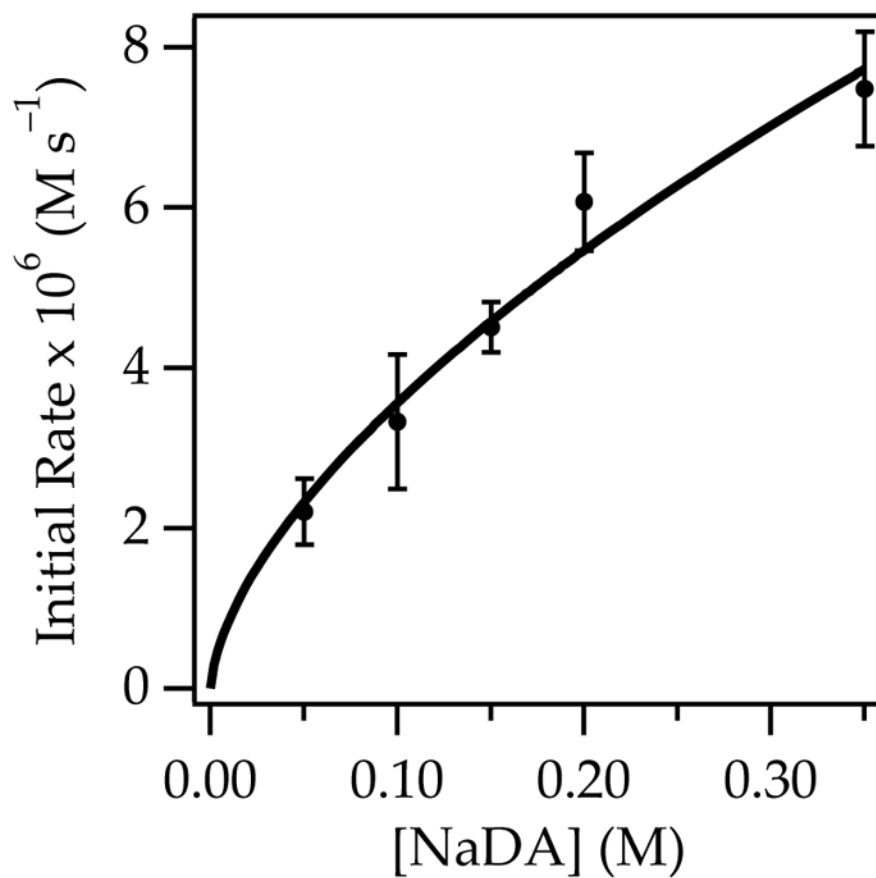


Figure 3. Plot of initial rate versus NaDA concentration for the orthometalation of 0.010 M 1,3-dimethoxybenzene in 6.0 M THF/hexane at -78 °C. The curve depicts an unweighted least-squares fit to the function $f(x) = ax^b$: $a = 15 \pm 2$; $b = 0.62 \pm 0.07$.

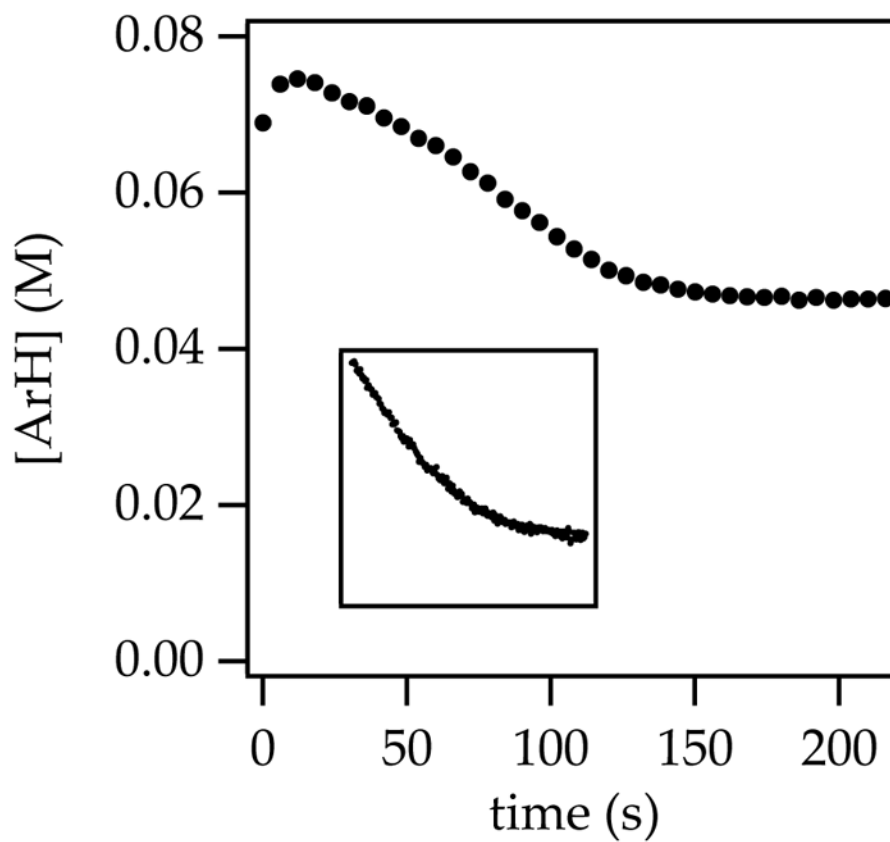


Figure 4. Plot of 1,2,4-trimethoxybenzene (**21**, ArH) concentration versus time for the metalation of 0.080 M ArH with 0.10 M NaDA in neat THF at $-78\text{ }^{\circ}\text{C}$. Inset: plot of arene concentration versus time (0–1200 s) for the metalation of low concentrations (0.010 M) of ArH with 0.10 M NaDA in neat THF at $-78\text{ }^{\circ}\text{C}$.

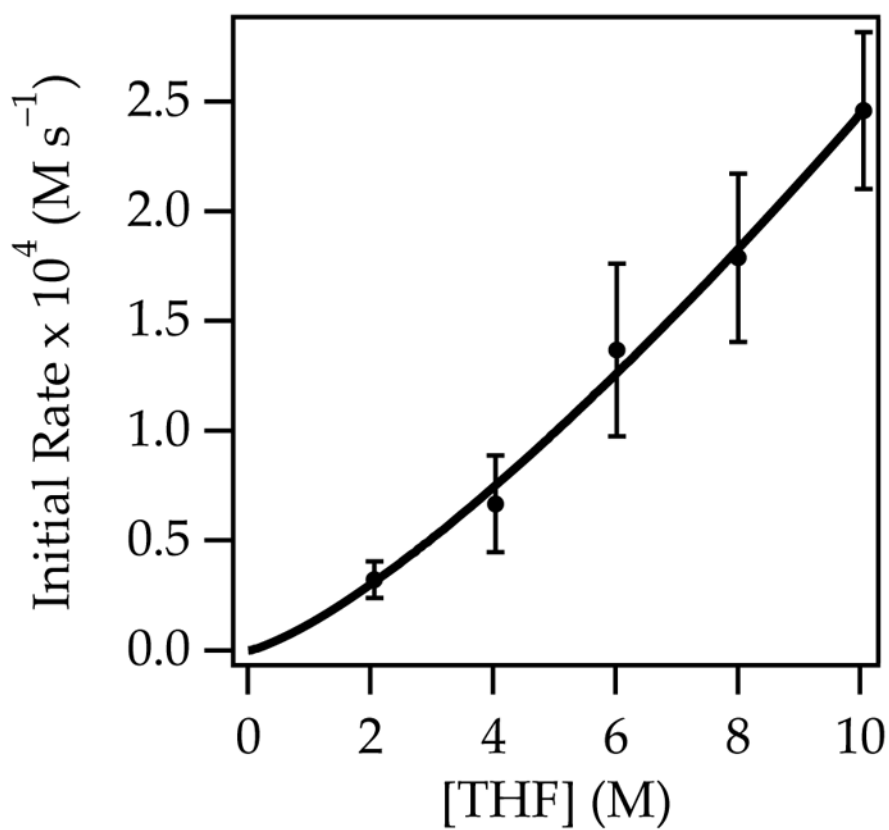


Figure 5. Plot of initial rate versus THF concentration for the isotopic exchange of 0.23 M benzene with 0.10 M NaDA and 1.04 M *i*-Pr₂ND in hexane cosolvent at 25 °C. The curve depicts an unweighted least-squares fit to the function $f(x) = ax^b$; $a = 0.12 \pm 0.02$; $b = 1.30 \pm 0.02$.

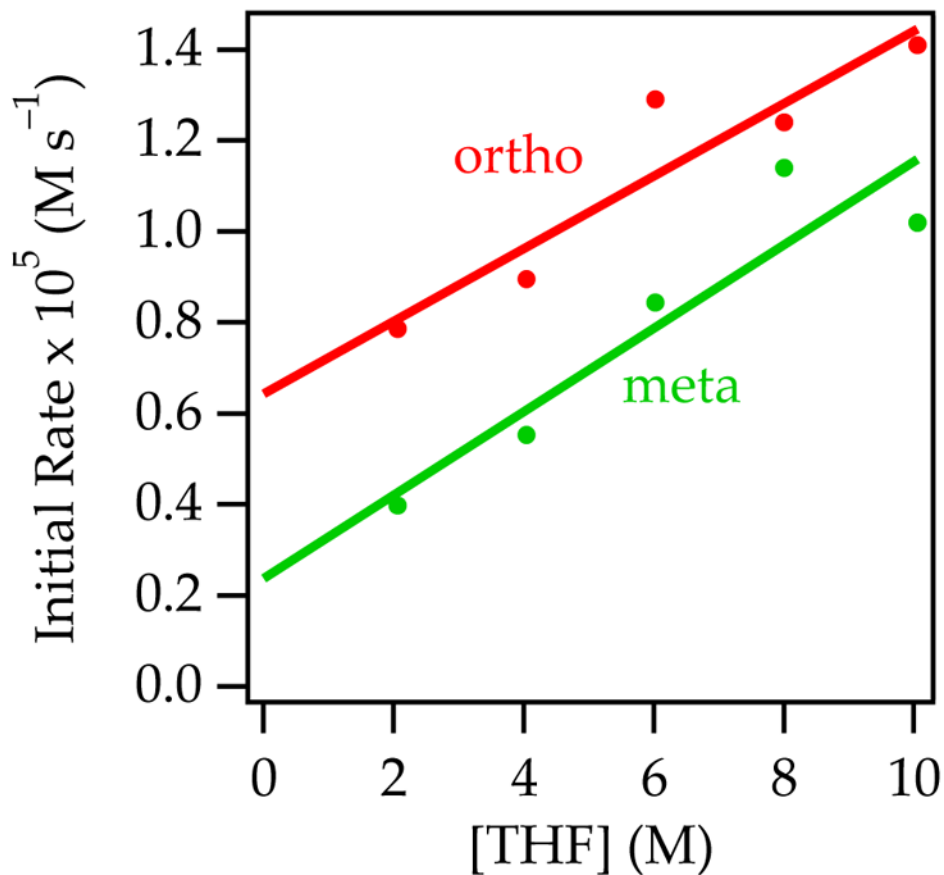


Figure 6. Plot of initial rate versus THF concentration for the isotopic exchange of 0.44 M *N,N*-dimethylaniline (**25**) with 0.10 M NaDA and 0.79 M *i*-Pr₂ND in hexane cosolvent at 25 °C. The curves depict unweighted least-squares fits to the function $f(x) = ax + b$: ortho: ($a = 0.08 \pm 0.02$; $b = 0.6 \pm 0.1$); meta: ($a = 0.09 \pm 0.02$; $b = 0.2 \pm 0.1$).

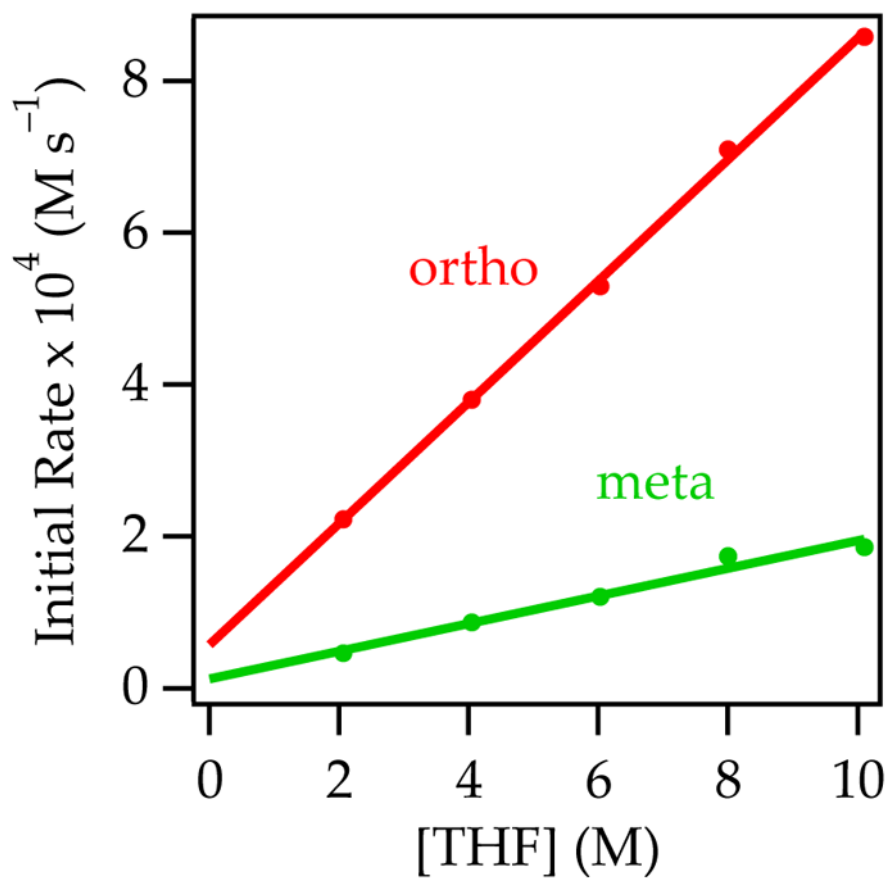


Figure 7. Plot of initial rate versus THF concentration for the isotopic exchange of 0.45 M α,α,α -trifluorotoluene (**28**) with 0.10 M NaDA and 0.79 M *i*-Pr₂ND in hexane cosolvent at -40 °C. The curves depict unweighted least-squares fits to the function $f(x) = ax + b$: ortho: ($a = 0.80 \pm 0.02$; $b = 0.6 \pm 0.1$); meta: ($a = 0.18 \pm 0.02$; $b = 0.1 \pm 0.1$).

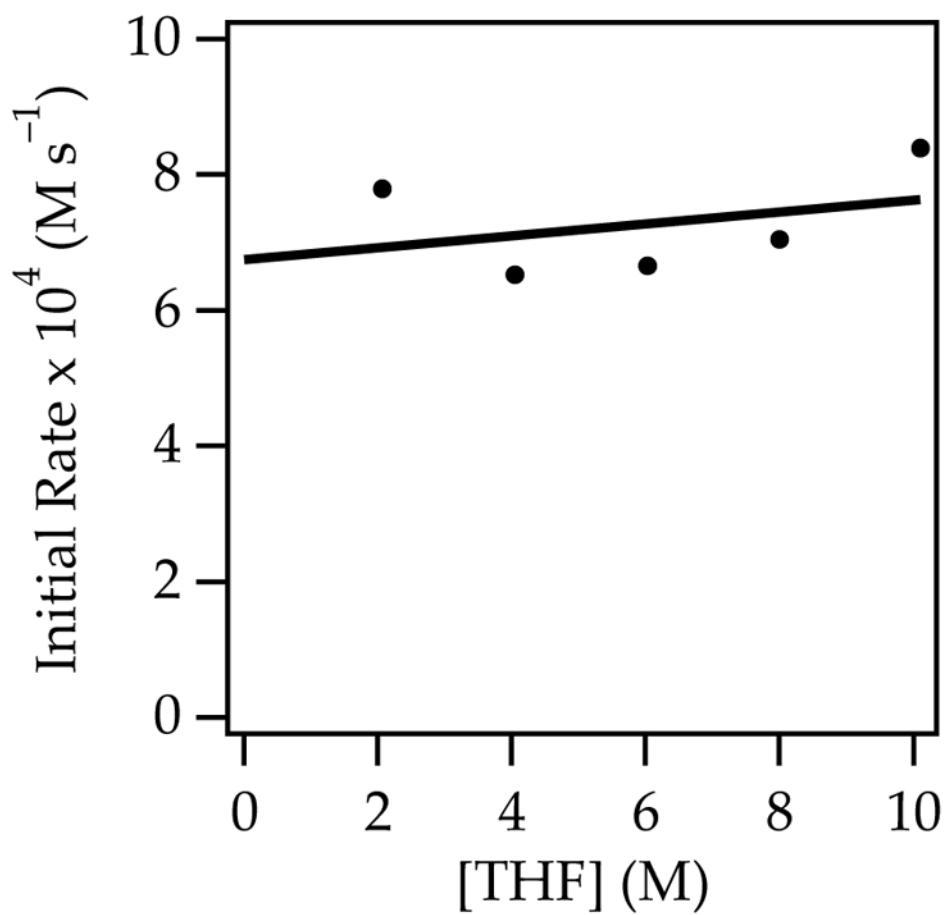


Figure 8. Plot of initial rate versus THF concentration for the ortho-selective isotopic exchange of 0.32 M 4,4-dimethyl-2-phenyl-2-oxazoline (**29**) with 0.10 M NaDA and 0.79 M *i*-Pr₂ND in hexane cosolvent at -40 °C. The curve depicts an unweighted least-squares fit to the function $f(x) = ax + b$: $a = 0.09 \pm 0.1$; $b = 6.8 \pm 0.9$.

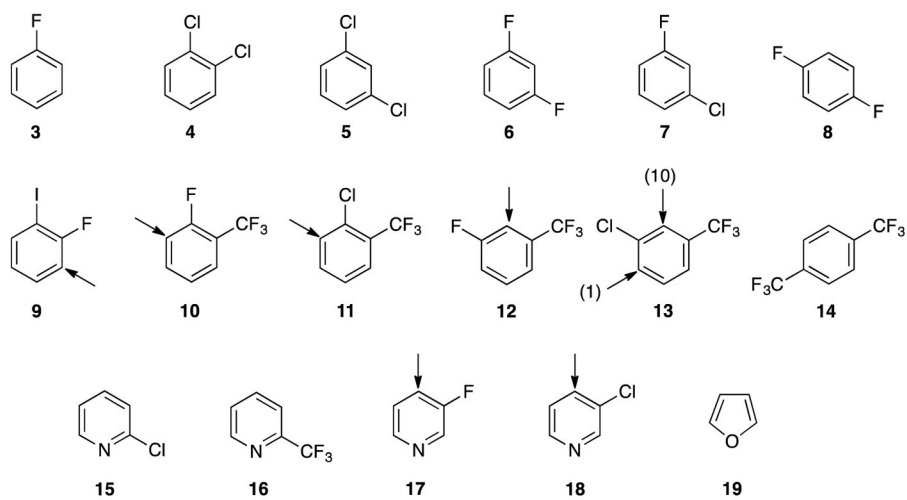


Chart 1.
Substrates that rapidly metalate.

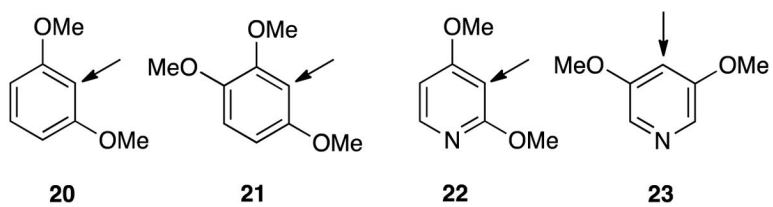


Chart 2.
Substrates that metalate at measurable rates.

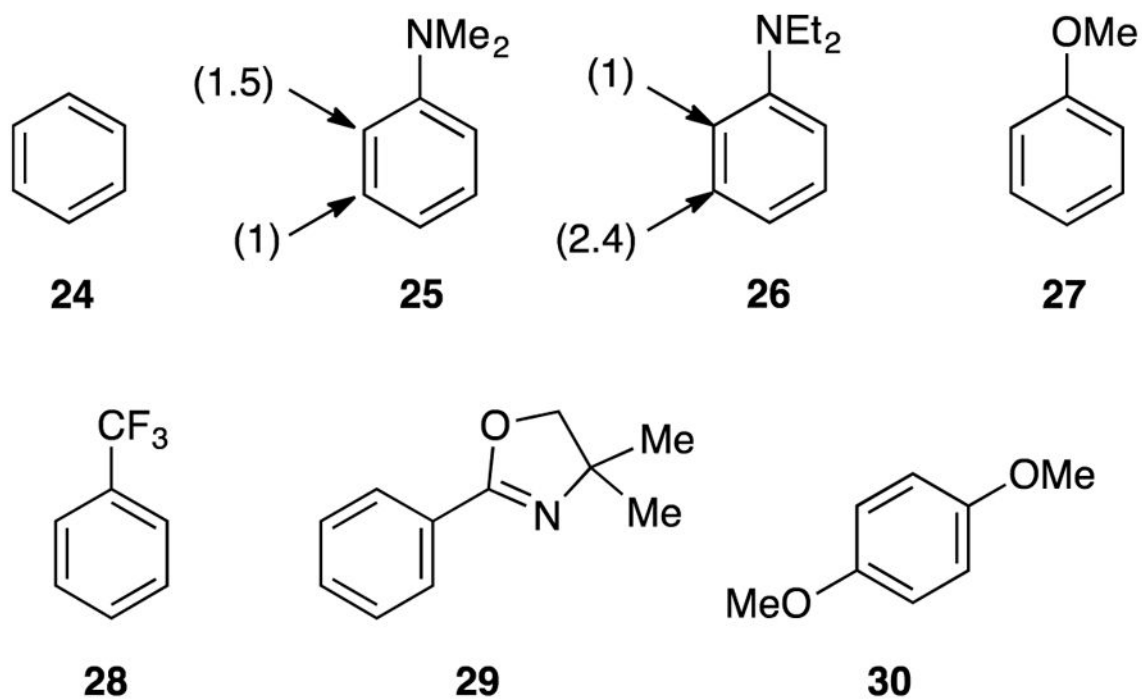


Chart 3.
Substrates that transiently metalate.

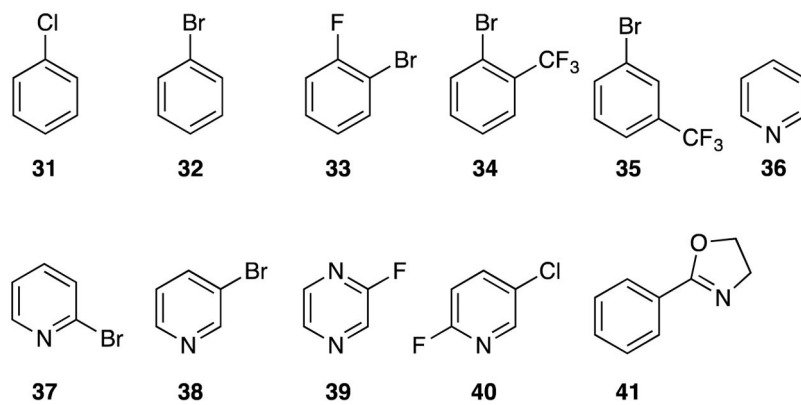


Chart 4.
Substrates that degrade on metalation.