

Supporting Information
for

Rev

Ortholithiation of Anisole by *n*-BuLi-TMEDA:
Reaction via Disolvated Dimers.

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EXPERIMENTAL SECTION

General Reagents and Solvents. Anisole (Aldrich) was vacuum transferred from a purple solution containing sodium benzophenone ketyl. Anisole-d₈ (Aldrich) was used without further purification. Pentane (Fisher) was distilled from a blue solution containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. Chlorotrimethylsilane (TMSCl, Aldrich) was freshly distilled from calcium hydride (Fisher) under nitrogen. Triethylamine (NEt₃, Fisher) was vacuum transferred from a blue solution of sodium benzophenone ketyl. The TMEDA was purchased from Aldrich and purified as described below. Other reagents were purchased from Aldrich or Fisher.

Purification of TMEDA. A 3 liter round bottom flask fitted with a stir bar was charged with 1500 mL of reagent grade methanol and 500 mL of TMEDA. The reaction was cooled in an ice bath, and 548 mL of concentrated hydrochloric acid were added slowly over 1.5 hr. An additional 600 mL of methanol were added, and the mixture was placed in a -40 °C freezer overnight. The solid was collected on a Buchner funnel and then resuspended in 1500 mL of refluxing methanol. Water (450 mL) was added step-wise until the solution became homogeneous. The mixture was allowed to cool to room temperature for two hours and was then placed in a -40 °C freezer overnight. The solid was collected again collected on a Buchner funnel and recrystallized once more from 1500 mL of methanol and 350 mL of water. The white crystalline solid was collected on a Buchner funnel and dried under a full vacuum for three hours. The free base of TMEDA was regenerated by adding 500 g of solid potassium hydroxide to the hydrochloride salt. After sufficient mixing, the liquid was decanted off and dried over fresh potassium hydroxide. The solution was again decanted and further dried sequentially with solid calcium hydride and KH in mineral oil. The liquid was vacuum transferred onto sodium and benzophenone. The resulting purple solution was vacuum transferred onto and stored over sodium-lead alloy. The TMEDA was freshly vacuum transferred immediately prior to use.

Purification of *n*-BuLi. A 300 mL Schlenk flask fitted with a stir bar was charged with 100 mL of a 1.6 M solution of *n*-BuLi in hexane via a cannula. The solvent was removed under full vacuum with warming in a water bath (50 °C) for two hours. Freshly distilled pentane (35 to 40 mL) was added, and the solution was titrated using diphenylacetic acid (Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879) to ensure that the molarity of the resulting solution is between 3.0 and 3.2 M. The solution was frozen solid in liquid nitrogen and then placed in a -94 °C freezer for ≥72 hr. The resulting suspension of crystals was placed in a -78 °C dry ice/acetone bath, and the solvent was decanted with a syringe fitted with a blunt

16 gauge needle. The crystals that remained were allowed to melt at room temperature and were again recrystallized from a 3.0-3.2 M pentane solution. The resulting crystals were allowed to melt at room temperature and were diluted with freshly distilled pentane to the desired molarity (typically 1.5-2.5 M) as measured by repeated titration. This solution was then used as described below.

Determination of the Rate Constants. Each rate constant was determined by quenching ten separate reaction vials as a function of time as described for the following representative procedure: Ten oven-dried, nitrogen-flushed 5 mL serum vials (Kimble) fitted with rubber septa and stir bars were charged sequentially with TMEDA (302 μ L, 2.0 mmol), pentane (553 μ L), and *n*-BuLi (125 μ L, 0.30 mmol, 2.40 M) at 0 °C. A stock solution of substrate was prepared by dissolving anisole, **1**, (109 μ L, 1.00 mmol) and dodecane (125 μ L, 0.55 mmol) in 2.0 mL of pentane under nitrogen. A second stock solution was prepared by dissolving TMSCl (3.81 mL, 30 mmol) and NEt₃ (4.18 mL, 30 mmol) in 50 mL of pentane. (The NEt₃ precipitates the residual HCl.) The reactions were initiated by adding aliquots of the anisole pentane solution (20 μ L, 0.01 mmol of anisole) to each vial. The reactions were quenched at varying times (3-120 minutes) by adding aliquots of the TMSCl/NEt₃ solution (1 mL, 0.60 mmol of TMSCl) and allowing the reactions to warm to room temperature for 30 minutes. Water (2 mL) was added to each vial and, after complete mixing, the organic layer was removed for direct GC analysis. Control experiments showed no significant partitioning of the anisole, 2-(trimethylsilyl)anisole, and dodecane.

Data Analysis: Gas Chromatography was performed on a Hewlett Packard 5890 Series II Gas Chromatograph fitted with a Hewlett Packard 6890 Series Autosampler Controller and a Hewlett Packard 3396 Series III Integrator. The data were analyzed on an IBM 466DX2/D computer running the Scientist™ software package from MicroMath® Scientific Software, Salt Lake City, Utah. All starting material and product intensities were normalized using the dodecane internal standard prior to least squares analysis.

The disappearance of anisole ("A") was fit to the expression

$$[A]/[A_0] = e^{-k_{\text{obsd}}t} \quad (1)$$

where [A] is the concentration of anisole (relative to the internal dodecane standard) at time "t" and [A₀] is the concentration of anisole at t = 0. The appearance of 2-(trimethylsilyl)anisole, **4**, ("P") was fit to the expression

$$[P] = [P_{\infty}](1 - e^{-k_{\text{obsd}}t}) \quad (2)$$

where $[P]$ is the measured concentration of product at time "t", $[P_{\infty}]$ is the concentration of product at $t = \infty$. The measured values of k_{obsd} were equal to those determined according to eq 1 ($\pm 10\%$).

We evaluated a third equation for determining the pseudo first order rate constant of the form:

$$[A]/[A]_{t=0} = e^{-k_{\text{obs}}t} + b \quad (3)$$

where "b" is a measure of the amount of anisole remaining at $t = \infty$. The rate constants were not significantly different and the values of b were typically a positive number equal to about 5% of $[A_0]$. We report rate constants derived solely from equation 1 for the paper. A representative data analysis is illustrated in Figures 1 and 2.

Determination of the Kinetic Isotope Effect. Method A: The procedure described above was employed using deuterated anisole **1-d₈**. The reported value of k_D ($2.58 \pm 0.33 \times 10^{-5}$) is the average of 5 runs. The kinetic isotope effect is 20 ± 3 (Figure 3).

Determination of the Kinetic Isotope Effect. Method B: The rate for the disappearance of **1** and **1-d₈** were determined using a 1:1 mixture of **1** and **1-d₈**. Substrates **1** and **1-d₈** resolved by GC only up to three half-lives. (See Stratakis, M. *J. Org. Chem.* **1997**, *62*, 3024.) Although the reproducibility was poor, $k_H/k_D \geq 20$ in four independent runs.

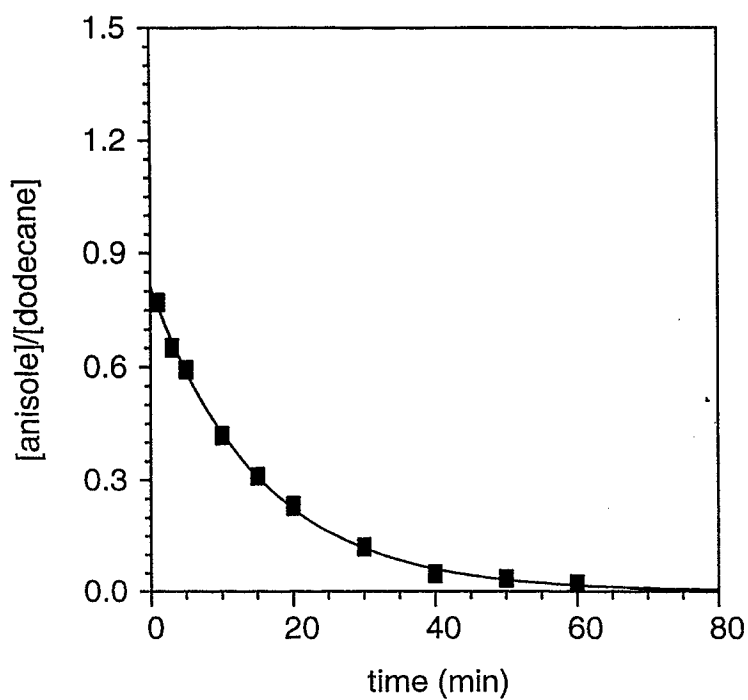


Figure 1. Plot of anisole concentration vs. time in pentane cosolvent at 0 °C. The initial concentrations of anisole, *n*-BuLi, and TMEDA were 0.004 M, 0.9 M, and 2.9 M, respectively. The rate constant derived from an unweighted least-squares fit of eq 1 is $1.08 \pm 0.02 \times 10^{-3} \text{ sec}^{-1}$.

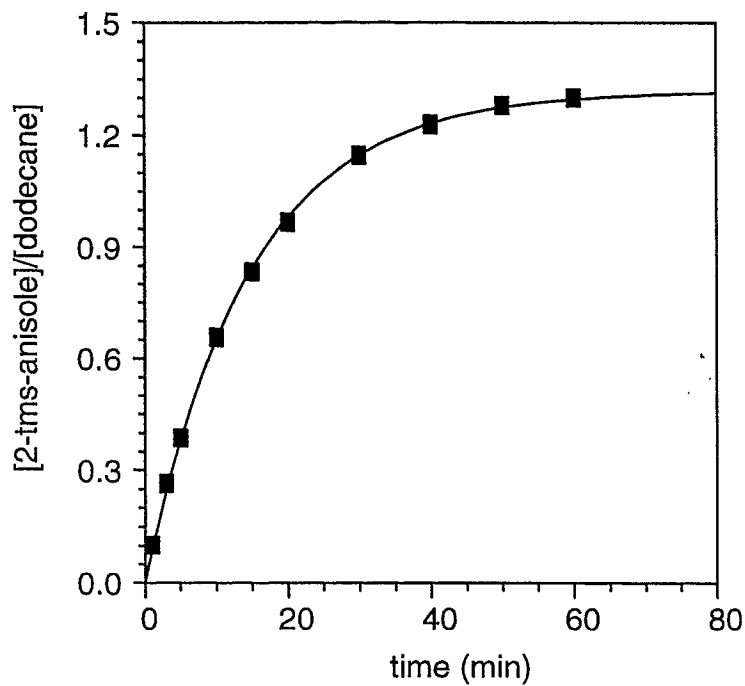


Figure 2. Plot of the 2-(trimethylsilyl)anisole concentration vs. time in pentane cosolvent at 0 °C. The initial concentrations of anisole, *n*-BuLi, and TMEDA were 0.004 M, 0.9 M, and 2.9 M, respectively. The rate constant derived from an unweighted least-squares fit to eq 2 is $1.14 \pm 0.02 \times 10^{-3} \text{ sec}^{-1}$.

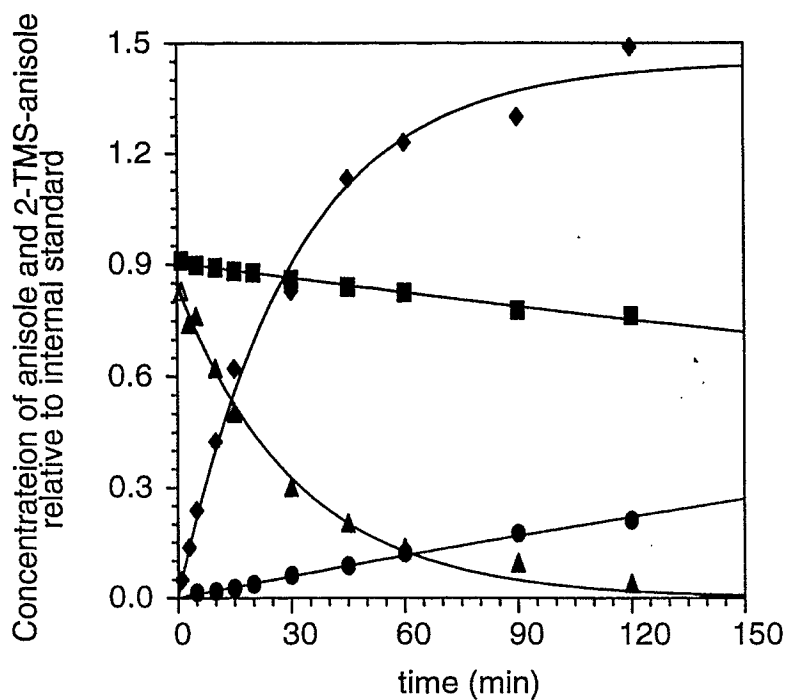


Figure 3. Plots of the concentrations of anisole- d_0 (**1**, ▲), anisole- d_8 (**1-d₈**, ■), 2-(trimethylsilyl)anisole (**4**, ◆), and 2-(trimethylsilyl)anisole- d_7 (**4-d₇**, ●) as a function of time in pentane cosolvent at 0°C. The initial concentrations of substrate (**1** or **1-d₈**), *n*-BuLi, and TMEDA were 0.01 M, 0.3 M, and 2.3 M, respectively. The rate constants were determined according to eqs 1 and 2 are as follows: **1**, $5.30 \pm 0.30 \times 10^{-4} \text{ sec}^{-1}$; **4**, $5.45 \pm 0.45 \times 10^{-4} \text{ sec}^{-1}$; **1-d₈**, $2.55 \pm 0.11 \times 10^{-5} \text{ sec}^{-1}$; **4-d₇**, $2.47 \pm 0.04 \times 10^{-5} \text{ sec}^{-1}$. To determine k_{obsd} for formation of **4d**, we set $[P_{\infty}] = 1.35$ based upon other (higher conversion) runs.

Table 1: k_{obsd} for the metalation of anisole by *n*-BuLi at various TMEDA concentrations.^a

Entry #	Excess ^b TMEDA (M)	k_{obsd} ($\times 10^{-4}$) (sec ⁻¹)	Average k_{obsd} ($\times 10^{-4}$) (sec ⁻¹)
1	1.0	4.42, 3.93, 4.68	4.34 \pm 0.38
2	2.0	4.77, 4.68	4.73 \pm 0.06
3	3.0	5.28, 5.02	5.15 \pm 0.18
4	4.0	5.67, 5.75	5.71 \pm 0.06
5	5.2	5.97, 6.57, 5.80	6.11 \pm 0.40

^aAll reactions were run using 0.3 M *n*-BuLi and 0.01 M anisole.

^bConcentration of free (unbound) TMEDA.

Table II. k_{obsd} for the metalation of anisole by *n*-BuLi/TMEDA at various *n*-BuLi concentrations.^a

Run #	<i>n</i> -BuLi (M)	k_{obsd} ($\times 10^{-4}$) (sec ⁻¹)
1	0.050	0.992
2	0.050	1.30
3	0.10	1.97
4	0.10	2.05
5	0.15	2.92
6	0.20	3.15
7	0.30	5.30
8	0.40	5.13
9	0.50	7.02
10	0.60	9.08
11	0.70	12.2
12	0.80	11.6
13	0.90	11.6
14	1.0	15.8
15	1.1	17.5
16	1.2	17.8

^aAll reactions were run using a 2.0 M excess of TMEDA and 0.004 M anisole.

Table III. k_{obsd} for the metalation of anisole by *n*-BuLi/TMEDA at various anisole concentrations.^a

Run #	anisole (M)	k_{obsd} ($\times 10^{-4}$) (sec ⁻¹)
1	0.0010	6.38
2	0.0020	6.90
3	0.0030	7.35
4	0.0040	7.60
5	0.0050	7.38
6	0.010	7.27
7	0.015	7.47
8	0.020	7.77

^aAll reactions were run using 0.46 M *n*-BuLi and a 2.0 M free (unbound) TMEDA.