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# Directed Ortho-Metalation of Dimethylarylamines

Michael Timmons

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TIMMONS



DIRECTED ORTHO-METALATION OF DIMETHYLARYLAMINES

A Thesis

Presented to

the Faculty of the Department of Chemistry

Western Kentucky University

Bowling Green, Kentucky

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Michael Douglas Timmons

December 2002

DIRECTED ORTHO-METALATION OF DIMETHYLARYLAMINES

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“What a long, strange trip its been...”  
Grateful Dead, 1970

## TABLE OF CONTENTS

<u>Chapter</u>	<u>Page</u>
I. INTRODUCTION .....	1
A. Background .....	1
B. Directed Metalation Mechanism .....	2
C. Alkylolithium Reagents .....	9
D. Size of Chelate Ring .....	11
E. Trapping/Derivatizing Agents .....	12
F. Aryl Substrates Containing Directing Metalation Groups .....	13
1. Anisole ( <b>1</b> ) .....	16
2. Aniline ( <b>2</b> ) .....	21
3. N,N-Dimethylaniline ( <b>3</b> ) .....	21
4. N,N-Dimethylbenzylamine ( <b>4</b> ) .....	22
5. N,N,N',N'-Tetramethyl-1,4-phenylenediamine ( <b>5</b> ) .....	23
6. 3-Methoxy-N,N-Dimethylaniline ( <b>6</b> ) .....	23
7. 3-Methoxy-N,N-Dimethylbenzylamine ( <b>7</b> ) .....	24
G. Tables of Literature Studies .....	24
II. EXPERIMENTAL .....	40
A. Reagents .....	40
B. Procedure for Metalations in n-Hexane and Cyclohexane .....	41
C. Procedure for Metalations in Diethyl Ether and Other Neat Solvents .....	41
D. Sampling Procedures .....	42
E. Determination of the Extent of Metalation.....	42
F. Instrumental Analysis.....	42
G. Isolation of TMS- Derivatives .....	43
H. Standardization of GC Spectra .....	44
I. Derivatives Prepared .....	45
1. 2-Trimethylsilyl-N,N-Dimethylaniline ( <b>8</b> ) .....	45
2. 2-Trimethylsilyl-N,N-Dimethylbenzylamine ( <b>9</b> ) .....	46
3. $\alpha$ -Trimethylsilyl-N,N-Dimethylbenzylamine ( <b>10</b> ).....	46
4. 2-TMS-N,N,N',N'-Tetramethyl-1,4-phenylenediamine ( <b>11</b> ) .....	47
5. 2-Trimethylsilyl-3-Methoxy-N,N-Dimethylaniline ( <b>12</b> ) .....	47
6. 2-Trimethylsilyl-3-Methoxy-N,N-Dimethylbenzylamine ( <b>13</b> ) .....	48
J. Summary of Selected Metalation Reactions .....	48

III. RESULTS AND DISCUSSION .....	57
A. Objectives .....	57
B. Background .....	58
C. Directed ortho-Metalation of N,N-Dimethylaniline (DMA) ( <b>3</b> ) .....	58
1. Solvent Experiments .....	58
a. Hydrocarbons .....	58
b. neat THF .....	63
c. neat MTBE .....	63
2. Temperature Experiments .....	63
3. Reactions with TMEDA .....	67
4. Reactions with THF .....	72
5. Reactions with (-)-Sparteine .....	73
6. Comparison of Literature Studies with Experimental Results .....	73
D. Directed ortho-Metalation of N,N-Dimethylbenzylamine (DMBA) ( <b>4</b> ) .....	74
1. Solvent Experiments .....	75
a. Hydrocarbons .....	75
b. neat THF .....	77
c. neat TMEDA .....	80
d. neat Diethyl Ether .....	80
e. neat MTBE .....	80
2. Temperature Experiments .....	81
3. Reactions with TMEDA .....	83
4. Reactions with MTBE .....	87
5. Reactions with THF .....	90
6. Reactions with (-)-Sparteine .....	90
7. Comparison of Literature Studies with Experimental Results .....	90
E. Directed ortho-Metalation of N,N,N',N'-Tetramethyl-1,4-phenylenediamine (1,4-TMPDA) ( <b>5</b> ) .....	92
1. Reactions with TMEDA .....	93
2. Comparison of Literature Studies with Experimental Results .....	96
F. Directed ortho-Metalation of 3-Methoxy-N,N-Dimethylaniline (3-MDMA) ( <b>6</b> ) .....	97
1. Reactions with TMEDA .....	98
2. Reactions in neat THF .....	99
3. Reactions in Diethyl Ether .....	100
4. Comparison of Literature Studies with Experimental Results .....	100
G. Directed ortho-Metalation of 3-Methoxy-N,N-Dimethylbenzylamine (3-MDMBA) ( <b>7</b> ) .....	101

1. Reactions with TMEDA .....	101
2. Reactions with MTBE .....	102
3. Comparison of Literature Studies with Experimental Results .....	103
VI. CONCLUSIONS .....	104
V. REFERENCES .....	107
VI. BIBLIOGRAPHY .....	114
VII. APPENDIXES .....	120
A. List of Abbreviations .....	121
B. NMR Spectra of Isolated Derivatives .....	122
1. <sup>1</sup> H NMR Spectra of <b><u>8</u></b> .....	122
2. <sup>13</sup> C NMR Spectra of <b><u>8</u></b> .....	123
3. <sup>1</sup> H NMR Spectra of <b><u>9</u></b> .....	124
4. <sup>13</sup> C NMR Spectra of <b><u>9</u></b> .....	125
5. <sup>1</sup> H NMR Spectra of <b><u>11</u></b> .....	126
6. <sup>13</sup> C NMR Spectra of <b><u>11</u></b> .....	127



## LIST OF FIGURES

<u>Figure</u>	<u>Page</u>
1. Proposed mechanistic scheme for the DoM reactions of n-BuLi with arylamines .....	3
2. n-BuLi dimer with coordinating amine-DMG featuring the agostic ortho-H interaction .....	6
3. The “overriding” base intermediate which involves direct insertion into the ortho- C-H bond without prior-coordination .....	7
4. Bis-coordination of 1,3-dimethoxybenzene .....	8
5. Coordinately-stabilized dimer structure of n-BuLi .....	10
6. N,N-Dimethylaniline coordinated with the n-butyllithium dimer illustrating the pseudo four-membered ring chelate interaction .....	12
7. N,N-Dimethylaniline product with ortho-trimethylsilyl group .....	13
8. Directed metalation relative ortho-directing priorities .....	15
9. Alkyl substrates .....	17
10. Opposing $\pi$ -resonance .....	19
11. Deactivating resonance structures for N,N-dimethylaniline .....	22
12. Resonance structures for N,N,N',N'-Tetramethyl-1,4-phenylenediamine .....	23
13. 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi vs. increments TMEDA at 25°C (30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol) .....	60
14. 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi with maximizing eq. TMEDA at 25°C (30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol) .....	62

15. 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi vs. increments TMEDA at various temperatures (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	65
16. Progress of DoM of 1.0 eq. DMA ( <b>3</b> ) with 1.0 eq. n-BuLi containing maximizing eq. TMEDA; variation of yield with temperature (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	66
17. Progress of DoM of 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi with various eq. TMEDA at 25°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	68
18. Progress of DoM of 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi with various eq. TMEDA at 45°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	69
19. Progress of DoM of 1.0 eq. DMA ( <b>3</b> ); 1.0 eq. n-BuLi with various eq. TMEDA at 60°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	71
20. 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi vs. increments TMEDA at 25°C (30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol) .....	76
21. 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi with maximizing eq. TMEDA at 25°C (30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol) .....	78
22. Metalation of 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi in various media at 25°C (30 mL solvent; 1.0 eq. = 0.04 mol) .....	79
23. Progress of DoM of 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi containing maximizing eq. TMEDA; variation of yield with temperature (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	82
24. Progress of DoM of 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi with various eq. TMEDA at 45°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	84
25. Progress of DoM of 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi with various eq. TMEDA at 60°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol) .....	86

26. Progress of DoM with 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi with various eq. MTBE at 25°C (30mL n-hexane; 1.0 eq. = 0.04 mol) .....	88
27. Progress of DoM with 1.0 eq. DMBA ( <b>4</b> ); 1.0 eq. n-BuLi with various eq. MTBE at 60°C (30mL n-hexane; 1.0 eq. = 0.04 mol) .....	89
28. Progress of DoM of 1.0 eq. 1,4-TMEDA ( <b>5</b> ); 1.0 eq. n-BuLi at various temperatures (30 mL cyclohexane; 1.0 eq. = 0.02 mol) .....	94
29. Comparison of DoM progress of 1.0 eq. DMA ( <b>3</b> ) and 1.0 eq. 1,4-TMPDA ( <b>5</b> ); 1.0 eq. n-BuLi at various temperatures in 30 mL cyclohexane (1 eq. = 0.02 mol 1,4-TMPDA, 1 eq. = 0.04 mol DMA) .....	95
30. <sup>1</sup> H NMR spectra of <b>8</b> .....	122
31. <sup>13</sup> C NMR spectra of <b>8</b> .....	123
32. <sup>1</sup> H NMR spectra of <b>9</b> .....	124
33. <sup>13</sup> C NMR spectra of <b>9</b> .....	125
34. <sup>1</sup> H NMR spectra of <b>11</b> .....	126
35. <sup>13</sup> C NMR spectra of <b>11</b> .....	127

## LIST OF TABLES

<u>Table</u>	<u>Page</u>
1. Lithiations of N,N-Dimethylaniline and its Homologs .....	25
2. Halogen Metal Exchange Reactions of N,N-Dimethylaniline and it's Homologs .....	30
3. Lithiations of N,N-Dimethylbenzylamine and its Homologs .....	31
4. Halogen Metal Exchange Reactions of N,N-Dimethylbenzylamine and it's Homologs .....	39
5. Relevant Retention Times of Aryl Substrates and Products .....	43
6. Calculated Correction Factors for TMS Products .....	44
7. Summary of Conditions and Yields for Selected Metalations of DMA ( <b>3</b> ) .....	49
8. Summary of Conditions and Yields for Selected Metalations of DMBA ( <b>4</b> ) .....	51
9. Summary of Conditions and Yields for Selected Metalations of 1,4-TMPDA ( <b>5</b> ) .....	55
10. Summary of Conditions and Yields for Selected Metalations of 3-MDMA ( <b>6</b> ) .....	55
11. Summary of Conditions and Yields for Selected Metalations of 3-MDMBA ( <b>7</b> ) .....	56
12. Failed Conditions for Metalation of DMA .....	63
13. Comparison of DMA Literature Studies with Experimental Results .....	74
14. Comparison of DMBA Literature Studies with Experimental Results .....	91
15. Comparison of 1,4-TMPDA Literature Studies with Experimental Results .....	97
16. DoM Reactions Conducted with 3-MDMA .....	99
17. Comparison of 3-MDMA Literature Studies with Experimental Results .....	100

18. DoM Reactions Conducted with 3-MDMBA .....	102
19. Comparison of 3-MDMBA Literature Studies with Experimental Results .....	103
20. List of Abbreviations .....	121

## DIRECTED ORTHO-METALATION OF DIMETHYLARYLAMINES

Michael Douglas Timmons

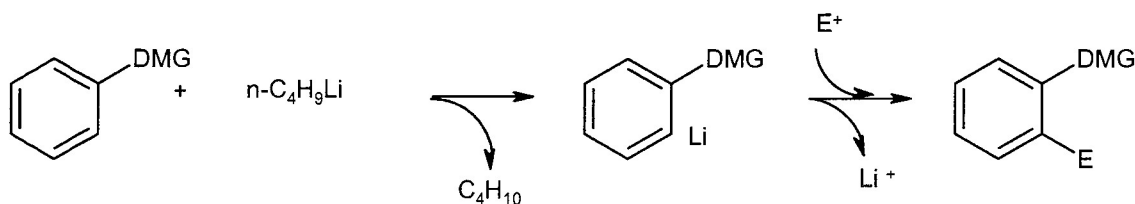
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Department of Chemistry

Western Kentucky University

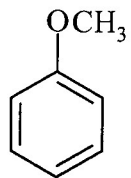
Site-specific product(s) from the reaction of benzene derivatives with various reagents is a need of researchers at numerous laboratories, particularly those in the pharmaceutical industry. Such derivatives can be synthesized directly, i.e., by substitution of a proton, using either of two procedures: electrophilic aromatic substitution (EAS) or directed ortho-metalation (DoM). Directed ortho-metalation (DoM) is an alternative aromatic substitution process initiated by organolithium reagents which provides regiospecific substitution exclusively at the ortho- position (equation).



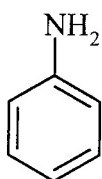
The focus of this study is to find hydrocarbon media that will permit the maximum extent of metalation of several dimethylarylamines. The dimethylamine-containing substituents constitute directing metalation groups (DMG's) for the various aryl systems investigated. Maximization of the extents of ortho-lithiation of dimethylaniline [DMG =  $-\text{N}(\text{CH}_3)_2$ ] and dimethylbenzylamine [DMG =  $-\text{CH}_2\text{N}(\text{CH}_3)_2$ ] have now been achieved using



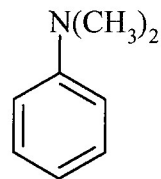
novel combinations of solvent, temperature and increments of catalyst. Studies of substituted dimethylanilines and dimethylbenzylamines containing a second DMG have yielded mixed results. Both metalation condition parameters as well as certain mechanistic aspects are altered by inclusion of a second DMG into these two parent systems.



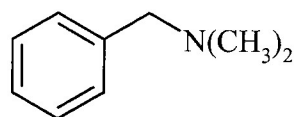
Anisole  
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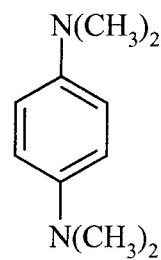
Aniline  
(2)



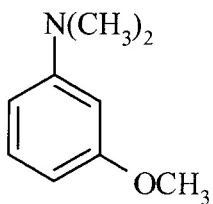
N,N-Dimethylaniline  
(DMA)  
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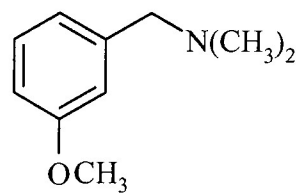
N,N-Dimethylbenzylamine  
(DMBA)  
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N,N,N',N'-Tetramethyl-1,4-phenylenediamine  
(1,4-TMPDA)  
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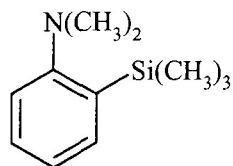


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(3-MDMA)  
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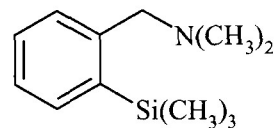


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(3-MDMBA)  
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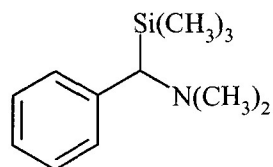
### Structures of Dimethylarylamine Substrates and Related Compounds



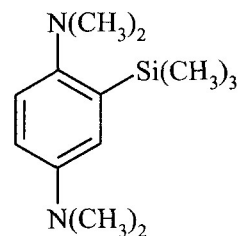
2-TMS-N,N-dimethylaniline  
(2-TMSDMA)  
**(8)**



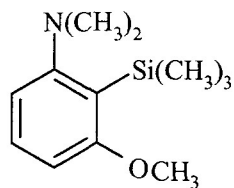
2-TMS-N,N-dimethylbenzylamine  
(2-TMSDMBA)  
**(9)**



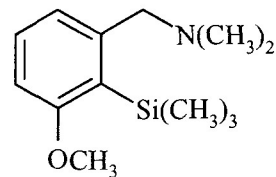
α-TMS-N,N-dimethylbenzylamine  
(α-TMSDMBA)  
**(10)**



2-TMS-N,N,N',N'-Tetramethyl-1,4-phenylenediamine  
(2-TMS-1,4-TMPDA)  
**(11)**



2-TMS-3-methoxy-N,N-dimethylaniline  
(2-TMS-3-MDMA)  
**(12)**



2-TMS-3-methoxy-N,N-dimethylbenzylamine  
(2-TMS-3-MDMBA)  
**(13)**

Structures of dimethylarylamine derivatives

## I. INTRODUCTION

### A. Background

The chemical industry, in particular the pharmaceutical industry, demands processes that can produce desired compounds in high yields with little or no secondary products and minimum amounts of unreacted starting materials. For regioselective reactions, desired products must be separated from their isomers and other by-products, which is both costly and time-consuming. Therefore, it is advantageous to produce a single product. However, there are few reactions that are specific enough to produce one product while still being cost effective, i.e., to exhibit “atom-economy.”<sup>1</sup>

The process of adding a substituent to a benzene ring is a valuable tool in organic synthesis.<sup>2</sup> Numerous pharmaceutical laboratories use this procedure to develop precursors for modern pharmaceuticals. There are two basic pathways used to obtain substituted aromatic rings, electrophilic aromatic substitution (EAS) and directed ortho-metalation (DoM). These are the only procedures that involve direct replacement of proton(s) on aromatic systems. All other aromatic substitution processes require an already substituted aromatic.

Electrophilic aromatic substitution (EAS) was developed approximately 100 years ago. Because of its usefulness and simplicity, it has remained a standard procedure in organic synthesis. Orientation in EAS is controlled by either an ortho-/para- directing group or a meta- directing group. Since the topic of this thesis is concerns with adding

substituents to the ortho- positions, it is the ortho-/para- EAS directors that are of interest.

The limitation with such EAS directors is that they usually do not produce site-specific products. Many directing groups in EAS produce a mixture of products with the substituent introduced into either the ortho- or para- position.<sup>3,4</sup> If only the ortho- product is desired, this limitation can be circumvented by using an alternative method, directed ortho-metalation (DoM).

Directed ortho-metalation is a process by which site-specific substituted aromatic compounds can be synthesized. This reaction, first observed in the late 1930's, involves a regiospecific exchange of an ortho-hydrogen and a lithium atom of an alkyllithium reagent.<sup>5,6</sup> Similar to the EAS reaction, directed ortho-metalation is controlled by a directing metalation group (DMG), but unlike EAS this directing group will only activate the ortho-position.<sup>7,8</sup>

#### B. Directed Metalation Mechanism

In 1939, two researchers, Henry Gilman<sup>6</sup> and George Wittig<sup>5</sup>, separately observed the process we now know as directed ortho- metalation. The exact pathway of the directed ortho-metalation is still unknown. Our group has proposed a step-by-step process for the reaction (Figure 1). In hydrocarbon media the principal oligomer structure of n-BuLi is the hexamer. With the aid of an additive such as THF or TMEDA, deoligomerization can be achieved to afford concentrations of the n-BuLi dimer structure, the most reactive form of n-BuLi for DoM.<sup>9</sup> The loss of one ligand from the dimer structure allows coordination by the directing metalation group (DMG). Loss of a second coordinating ligand from the same lithium affords an adjacent electrophilic site. Simple rotation of this coordinated structure allows the formation of an agostic interaction<sup>10</sup> between the ortho-hydrogen and the electron

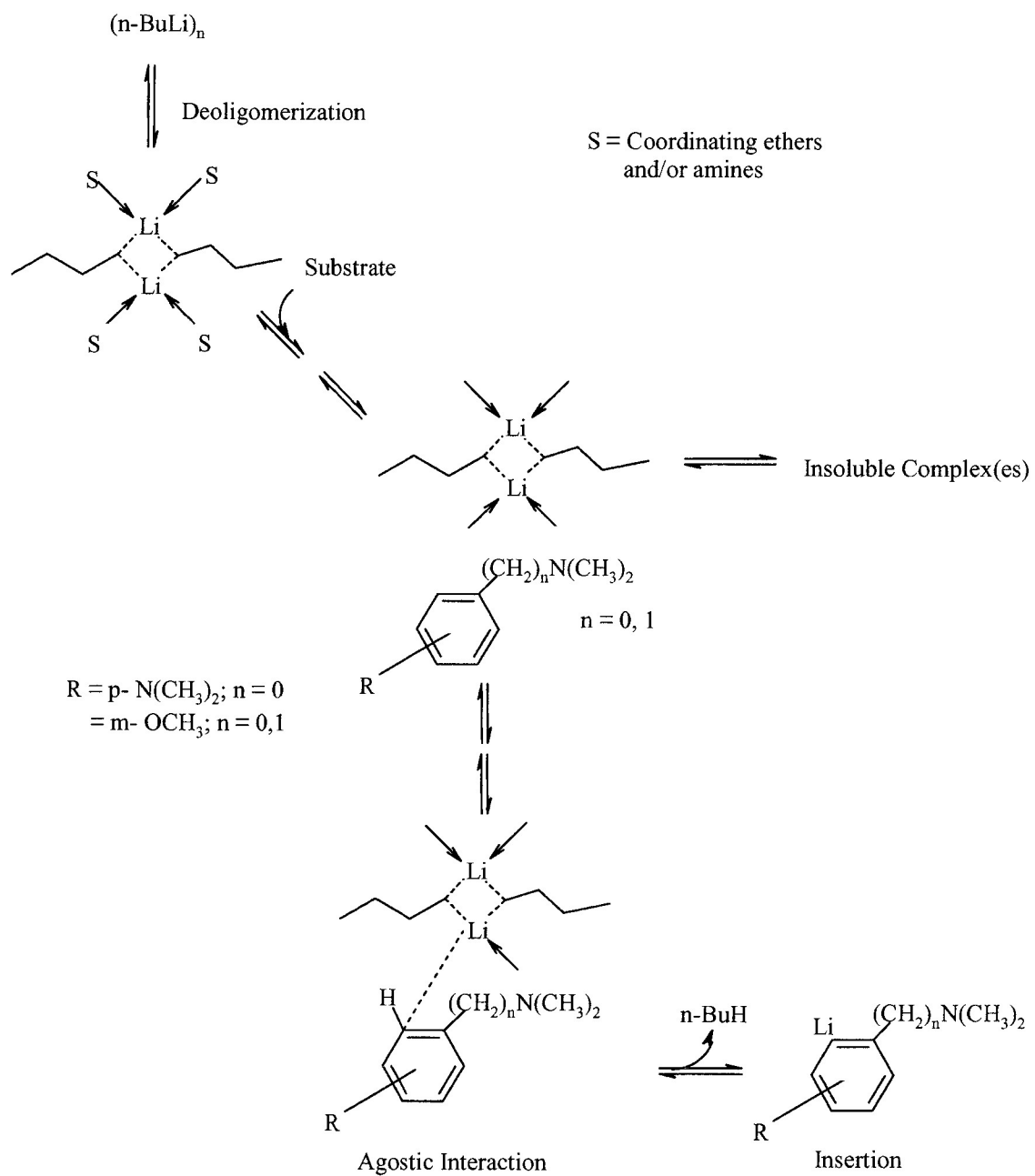


Figure 1. Proposed mechanism scheme for the DoM reaction of  $n\text{-BuLi}$  with arylamines



deficient orbital of the lithium.<sup>11</sup> This prior-coordination of the DMG and an alkyllithium reagent affords both entropic and electronic facilitation of the reaction. Articulated as the complex-induced proximity effect (CIPE)<sup>12</sup>, the formation of such complexes facilitates the observed ortho- regioselectivity of the DoM reaction.<sup>13</sup> The last step, which is rate determining, involves insertion of the lithium atom at the ortho- position of the substrate.

In directed metalation reactions, the lithium atom is directed to a proton site ortho- to the directing substituent of an arene substrate. This interaction between the electron-deficient lithium and the ortho-hydrogen is the result of various combinations of electronegativity and coordination effects. Throughout the development of the DoM procedure many different reasons have been proposed for its specificity. Bryce-Smith<sup>14</sup> theorized that the position of metalation is influenced by the thermodynamic stability of the carbon-hydrogen bond undergoing scission.<sup>15</sup> Benkeser<sup>16</sup> proposed that kinetics controls the initial attack, while thermodynamic stabilities determine the final position of the metalated product;<sup>15</sup> whereas, Reich has stated that solution structure, activity, and selectivity of alkyllithium reagents are dominated by coordination to Lewis bases through intermolecular and intramolecular forces.<sup>17</sup> However, researchers have shown through NMR and computational studies that both kinetic and thermodynamic factors influence the progress of the ortho-lithiation reaction.<sup>18</sup> Hommes and Schleyer have stated that the directing and accelerating abilities of DMG's is due to stabilization in the transition complex with the alkyllithium.

The concept of coordination between the alkyllithium metal and the substrate was first proposed by Roberts and Curtin.<sup>19</sup> These researchers conducted reactions under DoM conditions, using a known meta- director in EAS, the trifluoromethyl group. The reaction of benzotrifluoride and n-butyllithium in ether at reflux followed by carbonation yielded 48%

metalated product. Analysis of the product mixture revealed a 5-to-1 ratio of o- and m-trifluoromethylbenzoic acids. The trifluoromethyl group was thus demonstrated to activate the ring towards metalation. However, as proven by a competitive experiment between benzotrifluoride and anisole, the activation was less than that of the methoxy group. This data proved inconsistent with the hypothesis that the inductive effect was solely responsible for activation under DoM conditions. Two conclusions were drawn from these experiments, the first was that the methoxy group controlled DoM partly through prior-coordination with the alkyllithium reagent, which is an activation option unavailable to the trifluoromethyl group. The second was that coordination to a lithium atom by a DMG represents a flow of electron density out of the aromatic ring thereby increasing the acidity of the ortho-hydrogens.

Four related mechanisms can be proposed for the DoM reaction. All four mechanisms must ultimately involve insertion of a lithium atom into an ortho C-H bond. They differ in the pre-equilibria involved in the various self-assemblies necessary to approach the configurations(s) for the ultimate transition state. Each of these mechanistic variations will involve relevant solvation of the transition state, which necessarily will involve differing CIPE contributions by DMG's as well as varying coordination contributions by solvents and catalysts. Each of these four mechanisms will be defined by the relative contributions of these variables.

The first of these mechanisms involves prior-coordination of the substrate and the alkyllithium reagent (Figure 2). For this mechanism the DMG coordinates with the alkyllithium dimer allowing an ortho-hydrogen to obtain the proper orientation to react with the lithium atom. This interaction is known as the complex induced proximity effect.<sup>12,20</sup>

The DMG coordinates with the electron-deficient lithium resulting in an ortho-hydrogen becoming proximate to the electrophilic lithium atom. For this reaction to be successful promotion of dimer formation is necessary by use of additives and/or ether solvents. Examples of DMG's of this type are:  $-\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2$  (in a cyclic acetal structure),  $-\text{CHOHCH}_2\text{N}(\text{CH}_3)_2$ , etc.

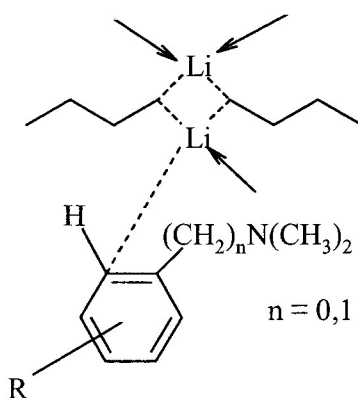


Figure 2. n-BuLi dimer with coordinating amine-DMG featuring the agostic ortho-H interaction

The second mechanism is controlled by the acidity of the ortho-hydrogen. This pathway, known as the “overriding base” mechanism, does not require any prior-coordination but rather direct agostic interaction of an electrophilic lithium site on the n-BuLi dimer with an ortho C-H bond (Figure 3). The basis behind the “overriding base” mechanism is controlled by the DMG’s electron-withdrawing capabilities. The acidity of the ortho-hydrogen is increased with the withdrawal of electron density from the aromatic ring by the DMG. The withdrawal of electron density through  $\sigma$ -bonds is known as the inductive effect. An example of a metalation reaction proceeding only through the inductive effect is that of benzonitrile.<sup>19</sup> Again, n-BuLi dimer formation must be effected for metalation by this mechanism.

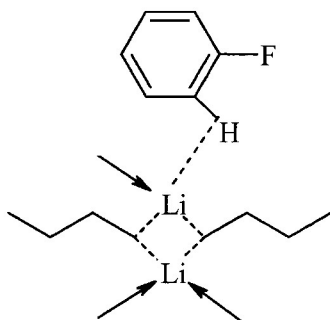


Figure 3. The “overriding” base intermediate which involves direct insertion into the ortho- C-H bond without prior-coordination.

The third mechanism is a combination of prior-coordination and “overriding base” effects. This combined mechanism is a signature of substrates with DMG’s that exhibit withdrawal of electron density through  $\sigma$ -bonds while donating electron density through  $\pi$ -orbitals. In such cases the DMG has the ability to coordinate with the alkyllithium which inhibits electron donation of electron density into the ring. The overall effect raises the acidity of the ortho- hydrogens. Examples of such substituents are:  $-\text{OCH}_3$ ,  $-\text{N}(\text{CH}_3)_2$ , etc.

A fourth limiting pathway for the directed metalation reaction involves the substrate catalyzing its own metalation. During a reaction the substrate promotes the formation of the n-BuLi dimer and thereby facilitates the formation of the n-BuLi dimer-substrate complex.<sup>21</sup>

A substrate that contains multiple directing groups that are ortho- and/or meta- to each other can act in a similar fashion to a bis-chelating amine. The substrate uses its DMG’s to increase deoligomerization through coordination with the alkyllithium.<sup>21</sup> The coordination can best be detected in hydrocarbon solvents, since there is no competing coordination effects as there are with ether solvents. The substrate can coordinate to the lithium aggregate through two unique configurations. This coordination can occur when the substrate has DMG’s in the 1- and 3- positions or the 1- and 2-positions.<sup>22</sup> Coordination of n-BuLi by 1,2- compounds (such as 1,2-DMB) occur at a faster rate because of the opposing  $\pi$ - resonance

effect, in which each DMG donates an equal amount of electron density to the ring, but each contribution is diminished by the contribution of the other. The diminished contribution of electron density results in a greater localization of unshared electron pairs remaining on each DMG resulting in better coordinating ability of each group with the alkyllithium reagent and a faster, more selective DoM.

Saa has proposed that 1,3-bis-coordination activates the 2-position proton by a process called the “tweezer” effect.<sup>23</sup> This configuration places each DMG in an orientation to coordinate with separate lithium atoms in the dimer complex (Figure 4).

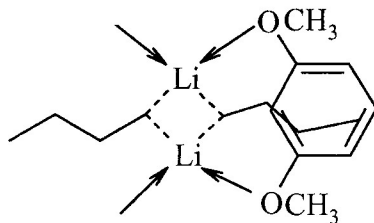


Figure 4. Bis-coordination of 1,3-dimethoxybenzene

The mechanism of the tweezer effect will lead to metalation ortho- to both substituents since the 2-position hydrogen is placed in a position to facilitate ortho C-H interaction. It should also be noted that with these substrates both DMG's do not have to be the same. It is noteworthy that several researchers have published papers with conflicting findings on the proposed mechanisms when reporting reaction rates, compared to anisole, for substrates with multiple methoxy directing groups.<sup>24,25</sup>

The advantage with the substrate-catalyzed mechanism is that it does not require coordinating solvents or bis-chelating amines. The disadvantage with the substrate-catalyzed mechanism is that it can only work for appropriate substrates, ones that possess at least two DMG's situated 1,2- or 1,3- on an arene ring. Substrates that could undergo

directed ortho-metalation through the substrate-catalyzed mechanism should contain directing metalation groups that can act as bis-coordinating substituents, which help to promote RLi dimer formation. This bis-chelation from the directing metalation groups stabilizes the lithium dimer in the same manner as a bis- chelating amine, such as TMEDA. Appropriate 1,2- and 1,3- disubstituted substrates would undergo metalation at the 3- and 2- positions, respectively.

Although the exact specifics of the DoM mechanism are unknown, most reactions probably proceed by a combination of at least two pathways. Both the prior-coordination and the “overriding base” mechanisms require a coordinating ether solvent or a bis-chelating amine. A coordinating solvent can be any solvent that facilitates the formation of the n-BuLi dimer. Two examples of coordinating solvents are diethyl ether and THF. The former favoring formation of the n-BuLi tetramer, the latter a tetramer-dimer equilibrium. A bis-chelating amine will also promote formation of the n-BuLi dimer complex even in hydrocarbon solvents. This intramolecular coordination of a promoter strongly stabilizes the lower oligomeric forms of the alkyllithium reagent.<sup>26</sup>

### C. Alkyllithium Reagent

A critical factor in a DoM reaction is the type of alkyllithium reagent employed. Several types of alkyllithium reagents exist, and each will differ in the rate and extent that it affects ortho- metalation. n-Butyllithium is the most common organolithium reagent used in the DoM process. However, other reagents such as n-hexyllithium, n-heptyllithium, sec-butyllithium, t-butyllithium, and phenyllithium have also been utilized. In this investigation all experiments were performed using n-butyllithium.



All oligomeric forms of organolithium reagents are electron-deficient species that can interact with a lone pair on the directing metalation group. This interaction places the alkyllithium in the vicinity of the ortho-hydrogen. If decoordination from this saturated intermediate takes place, an empty lithium orbital is produced that attacks the electron pair of the ortho- position C-H bond. The lithium, acting as an electrophile, reacts with the activated ortho-hydrogen's electrons and inserts itself into the bond resulting in a Li/H exchange.

It has been proposed by numerous researchers that organolithium reagents must deaggregate to support ortho-metalation. The size of the organolithium aggregate is dependent on the structural features of the alkyl group and the temperature of the reaction.<sup>27,28,29</sup> n-BuLi is known to aggregate primarily into three different oligomer structures: dimer, tetramer, and hexamer.<sup>30,31,32,33,34</sup>

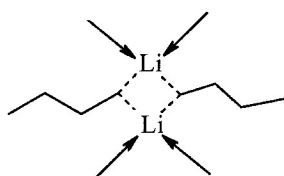


Figure 5. Coordinately-stabilized dimer structure of n-BuLi.

Each of these organolithium aggregates will have different coordination abilities and, therefore, different reactivities. It is the interaction between the solution and/or catalyst with the organolithium that is responsible for forming these oligomer structures. The addition of a bis-chelating amine, such as TMEDA, is known to aid in the formation of the favorable dimer oligomer.<sup>35,36</sup>

With knowledge of the various n-BuLi oligomer structures, it would be beneficial to determine the most reactive structure and the most advantageous solvent systems to promote

its formation. Numerous studies have concluded that the dimer structure of n-BuLi is the most reactive aggregate.<sup>37,38</sup> In addition, the dimer structure of an RLi reagent is the only one to possess two coordination sites on the same Li atom. An examination of the solvents used in the DoM process found that ether, the most commonly used solvent for DoM, supported the formation of the moderately reactive tetramer structure.<sup>31</sup>--which begs the question whether catalyzed reactions in ether proceed via the tetramer or via a hitherto undetected small concentration of the dimer. The fact that ether will not promote the formation of the dimer decreases its effectiveness as a DoM solvent.

An additional problem with ether solvents is that they slowly react with organolithium bases in storage.<sup>39</sup> n-Hexane and cyclohexane afford only the least reactive aggregate, the hexamer structure.<sup>30</sup> Hydrocarbon solvents are known to stabilize alkyllithium reagents; however, since these solvents promote formation of the hexamer, a catalyst usually is used to facilitate the reaction. It has been found that through coordination tetramethylethylenediamine (TMEDA) deoligomerizes the tetramer aggregate of n-BuLi to the dimer.<sup>17,40</sup> This intermolecular coordination with a bis-chelating amine strongly stabilizes the binding modes of the dimer form of n-butyllithium.

#### D. Size of Chelate Ring

Another concern of the DoM protocol is the size of a ring formed during the interaction between the alkyllithium and the substrate. In Figure 6, N,N-dimethylaniline is coordinated with a butyllithium dimer, forming a pseudo four-membered ring between the substrate and the alkyllithium. If the substrate were N,N-dimethylbenzylamine, a pseudo five-membered ring would be formed. Thermodynamic principles indicate that five- and six-membered

rings are favored over four-membered rings.<sup>36,41,42</sup> The actual ring size depends on the transition state of DoM and that is still under investigation.

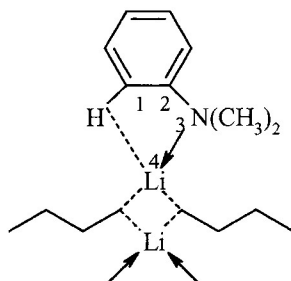


Figure 6. N,N-Dimethylaniline coordinated with the n-butyllithium dimer illustrating the pseudo four-membered ring chelate interaction

#### E. Trapping/Derivatizing Agents

The product of the reaction of an alkyllithium reagent with a DMG-containing aryl substrate forms an ortho-lithio intermediate.<sup>11</sup> Upon exposure to moisture and/or air this intermediate will readily undergo protonation. The ortho-lithio intermediate, after protonation, will then be converted back to the reactant. Therefore, it is necessary to react this intermediate with suitable electrophiles under an inert atmosphere.<sup>43</sup> Such weak electrophiles used herein are known as trapping agents.

The reaction with a trapping agent quantitatively replaces the ortho-lithium with a stable substituent. The type of analysis performed on the reaction mixture determines the appropriate type of trapping agent used. Trapping agents differ from one another by the side groups they add to the aryl product. For the purpose of this thesis, all reaction products were condensed with chlorotrimethylsilane (ClTMS). The trapping agent replaces the ortho-lithium with a trimethylsilyl group,  $-\text{Si}(\text{CH}_3)_3$  (Figure 7). The amount of product was quantitatively measured by gas chromatography (GC).

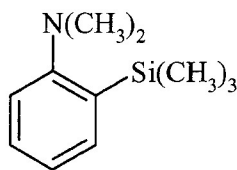


Figure 7. N,N-Dimethylaniline product with ortho-trimethylsilyl group.

The amount of intermediate generated is independent of the trapping agent employed. However, the reaction between the trapping agent and the intermediate should be complete. Numerous of other trapping agents have been employed, including benzophenone, methyl iodide, dry ice, and  $\text{D}_2\text{O}$ .<sup>44,45</sup> If all the intermediate does not react with the trapping agent, it will be protonated back to the starting material upon hydrolytic work up. The result will be a lower observed product yield.

#### F. Aryl Substrates Containing Directing Metalation Groups

Numerous factors play a role in the process of the directed metalation reaction. The most significant of these is the directing metalation group (DMG) itself. The directing metalation group controls the rate and extent to which metalation occurs at the ortho-position.

The process of DoM is controlled by a directing metalation group (DMG) that is attached to an aromatic ring system. Since the discovery of DoM, the number of directing metalation groups has grown substantially.<sup>46,47,48</sup> In order for a substituent to effectively direct metalation to the ortho- position, it must fulfill two criteria: First, it must be resistant to nucleophilic and base attack by the alkyllithium reagent. Second, it usually contains at least one heteroatom, which can coordinate with the incipient vacant site on the organolithium dimer. Both of these criteria must be met for most DMG's to be effective. Other important considerations for DMG are the ring size formed upon coordination and induction withdrawal by the DMG, which increases the ortho-H acidity.<sup>7,49</sup>

Most DMG's exhibit directing abilities reflecting combinations of coordination and electronic effects. The DMG activity series compares a list of directing metalation groups, ranked in order of decreasing reactivity each of which represent various combinations of these two features (Figure 8).<sup>13</sup> The activity series of the DMG's ability to promote ortho-lithiation is important for assessing the site of lithiation when two or more directing groups are located on the same ring.<sup>50,51,52,53</sup>

There are two factors that contribute to the effectiveness of each directing metalation group. The first factor is the ground state acidity of the ortho-hydrogen; the second one is the coordination ability of unshared electron pair(s) on the directing group.<sup>54</sup> The ground state acidity of the ortho-hydrogen can be affected by inductive and resonance characteristics of the directing group.<sup>55</sup> An inductive effect occurs when the directing group withdraws electron density away from the ring through  $\sigma$  bonds. The greater the inductive effect, the more electron density that will be pulled from the aromatic ring; thereby causing an increase in acidity of the ortho-hydrogen. The inductive characteristic of a DMG is a favorable effect since it helps to facilitate a reaction between the alkyllithium and an ortho-hydrogen.

Ground state resonance effects involve electron donation from the DMG to the ring through  $\pi$ -orbitals or lone pairs. These effects create a reduction in metalation potential for two reasons. First, the added electron density to the aromatic ring will lower the acidity of the ortho-hydrogens. Second, delocalization of an electron pair into the ring decreases its availability for coordination with the n-BuLi dimer complex. Of these two factors, the second is the most damaging to the prior-coordination metalation mechanism.

The coordination ability of the directing group is possibly the single most important factor during the DoM reaction. Coordination is the process in which the directing group

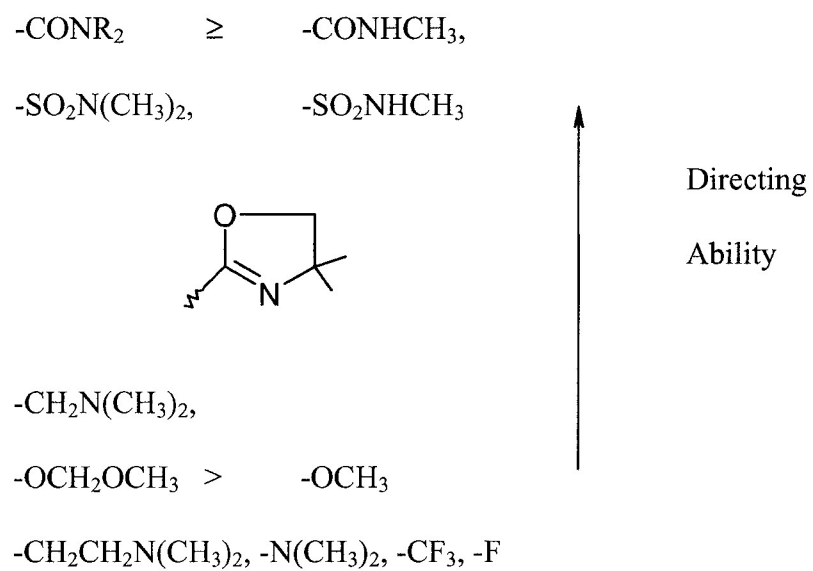


Figure 8. Relative ortho-directing ability in DoM<sup>7</sup>

interacts with the lithium atom. The significance of coordination can be proven when comparing the two limiting mechanisms of prior-coordination and “overriding base.” Prior-coordination brings the substrate and the alkyllithium dimer together so that the complex induced proximity effect can operate.<sup>11</sup> Without the substrate and the alkyllithium interacting in this manner, reaction of the ortho-hydrogen with the lithium dimer would not be facilitated. Coordination to the dimer by a DMG initiates a flow of electron density out of the ring thereby increasing the acidity of the ortho-hydrogens.<sup>19</sup> Because the lithium structure is an electron deficient species, it interacts with electron rich atoms. Coordination is commonly believed to occur through lone electron pairs on the DMG and vacant orbitals of an alkyllithium aggregate. Therefore to maximize the coordination ability of a DMG, it must localize its lone pair(s).

Because countless varieties of substrates used in the DoM reaction exist, the topic will be narrowed to a select few. The focus of this thesis is to find hydrocarbon media that will permit the maximum extent of metalation of several dimethylarylamines. The dimethylamine-containing substituents constitute directing metalation groups for the various aryl systems investigated. Figure 9 illustrates all of the substrates reviewed for the topic of this thesis.

#### 1. Anisole (**1**)

Since the development of the directed ortho-metalation reaction, anisole has been perhaps the most explored substrate. Gilman<sup>6</sup> and Wittig<sup>5</sup> studied anisole exclusively during their pioneering metalation experiments. The reason behind this is that anisole contains one of the most common directing groups, the methoxy group. The most appealing aspect of the anisole substrate is its ability to have numerous other directing groups in the ortho-, meta-,

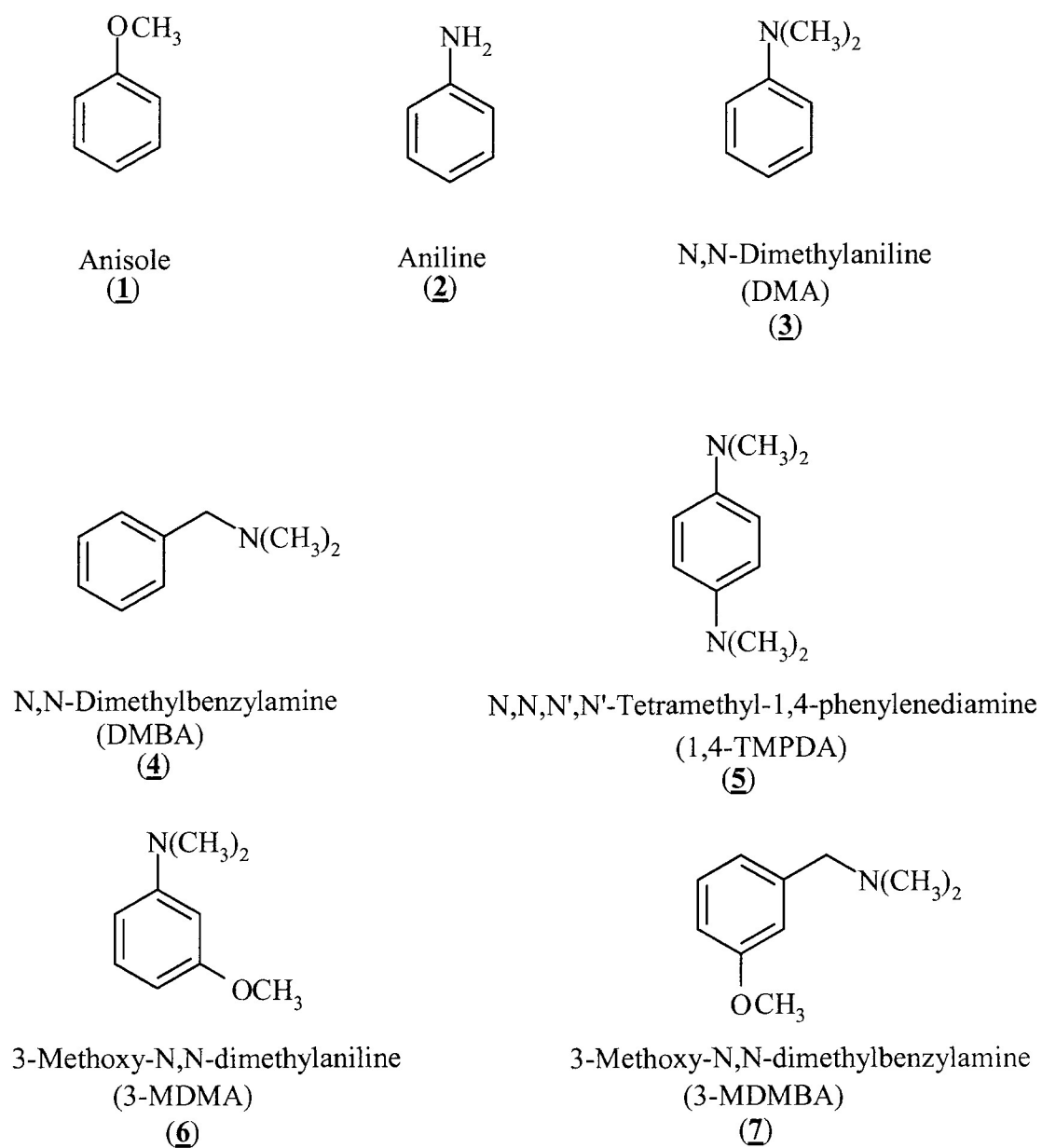


Figure 9. Dimethylarylamine substrates and related compounds



and para- position(s). Because the list of substituents that could be added to the anisole ring is so vast, this discussion will be limited to the following substituents: p-halo-, o-, m-, p-methyl, and o-, m-, p-methoxy (dimethoxybenzenes).

Halogen groups placed on an aromatic system are known to exert strong electronic effects. However, there are multiple problems associated with these substituents.<sup>56</sup> Under certain conditions p-bromoanisole can be metalated ortho- to the methoxy substituent.<sup>57</sup> However, both bromo- and iodo-anisoles will readily undergo a halogen/metal exchange in ether solvents.<sup>50</sup> Therefore, bromo- and iodo- substituents are of little use when reacted through most DoM conditions. When a fluorine group is in the para- position metalation can be made to predominantly occur ortho- to either the fluorine substituent or the methoxy group.<sup>50, 58, 59</sup> The objective of the DoM reaction is to produce a single product; therefore, this pattern is undesirable. p-Fluoroanisole has been regiospecifically metalated ortho- to the fluorine. However, an interesting point about p-fluoroanisole is that it displays an accelerated rate of metalation ortho- to the methoxy group, which can partially be explained by the opposing  $\pi$ - resonance effect (Figure 10) and an inductive effect. The fluorine substituent is interesting because it provides resonance donation to the ring but has a larger inductive withdrawal effect. The opposing  $\pi$ - resonance effect serves to increase localization of the electron pairs on oxygen, thereby facilitating coordination to the n-butyllithium dimer. Inductive withdrawal by both substituents increases the acidity of both sets of hydrogens. Both the electron-withdrawal and the increased coordinating ability would facilitate DoM.

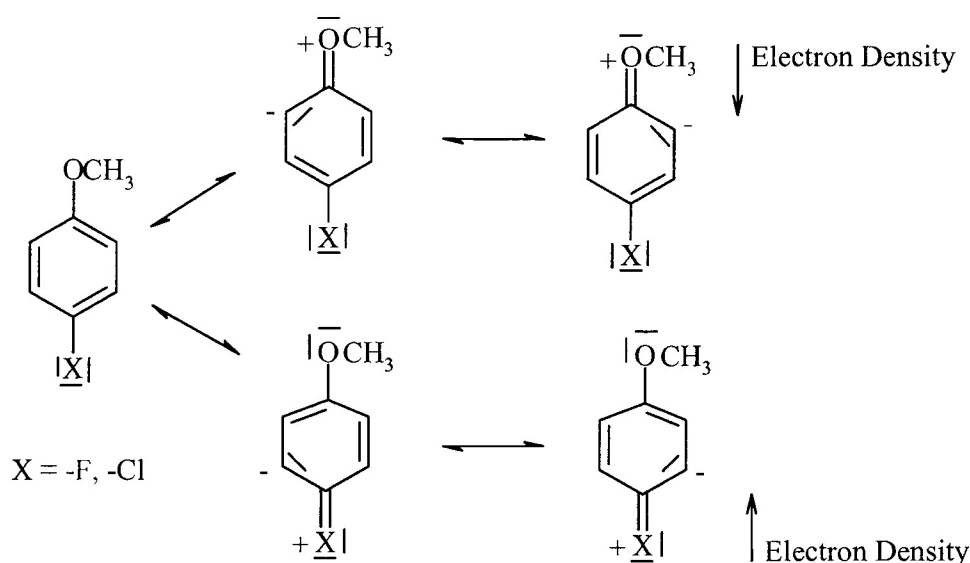


Figure 10. Opposing  $\pi$ -resonance  
(arrows indicate  $\pi$ -electron density flow)

p-Chloroanisole will undergo metalation ortho- to the chlorine substituent, and/or metalation ortho- to the methoxy group. Reactions conducted in n-hexane and cyclohexane using increments of TMEDA or neat THF resulted in metalation ortho- to the chlorine group with immediate formation of a benzyne intermediate.<sup>42,50,60</sup> Reactions under milder conditions, namely, fractional equivalents of THF in cyclohexane, produced metalation ortho- to the methoxy group with no evidence of benzyne intermediate formation.<sup>60</sup> This product formation leads to the hypothesis that the strong base prompted the “overriding base” mechanism while less aggressive conditions allowed the CIPE mechanism to assume control. Upon examining the halo-anisoles, p-chloroanisole is the most conducive to the DoM reaction. For the other halo-anisoles it would be useful to find a pathway that minimizes side reactions while still promoting metalation ortho- to the methoxy group.

For ortho- methylanisole, two primary metalation sites exist. One site is that at the  $\alpha$ - position. The second possibility is that metalation will occur ortho- to the methoxy group.<sup>61</sup> Studies have shown that a mixture of the two products are produced under all conditions investigated.<sup>62</sup>

When a methyl group is meta- to the methoxy group metalation can occur at both ortho- positions. Reactions conducted in ether with catalytic TMEDA resulted in metalation at the 2- and 6- positions at equal rates. Reactions in neat ether produced a 2:1 metalation favoring, presumably, the 6- position. Similar reactions in THF/n-hexane also favored metalation at the 6- position in a 2:1 ratio to that at the 2-position.<sup>63,64</sup>

For p-methylanisole metalation can occur ortho- to the methoxy group or, less likely, on the methyl group.<sup>65</sup> Since toluene will undergo benzylic metalation in the presence of n-BuLi and TMEDA, p-methylanisole (p-MA) allows competitive examination of the two possible sites of metalation. Reactions in ether with incremental amounts of TMEDA yielded >90% ortho-lithiation accompanied by 2-3% benzylic metalation.<sup>66</sup> However, the extent of benzylic metalation was decreased to <1% by use of the designed metalation media of THF/n-hexane.<sup>8</sup> Again, use of less aggressive conditions decreased the extent of metalation via the “overriding base” mechanism, the mechanism that must be operating to produce benzylic metalation in the p-position.

In comparison, metalation of 1,2-dimethoxybenzene (1,2-DMB) should occur at a rate faster than that of anisole or o-methylanisole. This rate of reaction can be explained by opposing  $\pi$ -resonance, in which each methoxy group donates an equal amount of electron density to the ring system, but each contribution is diminished by the contribution of the other. This involves resonance structures similar to those depicted in Figure 10. This

affords each methoxy group increased electron density available for coordination. According to this theory 1,3-DMB should undergo metalation at a slower rate than that of 1,2-DMB, since 1,3-DMB does not possess opposing  $\pi$ -resonance. However, 1,3-DMB does exhibit a larger combined inductive effect from the two methoxy groups resulting in an increased acidity of the hydrogen at the 2-position. 1,4-DMB will also exhibit the effect known as opposing  $\pi$ -resonance. This effect occurs when a donation of electron density from a substituent is opposed by a similar donation of electron density in the opposite direction. Figure 10 shows an example of how this occurs ( $X = -OCH_3$ ). The result of this effect is that a greater localization of unshared electron pairs will remain on each methoxy resulting in better coordinating ability of each methoxy group and a faster, more selective, DoM.

## 2. Aniline (2)

Aniline has a primary amine group as the directing metalation group. Nitrogen-containing substituents inductively enhance the acidity of ortho-hydrogens, but the lone pair on nitrogen is highly delocalized into the ring.<sup>67</sup> However, primary amine protons are fairly acidic. This provides the option of the alkyllithium abstracting an amine hydrogen rather than the desired ortho-hydrogen, since the hydrogens on the amine are more acidic. Because of this fact, aniline is not useful as a DoM substrate.

## 3. N,N-Dimethylaniline (3)

The metalation of N,N-dimethylaniline (DMA) occurs at a slower rate than that of anisole. The reason for this decreased rate is the ground state delocalization of the free electron pair from nitrogen (Figure 11).

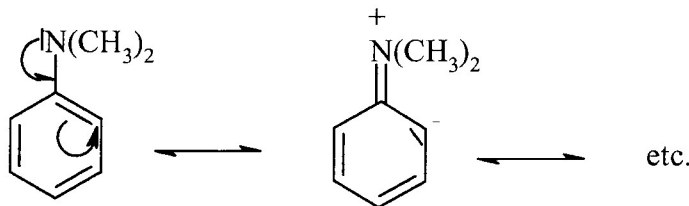


Figure 11. Deactivating resonance structures for N,N-dimethylaniline

Three of these structures place a double between nitrogen and the ring, with a positive charge on the nitrogen atom; thus effectively decreasing the coordination ability of the nitrogen. In addition, the added electron density in the ring will lower the acidity of the ortho-hydrogens.

#### 4. N,N-Dimethylbenzylamine (4)

The difference between N,N-dimethylbenzylamine and N,N-dimethylaniline is a  $\text{CH}_2$  group that removes the restrictions of direct electronic contact with the aromatic ring. The ortho-metalation of N,N-dimethylbenzylamine (DMBA) should occur at a faster rate than that of N,N-dimethylaniline, even though the methylene group essentially insulates the ring from the inductive influence of the nitrogen atom.<sup>15</sup> With the dimethylamino group separated from the ring, the lone pair displays no resonance effect. The lone electron pair of nitrogen is localized on the amine group. With the lone pair of electrons isolated on the amine it increases the coordination ability of the nitrogen group, as compared to dimethylaniline. Without the lone pair of electrons from the nitrogen being donated to the ring, the acidity of the ortho- hydrogens will not be compromised. Since there is no contribution of induction, metalation at an ortho- position should take place via CIPE only. With the nitrogen retaining its electron pair, the coordination ability of the DMG will predominate and ortho-metalation should readily take place. Therefore, a comparison of the

reactivity of dimethylbenzylamine and dimethylaniline will demonstrate the importance of coordination.

5. N,N,N',N'-Tetramethyl-1,4-phenylenediamine (5)

Since the lone pair of electrons on the dimethylamino group undergoes delocalization into the ring, addition of a second dimethylamino group on the ring in the para- position should provide a test of the opposing  $\pi$ -resonance effect. According to this concept, both dimethyl amine groups should equally donate part of their electron density to the ring. The result is that each amine group contributes electron density to the ring, but the effect for each is diminished due to opposing  $\pi$ -resonance. Thus, each unshared electron-pair is more available for coordination (Figure 12). Therefore, electron density is more localized on each nitrogen. It should be noted that with the addition of a second DMG group the number of ortho- hydrogens is doubled. It may be possible to promote dimetalation by using a ratio of equivalents of n-BuLi to substrate of at least 2:1.

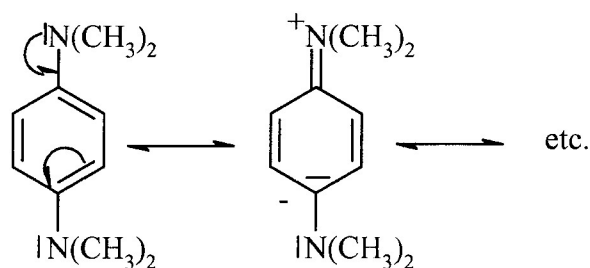


Figure 12. Resonance structures for N,N,N',N'-Tetramethyl-1,4-phenylenediamine

6. 3-Methoxy-N,N-Dimethylaniline (6)

With the addition of a methoxy group at a position meta- to the dimethylamino directing group, metalation should be significantly enhanced. Metalation could occur via the

substrate-catalyzed pathway. Under such conditions metalation will occur ortho- to both substituents.

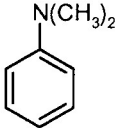
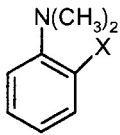
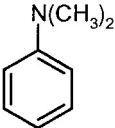
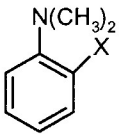
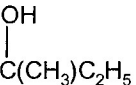
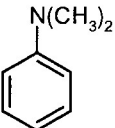
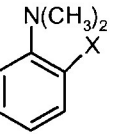
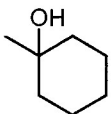
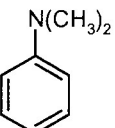
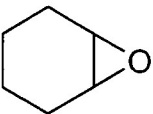
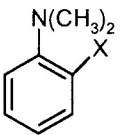
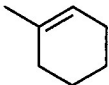
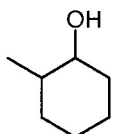
#### 7. 3-Methoxy-N,N-Dimethylbenzylamine (7)

Adding a methoxy group at a position meta- to a dimethylamino directing group may promote metalation through the substrate-catalyzed pathway. Under such conditions metalation should occur ortho- to both substituents, supporting the concept that steric hindrance is not an overriding factor during the reaction.

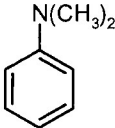
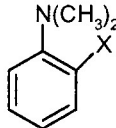
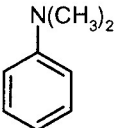
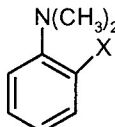
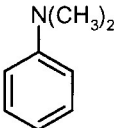
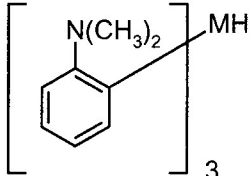
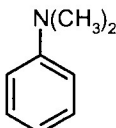
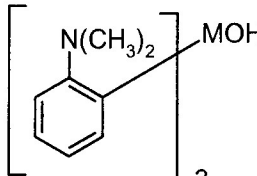
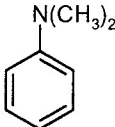
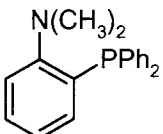
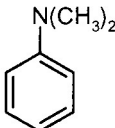
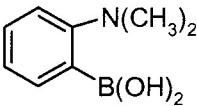
#### G. Tables of Literature Studies

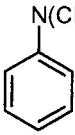
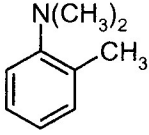
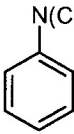
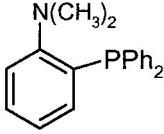
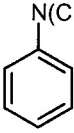
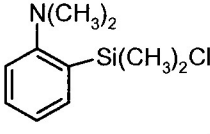
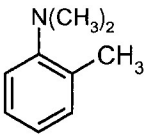
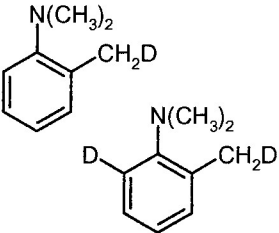
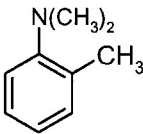
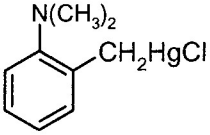
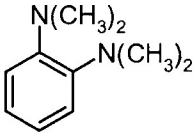
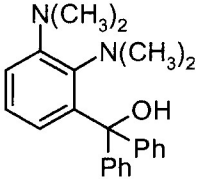
Over the years, there have been numerous review articles published regarding directed ortho- metalation reactions. However, the shortcomings of these publications are that few of them extensively cover the reaction of amine directing groups.<sup>48,68</sup> Therefore, studying the literature for dimethylamines reactions can be difficult. The following is a review of lithiations performed on N,N-dimethylaniline, N,N-dimethylbenzylamine, and several analogs. This review is not intended to be comprehensive, but rather to present an overview of metalations and derivatives prepared by use of the dimethylamino- and the dimethylaminomethyl- DMG's.

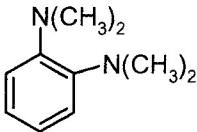
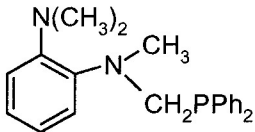
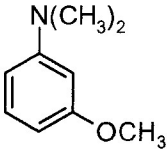
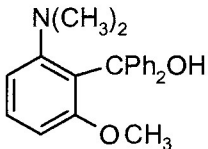
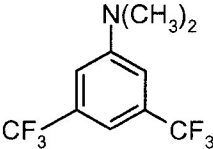
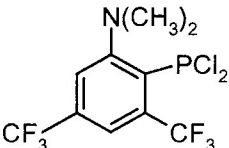
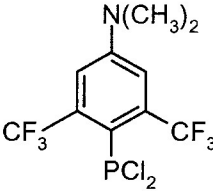
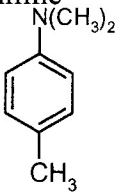
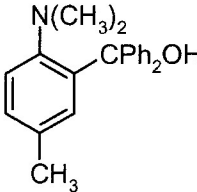
Table 1. Lithiations of N,N-Dimethylaniline and its Homologs.

Arene Lithiated	Conditions	Derivatization Agent	Product and Yield (%) (Reference)
N,N-Dimethylaniline 	n-BuLi/ n-hexane/ reflux/ 16 h	CF <sub>3</sub> COCF <sub>3</sub>	 X= -C(CF <sub>3</sub> ) <sub>2</sub> OH (49) <sup>69,48</sup>
N,N-Dimethylaniline 	n-BuLi/ n-hexane/ reflux/ 16 h	CH <sub>3</sub> COC <sub>2</sub> H <sub>5</sub>	 X=  (20) <sup>69,48</sup>
N,N-Dimethylaniline 	n-BuLi/ n-hexane/ reflux/ 16 h	Cyclo- hexanone	 X=  (31) <sup>69,48</sup>
N,N-Dimethylaniline 	n-BuLi/ n-hexane/ reflux/ 16 h		 X=  (14) <sup>69,48</sup> X=  (7) <sup>69,48</sup>



<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ n-hexane/ reflux/ 16 h</p>	<p>PhCOCH<sub>3</sub></p>	 <p>X= <math>-\text{C}(\text{CH}_3)_2\text{Ph}</math> (34)<sup>69,48</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ n-hexane/ TMEDA/ 25°C/ 4 h</p>	<p>Benzophenone Ph<sub>2</sub>CO</p>	 <p>X= -CPh<sub>2</sub>OH (71)<sup>48,69,70</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ THF/ TMEDA/ -78°C to 25°C</p>	<p>1.) (CH<sub>3</sub>O)<sub>4</sub>M M= Si, Ge 2.) LiAlH<sub>4</sub>/ THF</p>	 <p>M= Si (81) M= Ge (89)<sup>71</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ THF/ TMEDA/ -78°C to 25°C</p>	<p>1.) (CH<sub>3</sub>O)<sub>4</sub>M M= Si, Ge 2.) Silica Gel/ Hexane/ AcOEt</p>	 <p>M= Si (60) M= Ge (30)<sup>71</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ n-hexane/ TMEDA</p>	<p>Ph<sub>2</sub>PCl</p>	 <p>(43)<sup>72</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ ether/ TMEDA/ reflux/ 2 h</p>	<p>1.) Trimethyl- borate B(OCH<sub>3</sub>)<sub>3</sub> 2.) Hydrolysis</p>	 <p>(45)<sup>73</sup></p>

<p>N,N-Dimethylaniline</p> 	<p>s-BuLi/ THF/ TMEDA/ -90°C</p>	<p>CH<sub>3</sub>I/ -78°C</p>	<p>o-Methyl-N,N-dimethylaniline</p>  <p>(<math>&lt; 1</math>)<sup>74</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>n-BuLi/ n-hexane/ reflux/ 5 h</p>	<p>Ph<sub>2</sub>PCl/ -20°C/ reflux/ 5 h</p>	 <p>(85)<sup>75</sup></p>
<p>N,N-Dimethylaniline</p> 	<p>RLi/pentane/ 25°C/ 3 h</p>	<p>Dimethyl- dichlorosilane Si(CH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub></p>	<p>o-(Chlorodimethylsilyl)- N,N-dimethylaniline</p>  <p>(N.A.)<sup>76</sup></p>
<p>N,N-Dimethyl-o-toluidine</p> 	<p>n-BuLi/ ether/ 25°C/ 40 h</p>	<p>Deuterium oxide D<sub>2</sub>O</p>	 <p>(I+II, 94) (I:II, 1.5:1)<sup>48,70</sup></p>
<p>N,N-Dimethyl-o-toluidine</p> 	<p>n-BuLi/ ether or n-hexane</p>	<p>HgCl<sub>2</sub>/ THF/ -78°C</p>	 <p>(36)<sup>77</sup></p>
<p>N,N,N',N'-Tetramethyl-o-phenylenediamine</p> 	<p>n-BuLi/ n-hexane/ 55°C/ 48 h</p>	<p>1.) Benzo- phenone Ph<sub>2</sub>CO 2.) H<sup>+</sup></p>	 <p>(50-60)<sup>78</sup></p>

<p>N,N,N',N'-Tetramethyl-o-phenyldiamine</p> 	<p>n-BuLi/ n-hexane/ TMEDA</p>	<p>Ph<sub>2</sub>PCl</p>	 <p>(50)<sup>72</sup></p>
<p>3-Methoxy-N,N-dimethylaniline</p> 	<p>n-BuLi/ ether/ 35°C/ 12 h</p>	<p>Benzophenone Ph<sub>2</sub>CO</p>	<p>[2-(Dimethylamino)-6-methoxyphenyl]-diphenylmethanol</p>  <p>(71)<sup>48,52</sup></p>
<p>N,N-Dimethyl-3,5-bis(trifluormethyl)aniline</p> 	<p>n-BuLi/ n-hexane/ 12 h</p>	<p>PCl<sub>3</sub></p>	 <p>(70)</p>  <p>(7)<sup>79</sup></p>
<p>1,4-Methyl-N,N-dimethylaniline</p> 	<p>n-BuLi/ n-hexane/ TMEDA/ mild reflux/ 72 h</p>	<p>Benzo-phenone Ph<sub>2</sub>CO</p>	<p>2-N,N-Dimethyl-1,4-toluidine</p>  <p>(52)<sup>48,70</sup></p>

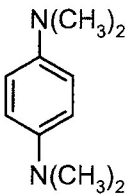
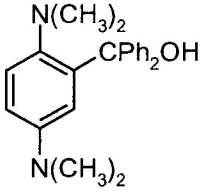
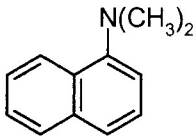
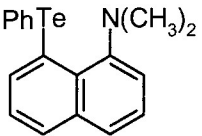
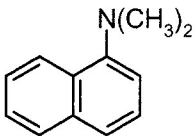
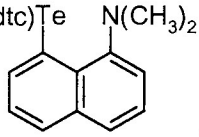
<p>N,N,N',N'-Tetramethyl-1,4-phenylenediamine</p> 	<p>n-BuLi/ n-hexane/ 55°C/ 48 h</p>	<p>1.) Benzo- phenone Ph<sub>2</sub>CO 2.) H<sup>+</sup></p>	 <p>(50-60)<sup>78</sup></p>
<p>N,N-Dimethylnaphthylamine</p> 	<p>n-BuLi/ ether/ 25°C/ 24 h</p>	<p>PhTeBr</p>	<p>8-(Dimethylamino)-1-naphthyl phenyl telluride</p>  <p>(26.3)<sup>80</sup></p>
<p>N,N-Dimethylnaphthylamine</p> 	<p>n-BuLi/ ether/ 25°C</p>	<p>Te(dtc)<sub>2</sub> dtc= diethyl- dithia- carbamate</p>	<p>8-[(Dimethylamino)-1-naphthyl]tellurium-diethyl dithiocarbamate</p>  <p>(70)<sup>81</sup></p>

Table 2. Halogen Metal Exchange Reactions of N,N-Dimethylaniline and its Homologs.

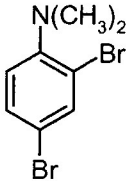
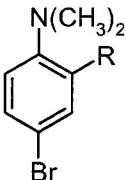
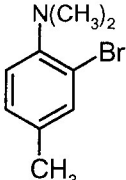
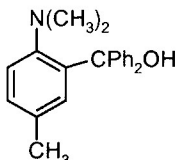
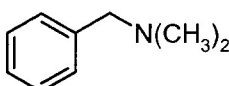
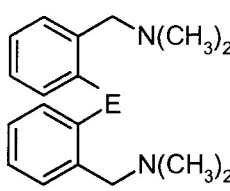
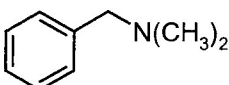
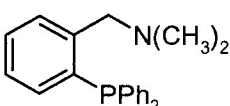
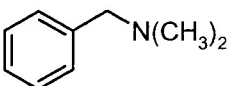
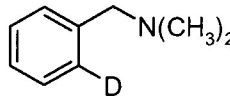
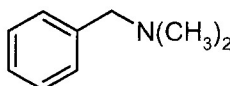
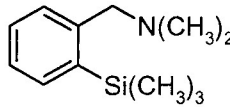
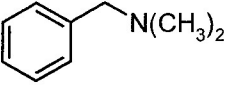
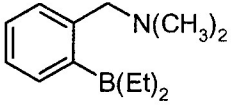
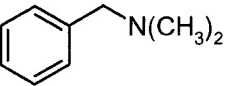
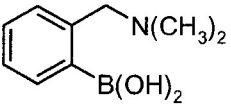
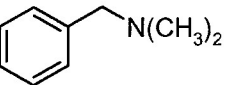
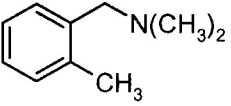
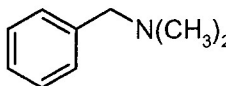
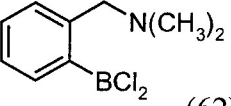
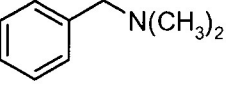
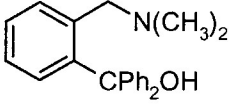
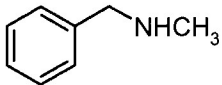
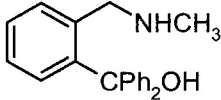
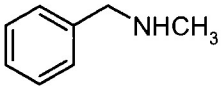
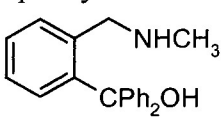
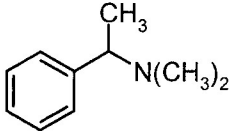
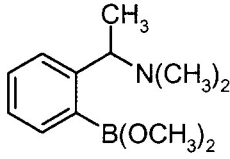
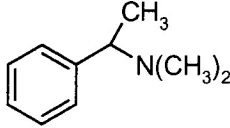
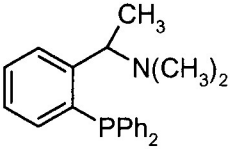
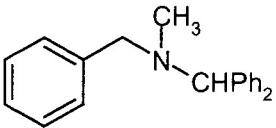
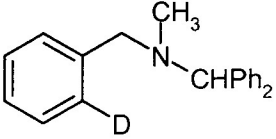
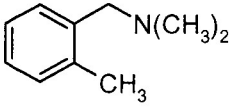
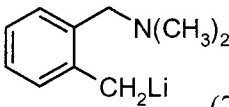
Arene Exchanged	Conditions	Derivatization Reagent	Product and Yield (%) (Reference)
2,4-Dibromo-N,N-dimethylaniline  	n-BuLi/ THF/ -90°C	R/ -90°C to 25°C	  R= CONEt <sub>2</sub> (19) R= CHO (73) R= CPh (74) R= COEt (22) R= CONHBu <sup>t</sup> (80) R= CH(OH)Et (76) <sup>82</sup>
2-Bromo-N,N-dimethyl-4-toluidine  	n-BuLi/ n-hexane/ ether/ 25°C/ 1.5 h	1.) Benzo- phenone Ph <sub>2</sub> CO 2.) H <sup>+</sup>	[6-(Dimethylamino)-3-tolyl]diphenylmethanol    (74) <sup>48,70</sup>

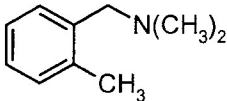
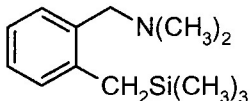
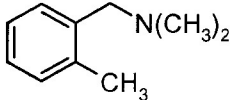
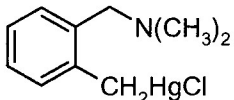
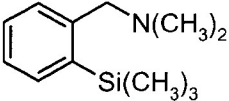
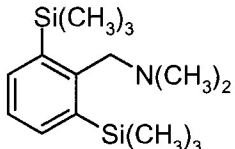
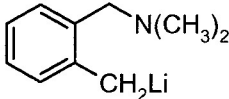
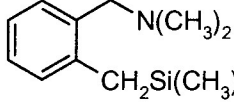
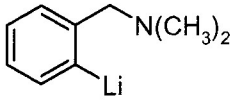
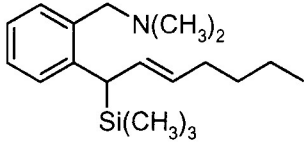
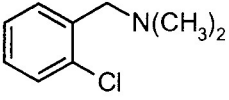
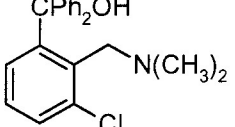
Table 3. Lithiations of N,N-Dimethylbenzylamine and its Homologs.

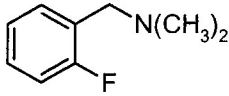
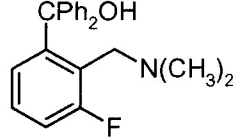
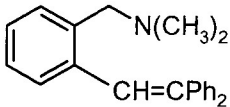
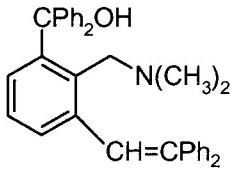
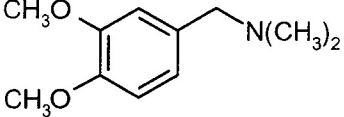
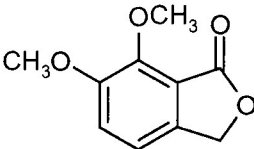
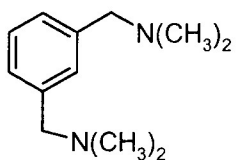
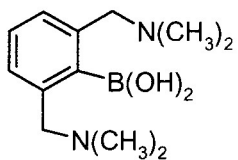
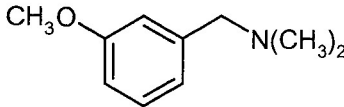
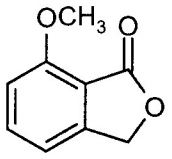
Arene Lithiated	Conditions	Derivatization Reagent	Product and Yield (%) (Reference)
N,N-Dimethylbenzylamine 	n-BuLi/ ether/ 25°C	E(dtc) <sub>2</sub> E= electro- phile dtc= diethyl- dithia- carbamate	 E= Se (97) E= Te (78) <sup>81</sup>
N,N-Dimethylbenzylamine 	n-BuLi/ n-hexane/ TMEDA	Ph <sub>2</sub> PCl	 (60) <sup>72</sup>
N,N-Dimethylbenzylamine 	n-BuLi/ ether/ 24 h	Deuterium oxide D <sub>2</sub> O	2-d-N,N- Dimethylbenzylamine  (75) <sup>83</sup>
N,N-Dimethylbenzylamine 	n-BuLi/ ether/ 24 h	Trimethylsilyl chloride Si(CH <sub>3</sub> ) <sub>3</sub> Cl	2-Trimethylsilylbenzyl- dimethylamine  (70) <sup>83</sup>

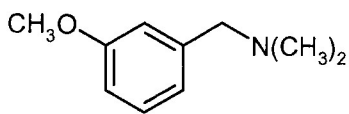
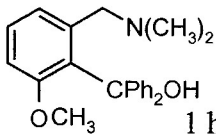
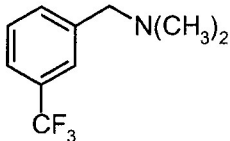
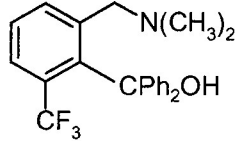
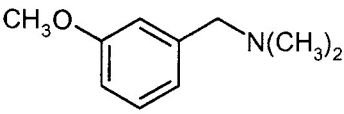
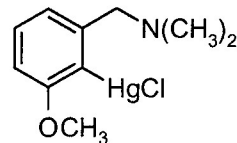
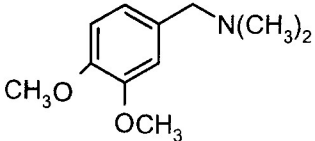
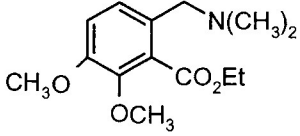
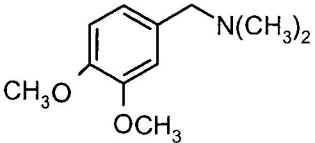
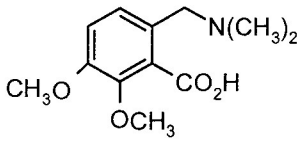
<p>N,N-Dimethylbenzylamine</p> 	<p>n-BuLi/ ether/ 25°C/ 20 h</p>	<p>BEt<sub>2</sub>(OCH<sub>3</sub>)</p>	<p>[2-((Dimethylamino)-methyl)phenyl]diethylborane</p>  <p>(20)<sup>84</sup></p>
<p>N,N-Dimethylbenzylamine</p> 	<p>n-BuLi/ ether/ TMEDA/ 25°C/ 8 h</p>	<p>1.) Trimethylborate B(OCH<sub>3</sub>)<sub>3</sub> 2.) Hydrolysis</p>	 <p>(60-65)<sup>73</sup></p>
<p>N,N-Dimethylbenzylamine</p> 	<p>s-BuLi/ THF/ TMEDA/ -90°C</p>	<p>CH<sub>3</sub>I/ -78°C</p>	<p>2-Methyl-N,N-dimethylbenzylamine</p>  <p>(&lt;1)<sup>74</sup></p>
<p>N,N-Dimethylbenzylamine</p> 	<p>n-BuLi/ n-hexane/ reflux/ 3 h</p>	<p>BCl<sub>3</sub>, -40°C</p>	<p>Dichloro(2-((dimethylamino)methyl)phenyl-C,N)boron</p>  <p>(62)<sup>85</sup></p>
<p>N,N-Dimethylbenzylamine</p> 	<p>LiBr/ Benzene, Octane/ 25°-30°C</p>	<p>Benzophenone Ph<sub>2</sub>CO</p>	<p>2-(dimethylamino-methyl)-triphenylcarbinol</p>  <p>(40)<sup>86</sup></p>

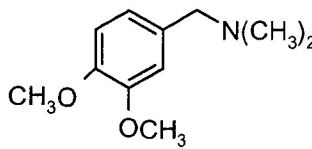
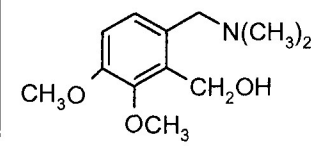
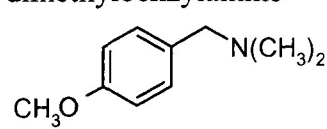
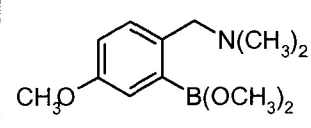
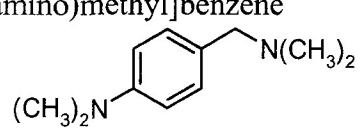
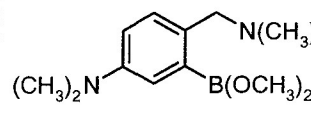
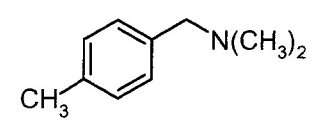
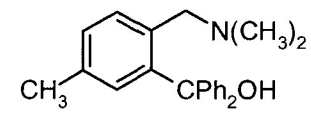
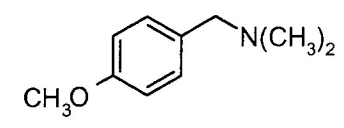
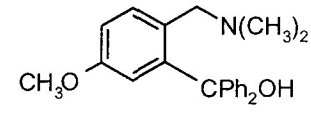
N-Methylbenzylamine 	n-BuLi/ ether/ n-hexane/ TMEDA/ 5 h	Benzophenone Ph <sub>2</sub> CO	2-(N-methylaminomethyl)- triphenylcarbinol  (50) <sup>87</sup>
N-Methylbenzylamine 	n-BuLi/ ether/ n-hexane/ TMEDA/ 5 h	Benzophenone Ph <sub>2</sub> CO	o-(N-methylaminomethyl)- diphenylcarbinol  (63) <sup>87</sup>
1-[(Dimethylamino)ethyl]- benzene 	n-BuLi/ ether/ TMEDA/ Reflux/ 7 h	Trimethyl- borate B(OCH <sub>3</sub> ) <sub>3</sub>	 (40-46) <sup>73</sup>
(-)(S)-N,N-Dimethyl-1- phenylethylamine 	n-BuLi/ n-hexane/ TMEDA	Ph <sub>2</sub> PCl	 (-)(S) (35) <sup>72</sup>
Dibenzylmethylamine 	n-BuLi/ ether/ 25°C/ 48 h	Deuterium oxide D <sub>2</sub> O	Dibenzylmethylamine-2d  (N.A.) <sup>88, 89</sup>
2-Methyl-N,N- dimethylbenzylamine 	n-BuLi/ ether/ 24 h	N.A.	2-N,N- Dimethylaminomethyl- benzyl lithium  (77) <sup>83</sup>



2-Methyl-N,N-dimethylbenzylamine 	n-BuLi/ THF/ 0°C	(CH <sub>3</sub> ) <sub>3</sub> SiCl	[2-((Trimethylsilyl)methyl)benzyl]- dimethylamine  (97) <sup>90</sup>
2-Methyl-N,N-dimethylbenzylamine 	n-BuLi/ ether or n-hexane	HgCl <sub>2</sub> / THF/ -78°C	 (55) <sup>77</sup>
2-Trimethylsilylbenzyl- dimethylamine 	n-BuLi/ ether/ 24 h	Trimethylsilyl chloride Si(CH <sub>3</sub> ) <sub>3</sub> Cl	2,6-Bis(trimethylsilyl)- benzyl dimethylamine  (64) <sup>83</sup>
2-N,N-Dimethylamino- methylbenzyl lithium 	N.A.	Trimethylsilyl chloride Si(CH <sub>3</sub> ) <sub>3</sub> Cl	2-Trimethylsilyl- methylbenzyl- dimethylamine  (55) <sup>83</sup>
2-Lithium-N,N-dimethylbenzylamine 	n-BuLi/ ether/ 25° to 30°C <sup>91,92</sup>	1- trimethylsilyl- hept-1-en-3-ol	 (50) <sup>93</sup>
2-Chloro-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	3-Chloro-2-(dimethylaminomethyl)- triphenylcarbinol  1 h (73) 24 h (81) <sup>92</sup>

2-Fluoro-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino- methyl)-3-fluoro- triphenylcarbinol  1 h (33) 24 h (0) <sup>92</sup>
	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino- methyl)-3- (diphenylvinyl)- triphenylcarbinol  1 h (23) 24 h (32) <sup>92</sup>
3,4-Dimethoxy-N,N-diethylbenzylamine 	n-BuLi/ ether/ 25° to 0°C/ 1 h	1.) ClCO <sub>2</sub> Et/ 0°C 2.) Hydrolysis 3.) 130°C/ 10-15 m	 95 (N.A. <sup>94</sup> )
2,6-Bis[(N,N-dimethylamino)- methyl]benzene 	n-BuLi/ ether/ TMEDA/ 25°C/ 8 h	1.) Trimethyl- borate B(OCH <sub>3</sub> ) <sub>3</sub> 2.) Hydrolysis	 (5-10) <sup>53</sup>
3-Methoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether/ 25° to 0°C/ 1 h	1.) ClCO <sub>2</sub> Et/ 0°C 2.) Hydrolysis 3.) 120-30°C/ 10-15 m	 (N.A. <sup>94</sup> ) <sup>95</sup>

3-Methoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino-methyl)-6-methoxy-triphenylcarbinol  1 h (26) 24 h (75) <sup>92</sup>
3-Trifluoromethyl-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino-methyl)-6-trifluoromethyl-triphenylcarbinol  1 h (72) 24 h (70) <sup>92</sup>
3-Methoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether or n-hexane	HgCl <sub>2</sub> / THF/ -78°C	 (71) <sup>77</sup>
3,4-Dimethoxy-N,N-dimethylbenzylamine 	n-BuLi/ 20°C/ 1-2 h	Ethyl chloroformate ClCO <sub>2</sub> Et 20°C/24 h	 (N.A.) <sup>94,96</sup>
3,4-Dimethoxy-N,N-dimethylbenzylamine 	n-BuLi/ 20°C/ 1-2 h	CO <sub>2</sub> /H <sub>3</sub> O <sup>+</sup>	 (71) <sup>96</sup>

3,4-Dimethoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether/ 0°C	(CH <sub>2</sub> O) <sub>n</sub> 15 h	 (92) <sup>97</sup>
4-Methoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether/ TMEDA/ 25°C/ 18 h	Trimethyl- borate B(OCH <sub>3</sub> ) <sub>3</sub>	 (70-80) <sup>53</sup>
4-N,N-Dimethylamino[(dimethylamino)methyl]benzene 	n-BuLi/ ether/ TMEDA/ 25°C/ 18 h	Trimethyl- borate B(OCH <sub>3</sub> ) <sub>3</sub>	 (74) <sup>53</sup>
4-Methyl-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino- methyl)-5-methyl- triphenylcarbinol  1 h (29) 24 h (82) <sup>92</sup>
4-Methoxy-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	2-(Dimethylamino- methyl)-5-methoxy- triphenylcarbinol  1 h (29) 24 h (70) <sup>92</sup>

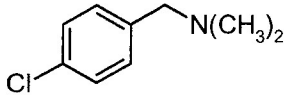
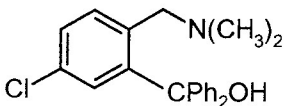
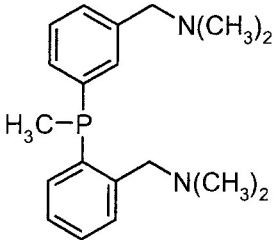
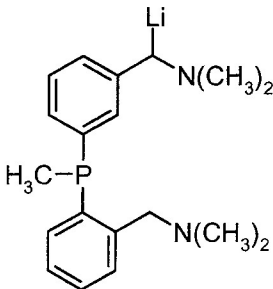
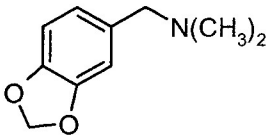
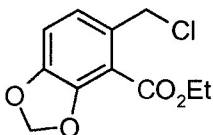
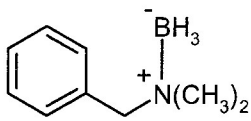

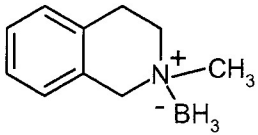
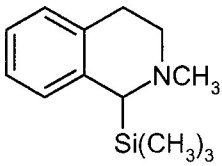
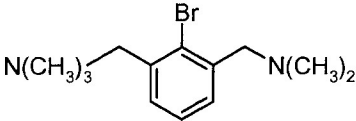
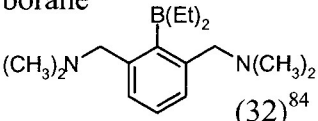
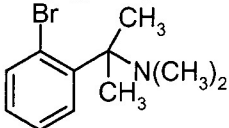
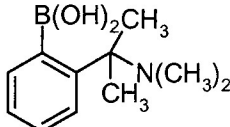
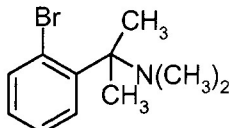
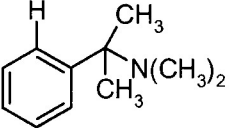
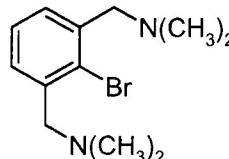
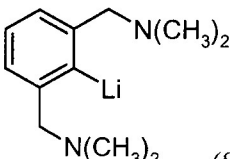
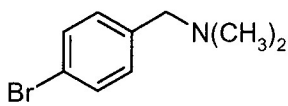
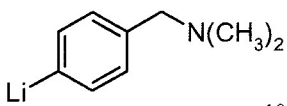
4-Chloro-N,N-dimethylbenzylamine 	n-BuLi/ ether/ n-hexane/ 25°-30°C	Benzophenone Ph <sub>2</sub> CO	5-Chloro-2-(dimethylaminomethyl)- triphenylcarbinol  1 h (72) 24 h (82) <sup>92</sup>
	t-BuLi/ Light Petroleum/ 1 h	N.A.	 (51) <sup>98</sup>
N,N-Dimethyl-3,4-(methylenedioxy)benzylamine 	n-BuLi/ THF/ -78°C/ 2 h	ClCO <sub>2</sub> Et/ -78°C to 23°C/ 3 h 45 m.	2-(Ethoxycarbonyl)-3,4-(methoxyenedioxy)- benzyl chloride  (45) <sup>99</sup>
	n-BuLi/ THF/ 25°C	1.) Trimethyl- silyl chloride Si(CH <sub>3</sub> ) <sub>3</sub> Cl 2.) EtOH/ reflux	 (71) <sup>100</sup>
	n-BuLi/ THF/ 25°C	1.) Trimethyl- silyl chloride Si(CH <sub>3</sub> ) <sub>3</sub> Cl 2.) EtOH/ reflux	 (64) <sup>100</sup>

Table 4. Halogen Metal Exchange Reactions of N,N-Dimethylbenzylamine and its Homologs.

Arene Exchanged	Conditions	Derivatization Reagent	Product and Yield (%) (Reference)
	n-BuLi/ 25°C, 23 h/ reflux, 4 h	BEt <sub>2</sub> (OCH <sub>3</sub> )	[2,6-Bis((dimethylamino)methyl)phenyl]diethylborane  (32) <sup>84</sup>
2-[1-(Dimethylamino)-1-methylethyl]phenyllithium 	n-BuLi/ ether/ 25°C/ 2 h	1.) B(OPr) <sub>3</sub> 2.) H <sup>+</sup>	 (9) <sup>101</sup>
2-[1-(Dimethylamino)-1-methylethyl]phenyllithium 	n-BuLi/ ether/ 25°C/ 2 h	1.) B(OPr) <sub>3</sub> 2.) H <sup>+</sup>	 (46) <sup>101</sup>
2-Bromo-N,N,N',N'-tetramethyl-3-phenylenediamine 	2 Li/ ether/	N.A.	2-Lithio-N,N,N',N'-tetramethyl-3-phenylenediamine  (80) <sup>102</sup>
4-Bromo-N,N-dimethylbenzylamine 	t-BuLi/ ether/ -78°C	N.A.	4-Lithio-N,N-dimethylbenzylamine  (80-90) <sup>103</sup>

## II. EXPERIMENTAL

### A. Reagents

Unless otherwise indicated, substrates and reagents were obtained from the Aldrich Chemical Company. n-Butyllithium (n-BuLi) was obtained from FMC Corp. (1.6 M in hexane, standardized by FMC prior to shipping) and Aldrich Chemical Company (10 M and 2.5 M in hexane and 2.0 M in cyclohexane) and refrigerated. N,N-dimethylbenzylamine (DMBA) (**4**) and N,N-dimethylaniline (DMA) (**3**) were kept over 4 Å molecular sieves. 3-Methoxy-N,N-dimethylbenzylamine (3-MDMBA) (**7**) was used without further purification. 3-Methoxydimethylaniline (3-MDMA) (**6**), and N,N,N',N'-tetramethyl-1,4-phenylenediamine (1,4-TMPDA) (**5**) were obtained from Lancaster Chemical Company and used without further purification. Chlorotrimethylsilane (ClTMS) was stored over 4 Å molecular sieves. For use as a derivatizing agent, ClTMS was diluted to a 2.0 M solution in dry n-hexane and the solution was stored over 4 Å molecular sieves. Both liquids were kept refrigerated. Tetrahydrofuran (THF) and tetramethylethylenediamine (TMEDA) were stored over 4 Å molecular sieves. Methyl tert-butyl ether (MTBE) was obtained from ACROS Chemical Company and dried over 4 Å molecular sieves. Cyclohexane and n-hexane were dried over 4 Å molecular sieves. Diethyl ether was obtained from EM Scientific and stored over 4 Å molecular sieves. Ethyl acetate was used without any modification. Silica gel 200-400 mesh, 60 Å was used without any modification.

Most of the reagents used during experimental procedures did not require any special preparation. However, alkyllithium reagents are spontaneously combustible in the presence of air and water; therefore special precautions were necessary. *n*-BuLi was supplied by Aldrich and contained within a sure/seal™ bottle. To extract the *n*-BuLi a 12", 18-20 gauge needle with syringe was placed through the sure/seal™ top, along with a second 1" needle connected to a nitrogen gas tank. Backpressure from the flow of nitrogen into the *n*-BuLi bottle pushed the *n*-BuLi into the syringe to achieve the desired volume of reagent.

#### B. Procedure for Metalations in *n*-Hexane and Cyclohexane

A 200 mL round bottom flask containing a magnetic stir bar was filled with dry *n*-hexane or dry cyclohexane and 0.04 mol of the DMA or DMBA substrate, (0.02 mol for 3-MDMA, 3-MDMBA, and 1,4-TMPDA). Next, varying molar equivalents of catalyst (TMEDA, THF, or MTBE) were added to the flask. After the flask was fitted with a septum and purged with nitrogen, it was placed in a constant temperature bath set at 25°C, 45°C, or 60°C. Once temperature equilibration was reached, 0.02 or 0.04 eq. of *n*-BuLi (10.0 M or 2.0 M in hexanes or 2.5 M in cyclohexane) was added via syringe. A 1:1 ratio of reactants was always maintained. Since the *n*-BuLi was used as a solution in hexanes (or cyclohexane), the volume of solvent added initially was 30 mL minus the volume of *n*-BuLi added to the reaction. The initial solutions were thus 0.02 mol in 30 mL solvent (0.67 M) or 0.04 mol in 30 mL solvent (1.3 M).

#### C. Procedure for Metalations in Diethyl Ether and Other Neat Solvents

A 200 mL round bottom flask containing a magnetic stir bar was filled with 30 mL of ether or other neat solvents (MTBE, TMEDA, THF) and 0.04 mol of the DMA or DMBA substrate (0.02 mol for 3-MDMA, 3-MDMBA, and 1,4-TMPDA). The flask was then placed



in a constant temperature bath set at 25°C, 45°C, or 60°C. Once temperature equilibration was reached, 0.04 eq. of n-BuLi (4 mL of 10 M in hexanes) was added via syringe.

#### D. Sampling Procedures

One-milliliter aliquots of the reactions were taken using a 5 or 10 mL syringe fitted with a 12", 18-20 gauge needle. Some of the reactions produced excess pressure, which was vented before sampling by the insertion of a 1" needle through the septum. Samples were taken from the solution in such a manner as to not disturb the stir bar. The majority of reactions conducted contained a significant amount of flocculent precipitate; therefore, rapid stirring was required and the sample was taken with a wide-bore 12" needle to ensure as homogeneous a sample as possible.

#### E. Determination of the Extent of Metalation

During the reaction 1.0 mL aliquots were removed from the reaction flask at 2, 10, 30 m, and 1, 2, 3, 4, 6, 8, 24, and 26 h. These aliquots were added to vials containing 1.0 mL solution of 2.0 M CITMS. These samples were worked up by the addition of 4.0 mL of saturated Na<sub>2</sub>CO<sub>3</sub> and 3.0 mL of n-hexane to each vial followed by analysis of the organic layer by GC and GC/MS.

#### F. Instrumental Analysis

Analyses were performed on a HP 5890 gas chromatograph with an OV-17 packed column and a FID detector. Standard conditions used involved the injector and detector temperature being held at 250°C, and the column temperature being ramped from 120°C to 300°C at a rate of 10 degrees/min. The flow rate of the carrier gas, N<sub>2</sub>, was kept between 30 psi and 40 psi. Peak areas were determined using digital integration. Relevant retention times, in minutes, are given in Table 5.

Table 5. Relevant Retention Times of Aryl Substrates and Products.

Substrate	Retention Times (min.)
N,N-Dimethylaniline ( <b>3</b> )	2.2
2-TMS-N,N-dimethylaniline ( <b>8</b> )	2.8
N,N-Dimethylbenzylamine ( <b>4</b> )	0.9
2-TMS-N,N-dimethylbenzylamine ( <b>9</b> )	2.5
$\alpha$ -TMS-N,N-dimethylbenzylamine ( <b>10</b> )	2.4
N,N,N',N'-Tetramethyl-1,4-phenylenediamine ( <b>5</b> )	5.5
2-TMS-N,N,N',N'-Tetramethyl-1,4-phenylenediamine ( <b>11</b> )	6.1
3-Methoxy-N,N-dimethylaniline ( <b>6</b> )	6.1
2-TMS-3-methoxy-N,N-dimethylaniline ( <b>12</b> )	8.7
3-Methoxy-N,N-dimethylbenzylamine ( <b>7</b> )	3.9
2-TMS-3-methoxy-N,N-dimethylbenzylamine ( <b>13</b> )	5.8

Percent metalation was determined by taking the ratio of the product peak to the total area of the product plus the starting material after application of a correction factor (see Section H). Uncorrected percentage(s) of secondary products were also determined.

NMR analysis was performed using a JEOL CPF 270 with broad band and variable temperature capabilities. GC/MS analysis was conducted on an Agilent 5973 MSD with 6890 N Network GC system.

#### G. Isolation of TMS- Derivatives

After a designated period of time each metalated intermediate was derivatized by addition of undiluted (neat) ClTMS to the reaction solution. The reaction mixtures were concentrated by evaporation of excess solvent. Column chromatography was used to separate the concentrated TMS product mixture from starting material and by-product(s). One gram of a

selected reaction mixture containing a high yield of each of the indicated substrates in Table 6 was run through a column containing 200-400 mesh, 60 Å silica gel with a 10% ethyl acetate/n-hexane solution. Samples were collected from the column and tested by GC for extent of 2-TMS product. Samples containing only the TMS product were combined and the remaining solvent evaporated. The concentrated product sample was then analyzed, characterized and used to standardize GC spectra (see Section H).

#### H. Standardization of GC Spectra

Separate solutions in n-hexane, with equal moles, of both the starting material and the TMS-product were made in 50 mL volumetric flasks. Using a pipet, solutions of starting material to product ratios were made: 1/5, 2/4, 3/3, 4/2, and 5/1. GC analysis was performed on each of the samples, and the mol ratio of the starting material to the product was plotted against the corresponding GC area ratio of starting material to the product. The result was a straight line with the slope being the correction factor. Table 6 lists the calculated correction factors for all substrates isolated.

Table 6. Calculated Correction Factors for TMS Products.

Product	Correction Factor
2-TMS-N,N-dimethylaniline ( <b>8</b> )	0.77
2-TMS-N,N-dimethylbenzylamine ( <b>9</b> )	0.63
$\alpha$ -TMS-N,N-dimethylbenzylamine ( <b>10</b> )	Not Isolated
2-TMS-N,N,N',N'-Tetramethyl-1,4-phenylenediamine ( <b>11</b> )	0.64
2-TMS-3-methoxy-N,N-dimethylaniline ( <b>12</b> )	Not Isolated
2-TMS-3-methoxy-N,N-dimethylbenzylamine ( <b>13</b> )	Not Isolated

The correction factors were applied to the formula for determination of percent yield. The general formula of percent yield used for each substrate was the following:

$$[(\text{ortho-product} \times \text{CF}) / ((\text{SM}) + (\alpha\text{-product}) + (\text{ortho-product} \times \text{CF}))] \times 100 = \% \text{ yield}$$

Where CF is the GC correction factor for a particular ortho-product and SM represents the area under the starting material peak. The area under the ortho- and  $\alpha$ - (applicable only for DMBA) product peaks is entered in the appropriate places. Determination of  $\alpha$ -product yield can be made by replacing the (ortho-product  $\times$  CF) in the numerator with ( $\alpha$ -product). As the CF for the  $\alpha$ -product was not determined, calculations provide only an uncorrected yield for the  $\alpha$ -product.

## I. Derivatives Prepared

### 1. 2-Trimethylsilyl-N,N-Dimethylaniline (8)

A 1:1:0.1 DMA:n-BuLi:TMEDA metalation in cyclohexane at 60°C was performed using twice the usual amounts (0.08 mol DMA, 0.08 mol n-BuLi and 0.008 mol TMEDA in 60 mL cyclohexane). After 26 h the reaction was quenched with 3.9 eq. of dry ClTMS and then washed with 30 mL of saturated Na<sub>2</sub>CO<sub>3</sub>. Analysis of the reaction solution by GC indicated an ortho-TMS percent yield of 69.9%. The organic layer was separated by extraction, and left to evaporate until approximately 5 mL remained. Column chromatography was used to separate the TMS product from starting material and by-product(s). After product isolation procedures the pure sample of **8** was analyzed by GC/MS, NMR, and elemental analysis. The correction factor standard for the isolated product was  $8.4 \times 10^{-3}$  M and the starting material standard was  $7.9 \times 10^{-3}$  M.

GC/MS: m/z % relative abundance, assignment: 193 (48, M+), 178 (90, M-15), 163 (85, M-30), 148 (10, M-45), 120 (100, M-73).

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  0.28 (s, 9H), 2.61 (s, 6H), 7.28-7.47 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.15, 22.72, 31.66, 46.93, 121.58, 124.93, 130.27, 135.28.

Anal.<sup>104</sup>  $\text{C}_{11}\text{H}_{19}\text{NSi}$  calc'd.: C, 68.33%; N, 7.24%. Found: C, 68.43%; N, 6.70%.

## 2. 2-Trimethylsilyl-N,N-Dimethylbenzylamine (9)

A 1:1:0.8 DMBA:n-BuLi:TMEDA metalation in cyclohexane at 60°C was performed using twice the usual amounts (0.08 mol DMBA, 0.08 mol n-BuLi and 0.064 mol TMEDA in 60 mL cyclohexane). After 26 h the reaction was quenched with 3.1 eq. of dry ClTMS and then washed with 30 mL of saturated  $\text{Na}_2\text{CO}_3$ . Analysis of this solution by GC indicated an ortho-TMS percent yield of 94.6%. The organic layer was then separated by extraction, and left to evaporate until approximately 5 mL remained. Column chromatography was used to separate the concentrated TMS product mixture from starting material and by-product(s). After product isolation procedures the pure sample of **9** was analyzed by GC/MS and NMR. This data was consistent with the characterization performed by C. T. Viswanathan et al<sup>83</sup>. The correction factor standard for the isolated product was 0.203 M and the starting material standard was 0.207 M.

GC/MS: m/z % relative abundance, assignment: 207 (33, M<sup>+</sup>), 192 (100, M-15), 177 (8, M-30), 162 (3, M-45), 149 (47, M-58), 134 (19, M-73), 73 (29, TMS<sup>+</sup>), 58 (90,  $[\text{CH}_2=\text{N}(\text{CH}_3)_2]^+$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  0.34 (s, 9H), 2.25 (s, 6H), 3.51 (d, 2H), 7.2-87.55 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  45.34, 64.67, 126.24, 128.90, 128.99, 134.83, 138.87, 145.37, 155.01.

## 3. $\alpha$ -Trimethylsilyl-N,N-Dimethylbenzylamine (10)

DMBA metalation solutions prepared under all conditions were analyzed for evidence of the known product of lateral ( $\alpha$ ) metalation. This product was found under most conditions.

Although this product was not isolated, a sample containing **10** was analyzed by GC/MS.

GC/MS: m/z % relative abundance, assignment: 207 (2, M<sup>+</sup>), 134 (100, M-73).

#### 4. 2-TMS-N,N,N',N'-Tetramethyl-1,4-phenylenediamine (11)

A 1:1:0.1 1,4-TMPDA:n-BuLi:TMEDA metalation in cyclohexane at 60°C was performed using twice the usual amounts (0.04 mol 1,4-TMPDA, 0.04 mol n-BuLi, 0.004 mol TMEDA in 60 mL cyclohexane). After 26 h the reaction was quenched with 3.9 eq. of dry ClTMS and then washed with 30 mL of saturated Na<sub>2</sub>CO<sub>3</sub>. Analysis of this solution by GC indicated production of the 2-TMS product in 92.8% yield. The organic layer was then separated by an extraction process, and left to evaporate until approximately 10 mL of solution remained. Column chromatography was used to separate the TMS product from starting material and by-product(s). After product isolation procedures, the pure sample of **11** was analyzed by GC/MS, NMR, and elemental analysis. The correction factor standard for the isolated product was 0.146 M and the starting material standard was 0.146 M.

GC/MS: m/z % relative abundance, assignment: 236 (78, M<sup>+</sup>), 221 (26, M-15), 206 (95, M-30), 191 (18, M-45), 163 (40, M-73), 146 (8, M-90), 73 (100, TMS<sup>+</sup>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.31 (s, 9H), 2.6 (s, 6H), 2.95 (s, 6H), 6.8–δ6.87 (m, 2H), 7.22–δ7.25 (d, 1H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 41.13, 47.28, 115.0, 118.90, 122.35, 138.91, 148.20, 151.19.

Anal.<sup>105</sup> C<sub>13</sub>H<sub>24</sub>N<sub>2</sub>Si calc'd.: C, 66.04%; H, 10.23%. Found: C, 65.53%; H, 10.51%.

#### 5. 2-Trimethylsilyl-3-Methoxy-N,N-Dimethylaniline (12)

Analysis was performed on several product solutions resulting from metalation of 3-MDMA. Evidence of production of **12** in low yield was found in several of these. Although

this product was not isolated, a mass spectrum of **12** was obtained by GC/MS.

GC/MS: m/z % relative abundance, assignment: 223 (100, M<sup>+</sup>), 208 (93, M-15), 193 (34, M-30), 178 (87, M-45), 73 (8, TMS<sup>+</sup>).

6. 2-Trimethylsilyl-3-Methoxy-N,N-Dimethylbenzylamine (13)

Analysis was performed on several product solutions resulting from metalation of 3-MDMBA. Evidence of production of **13** in low yield was found in several of these. Although this product was not isolated, a mass spectrum of **13** was obtained by GC/MS.

GC/MS: m/z % relative abundance, assignment: 237 (3, M<sup>+</sup>), 222 (70, M-15), 194 (100, M-43), 73 (42, TMS<sup>+</sup>), 58 (65, [CH<sub>2</sub>=N(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>).

J. Summary of Selected Metalation Reactions

During the course of experimentation numerous reaction conditions were attempted to achieve maximum DoM. The collection of data obtained from these experiments would be far too comprehensive for inclusion in this thesis. Below are five tables highlighting the reactions conditions for each of the five substrates. Selections included within these tables were chosen to illustrate a variety of conditions involving variation in solvents, concentration, type of catalyst, and temperature. Many of the reactions included in these tables are the focus of graphs and discussion in the next section.

Table 7. Summary of Conditions and Yields for Selected Metalations of DMA (3)

## 1.) Equivalent Amounts of TMEDA at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number(s)	DMA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT/RS/MC <sup>106</sup> 1, 2	1:1:0.1	25	18.8(6 h), 20.6(6 h)
MT/RS/MC <sup>106</sup> 3, 4	1:1:0.3	25	60.3(6 h), 58.8(6 h)
MT/RS/MC <sup>106</sup> 5, 6	1:1:0.5	25	67.4(6 h), 66.5(4 h)
MT/RS/MC <sup>106</sup> 7, 8	1:1:0.8	25	62(6 h), 65.7(6 h)
MT/RS/MC <sup>106</sup> 9, 10	1:1:1	25	64(6 h), 57(6 h)
MT/RS/MC <sup>106</sup> 11, 12	1:1:1.5	25	59(6 h), 54.1(6 h)
MT/RS/MC <sup>106</sup> 13, 14	1:1:2	25	55.8(4 h), 60(4 h)
MT/DC <sup>107</sup> 56, 57	1:1:0.05	45	63.9(26 h), 69.5(24 h)
MT/DC <sup>107</sup> 58, 59	1:1:0.2	45	70.6(24 h), 60.6(4 h)
MT/DC <sup>107</sup> 68	1:1:0.05	60	28.6(26 h)
MT/DC <sup>107</sup> 69	1:1:0.1	60	77.4(24 h)
MT/DC <sup>107</sup> 70	1:1:0.2	60	69.8(24 h)

## 2.) Equivalent Amounts of TMEDA at 0.04 mol/eq. in 30 mL Cyclohexane

Run Number(s)	DMA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT/RS/MC <sup>106</sup> 15, 40, 44	1:1:0.1	25	29.5(6 h), 36(6 h), 36.3(6 h)
MT/RS/MC <sup>106</sup> 17, 18	1:1:0.3	25	67.2(6 h), 68.8(6 h)
MT/RS/MC <sup>106</sup> 19, 20	1:1:0.5	25	63.5(4 h), 68(6 h)
MT/RS/MC <sup>106</sup> 21, 22	1:1:0.8	25	71(6 h), 67.3(6 h)
MT/RS/MC <sup>106</sup> 23, 24	1:1:1	25	64.7(4 h), 67.5(6 h)
MT/RS/MC <sup>106</sup> 25, 42, 46	1:1:1.5	25	64.3(22 h), 61(6 h), 67.7(6 h)
MT/RS/MC <sup>106</sup> 26, 30, 43, 47	1:1:2	25	57(6 h), 71(6 h), 54.1(6 h), 61.6(6 h)
MT/AW <sup>108</sup> 84	1:1:0.01	45	70.8(26 h)
MT/AW <sup>108</sup> 81	1:1:0.1	45	80.6(24 h)
MT/AW <sup>108</sup> 82	1:1:0.2	45	84.9(6 h)
MT/AW <sup>108</sup> 83	1:1:0.5	45	80.3(6 h)
MT/AW <sup>108</sup> 85	1:1:1	45	67.9(4 h)
MT/AW <sup>108</sup> 87	1:1:2	45	63.6(2 h)



MT/AW <sup>108</sup> 76, 97	1:1:0.01	60	63.3(26 h), 59.5(26 h)
MT/AW <sup>108</sup> 64, 72, 89, 98	1:1:0.05	60	82.8(26 h), 83.2(24 h), 85.5(26 h), 82.3(24 h)
MT/AW <sup>108</sup> 65, 73, 90	1:1:0.1	60	83(6 h), 90.3(26 h), 88(26 h)
MT/AW <sup>108</sup> 66, 74	1:1:0.2	60	87(6 h), 86.6(26 h)
MT/AW <sup>108</sup> 67, 75	1:1:0.5	60	80.4(6 h), 74.8(26 h)
MT/AW <sup>108</sup> 77, 93	1:1:1	60	60.5(4 h), 67.2(4 h)
MT/AW <sup>108</sup> 94, 101	1:1:1.5	60	58.6(1 h), 58.44(1 h)
MT/AW <sup>108</sup> 95, 102	1:1:2	60	58.2(1 h), 58.9(1 h)

3.) Equivalent Amounts at 0.04 mol/eq. in 30 mL THF

Run Number(s)	DMA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT/DC <sup>107</sup> 62,63	1:1	45	11(30 m), 15(30 m)
MT/DC <sup>107</sup> 60,61	1:1	60	9.8(2 h), 15(30 m)

4.) Equivalent Amounts at 0.04 mol/eq. in 30 mL MTBE

Run Number	DMA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT 126	1:1	25	5(24 h)

5.) Equivalent Amounts of THF at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number	DMA:n-BuLi:THF	Temp (°C)	Maximum Percent Yield Attained
MT/RS/MC <sup>106</sup> 32	1:1:1	25	2.5(6 h)
MT/RS/MC <sup>106</sup> 34	1:1:3	25	10.9(6 h)
MT/RS/MC <sup>106</sup> 36	1:1:5	25	19.9(6 h)
MT/RS/MC <sup>106</sup> 37	1:1:6	25	20.3(6 h)
MT/RS/MC <sup>106</sup> 38	1:1:7	25	15.2(4 h)

6.) Equivalent Amounts of (-)-Sparteine at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number(s)	DMA:n-BuLi:(-)-Sparteine	Temp (°C)	Maximum Percent Yield Attained
MT/RS/MC <sup>106</sup> 48,51	1:1:0.05	25	9.8(6 h), 5.6(6 h)
MT/RS/MC <sup>106</sup> 49,50	1:1:0.1	25	9.1(6 h), 9.8(6 h)

Table 8. Summary of Conditions and Yields for Selected Metalations of DMBA (4)

1.) Equivalent Amounts of TMEDA at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number(s)	DMBA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT 11, 12	1:1:0	25	o- 26.7(4 h), 26.7(4 h) α- 0,0
MT 37, 38, 84, 85	1:1:0.03	25	o- 43(6 h), 39.5(6 h), 47.3(6 h), 48.2(6 h) α- 5.1(6 h), 3.8(6 h), 0.97(6 h), 0.97(6 h)
MT 39, 40, 86, 87	1:1:0.05	25	o- 52(6 h), 50.4(6 h), 53.9(6 h), 58.3(6 h) α- 6(6 h), 4.4(6 h), 3.7(6 h), 3.8(6 h)
MT 15, 16, 92, 93	1:1:0.1	25	o- 72.7(6 h), 85.6(6 h), 57.2(6 h), 54.5(6 h) α- 10(6 h), 11(6 h), 7.9(6 h), 7.8(26 h)
MT 41, 42	1:1:0.2	25	o- 65.5(4 h), 66.4(3 h) α- 16(3 h), 14.9(3 h)
MT 17, 18, 94, 95	1:1:0.3	25	o- 65.5(4 h), 56.6(3 h), 59.5(6 h), 54(6 h) α- 17.2(4 h), 18.2(6 h), 16.7(24 h), 15.2(6 h)
MT 43, 44, 96, 97	1:1:0.4	25	o- 61(3 h), 60.5(4 h), 57.6(2 h), 49.8(6 h) α- 25.7(2 h), 19.7(3 h), 17.1(2 h), 15.7(26 h)
MT 19, 98, 99	1:1:0.5	25	o- 47.1(4 h), 54.3(26 h), 46.7(4 h) α- 14.4(4 h), 18.3(26 h), 20.6(24 h)
MT 61A, 61B	1:1:1	25	o- 42(24 h), 44.3(24 h) α- 26.5(24 h), 26.4(24 h)
MT 23	1:1:2	25	o- 38(2 h) α- 18.3(2 h)

## 2.) Equivalent Amounts of TMEDA at 0.04 mol/eq. in 30 mL Cyclohexane

Run Number(s)	DMBA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT 25, 26	1:1:0	25	o- 32(6 h), 33(6 h) α- 0,0
MT 47, 48	1:1:0.05	25	o- 34.7(6 h), 30(3 h) α- 3.7(6 h), 3.7(6 h)
MT 27, 28	1:1:0.1	25	o- 58.8(6 h), 55(6 h) α- 12.8(6 h), 12.8(6 h)
MT 29, 30	1:1:0.3	25	o- 59(4 h), 54.5(4 h) α- 21.3(4 h), 21(4 h)
MT 31, 32	1:1:0.5	25	o- 55(6 h), 54.5(6 h) α- 21.7(6 h), 25(6 h)
MT 33, 34	1:1:1	25	o- 50(6 h), 60.4(3 h) α- 22.8(6 h), 25.1(4 h)
MT 35, 36	1:1:2	25	o- 53(4 h), 52.5(4 h) α- 21(6 h), 23(4 h)
MT 141	1:1:0	45	o- 57.6(26 h) α- 0.5(2 h)
MT 111, 142	1:1:0.05	45	o- 75.6(24 h), 79(6 h) α- 5.1(3 h), 5.6(4 h)
MT 112, 143	1:1:0.1	45	o- 77.5(24 h), 87.7(6 h) α- 8.7(3 h), 9(2 h)
MT 114, 145	1:1:0.5	45	o- 74.1(6 h), 59.7(26 h) α- 27(24 h), 27.7(2 h)
MT 128, 129	1:1:0	60	o- 33.9(6 h), 55.8(6 h) α- 0.4(30 m), 0.3(1 h)
MT 115, 132	1:1:0.05	60	o- 84.8(6 h), 68.2(26 h) α- 2.2(2 h), 3.6(10 m)
MT 116, 119, 133	1:1:0.1	60	o- 88.6(24 h), 70.2(24 h), 72.8(3 h) α- 5(10 m), 8.1(30 m), 7.2 (30 m)
MT 117, 138	1:1:0.2	60	o- 78.1(6 h), 75.6(6 h) α- 9.2(30 m), 13.4(2 h)
MT 118, 139	1:1:0.5	60	o- 64.5(6 h), 68.8(6 h) α- 18.4(3 h), 21.1(1 h)
MT 127, 131	1:1:1	60	o- 54.2(26 h), 58(24 h) α- 26.1(30 m), 29.4(30 m)

## 3.) Equivalent Amounts at 0.04 mol/eq. in 30 mL THF

Run Number(s)	DMBA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT 78, 79	1:1	25	o- 47.7(26 h), 29(6 h) α- 9.8(2 h), 9.5(30 m)
MT 107, 108	1:1	45	o- 47.8(4 h), 40.7(4 h) α- 8.4(1 h), 12(10 m)
MT 109, 110	1:1	60	o- 46.7(2 h), 39.2(2 h) α- 12(10 m), 9.3(10m)

## 4.) Equivalent Amounts at 0.04 mol/eq. in 30 mL TMEDA

Run Number(s)	DMBA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT 80, 81	1:1	25	o- 33(26 h), 29.4(26 h) α- 16.4(24h), 14.2(26 h)

## 5.) Equivalent Amounts at 0.04 mol/eq. in 30 mL Ether

Run Number	DMBA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT 161	1:1	25	o- 69.9(3 h) α- 0.86(4 h)

## 6.) Equivalent Amounts at 0.04 mol/eq. in 30 mL MTBE

Run Number	DMBA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT 125	1:1	25	o- 63.9(24 h) α- 0.8(1 h)

## 7.) Equivalent Amounts of MTBE at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number(s)	DMBA:n-BuLi:MTBE	Temp (°C)	Maximum Percent Yield Attained
MT 151	1:1:0.7	25	o- 62.5(6 h) α- 0.87(4 h)
MT 152	1:1:1	25	o- 75(6 h) α- 1.03(4 h)
MT 179, 180	1:1:0	60	o- 57.6(7 h), 56.3(5 h) α- 1.3(2 h), 1.5(2 h)

MT 157, 163, 183	1:1:0.7	60	o- 94.7(4 h), 94.9(7 h), 94.1(7 h) α- 2.2(30 m), 2.1(30 m), 2(1 h)
MT 147, 158, 185	1:1:1	60	o- 90.3(2 h), 95(4 h), 94(6 h) α- 1.1(30 m), 2.1(1 h), 2.2(1 h)
MT 165, 186	1:1:1.5	60	o- 86(7 h), 88.6(4 h) α- 1.9(10m), 1.5(10m)

## 8.) Equivalent Amounts of MTBE at 0.04 mol/eq. in 30 mL Cyclohexane

Run Number(s)	DMBA:n-BuLi:MTBE	Temp (°C)	Maximum Percent Yield Attained
MT 169, 176	1:1:0.7	60	o- 74.4(8 h), 78(6 h) α- 1.4(1 h), 1.3(30 m)
MT 170, 177	1:1:1	60	o- 92.5(5 h), 99(4 h) α- 1.6(10 m), 1.5(1 h)
MT 171, 178	1:1:1.5	60	o- 67(2 h), 92(7 h) α- 1.4(10 m), 3.8(10 m)

## 9.) Equivalent Amounts of THF at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number(s)	DMBA:n-BuLi:THF	Temp (°C)	Maximum Percent Yield Attained
MT 62, 63	1:1:1	25	o- 33.6(6 h), 28.4(1 h) α- 3.3(6 h), 2.2(6 h)
MT 66, 67	1:1:4	25	o- 36.3(6 h), 33.3(4 h) α- 8.2(3 h), 8.6(4 h)

## 10.) Equivalent Amounts of THF at 0.04 mol/eq. in 30 mL Cyclohexane

Run Number(s)	DMBA:n-BuLi:THF	Temp (°C)	Maximum Percent Yield Attained
MT 72, 73	1:1:1	25	o- 34(26 h), 32.7(6 h) α- 2.9(6 h), 2.9(6 h)
MT 70	1:1:4	25	o- 54.8(26 h) α- 7.6(4 h)

## 11.) Equivalent Amounts of (-)-Sparteine at 0.04 mol/eq. in 30 mL n-Hexanes

Run Number	DMBA:n-BuLi:(-)-Sparteine	Temp (°C)	Maximum Percent Yield Attained
MT 123	1:1:0.05	25	o- 69.5(26 h) α- 2.7(4 h)
MT 124	1:1:0.1	25	o- 65.6(24 h) α- 4.4(4 h)

Table 9. Summary of Conditions and Yields for Selected Metalations of 1,4-TMPDA (5)

## 1.) Equivalent Amounts of TMEDA at 0.02 mol/eq. in 30 mL Cyclohexane

Run Number(s)	1,4-TMPDA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT/JT <sup>109</sup> 27	1:1:0.1	25	41.4(2 h)
MT/JT <sup>109</sup> 28	1:1:0.2	25	58.1(2 h)
MT/JT <sup>109</sup> 10, 14, 23	1:1:0.1	60	87(6 h), 92.8(26 h), 90.8(6 h)
MT/JT <sup>109</sup> 11, 24	1:1:0.2	60	93.6(1 h), 91.1(26 h)

Table 10. Summary of Conditions and Yields for Selected Metalations of 3-MDMA (6)

## 1.) Equivalent Amounts of TMEDA at 0.02 mol/eq. in 30 mL Cyclohexane

Run Number(s)	3-MDMA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT/JT <sup>109</sup> 45, 46	1:1:0	60	3.7(1.5 h), 3.7(4 h)
MT/JT <sup>109</sup> 29, 30	1:1:0.05	60	19.2(2 m), 18.6(1.5 h)
MT/JT <sup>109</sup> 5, 33	1:1:0.1	60	7.8(3 h), 13.9(2 m)
MT/JT <sup>109</sup> 6, 34, 38	1:1:0.2	60	6(1 h), 6.5(30 m), 6.2(10 m)

## 2.) Equivalent Amounts at 0.02 mol/eq. in 30 mL THF

Run Number	3-MDMA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT/JT <sup>109</sup> 26	1:1	25	20.9(2 h)

## 3.) Equivalent Amounts at 0.02 mol/eq. in 30 mL Ether

Run Number	3-MDMA:n-BuLi	Temp (°C)	Maximum Percent Yield Attained
MT/JT <sup>109</sup> 9	1:1	25	9.6(4 h)

Table 11. Summary of Conditions and Yields for Selected Metalations of 3-MDMBA (7)

## 1.) Equivalent Amounts of TMEDA at 0.02 mol/eq. in 30 mL Cyclohexane

Run Number(s)	3-MDMBA:n-BuLi:TMEDA	Temp (°C)	Maximum Percent Yield Attained
MT/JT <sup>109</sup> 43, 44	1:1:0	60	45.5(4 h), 41.8(4 h)
MT/JT <sup>109</sup> 31, 32	1:1:0.05	60	54(2 h), 72.7(2 h)
MT/JT <sup>109</sup> 12, 35	1:1:0.1	60	74.7(2 m), 53.1(1 h)
MT/JT <sup>109</sup> 4, 13	1:1:0.2	60	76.6(1 h), 85.7(10 m)

## 2.) Equivalent Amounts of MTBE at 0.02 mol/eq. in 30 mL n-Hexane

Run Number	3-MDMBA:n-BuLi:MTBE	Temp (°C)	Maximum Percent Yield Attained
MT 167	1:1:0.7	60	56.2(6 h)
MT 168	1:1:1	60	46(5 h)

## 3.) Equivalent Amounts of MTBE at 0.02 mol/eq. in 30 mL Cyclohexane

Run Number	3-MDMBA:n-BuLi:MTBE	Temp (°C)	Maximum Percent Yield Attained
MT 173	1:1:0.7	60	44(6 h)
MT 174	1:1:1	60	41(8 h)

### III. RESULTS AND DISCUSSION

#### A. Objectives

This project involved the investigation of the catalyzed ortho-metalation (DoM) of dimethylarylamine substrates, N,N-dimethylaniline (**3**), N,N-dimethylbenzylamine (**4**) and related arylamines (**5**, **6**, and **7**) in hydrocarbon solvents. The response to various catalytic systems as measured by rates and extents of metalation has resulted in more efficient metalation procedures for both substrates, the principal goal of the project. New insights into the mechanism of the DoM reaction have been gained as well. The importance of coordination can be expanded from the data obtained from the DoM of these two substrates. After extensive studies on these two principal substrates, it was of interest to explore the effect on DoM by adding a second DMG group to each of these two principal arylamine systems. Two of these compounds possessed a methoxy group in the meta- position to either a dimethylamino- or dimethylaminomethyl- DMG, namely, 3-methoxy-N,N-dimethylaniline (**6**) and 3-methoxy-N,N-dimethylbenzylamine (**7**). The expected result is that each of these compounds would produce higher yields and a faster rate of metalation than those of the monosubstituted analogs. The rationale behind this theory is that the added electron withdrawing capabilities as well as coordinating abilities of the methoxy group would both increase the acidity of the ring hydrogens as well as the n-BuLi activation ability. In addition, it may be possible for each of these compounds to undergo metalation via the substrate-catalyzed mechanism. Neither of these hypotheses were realized.



The final compound, N,N,N',N'-tetramethyl-1,4-phenylenediamine (**5**), possessed two dimethylamino substituents oriented para to each other on a benzene ring. Metalation of this substrate revealed a hypothesized contribution of the opposing  $\pi$ -resonance effect.

## B. Background

The initial study of the metalation of anisole in hydrocarbon solvents at 25°C revealed that, uncatalyzed, only 6-8% extent of metalation took place in 24 h.<sup>8</sup> The addition of 3 eq. THF, as a catalyst, to the reaction mixture increases this yield to 85%. A similar reaction with 0.1 eq. TMEDA and 1.0 eq. anisole produced yields over 90% at 60°C. In anticipation of repeating the success achieved with anisole, both of the principal substrates were metalated under similar and related conditions.

## C. Directed ortho-Metalation of N,N-Dimethylaniline (DMA) (**3**)

As with anisole, the DoM of DMA was conducted under a variety of conditions (i.e. variations of hydrocarbon solvent, temperature, and catalyst) with the goal of designing a media that would afford the highest extent of metalation. Initial studies were centered on which hydrocarbon solvent best facilitated ortho-metalation. Extents of metalation were measured by GC analysis of the TMS product (**8**) with the assumption that the ortho-lithio intermediates were 100% derivatized by the CITMS reagent.

### 1. Solvent Experiments

#### a. Hydrocarbons

The basic mechanism of DoM indicates that the dimer configuration of the organolithium is the most reactive aggregate.<sup>37,38</sup> Therefore a solvent that could promote formation of this dimer should be the most conducive towards metalation. As stated before it has been shown that hydrocarbon solvents containing a bis-chelating amine will promote

formation of the dimer structure.<sup>17,30,40</sup> Therefore both n-hexane and cyclohexane containing TMEDA were investigated as media for efficient ortho-metalation studies.

The results comparing the reaction of DMA with increments of TMEDA in n-hexane and cyclohexane at 25°C can be seen in Figure 13. Cyclohexane uniformly produced higher yields of TMS product with less TMEDA present than did n-hexane. The reaction performed in cyclohexane attains a maximum extent of metalation of 69%, while the reaction conducted in n-hexane achieves no better than 67%. Another interesting point about these results is that the percent of TMS product drops off, in both solvents, with higher equivalents of TMEDA present. There are two important reasons postulated for this phenomenon. The first of these involves the conformation of the TMEDA molecule. Under standard conditions most TMEDA molecules will reside in a staggered conformation; however, at higher temperatures a greater concentration of TMEDA in the less stable eclipsed conformation will be formed. It is this eclipsed conformation that is responsible for bis-coordination to n-BuLi and forming the dimer structure. Energy put into a metalation system increases the accessibility of TMEDA in the eclipsed form (*vide infra*). The result is that at higher concentrations, and higher temperatures, a greater proportion of TMEDA will exist in the eclipsed conformation. A saturation point is reached when enough TMEDA is present to coordinate with all the available n-BuLi and to compete for open sites on the dimer complex. The equivalents needed to reach the saturation point will vary depending on the substrate, catalyst, solvent, and temperature of the reaction.

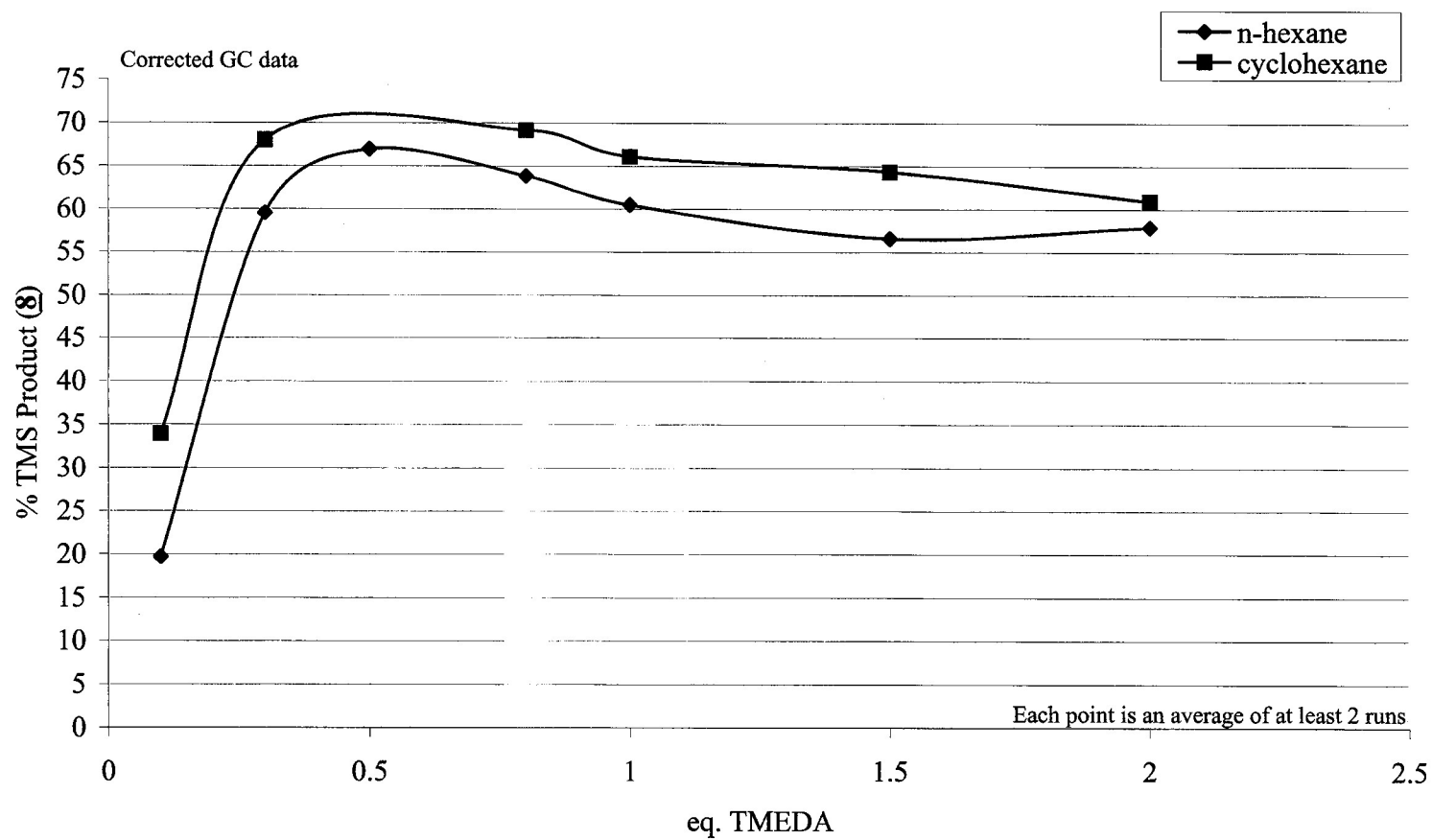


Figure 13. 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi vs. increments TMEDA at 25°C  
(30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol)

The second factor has to do with the coordination ability of the substrate. As stated before DMA has poor coordination characteristics with n-BuLi, due to resonance delocalization of the electron pair on nitrogen into the ring system. Therefore, at the saturation point, DMA cannot effectively compete with TMEDA for coordination sites on n-BuLi, illustrating that over-stabilization of the n-BuLi dimer by TMEDA is counter-productive. Both of these factors are believed to contribute to decrease the extent of metalation at higher concentrations of TMEDA.

Figure 14 compares the extents of reaction of DMA with maximizing eq. of TMEDA in n-hexane and cyclohexane. Using the data from Figure 13, the maximizing eq. of TMEDA in both solvents were plotted against time to show the extent of metalation. The maximizing amount of TMEDA in n-hexane was found to be 0.5 eq. (67%). The maximizing amount of TMEDA in cyclohexane was 0.8 eq. (69%). The plots clearly indicate that cyclohexane produced a faster rate and extent of metalation than that performed in n-hexane.

In fact, according to Table 7 (Experimental section), reactions in cyclohexane with 0.3 eq. TMEDA produced higher yields (68%) than the maximizing eq. of TMEDA for reactions in n-hexane. Therefore less TMEDA was necessary in cyclohexane than in n-hexane to achieve higher yields of ortho-product. The conclusion reached from these experiments was that cyclohexane was a better hydrocarbon solvent for the facilitation of the ortho-metalation of this substrate. Because of these findings cyclohexane was employed for the majority of the experiments in this research project.

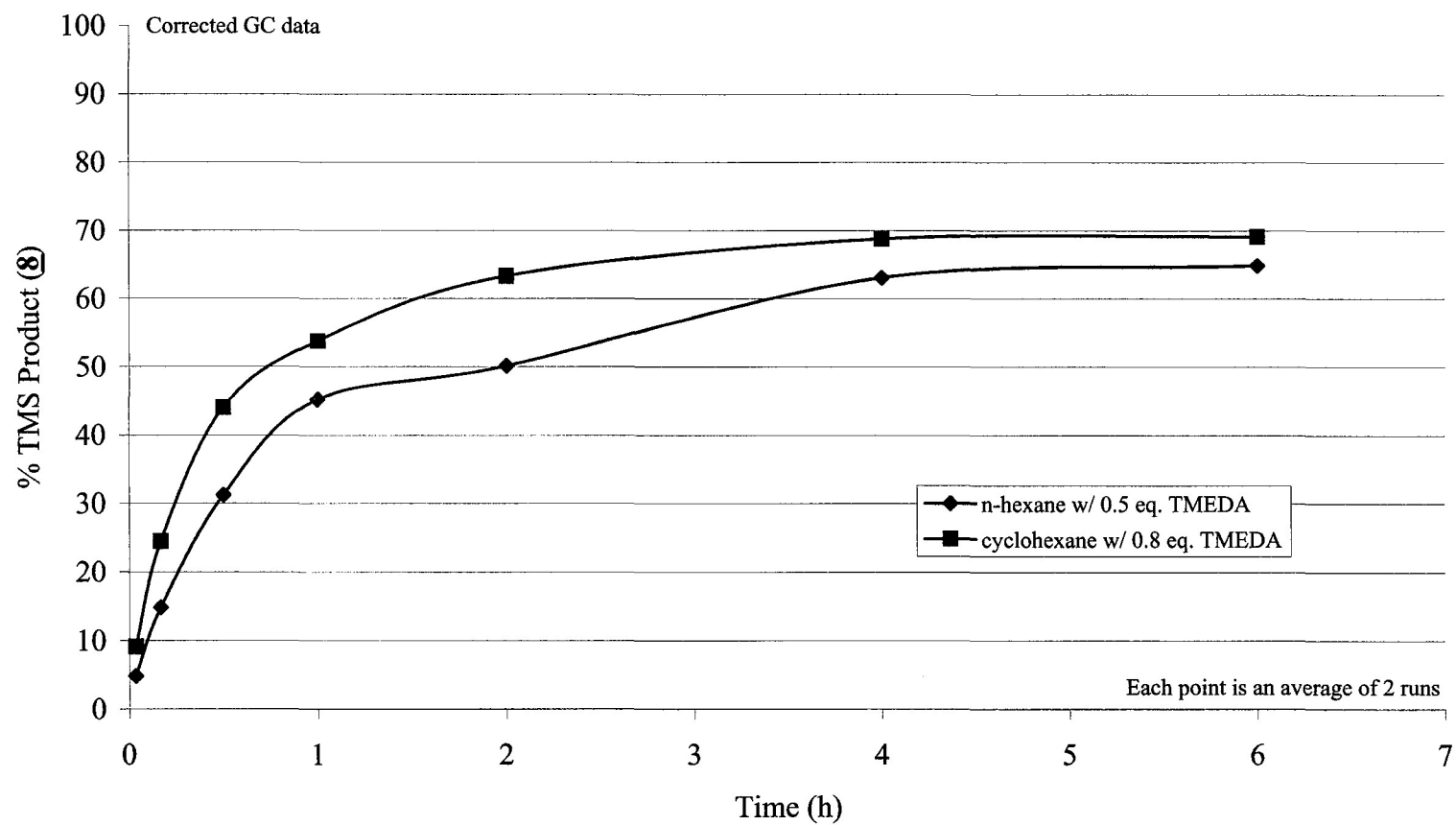


Figure 14. 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi with maximizing eq. TMEDA at 25°C  
(30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol)

b. neat THF

Reactions conducted in neat ether solvents should more than saturate all the coordination sites on n-BuLi. In other words, the solvent itself serves as a bulk deoligomerization catalyst. Since the substrate would be competing for coordination sites with saturating amounts of catalyst, product yields might not be maximized. The reactions of DMA in neat THF at 45°C exemplifies the theory that saturating amounts of catalyst are counter-productive to the DoM reaction. The average of the two runs produced 13% product early in the reaction, then dropped in yield. The reactions of DMA in neat THF at 60°C produced similar results, as the average ortho-TMS yield reached 12%, then dropped in yield. Results for these and additional DMA reactions can be seen in Table 12.

c. neat MTBE

A reaction of DMA and a second neat solvent was also attempted. This reaction performed in neat MTBE, methyl tert-butyl ether, produced 5% TMS product (Table 12).

Table 12. Failed Conditions for Metalation of DMA

Reaction Components <sup>110</sup> (Equivalent Ratios)	Solvent	Temp (°C)	Maximum Percent GC Yield (Time)
DMA:n-BuLi (1:1)	THF	45	13(30 m)
DMA:n-BuLi (1:1)	THF	60	12(30 m)
DMA:n-BuLi (1:1)	MTBE	25	5(24 h)
DMA:n-BuLi:THF (1:1:6)	n-Hexane	25	20.3(6 h)
DMA:n-BuLi:(-)-Sparteine (1:1:0.1)	n-Hexane	25	9.4(6 h)

2. Temperature Experiments

The next task was to explore the effect of temperature on the rate and extent of metalation. A series of reactions was performed with DMA and increments of TMEDA at 25°, 45°, and 60°C.

To be an effective bis-chelating agent, TMEDA must first interconvert into the less-stable eclipsed conformation, meaning that the more energy supplied to a reaction the greater likelihood that the eclipsed conformation will predominate. The results for running reactions at 25°, 45°, and 60°C with 1.0 equivalent DMA, 1.0 eq. n-BuLi, and increments of TMEDA can be seen in Figure 15.

The results indicate that the rate of reaction and extent of metalation increase with increasing temperature. The graph also shows that at higher temperatures fewer eq. of TMEDA are required to achieve maximum extent of metalation. Another interesting point on this graph is that at temperatures of 45° and 60°C there is a dramatic drop in extent of metalation with higher concentrations of TMEDA. With greater concentrations of TMEDA in the eclipsed conformations it is believed DMA cannot effectively compete for coordination sites on n-BuLi. Notice that a not as significant drop in metalation extent occurs at 25°C.

Figure 16 illustrates the progress, as a function of time, of 1.0 eq. DMA, 1.0 eq. n-BuLi, with the maximizing eq. of TMEDA at 25°, 45°, and 60°C. This data is very interesting because it shows that after achieving a maximized extent of metalation at 60°C with 0.1 eq. TMEDA, of 88%, the percent of metalated product falls off below the yields of reactions at 25°C and 45°C. Remember that DMA has poor coordination ability, because of this it has trouble competing with TMEDA for n-BuLi coordination sites. These results support the theory that over-saturation of the alkyllithium with catalysts is counter-productive to the DoM reaction.

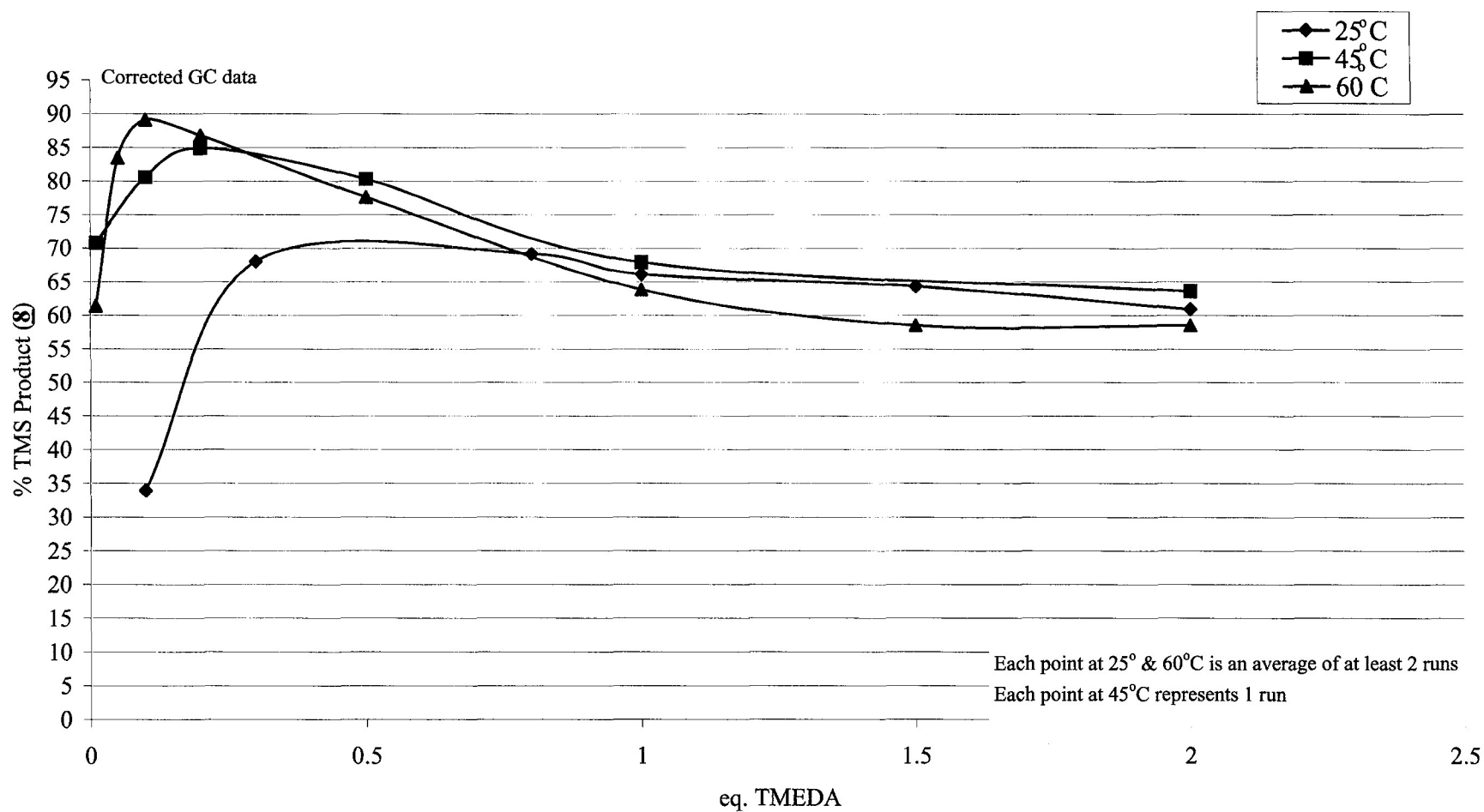


Figure 15. 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi vs. increments TMEDA at various temperatures (30 mL cyclohexane; 1.0 eq. = 0.04 mol)



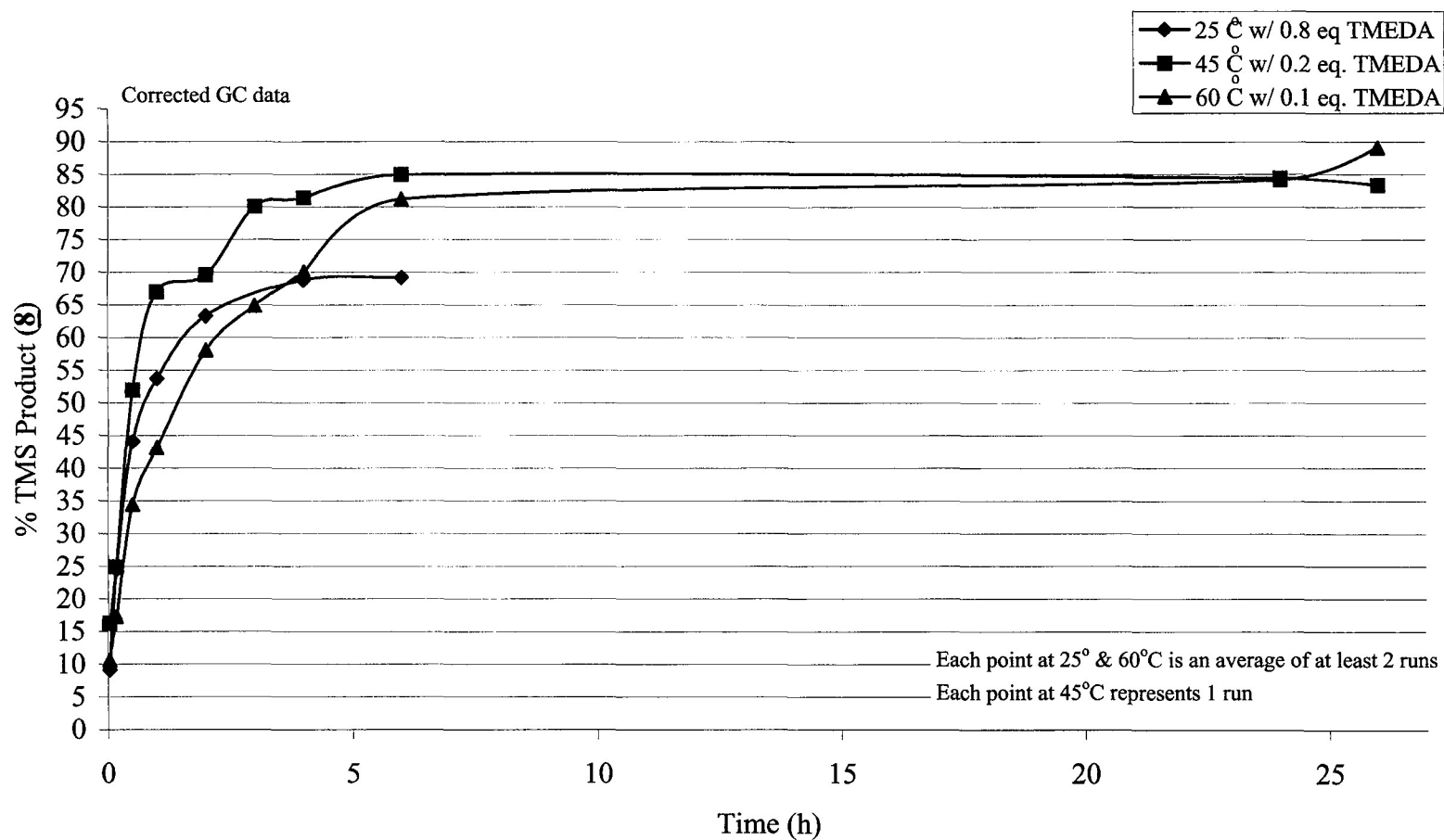


Figure 16. Progress of DoM of 1.0 eq. DMA (**3**) with 1.0 eq. n-BuLi containing maximizing eq. TMEDA; variation of yield with temperature (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

### 3. Reactions with TMEDA

The DoM mechanism is fairly sensitive in that altering reaction parameters often results in a significant change in percent yield. A series of reactions were performed to examine the effects when temperature and concentration of TMEDA are varied. This reaction series monitored the progress of reacting 1.0 eq. DMA, 1.0 eq. n-BuLi, with three different eq. of TMEDA at 25°, 45°, and 60°C.

The first set from this series were reactions at 25°C (Figure 17). As the data from Figures 15 and 16 demonstrates, at 25°C the percent yield of ortho- TMS product remains moderately low because few of the TMEDA molecules reside in the eclipsed conformation. The percent yield for 0.1 eq. TMEDA remained quite low (34%). The percent yield for 0.8 and 1.0 eq. had enough TMEDA in the eclipsed conformation to effect ortho-metalation, achieving results of 69% and 64%, respectively. As previously stated, at 25°C TMEDA exists as an equilibrium between the staggered conformation and the eclipsed conformation. Therefore, increasing the eq. of TMEDA increases the concentration of TMEDA in the eclipsed conformation. At 25°C the saturation point of TMEDA was reached at 0.8 eq. of TMEDA and exceeded at 1.0 eq. TMEDA (Figure 17).

The next set of reactions, performed at 45°C, used the same methodology while slightly varying the ratios of reagents from the reactions at 25°C. Figure 18 illustrates the difference in percent yield of metalations containing 0.1, 0.5, and 1.0 eq. of TMEDA conducted at 45°C. As a result of the increased temperature, the yields obtained from these experiments are noticeably higher than those conducted at 25°C (Figure 17).

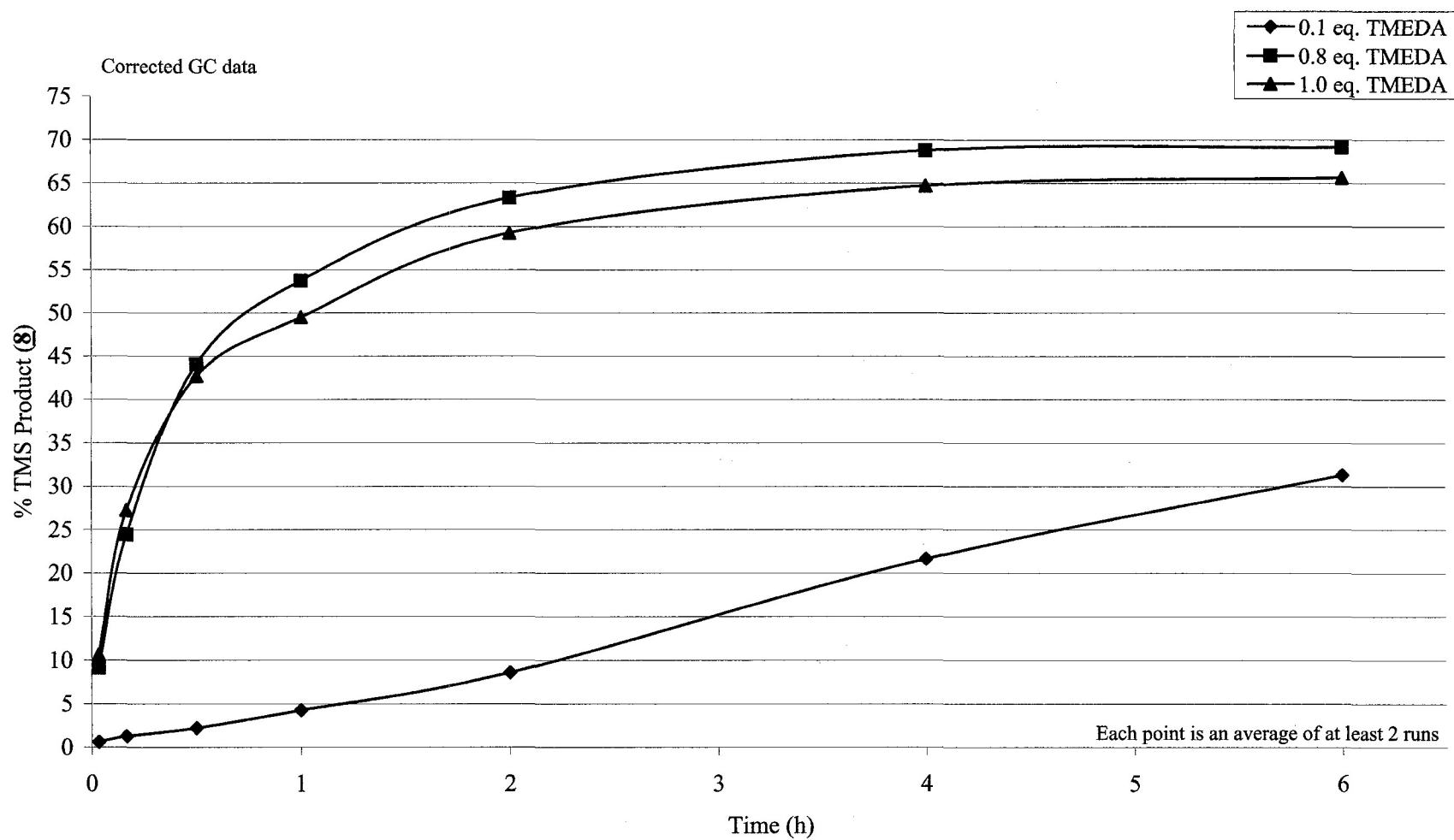


Figure 17. Progress of DoM of 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi with various eq. TMEDA at 25°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

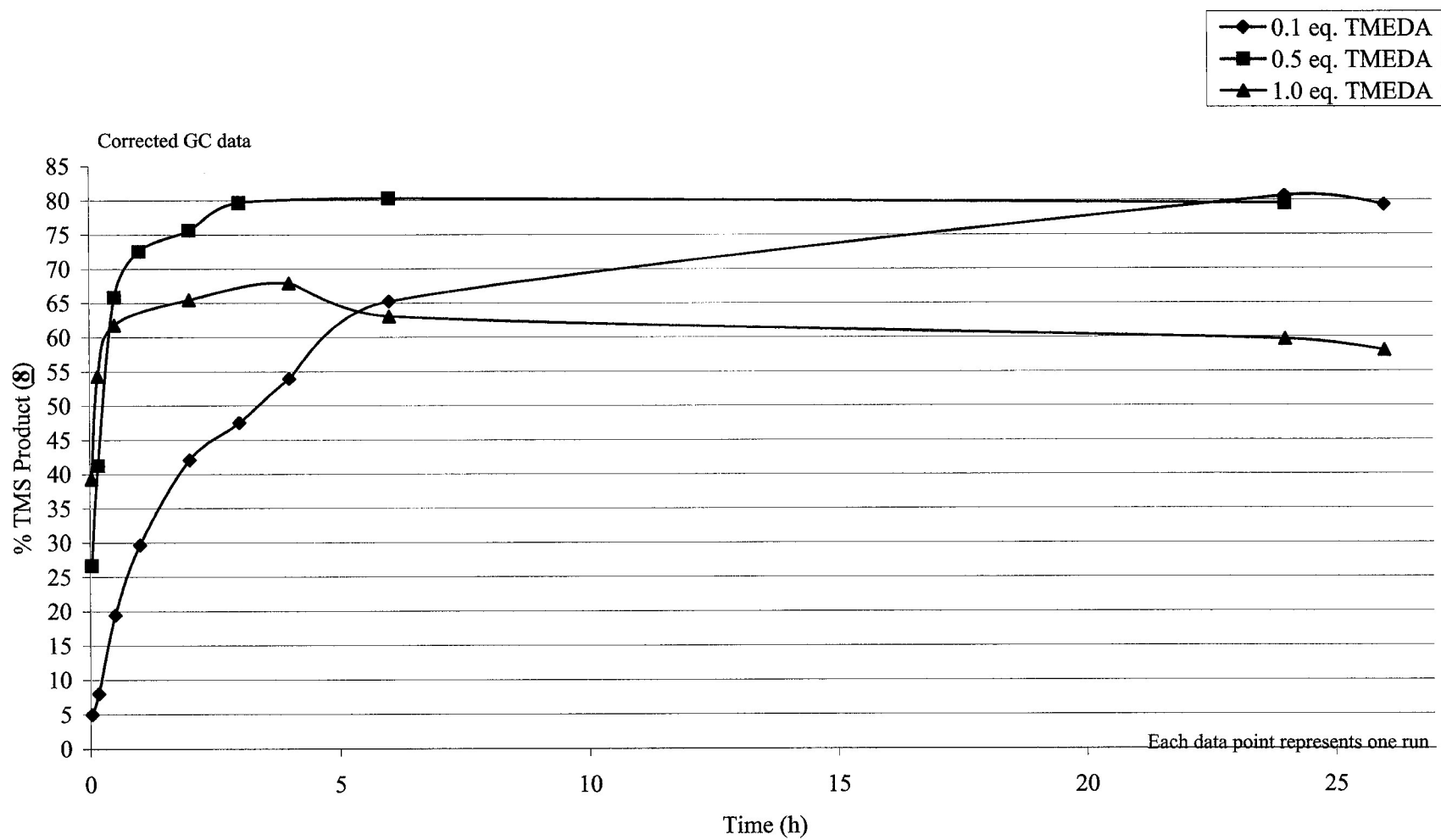


Figure 18. Progress of DoM of 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi with various eq. TMEDA at 45°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

Reactions conducted at 45°C also exhibited an inverse relationship with yield at higher concentrations of TMEDA. Reactions with 1.0 eq. of TMEDA had the lowest maximum percent yield, 68%, over a 26-hour period. The maximum percent yield for 0.5 eq. TMEDA was 77%. The highest yield from this set of experiments was 0.1 eq. TMEDA at 81% (Figure 18). However, this high yield was only achieved at 24 and 26 hours into the reaction. Comparing the yields at 4 hours the reaction at 0.5 eq. has achieved it's maximum at 77% metalation, whereas the reaction at 0.1 eq. had only reached 70% metalation. Reactions at 0.5 and 1.0 eq. of TMEDA had a faster rate of reaction than that containing 0.1 eq. It should be noted that results obtained from reactions at 45°C are only indicative since only one run was used for each data point.

The explanation for these results once again is believed to stem from the concentration of TMEDA in the eclipsed conformation. At 45°C with 1.0 eq. TMEDA, DMA struggles to compete for coordination sites on n-BuLi. The rapid rate of reaction indicates that during the initial hours of the reaction DMA competes effectively for coordination sites on n-BuLi. However, by 6 hours the percent yield dropped, indirectly indicating that TMEDA predominately occupies the coordination sites on n-BuLi.

The last reaction set, Figure 19, was conducted at 60°C. The two higher TMEDA concentrations, 0.5 and 1.0 eq., produced lower percent yields than their respective eq. at 45°C. For both of these reactions with 0.5 and 1.0 eq. TMEDA the percent yields are approximately 3-4% lower at 60°C than at 45°C. In contrast, the 0.1 eq. TMEDA reaction increased in percent yield, 89%, at the higher temperature representing almost a 9% higher yield than observed at 45°C. The rate of reaction with 0.1 eq. of TMEDA at 60°C was faster

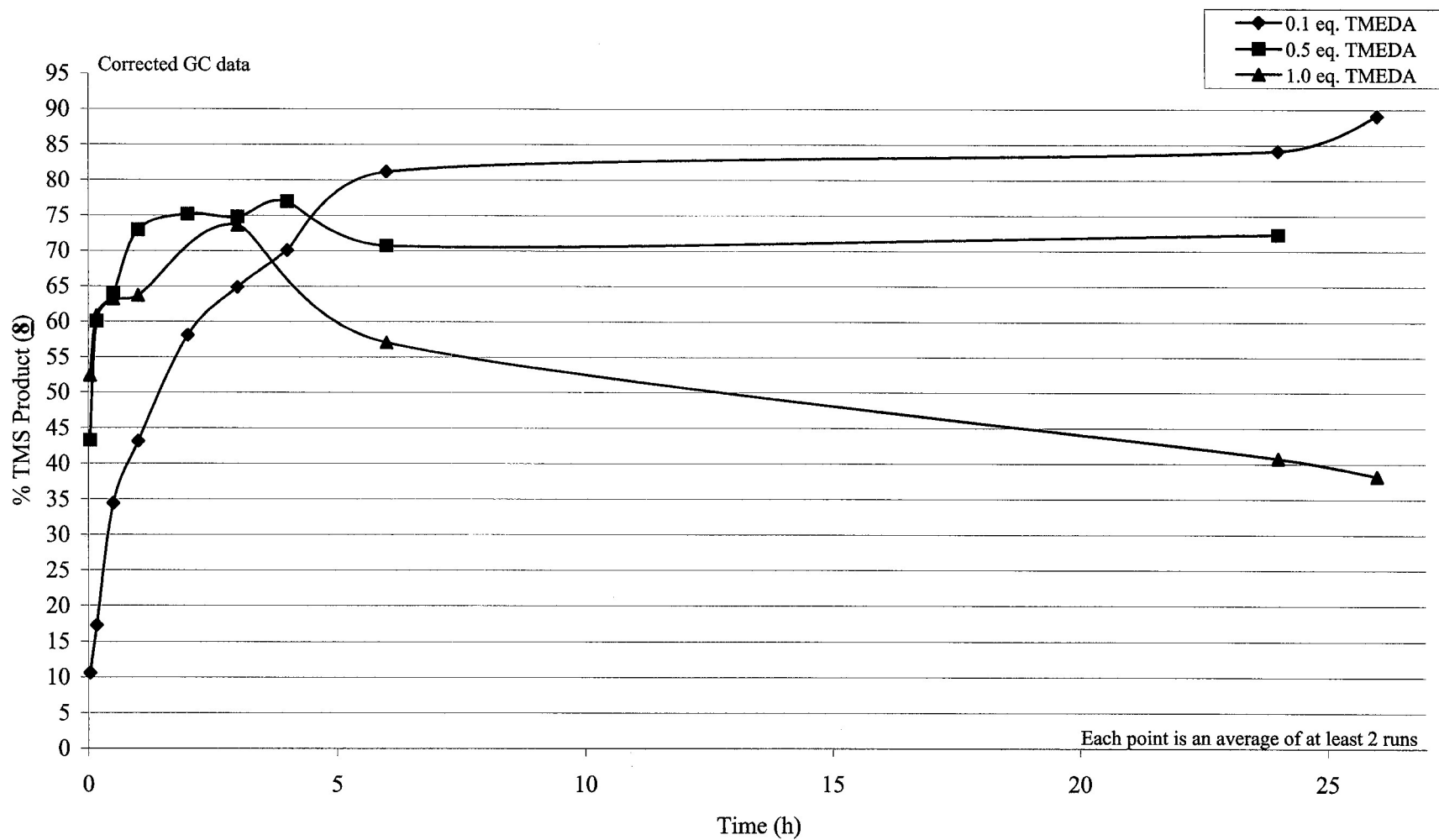


Figure 19. Progress of DoM of 1.0 eq. DMA (**3**); 1.0 eq. n-BuLi with various eq. of TMEDA at 60°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

than those at 45°C. The other two parameters, 0.5 and 1.0 eq. TMEDA, had a higher percent yield of product at the initial onset of the reaction, then they leveled off or began to decline in percent yield.

The summary for DoM reactions with DMA is that, at all temperatures investigated, a 1:1 ratio of n-BuLi and TMEDA is counter-productive. This is believed to be a result of the increased TMEDA concentration in the eclipsed conformation and the poor coordination capabilities of DMA. As the concentration of TMEDA in the eclipsed conformation increases it occupies all of the available coordination sites on n-BuLi. The resonance effects of the lone pair on the  $\text{N}(\text{CH}_3)_2$  group from DMA have decreased its coordination capabilities. This decrease in coordination results in DMA not being able to compete effectively for coordination sites on n-BuLi.

To counteract this effect, as the temperature of the reaction is increased the equivalents of TMEDA should be decreased. At lower temperatures greater equivalents of TMEDA are needed to achieve maximum ortho- metalation because the majority of TMEDA is not in the eclipsed conformation.

#### 4. Reactions with THF

The structure of THF is such that it takes four molecules to occupy the four coordination sites on the n-BuLi dimer. With TMEDA, a bis-chelating amine, only two molecules are needed to fill the n-BuLi dimer coordination sites. Therefore, the number of equivalents for THF and TMEDA used during the reaction cannot be directly compared.

For DMA, 6.0 eq. THF was found to be the maximizing equivalent. As is shown by Table 12, the yield for even the maximizing eq. of THF produced <20% metalation. Since

this produced far less product than that of TMEDA, THF is thought to be a less effective catalyst. Therefore experiments with THF were not pursued in depth.

#### 5. Reactions with (-)-Sparteine

(-)-Sparteine, a bis-chelating amine, has two nitrogen groups per molecule that bridge n-BuLi. Like TMEDA, two (-)-sparteine molecules will occupy all of the available coordination sites on the n-BuLi dimer. (-)-Sparteine is unlike TMEDA in that it exhibits little conformational mobility. The two nitrogen groups for (-)-sparteine are locked into the eclipsed conformation, therefore increasing the temperature should not affect the percent yield as dramatically as it would with TMEDA. Because of this restricted conformation all of the (-)-sparteine involved in the reaction is functional towards binding to n-BuLi. The DMA reaction with 0.1 eq. (-)-sparteine produced less than 10% of TMS product (Table 12). The low yield of product with (-)-sparteine could be due to steric factors. Because of the failure to produce reasonable amounts of TMS product, these reactions were not pursued in depth.

#### 6. Comparison of Literature Studies with Experimental Results

A comparison between the DMA experimental results (Table 7) and the summary of DMA reactions reported in Table 1 would be beneficial in evaluating results obtained during experimental procedures. In many cases a direct comparison between two reactions might be difficult because of differing reaction conditions and derivatizing agents. However comparing a few examples should illustrate that results obtained from experiments for this thesis produced comparable yields of ortho- product under similar or more moderate conditions than previously reported experiments.



Table 13. Comparison of DMA Literature Studies with Experimental Results

## 1.) Examples from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/ n-hexane/ TMEDA/ 25°C/4 h <sup>111</sup>	Ph <sub>2</sub> CO	71 <sup>48,69,70</sup>
n-BuLi/ n-hexane/ reflux/ 5 h <sup>112</sup>	Ph <sub>2</sub> PCl	85 <sup>75</sup>

## 2.) Examples from Experimental Results

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/ n-hexane/TMEDA/ 25°C/ 6 h	CITMS	67.4 <sup>113</sup>
n-BuLi/ cyclohexane/ TMEDA/ 60°C/ 26 h	CITMS	86.6 <sup>114</sup>

The first examples from each section compares reactions conducted with DMA, n-BuLi, and TMEDA at 25°C. Although the first literature reaction yielded higher product than the first experimental example the two reactions differed by less than 4%. The second reactions compare a difference of temperature combined with use of a catalyst. Instead of performing a reaction at reflux, as in the literature example, the experimental example temperature was only raised to 60°C and 0.2 eq. TMEDA was used to achieve a slightly higher yield.

D. Directed ortho-Metalation of N,N-Dimethylbenzylamine (DMBA) (4)

The DoM of DMBA was studied under conditions similar to those studied for DMA. The comparison of data between DMBA and DMA will provide insight into the mechanism of DoM. N,N-Dimethylbenzylamine has a methylene (CH<sub>2</sub>) group between the ring and the dimethylamino group [N(CH<sub>3</sub>)<sub>2</sub>]. This methylene group isolates the lone pair of electrons on nitrogen preventing any electron donation to the ring. Without donation of the lone pair, the coordination abilities of DMBA are not compromised, as they are with DMA.

However, this methylene group provides an additional location for metalation.

Metalation on the methylene group, better known as lateral metalation, results in an  $\alpha$ -TMS product. The advent of this second product limits the usefulness of DMBA as a viable substrate for DoM. The focus of reactions with DMBA centered on maximizing ortho-metalation, while minimizing lateral metalation. Initial studies were performed to determine the optimum solvent for DoM of this substrate.

## 1. Solvent Experiments

### a. Hydrocarbons

Reactions were conducted using 1.0 eq. DMBA, 1.0 eq. n-BuLi at 25°C in both n-hexane and cyclohexane (Figure 20). The metalation of DMBA produced slightly higher ortho-product yields in cyclohexane than in n-hexane. Reactions in n-hexane showed a reduction in ortho-product yields beginning at 0.4 eq. TMEDA. Reactions in cyclohexane only gave a reduction in ortho-product with 2 eq. TMEDA. The information provided on this graph also shows the yield of the  $\alpha$ -product. It is evident that cyclohexane produced 4 to 10% higher yields of  $\alpha$ -product than reactions in n-hexane. Although this is an undesirable side-product two worthwhile observations can be derived from these results. The first is that cyclohexane seems to better facilitate metalation when compared to n-hexane. Secondly, if a designer media could be developed to minimize lateral metalation, cyclohexane should prove to be the solvent of choice for DoM of DMBA.

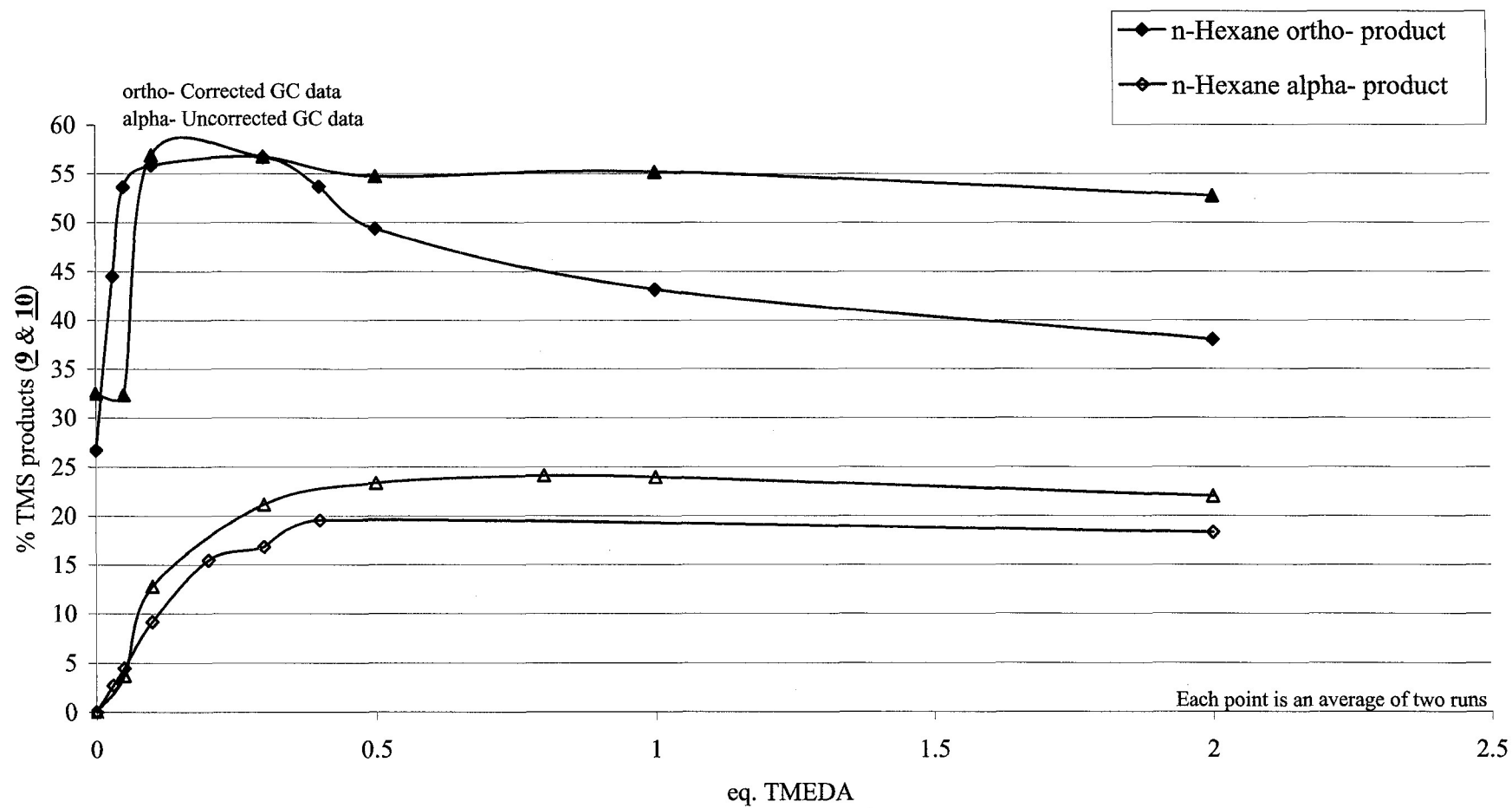


Figure 20. 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi vs. increments TMEDA at 25°C  
(30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol)

The next set of experiments elaborated upon the data displayed in Figure 20. Maximizing eq. of TMEDA in both hydrocarbon solvents were plotted against time. The results (Figure 21) show the progress of 1.0 eq. DMBA, 1.0 eq. n-BuLi with 0.3 eq. of TMEDA in n-hexane and cyclohexane. Even though the maximizing eq. in cyclohexane was found to be 0.8, 0.3 eq. was chosen to give an even comparison of ortho- and  $\alpha$ - yields between the two solvents. Consistent with previous results, cyclohexane and n-hexane produced comparable ortho-product yields and rates of reaction. When percent yields of ortho- and  $\alpha$ -products were added together the majority of reactions in cyclohexane had a higher product yield. Cyclohexane seemed to be the more activating solvent; however it was less discriminatory towards metalation position. Because of this cyclohexane was used in the majority of the remaining experiments, in an attempt to design a media that would maximize metalation while minimizing lateral metalation.

b. neat THF

Ether solvents should permit saturation of all the coordination sites on n-BuLi oligomers. Since the substrate will be competing for coordination sites with saturating amounts of catalyst, product yields should be lower. With neat THF, DMBA produced greater than 47% ortho- product at 25°C, moreover nearly 12% of  $\alpha$ - product was also produced. Figure 22 shows the yields of ortho- and  $\alpha$ - products from a variety of solvent experiments at 25°C. Several other reactions in neat THF were conducted at 45° and 60°C, both of these series produced an average of <50% ortho- product and >10%  $\alpha$ - product. For DMBA, the saturation did not affect the production of ortho- TMS product in such a dramatic fashion

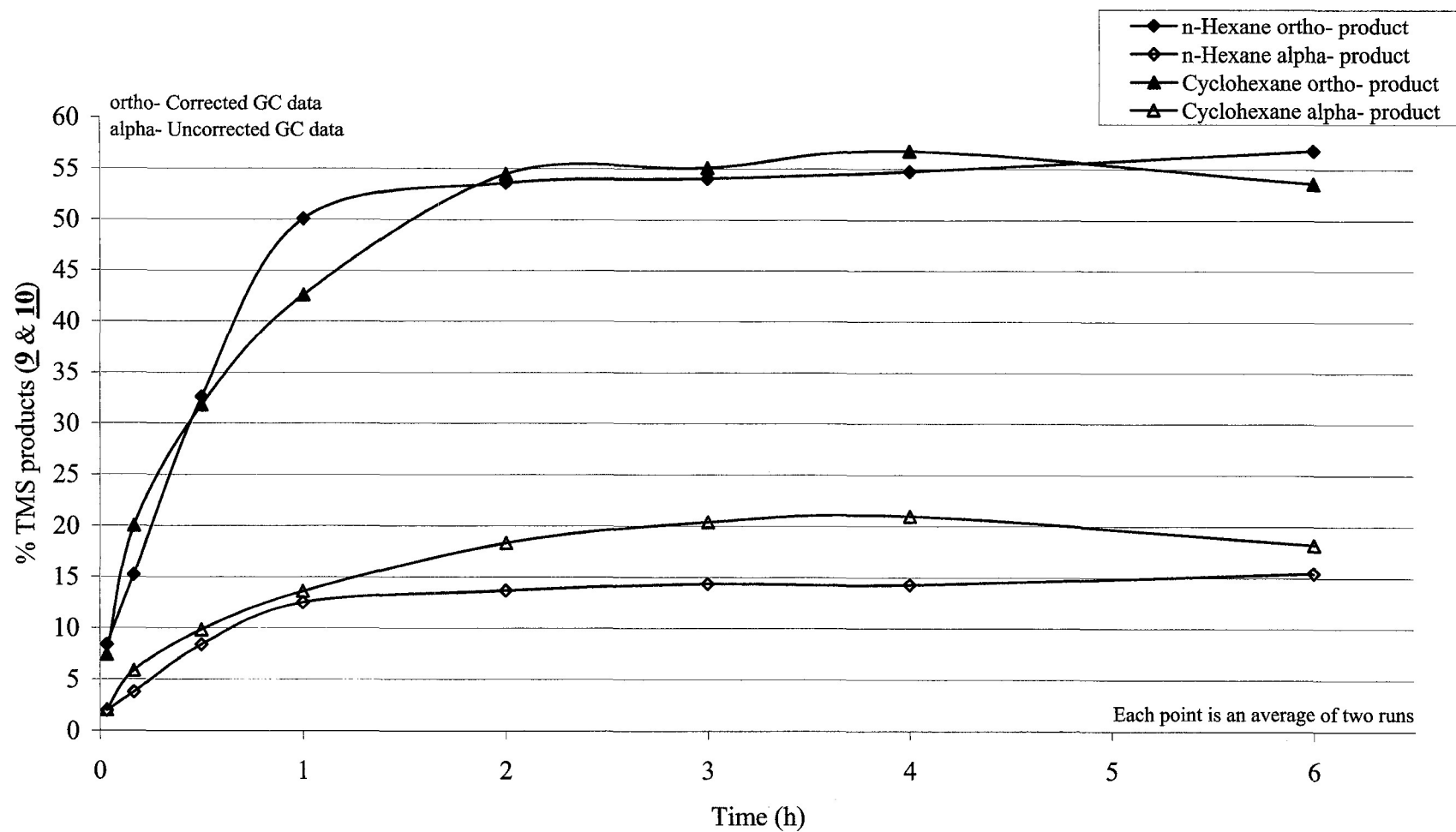


Figure 21. 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi; 0.3 eq. TMEDA at 25°C  
(30 mL hydrocarbon solvent; 1.0 eq. = 0.04 mol)

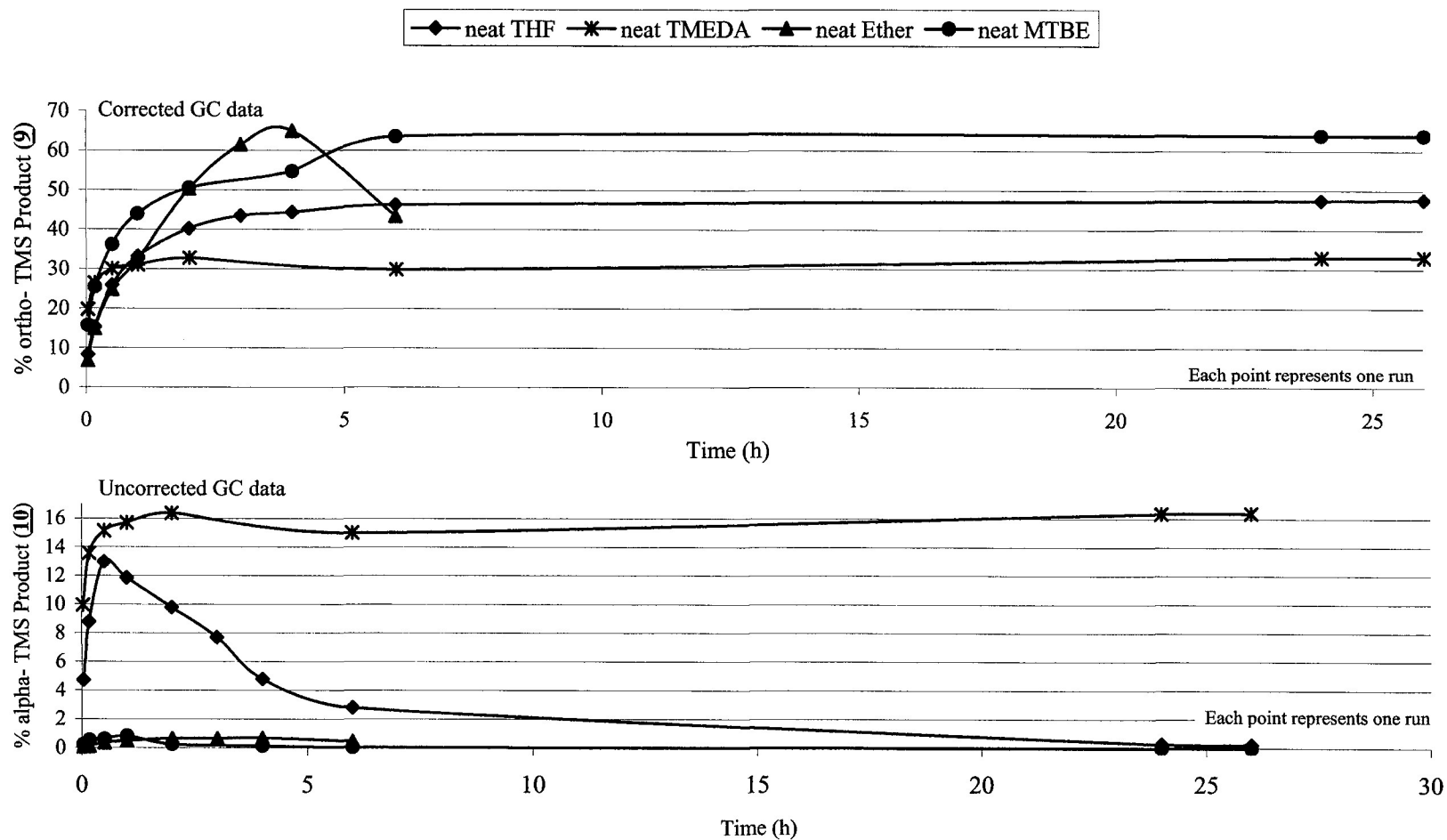


Figure 22. Metalation of 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi in various media at 25°C (30 mL solvent; 1.0 eq. = 0.04 mol)

as it did for DMA. Even at high levels of catalyst DMBA could still compete for coordination sites around n-BuLi, but not very effectively.

c. neat TMEDA

The catalytic properties that TMEDA exhibited with anisole and DMA were tested with DMBA. In neat TMEDA, DMBA was only able to produce 33% ortho- product and 16%  $\alpha$ - product. From this experimental data neat TMEDA was not pursued as a solvent for DoM; however experiments with incremental amounts of TMEDA were still conducted.

d. neat Diethyl Ether

Studies of the solvents used in DoM reactions found that ether supported the formation of the intermediately reactive tetramer structure.<sup>31</sup> The fact that ether will not promote the formation of the dimer decreases its effectiveness as a DoM solvent. An additional problem with ether solvents is that they react slowly with organolithium bases in storage.<sup>39</sup> Nevertheless, ether solvents have been reported to selectively promote ortho- metalation over lateral metalation. For this reason reactions with 30 mL diethyl ether were attempted. The data revealed that diethyl ether produced close to 65% ortho- product with <1% lateral metalation. As indicated by Figure 22 after the 4-hour maximum point, a dramatic drop-off in yield occurred, down to 43%. Presumably, this could be the result of degradation of n-BuLi by the ether solvents. Because of reasons stated above and safety concerns, reactions in neat ether and incremental ether were not pursued further.

e. neat MTBE

In an attempt to design media to mimic the regioselectivity in diethyl ether, while increasing the yield, reactions were conducted in neat methyl tert-butyl ether (MTBE). The reaction in neat MTBE gave a surprising 64% ortho- TMS yield, and the yield of  $\alpha$ - product

was particularly interesting. A maximum of <1%  $\alpha$ - product was present within 1 hour of the reaction; however after 6 hours only 0.05% of  $\alpha$ - product was detected. By the 24 and 26-hour points the  $\alpha$ - product peak was no longer apparent over the background instrument noise. Further reactions would later be conducted with incremental amounts of MTBE.

## 2. Temperature Experiments

Using the maximizing eq. of TMEDA with DMBA at 25°, 45°, and 60°C the maximum percent yields of ortho- and  $\alpha$ - products, were plotted as a function of time to monitor the progress of each reaction. This data, Figure 23, provided evidence on how these reactions progress over a period of time. The presented data supports a previously discussed topic, the direct correlation between temperature and product yield.

According to the experimental data, the 60°C reaction exhibited the fastest rate of metalation. However, within 6 hours the reaction at 45°C had slightly surpassed the ortho-product yield of the reaction at 60°C. The reaction at 60°C yielded less  $\alpha$ - TMS product than the reaction at 45°C, with 0.1 eq. TMEDA. The reaction at 25°C, with 0.3 eq. TMEDA, yielded the highest percent of  $\alpha$ - product.

A possible explanation for these observations could be a result of variations in eq. TMEDA. The 25°C reaction had 0.3 eq. TMEDA and produced the highest percentage of  $\alpha$ - product. The graph shows that the reaction with the higher TMEDA concentration produced the highest yield of  $\alpha$ -product. It appears that lateral metalation occurs more abundantly under stronger DoM conditions. Later results will support this theory that higher TMEDA concentrations lead to greater amounts of lateral metalation product. Lateral metalation



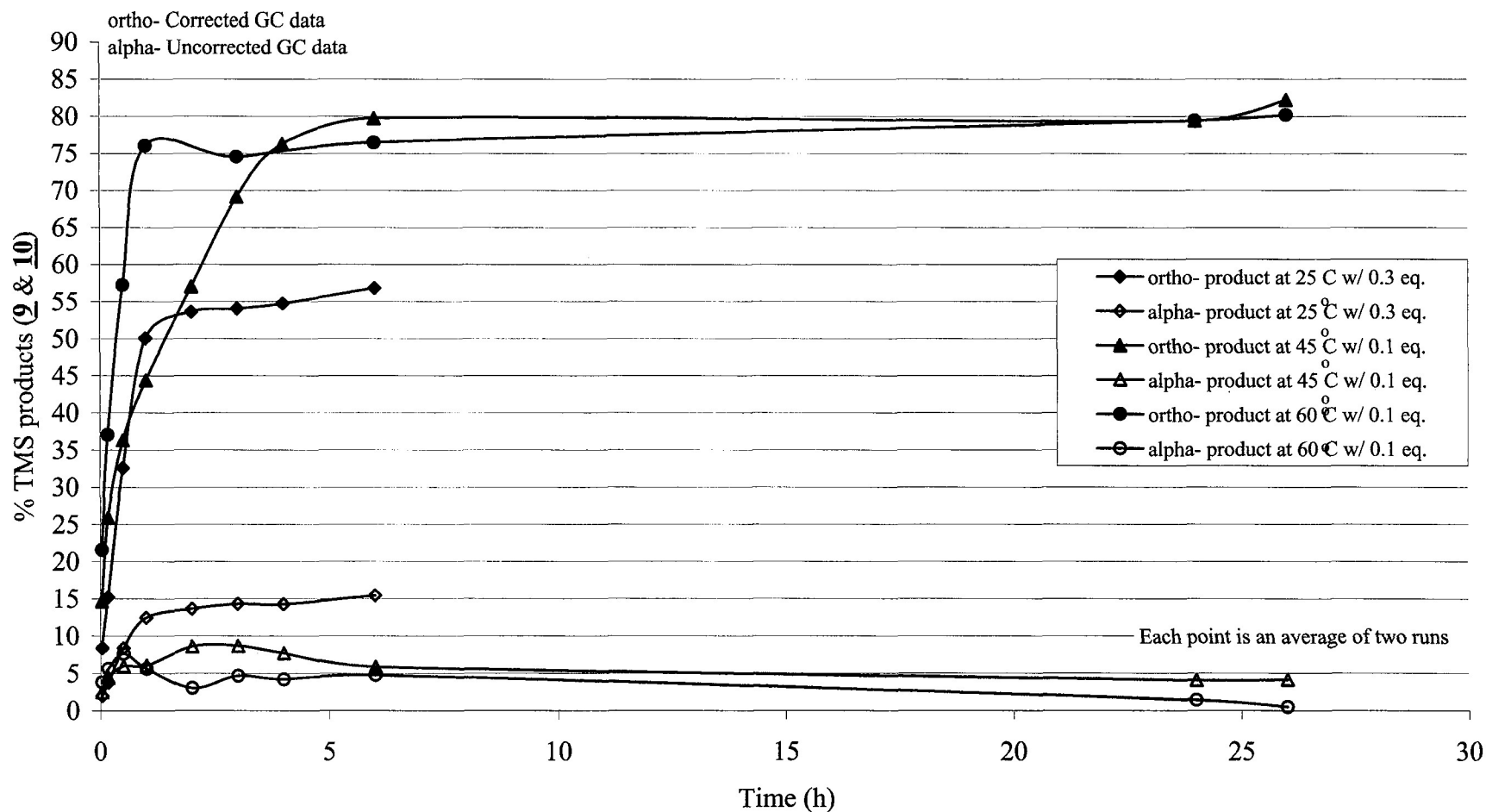


Figure 23. Progress of DoM of 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi containing maximizing eq. TMEDA; variation of yield with temperature (30 mL cyclohexane; 1 eq. = 0.04 mol)

would be compounded when high concentrations of TMEDA are combined with increased temperatures. Therefore modest fractional amounts of TMEDA and elevated temperature could maximize ortho-metalation while minimizing lateral metalation.

### 3. Reactions with TMEDA

Numerous experimental conditions were attempted to minimize the  $\alpha$ - product while yielding >80% ortho- product. To examine how changing DoM reaction parameters, such as temperature and eq. of catalyst, affects the progress and product yield, three sets of reactions were conducted with DMBA at 25°, 45°, and 60°C. These reactions compared the rate and extent of DoM with three different eq. of TMEDA. The specific eq. of TMEDA examined were chosen as to give a broad range of concentrations.

The first reaction set utilized 1.0 eq. DMBA, 1.0 eq. n-BuLi, with 0.1, 0.3, and 0.5 eq. TMEDA at 25°C (results not shown). These three reactions were monitored over a period of 6 hours and plotted against percent TMS product. The highest yield of ortho- product approached 56% and yielded 21% of  $\alpha$ - product with 0.3 eq. TMEDA at 4 hours. It was therefore determined that 25°C was not the optimum temperature for significant DoM product yield.

The next reaction set examined was 1.0 eq. DMBA, 1.0 eq. n-BuLi, with 0.05, 0.1, 0.5 eq. TMEDA at 45°C. These three reactions, plotted in Figure 24, provided a good representation of how one minor change in the reaction parameters can affect the yield in these experiments. The reactions with 0.05 and 0.1 eq. TMEDA provided 77% and 79% ortho-product yield, respectively. The extent of  $\alpha$ - product yielded for the 0.05 experiment was 5% and 0.1 eq. was 9%. The experiment with the highest concentration of TMEDA, 0.5 eq.,

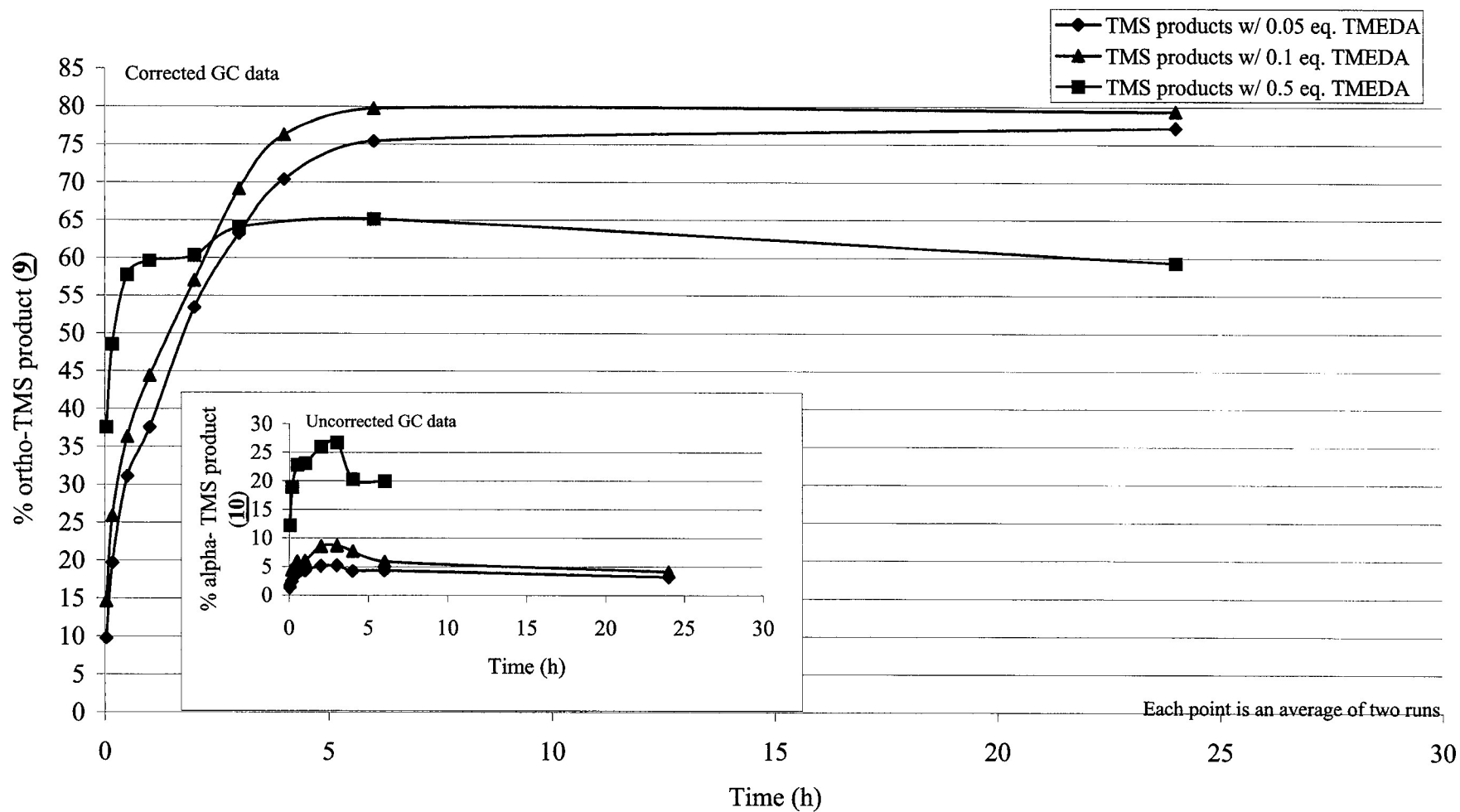


Figure 24. Progress of DoM of 1.0 eq. DMBA (4); 1.0 eq. n-BuLi with various eq. TMEDA at 45°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

produced the lowest yield of ortho- product, 65%, and the highest yield of  $\alpha$ - product, 27%. These results supported the previously discussed trend that lateral metalation occurs more frequently under harsh DoM conditions, greater concentrations of TMEDA and/or increased temperature. It was again concluded that fractional amounts of TMEDA and an increase in temperature could maximize ortho- metalation and minimize lateral metalation.

The final reaction set examined was 1.0 eq. DMBA, 1.0 eq. n-BuLi, with 0.05, 0.1, and 0.5 eq. TMEDA at 60°C (Figure 25). The reaction with 0.05 eq. TMEDA achieved >75% ortho- product and generated the least  $\alpha$ - product, <3%. The highest production of ortho-product yield, 77%, was from the 0.1 eq. reaction along with 7%  $\alpha$ - product. The lowest ortho- product yield, 61%, resulted from the 0.5 eq. TMEDA reaction which also produced the highest  $\alpha$ - product yield, over 19%. The reduction in yield of the 0.5 eq. reaction could be somewhat anticipated following data observed from DMA. At higher temperatures reactions maximized with lower equivalents of catalyst. Once again the appearance of  $\alpha$ - product could be directly linked to the concentration of TMEDA. The highest concentration of TMEDA, 0.5 eq., produced the highest percent of  $\alpha$ - product, >19%. The insert graph within Figure 25 displays significant decrease in extent of  $\alpha$ - product with time. With 0.5 eq. TMEDA a minimum of <10%  $\alpha$ - product was produced after 24 hours. Similar observations were made for the reactions conducted with lower concentrations of TMEDA. For these reasons the exploration of different reaction media had a time component added for consideration.

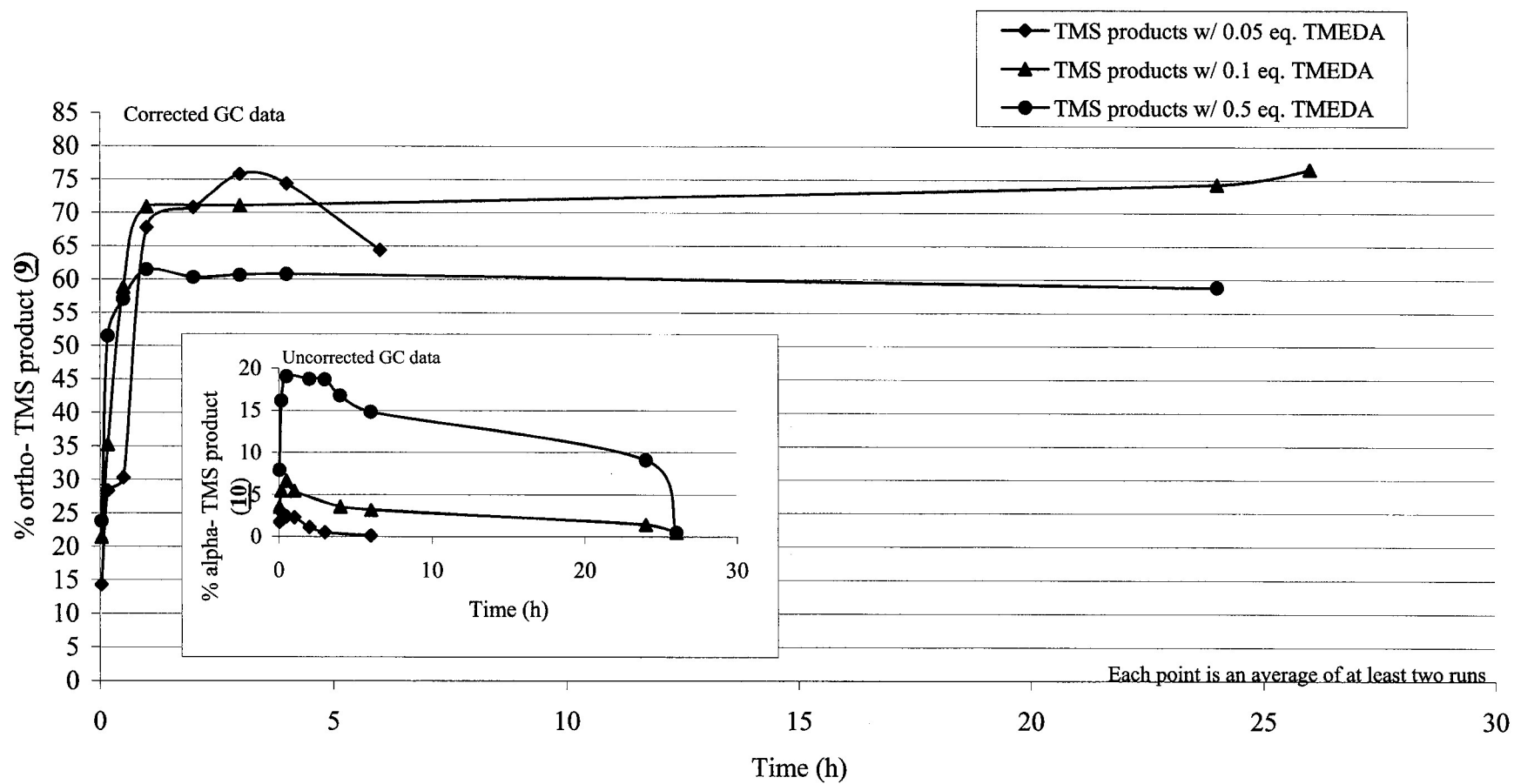


Figure 25. Progress of DoM with 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi with various eq. TMEDA at 60°C (30 mL cyclohexane; 1.0 eq. = 0.04 mol)

#### 4. Reactions with MTBE

Following the realization that reactions in neat MTBE afforded little  $\alpha$ -metalation, fractional eq. of MTBE in hydrocarbon solvent was investigated. Unlike the majority of other experimental systems studied, these reactions were conducted in n-hexane. An example of this abbreviated reaction series with MTBE at 25° and 60°C in n-hexane can be seen in Figures 26 and 27. At 25°C, 75% ortho-metalation was achieved accompanied by <1%  $\alpha$ -metalation. Success for the project was achieved at 60°C. The results for the DMBA/MTBE series at this temperature were that the ortho-product, >94%, was realized with only trace amounts of  $\alpha$ -product at both concentrations of MTBE additive. In addition to the highest ortho-product yield obtained thus far the results indicated that the percent of  $\alpha$ -product decreased over the course of the reaction, from 2% down to 0.03%. It could be conceived that with an extended reaction time the occurrence of lateral metalation might cease to be a problem. Because of time constraints, reactions to optimize the MTBE concentration for DoM were not conducted; however according to preliminary results it probably resides between 0.5 and 1.0 eq.

A second abbreviated series was attempted with MTBE in cyclohexane at 60°C. The reaction with 0.7 eq. MTBE produced an average of 76% ortho-product, approximately 18% lower than reactions in n-hexane. Two reactions with 1.0 eq. MTBE yielded an average of 95% ortho-product, which is the same average as that for the three reactions in n-hexane. Because the yields for the cyclohexane reactions with varying eq. of MTBE varied so significantly, the results were not considered as reliable as those in n-hexane.

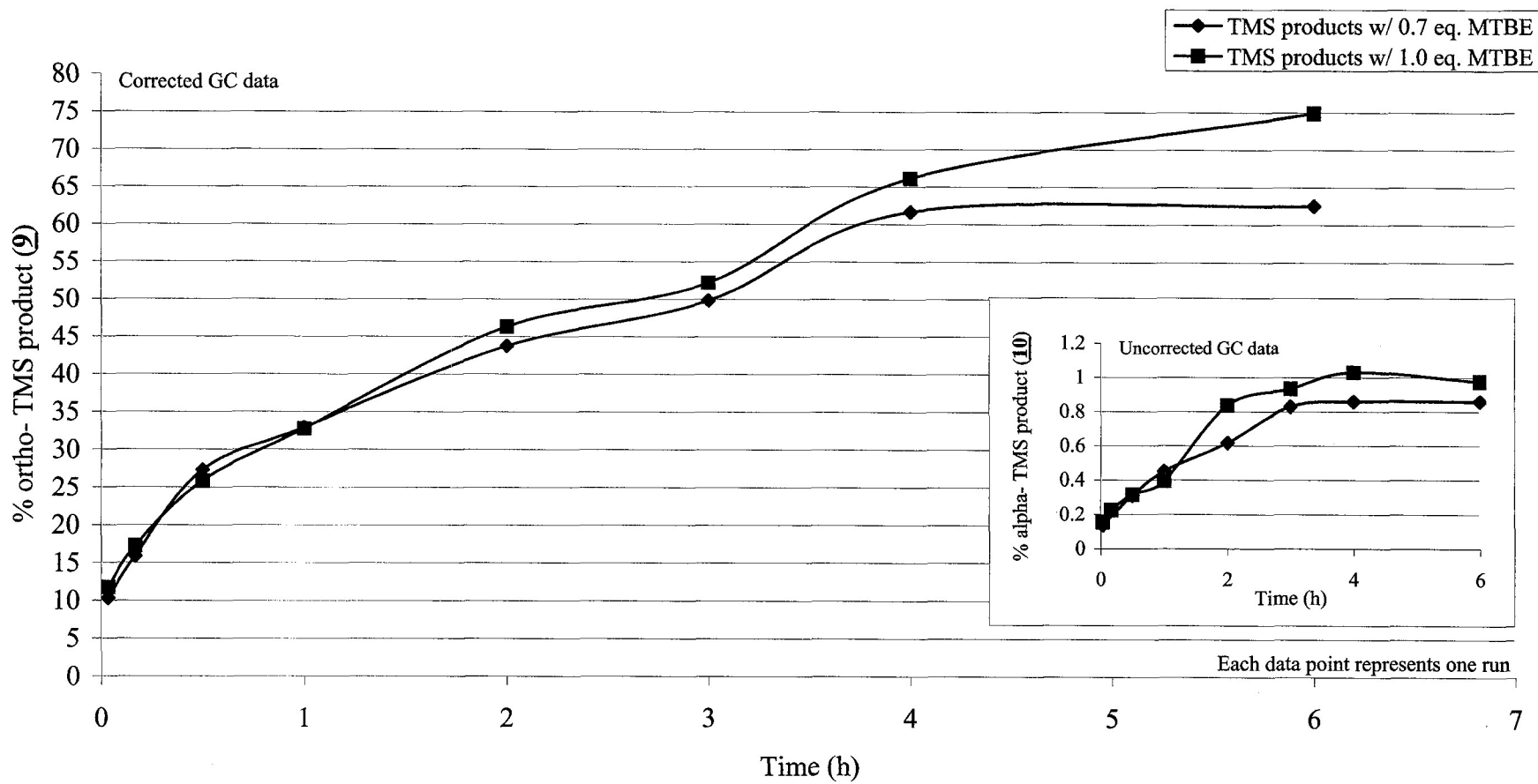


Figure 26. Progress of DoM with 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi with various eq. MTBE at 25°C (30mL n-hexane; 1.0 eq. = 0.04 mol)

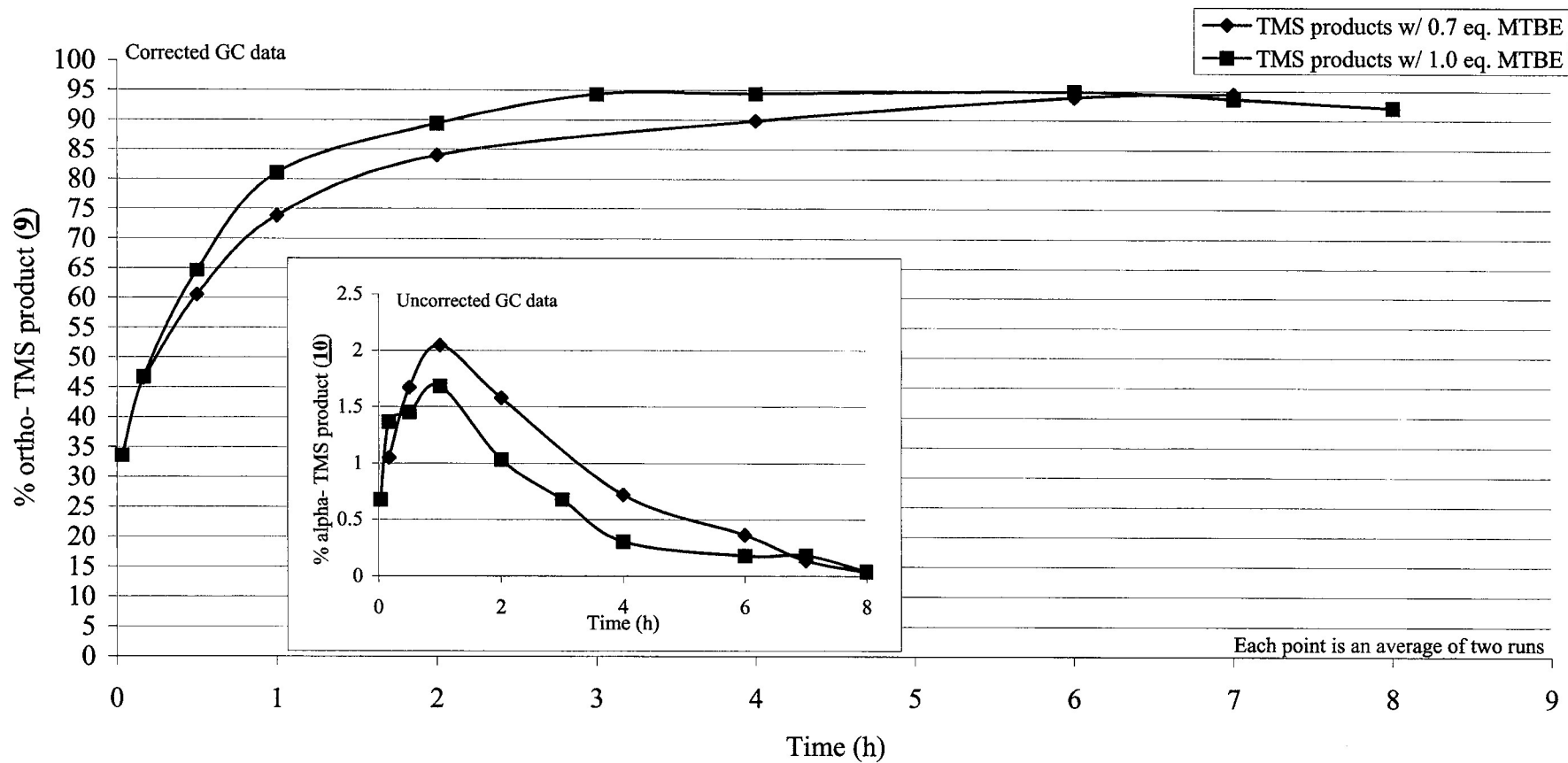


Figure 27. Progress of DoM with 1.0 eq. DMBA (**4**); 1.0 eq. n-BuLi with various eq. MTBE at 60°C (30mL n-hexane; 1.0 eq. = 0.04 mol)



## 5. Reactions with THF

A reaction with 4.0 eq. THF, 1.0 eq. DMBA, and 1.0 eq. n-BuLi in cyclohexane revealed that approximately 55% ortho- yield and 8%  $\alpha$ - product over a 26-hour time frame, Table 8. As with DMA the reaction with THF produced lower amounts of product than those with TMEDA, supporting the idea that THF was not as efficient a catalyst. Because of this the reaction series with THF was not explored in depth.

## 6. Reactions with (-)-Sparteine

The reaction of DMBA with (-)-sparteine, 0.05 eq., achieved slightly more than 69% ortho- product yield containing less than 3%  $\alpha$ - product (Table 8). Another reaction with 0.1 eq. (-)-sparteine produced slightly less ortho- yield, 65%, and an  $\alpha$ - product yield of >4%. As in the case with TMEDA, the reaction with the higher concentration of catalyst produced the higher yield of  $\alpha$ - product. Even though lateral metalation was diminished with (-)-sparteine the yield of ortho- product was significantly lower than the desired >90% extent of metalation. Because of this the reaction series with (-)-sparteine was not explored further.

## 7. Comparison of Literature Studies with Experimental Results

A comparison between the DMBA experimental results (Table 8) and the summary of DMBA reactions reported in Table 3 would be beneficial in evaluating results obtained during experimental procedures. In many cases, a direct comparison between two reactions might be difficult because of differing reaction conditions and derivatizing agents. However comparing a few examples should illustrate that results obtained from experiments for this thesis produced superior yields of ortho- product under similar or less aggressive conditions than previously reported experiments.

Table 14. Comparison of DMBA Literature Studies with Experimental Results

## 1.) DoM Examples from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/n-hexane/TMEDA <sup>115</sup>	Ph <sub>2</sub> PCl	60 <sup>72</sup>
n-BuLi/n-hexane/reflux/3 h <sup>116</sup>	BCl <sub>3</sub> , -40°C	62 <sup>85</sup>

## 2.) Halogen Metal Exchange Example from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
pBr-DMBA/t-BuLi/ether <sup>117</sup>	N.A.	80-90 <sup>103</sup>

## 3.) Example from Experimental Results

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/n-hexane/TMEDA/ 25°C/4 h	CITMS	o- 65.5 <sup>118</sup> α- 16
n-BuLi/n-hexane/MTBE/ 60°C/7 h	CITMS	o- 94.9 <sup>119</sup> α- 2.1

The best comparison between experiments conducted for this thesis and those found in the literature can be made from Table 14. The first reaction from the literature studies yielded only 60% ortho- product, whereas MT 41 yielded >65% ortho- product and 16% α-product. The temperature and time of the first literature reaction was not reported; therefore the comparison was made with a reaction at room temperature. The second reaction from the literature studies has a slightly higher yield; however, this reaction was conducted at reflux and should be expected to produce much higher yields. Since the yields reported from the literature studies were low, a halogen metal exchange reaction is shown to provide an example of alternatives employed with DMBA. The reaction MT 163 is reported to show how effective the catalyst, MTBE, can be when compared to a halogen metal exchange.

It is important to note that no reaction from the literature studies in Table 3 reported the appearance of a lateral metalation product. It would be remarkable if each of these reactions was regiospecific to the ortho- position; however if a second product was not detected or left unreported it could lower reported percent yields.

E. Directed ortho-Metalation of N,N,N',N'-Tetramethyl-1,4-phenylenediamine (1,4-TMPDA) (5)

Adding a second directing group in the para- position of a substrate could alter the results of a reaction dramatically. As stated before, adding a second DMG, such as a halogen, to an arene that already contains a DMG can alter the site of metalation.<sup>50,56,52,58,66</sup> Certain directing groups could invoke the opposing  $\pi$ -resonance effect.<sup>66</sup> This effect serves to increase localization of the electron pairs, thereby facilitating coordination to n-BuLi. Both increased electron-withdrawal and increased coordinating ability should facilitate DoM.

N,N,N',N'-Tetramethyl-1,4-phenylenediamine (1,4-TMPDA) is a unique substrate in that it contains two dimethylamino directing groups para- to each other. Each dimethylamino group donates electron density to the ring that is opposed by a similar donation from the other dimethylamino group. The result is that each group contributes electron density to the ring, but the effect for each is diminished due to the opposing  $\pi$ -resonance. Therefore each unshared electron-pair on both dimethylamino groups would be more available for coordination.

An interesting point is that both of the dimethylamino groups on the ring are equal so this increases the number of ortho-hydrogens from two to four. The advantage of using a substrate with the same directing groups is that it lessens the chance of a second product. With the substrate and n-butyllithium reagents reacted under conditions of a 1-to-1 ratio only

mono-metalation should occur; however, dimetalation could be achieved by doubling the n-BuLi equivalents. Reactions to achieve dimetalation were not performed.

#### 1. Reactions with TMEDA

Using information obtained from the reactions of DMA, four sets of experiments were conducted to test the same conditions on 1,4-TMPDA. These reactions, conducted at 25° and 60°C, compared product yield variation using 0.1 and 0.2 eq. TMEDA (Figure 28). The reaction performed at 60°C with 0.2 eq. TMEDA used the same parameters that produced a maximum percent yield for DMA, within a 6 hour timeframe.

Results for reactions with 1,4-TMPDA at 60°C did produce slightly higher yields and faster rates of reaction than corresponding reactions with DMA. Both of the reactions with 1,4-TMPDA at 60°C reached slightly over 90% ortho-metalation, as compared to 88% yield for similar reactions conducted with DMA (Figures 16 and 19). Reactions with 1,4-TMPDA at 25°C produced a significantly higher yield than similar reactions with DMA. The reaction with 0.2 eq. TMEDA generated a maximum metalation of 58% within 2 hours, thus supporting the theory that 1,4-TMPDA is better at competing for coordination sites on n-BuLi as a result of the opposing  $\pi$ -resonance effect.

A comparison between DMA and 1,4-TMPDA would provide a side-by-side assessment of the rate and extent of metalation afforded by both substrates. Figure 29 displays the reactions of 1.0 eq. DMA, 1.0 eq. n-BuLi and 1.0 eq. 1,4-TMPDA, 1.0 eq. n-BuLi both with 0.2 eq. TMEDA at 25° and 60°C. As indicated by the graph 1,4-TMPDA reached over 90% TMS product within 6 hours, as compared to 80% TMS product for DMA. As expected the rate of metalation is faster for 1,4-TMPDA.

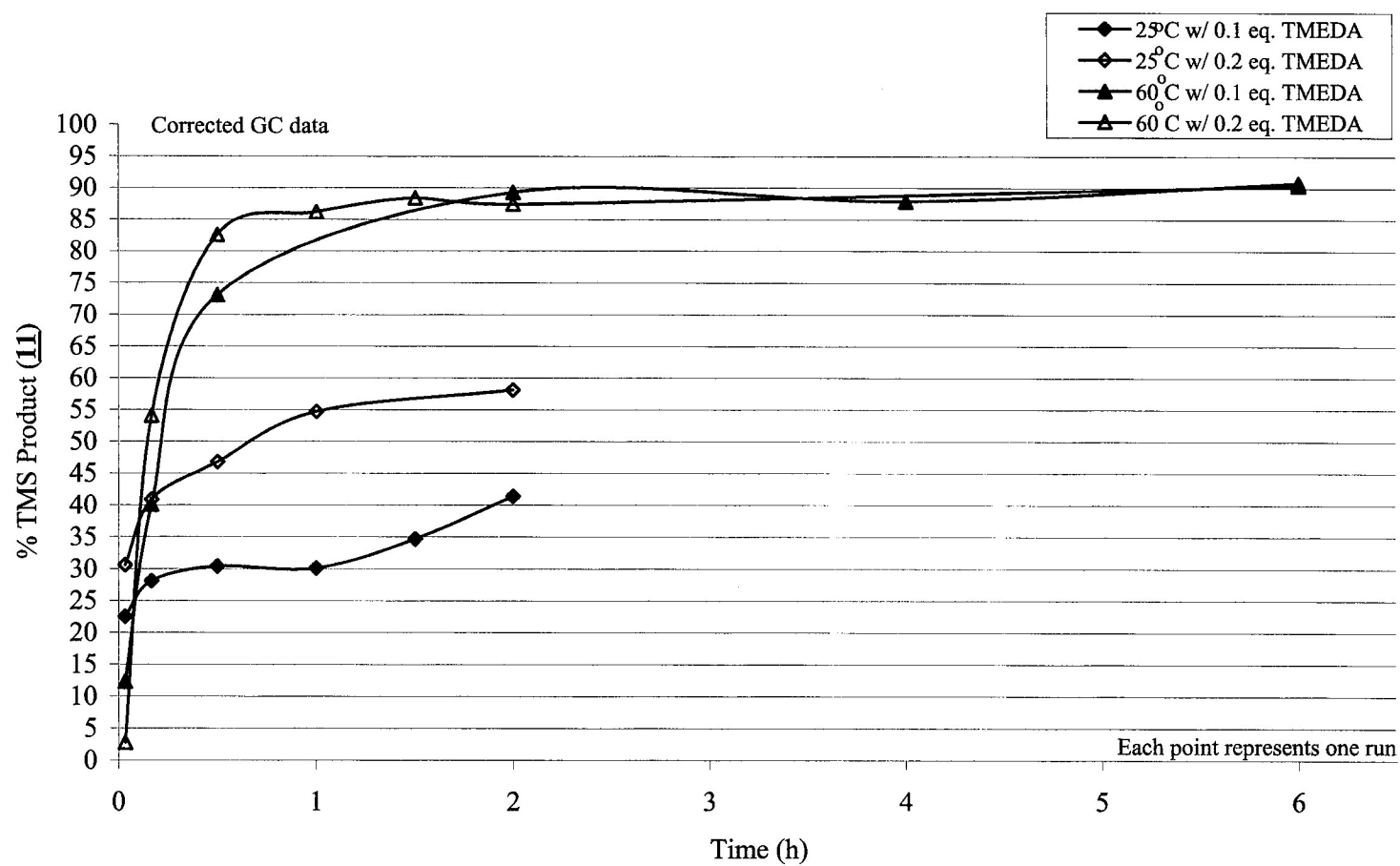


Figure 28. Progress of DoM of 1.0 eq. 1,4-TMPDA (**5**); 1.0 eq. n-BuLi at various temperatures (30 mL cyclohexane; 1.0 eq. = 0.02 mol)

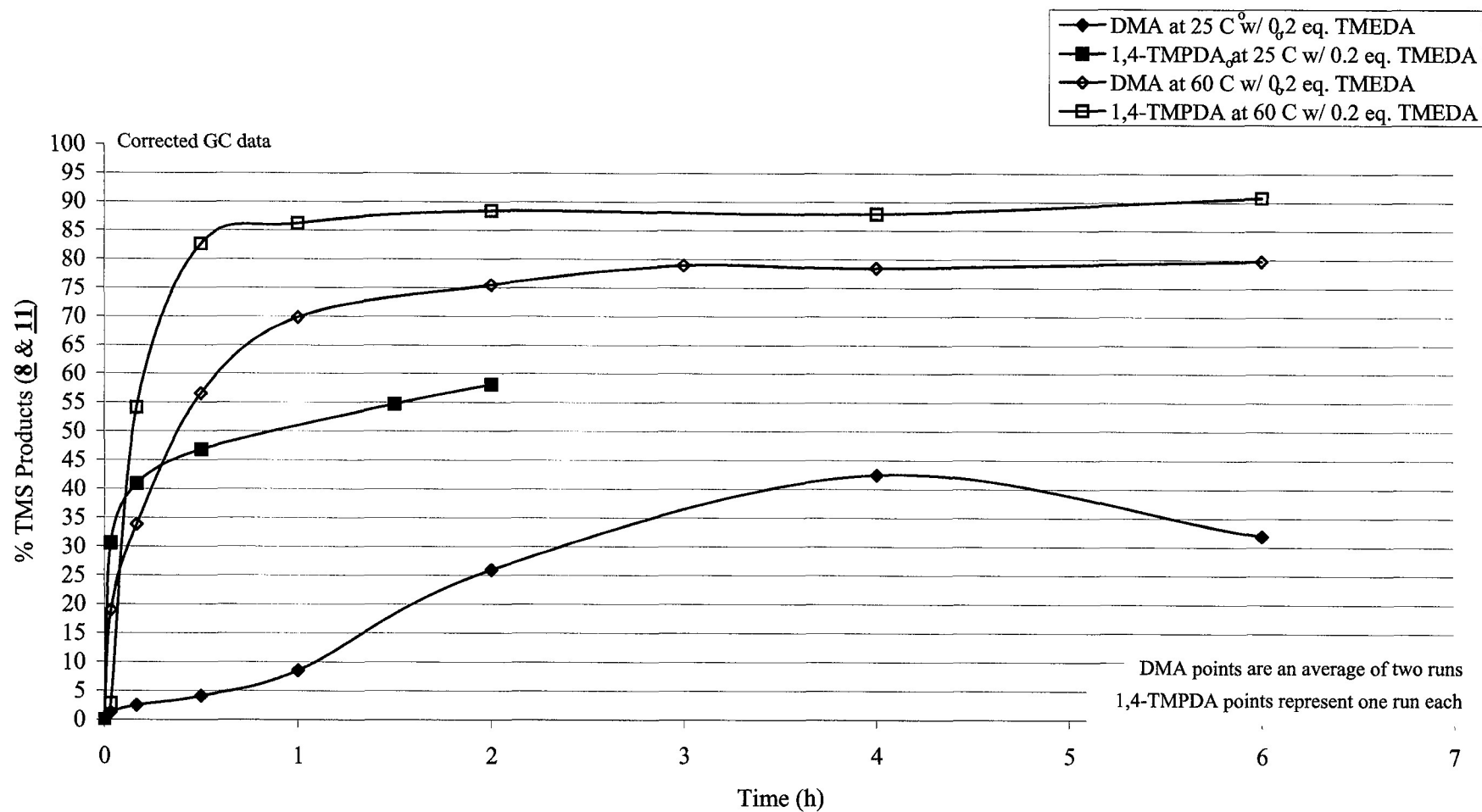


Figure 29. Comparison of DoM progress of 1.0 eq. DMA (**3**) and 1.0 eq. 1,4-TMPDA (**5**); 1.0 eq. n-BuLi at various temperatures in 30 mL cyclohexane (1 eq. = 0.04 mol DMA, 1 eq. = 0.02 mol 1,4-TMPDA)

Comparison of the reactions at 25°C reveals the difference in percent yield is much greater than those of the reactions at 60°C. Within 2 hours at 25°C 1,4-TMPDA yielded 58% TMS product, whereas DMA took 4 hours to achieve a maximum of little more than 42% TMS product. There is a marked increased rate attributable to the opposing  $\pi$ -resonance effect. The indirect evidence that the opposing  $\pi$ -resonance effect altered the 1,4-TMPDA reaction can be derived from this data. As previously stated, at 25°C TMEDA is not predominately in the eclipsed confirmation. With poor coordination capabilities DMA is reliant upon TMEDA to help form the n-BuLi dimer. On the other hand, because of opposing  $\pi$ -resonance, 1,4-TMPDA is a better coordinator and better competes with TMEDA for reactive sites. Therefore, it can achieve higher yields at low temperatures.

Reactions with 1,4-TMPDA and the direct comparison with DMA have shown that adding a second directing group in the para- position altered the extent of DoM. If indeed 1,4-TMPDA was reacting under the influence of the opposing  $\pi$ -resonance effect it provided further evidence that an additional electron donating DMG can increase DoM. The direct comparison of 1,4-TMPDA and DMA reactions showed evidence that the opposing  $\pi$ -resonance effect was pronounced at 25°C, but is not as significant at 60°C.

## 2. Comparison of Literature Studies with Experimental Results

A comparison between the 1,4-TMPDA experimental results (Table 10) and the summary of 1,4-TMPDA reactions reported in Table 1 would be beneficial in evaluating results obtained during experimental procedures. In many cases a direct comparison between two reactions might be difficult because of differing reaction conditions and derivatizing agents.

Table 15. Comparison of 1,4-TMPDA Literature Studies with Experimental Results

## 1.) Example from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/n-hexane/55°C/48 h <sup>120</sup>	Ph <sub>2</sub> CO	50-60 <sup>78</sup>

## 2.) Example from Experimental Results

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/cyclohexane/TMEDA/60°C/ 26h	CITMS	91 <sup>121</sup>

The comparison between these two reactions is essentially the difference in using the catalyst TMEDA. With only 0.2 eq. TMEDA the observed yield is more than 30% higher than the reported literature study.

F. Directed ortho-Metalation of 3-Methoxy-N,N-Dimethylaniline (3-MDMA) (6)

Two compounds, 3-methoxy-N,N-dimethylaniline (3-MDMA) and 3-methoxy-N,N-dimethylbenzylamine (3-MDMBA), each contain one of the principal DMG's of this thesis. Building on previous experimental results and expectations these two compounds were reacted under conditions similar to those found for DMA and DMBA. The results for 3-MDMA and 3-MDMBA should provide additional insight into the DoM reaction.

The DoM of substrates with directing groups in the 1- and 3- positions are subject to react via several different scenarios. To simplify the characterization of these reactions it would be best to divide the substrates into two categories: those with the same DMG's in the 1- and 3- positions, and those substrates with different DMG's in the 1- and 3- positions.

Compounds that have the same DMG's in the 1- and 3- positions will also have three hydrogens in an ortho- position. One hydrogen between both DMG's and two hydrogens that



are ortho- to the DMG's separately. Since the two DMG's are the same, the hydrogens ortho- to only one directing group will be equivalent. DoM could occur on the hydrogen ortho- to both directing groups, or it could occur on the hydrogens ortho- to either one of the directing groups. The result of these reactions could be two distinct products: a 1,2,3-compound and/or a 1,3,4-compound.

Compounds that have different DMG's in the 1- and 3- positions, such as 3-MDMA and 3-MDMBA, will have three ortho- hydrogens in different environments. One hydrogen between both DMG's, one hydrogen ortho- to the dimethylamino group, and one hydrogen ortho- to the methoxy group. DoM could occur on the hydrogen ortho- to both directing groups, or it could occur on the hydrogens ortho- to either one of the directing groups. Since the groups are not equivalent these two hydrogens are not equivalent. The result of these reactions could be three distinct products: a 1,2,3-compound, and two different 1,3,4-compounds.

The withdrawal of electron density by the methoxy and/or dimethylamino group increases the acidity of ring hydrogens, especially the hydrogens in the 2-positions. This is particularly the case with 3-MDMA. Coordination between the dimethylamino group and n-BuLi increases the contribution of DoM through the CIPE. This applies to both substrates. The increased acidity and the CIPE should promote metalation on the hydrogen ortho- to both substituents. The result of this DoM between both substitutes is a 1,2,3-product.

#### 1. Reactions with TMEDA

Building on the knowledge gained from the best yield reactions of DMA, several experimental sets were conducted with 3-MDMA. Because of the increased acidity on the ring hydrogens DoM should occur more extensively and at a faster rate than with DMA.

Table 16 shows the results for reactions of 1.0 eq. 3-MDMA, 1.0 eq. n-BuLi, with 0, 0.05, 0.1, and 0.2 eq. TMEDA at 60°C in cyclohexane. The data included in the table revealed that the results for 3-MDMA are disappointing and not what was expected.

Table 16. DoM Reactions Conducted with 3-MDMA

Reaction Components <sup>122</sup> (Equivalent Ratios)	Solvent	Temp (°C)	Maximum Percent GC Yield (Time)
3-MDMA:n-BuLi (1:1)	Cyclohexane	60	3.7(4 h)
3-MDMA:n-BuLi:TMEDA (1:1:0.05)	Cyclohexane	60	18.9(1.5 h)
3-MDMA:n-BuLi:TMEDA (1:1:0.1)	Cyclohexane	60	10.8(3 h)
3-MDMA:n-BuLi:TMEDA (1:1:0.2)	Cyclohexane	60	6.2(30 m)
3-MDMA:n-BuLi (1:1)	THF	25	20.9(2 h)
3-MDMA:n-BuLi (1:1)	Ether	25	9.6(4 h)

Addition of a methoxy group in the meta- position should increase the percent yield; however, both reaction sets produced percent yields dramatically lower than DMA experiments run under similar conditions. They are also much lower than that from a metalation of this substrate recorded in the literature.<sup>48,52</sup> It might be possible that the hydrogen ortho- to both substituents is too sterically hindered to permit modest amounts of metalation in hydrocarbon solvent in which the substrate was only slightly soluble. However this is doubtful considering results from m-DMB experiments. Because of the failure to generate significant product from these reactions, isolation of the –TMS derivative and correction of the GC spectra was not pursued.

## 2. Reactions in neat THF

In an attempt to find a media to promote DoM of 3-MDMA a reaction in neat THF was conducted. The maximum yield for this reaction was 21% within 2 hours (Table 16), which

is only slightly above the 15% afforded by DMA in neat THF. Although 3-MDMA produced higher yields than DMA in neat THF, there was not as significant a difference as was expected.

### 3. Reactions in neat Diethyl Ether

In an attempt to design a media to promote significant metalation of 3-MDMA a reaction was conducted in neat ether. The maximum yield for this reaction was 10% within 4 hours (Table 16).

### 4. Comparison of Literature Studies with Experimental Results

A comparison between the 3-MDMA experimental results (Table 11) and the summary of 3-MDMA reactions reported in Table 1 would be beneficial in evaluating results obtained during experimental procedures.

Table 17. Comparison of 3-MDMA Literature Studies with Experimental Results

#### 1.) Example from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/ether/35°C/12 h <sup>123</sup>	Ph <sub>2</sub> CO	71 <sup>48,52</sup>

#### 2.) Examples from Experimental Results

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/ether/25°C/4 h	CITMS	9.6 <sup>124</sup>
n-BuLi/THF/25°C/2 h	CITMS	20.9 <sup>125</sup>

This is an interesting comparison since the reported literature study reaction in neat ether achieved 60% more ortho- product than the experimental result. The highest yield obtained in these studies for the 3-MDMA reactions was in neat THF, 21%, which is still 50% lower than previously reported studies. It is difficult to explain such a discrepancy in results. It is doubtful that the higher temperature of the literature reaction would account for a 60%

difference in percent yield. No conditions were found for a reasonable metalation of this substrate.

G. Directed ortho-Metalation of 3-Methoxy-N,N-Dimethylbenzylamine (3-MDMBA) (7)

The DoM of 3-methoxy-N,N-dimethylbenzylamine (3-MDMBA) should proceed quite readily at the 2-position. The theory is that the methoxy group can withdraw electron density from the ring and increase the acidity of ring hydrogens, while the lone pair of electrons remains on the dimethylamino group available for coordination. Metalation is expected to occur most readily at the hydrogen ortho- to both substituents.

As was the case with DMBA, the methylene group provides an additional location for metalation. Metalation on the methylene group, better known as lateral metalation, would result in an  $\alpha$ -TMS product. The advent of this second product would limit the usefulness of 3-MDMBA as a viable substrate for DoM. The focus of reactions with 3-MDMBA centered on trying to maximize ortho- metalation, while minimizing lateral metalation.

1. Reactions with TMEDA

Results of experiments with 1.0 eq. 3-MDMBA, 1.0 eq. n-BuLi, with 0, 0.05, 0.1, and 0.2 eq. of TMEDA at 60°C in cyclohexane, can be seen in Table 18. After 6 hours the reactions have achieved an average yield of 81% for 0.2 eq. and 64% for 0.1 eq. TMEDA. Comparing a similar experiment with DMBA from Figure 27 the maximum product yield with 0.1 eq. TMEDA at 60°C reached 71% within 24 hours.

Although the product yield obtained for 3-MDMBA was better than those for DMBA under similar conditions, anticipated results of >90% yield in hydrocarbon solvent was not realized. A possible explanation for this less-than-anticipated yield might be that because multiple metalation sites exist on 3-MDMBA, metalation occurs at different sites thus

lowering the observed ortho- product yield. As with DMBA it was possible and suspected that lateral metalation was occurring producing an  $\alpha$ -product. According to GC/MS data from 3-MDMBA reactions, three unique products might be present. The most abundant of these products possesses the  $M^+$  corresponding to 2-TMS-3-MDMBA (**13**). Moreover, this is the site of metalation reported in the literature.<sup>77,92,96</sup>

Table 18. DoM Reactions Conducted with 3-MDMBA

Reaction Components <sup>126</sup> (Equivalent Ratios)	Solvent	Temp (°C)	Maximum Percent GC Yield (Time)
3-MDMBA:n-BuLi (1:1)	Cyclohexane	60	43.6 (4 h)
3-MDMBA:n-BuLi:TMEDA (1:1:0.05)	Cyclohexane	60	63.4 (2 h)
3-MDMBA:n-BuLi:TMEDA (1:1:0.1)	Cyclohexane	60	63.9 (2 m)
3-MDMBA:n-BuLi:TMEDA (1:1:0.2)	Cyclohexane	60	81.2(1 h)
3-MDMBA:n-BuLi:MTBE (1:1:0.7)	n-Hexane	60	56.2(6 h)
3-MDMBA:n-BuLi:MTBE (1:1:0.7)	Cyclohexane	60	44(6 h)

## 2. Reactions with MTBE

Following the success of DoM with DMBA and MTBE in n-hexane, reactions were conducted with 3-MDMBA and MTBE. Although a TMS product(s) had not been isolated for 3-MDMBA, an increase in uncorrected GC product yield was anticipated. The results for experiments with 1.0 eq. 3-MDMBA, 1.0 eq. n-BuLi, with 0.7 eq. and 1.0 eq. MTBE at 60°C in n-hexane and cyclohexane were disappointing. The two reactions produced 56% with 0.7 eq. and 46% with 1.0 eq. MTBE during a 8 hour time frame. Similar results were obtained for reactions in cyclohexane; 44% with 0.7 eq. and 41% with 1.0 eq. MTBE (Table 18).

Once again the failure of 3-MDMBA to produce higher or equal yields to DMBA under comparable conditions was disappointing and hard to explain. Further reactions should center on finding the maximizing MTBE eq. for 3-MDMBA, as this substrate may function better at lower MTBE concentrations. As stated above, metalation occurring at different sites would lower the observed ortho- product yield.

### 3. Comparison of Literature Studies with Experimental Results

A comparison between the 3-MDMBA experimental results (Table 12) and the summary of 3-MDMBA reactions reported in Table 3 would be beneficial in evaluating results obtained during experimental procedures.

Table 19. Comparison of 3-MDMBA Literature Studies with Experimental Results

#### 1.) Example from Literature Studies

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/ether/25°-30°C/ 24 h <sup>127</sup>	Ph <sub>2</sub> CO	75 <sup>92</sup>

#### 2.) Example from Experimental Results

Conditions	Derivatization Reagent	Percent Yield (Reference)
n-BuLi/cyclohexane/ TMEDA/60°C/1 h	CITMS	76.6 <sup>128</sup>

Although the reaction conditions for these two examples are quite different it does illustrate that moderate yields for 3-MDMBA are possible. Reactions at 25°C for 3-MDMBA were not attempted for this thesis.

#### IV. CONCLUSIONS

The comparison of reactions between DMBA and DMA provided insight into the DoM mechanism and the importance of prior-coordination of n-BuLi with the DMG. The chemistry behind these results was centered on the coordination abilities of the two substrates. With the methylene separating the dimethylamino group from the ring system, the lone electron pair on DMBA cannot delocalize its coordinating unshared electron pair into the ring. This allows the lone pair uncompromised coordination with an empty  $sp^3$  orbital on the n-BuLi dimer. N,N-Dimethylaniline does not have a unit separating the dimethylamino DMG from the ring system. The lone pair in this case readily delocalized into the ring and was therefore less available for external coordination. This effect significantly decreases the ability to direct metalation by the prior-coordination mechanism (Figure 1).

N,N-Dimethylaniline (**3**) failed to achieve a decent percent yield under mild metalation conditions. Only with high temperature did DMA achieve significant yield of the ortho-TMS product, **8**. The highest percent of ortho-TMS product (88%) was achieved through a combination of high temperatures and low TMEDA concentrations. Reactions with high TMEDA concentrations at increased temperatures afforded lower ortho-TMS product yield.

N,N-Dimethylbenzylamine (**4**) had similar restrictions for DoM that at higher temperatures fewer eq. of catalyst were necessary to achieve maximum yield. In fact reactions conducted under strong conditions, such as increased temperatures and high

TMEDA concentrations, yielded a significant percent of  $\alpha$ - product. The proposed reason for this was the methylene segment separating the ring and dimethylamino group provided an additional site for metalation.

The complication of producing multiple metalation products could hinder DMBA's effectiveness when reacted under DoM conditions. Later experiments revealed that reactions of DMBA and fractional eq. of MTBE produced 94% ortho- TMS product with minor amounts of  $\alpha$ -product present. These studies also indicated that the percent  $\alpha$ -product diminished and then disappeared over the course of 8 hours.

Applying the knowledge obtain from data of DMA and DMBA reactions, metalation was attempted on three dimethylamine homologs. The DoM of tetramethyl-1,4-phenylenediamine (1,4-TMPDA) (**5**), 3-methoxy-N,N-dimethylaniline (3-MDMA) (**6**), and 3-methoxy-N,N-dimethylbenzylamine (3-MDMBA) (**7**) tested the reaction theories of DMA and DMBA.

The reactions of 1,4-TMPDA produced results that where consistent with predictions. Adding the second dimethylamino group increased the rate and extent of metalation of this substrate compared to similar metalation of DMA. The increased rate of metalation was attributed to an opposing  $\pi$ -resonance effect.

Both 3-methoxy-N,N-dimethylaniline and 3-methoxy-N,N-dimethylbenzylamine did not achieve expected yields. Studies with 3-MDMA failed to produce over 21% TMS product. Reactions with 3-MDMBA reached 70% metalation however this was lower than reactions with DMBA. In both cases adding the meta- methoxy group should increase the rate and extent of DoM, however this was not the case.



We were most fortunate to find hydrocarbon systems for metalation of three of the five substrates examined. Moreover, the yields realized were higher than those reported in the literature in ether media. No real understanding of why 3-MDMA and 3-MDMBA failed to undergo 90% ortho- metalation.

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- <sup>104</sup> Materials Characterization Laboratory, Western Kentucky University, Bowling Green, KY 42101.
- <sup>105</sup> Materials Characterization Laboratory, Western Kentucky University, Bowling Green, KY 42101.
- <sup>106</sup> Assistance by undergraduates Ryan Sullivan and Melinda Crawford.
- <sup>107</sup> Assistance by undergraduate Dave Cardwell.
- <sup>108</sup> Assistance by undergraduate Adam Watson.
- <sup>109</sup> Assistance by undergraduate John Thompson.
- <sup>110</sup> Each reaction was conducted at 0.04 mol/eq. in 30 mL solvent.

- <sup>111</sup> 0.825 eq. DMA:1.725 eq. n-BuLi:1.65 eq. TMEDA (0.04 mol/eq.).
- <sup>112</sup> 3.0 eq. DMA:2.5 eq. n-BuLi (0.04 mol/eq.).
- <sup>113</sup> 1.0 eq. DMA:1.0 eq. n-BuLi:0.5 eq. TMEDA (0.04 mol/eq.). Reaction MT/RS/MS 5.
- <sup>114</sup> 1.0 eq. DMA:1.0 eq. n-BuLi:0.2 eq. TMEDA (0.04 mol/eq.). Reaction MT/AW 74.
- <sup>115</sup> 1.6 eq. DMBA:1.6 eq. n-BuLi:1.6 eq. TMEDA (0.04 mol/eq.).
- <sup>116</sup> 18.5 eq. DMBA:123 eq. n-BuLi (0.04 mol/eq.).
- <sup>117</sup> 1.0 eq. DMBA:2.0 eq. t-BuLi (0.08 mol/eq.).
- <sup>118</sup> 1.0 eq. DMBA:1.0 eq. n-BuLi:0.2 eq. TMEDA (0.04 mol/eq.) Reaction MT 41.
- <sup>119</sup> 1.0 eq. DMBA:1.0 eq. n-BuLi:0.7 eq. MTBE (0.04 mol/eq.) Reaction MT 163.
- <sup>120</sup> 0.5 eq. DMBA:0.5 eq. n-BuLi (0.04 mol/eq.).
- <sup>121</sup> 1.0 eq. 1,4-TMPDA:1.0 eq. n-BuLi:0.2 eq. TMEDA (0.02 mol/eq.). Reaction MT/JT 24.
- <sup>122</sup> Each reaction was conducted at 0.02 mol/eq in 30 mL solvent.
- <sup>123</sup> 1.0 eq. 3-MDMA:1.0 eq. n-BuLi (0.04 mol/eq.).
- <sup>124</sup> 1.0 eq. 3-MDMA:1.0 eq. n-BuLi (0.02 mol/eq.). Reaction MT/JT 9.
- <sup>125</sup> 1.0 eq. 3-MDMA:1.0 eq. n-BuLi (0.02 mol/eq.). Reaction MT/JT 26.
- <sup>126</sup> Each reaction was conducted at 0.02 mol/eq. in 30 mL solvent.
- <sup>127</sup> 1.25 eq. 3-MDMBA:1.5 eq. n-BuLi (0.02 mol/eq.).
- <sup>128</sup> 1.0 eq. 3-MDMBA:1.0 eq. n-BuLi (0.02 mol/eq.). Reaction MT/JT 4.



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## VII. APPENDIXES

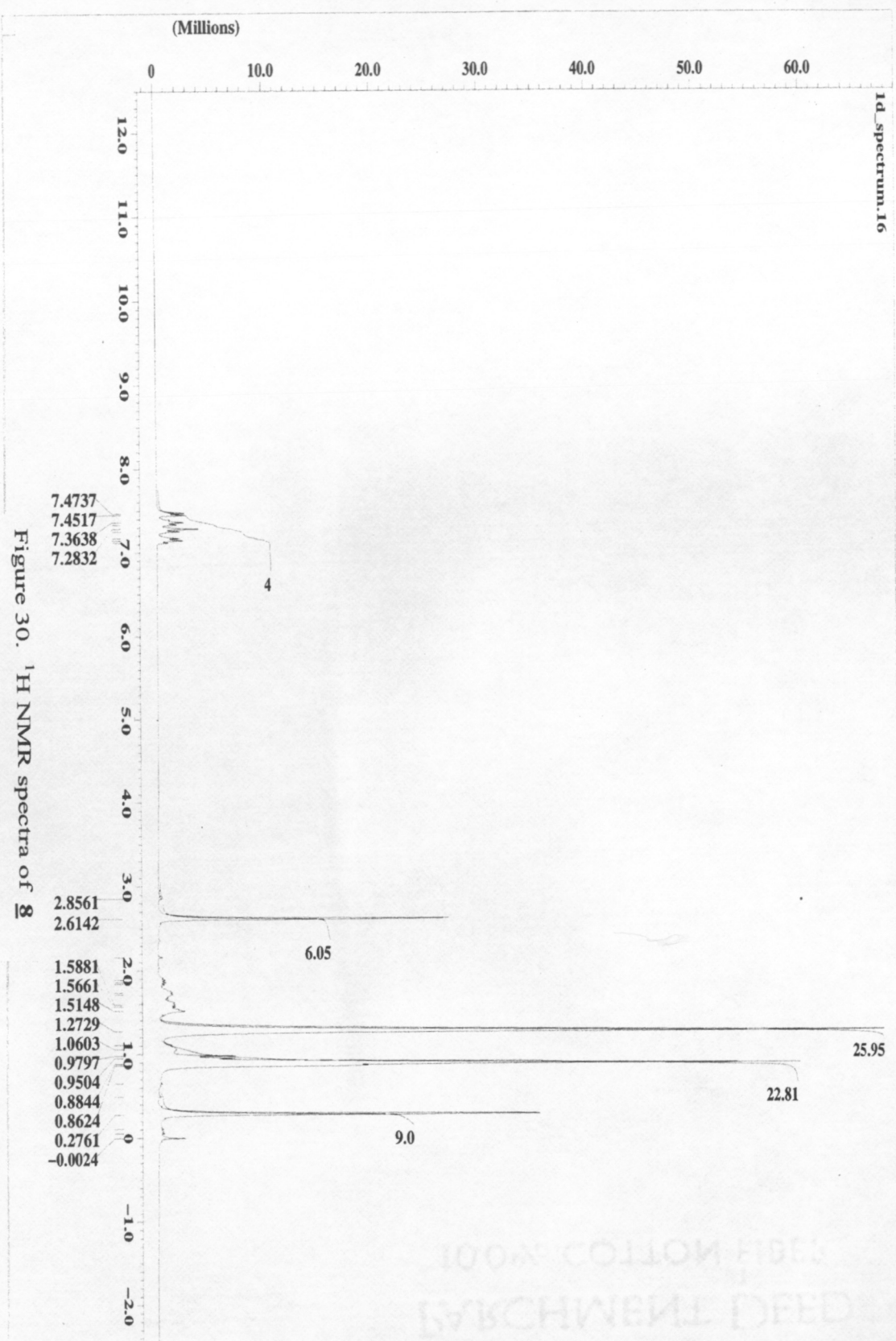
- A. List of Abbreviations
- B. NMR Spectra of Isolated Derivatives
  - 1.  $^1\text{H}$  NMR spectra of **8**
  - 2.  $^{13}\text{C}$  NMR spectra of **8**
  - 3.  $^1\text{H}$  NMR spectra of **9**
  - 4.  $^{13}\text{C}$  NMR spectra of **9**
  - 5.  $^1\text{H}$  NMR spectra of **11**
  - 6.  $^{13}\text{C}$  NMR spectra of **11**

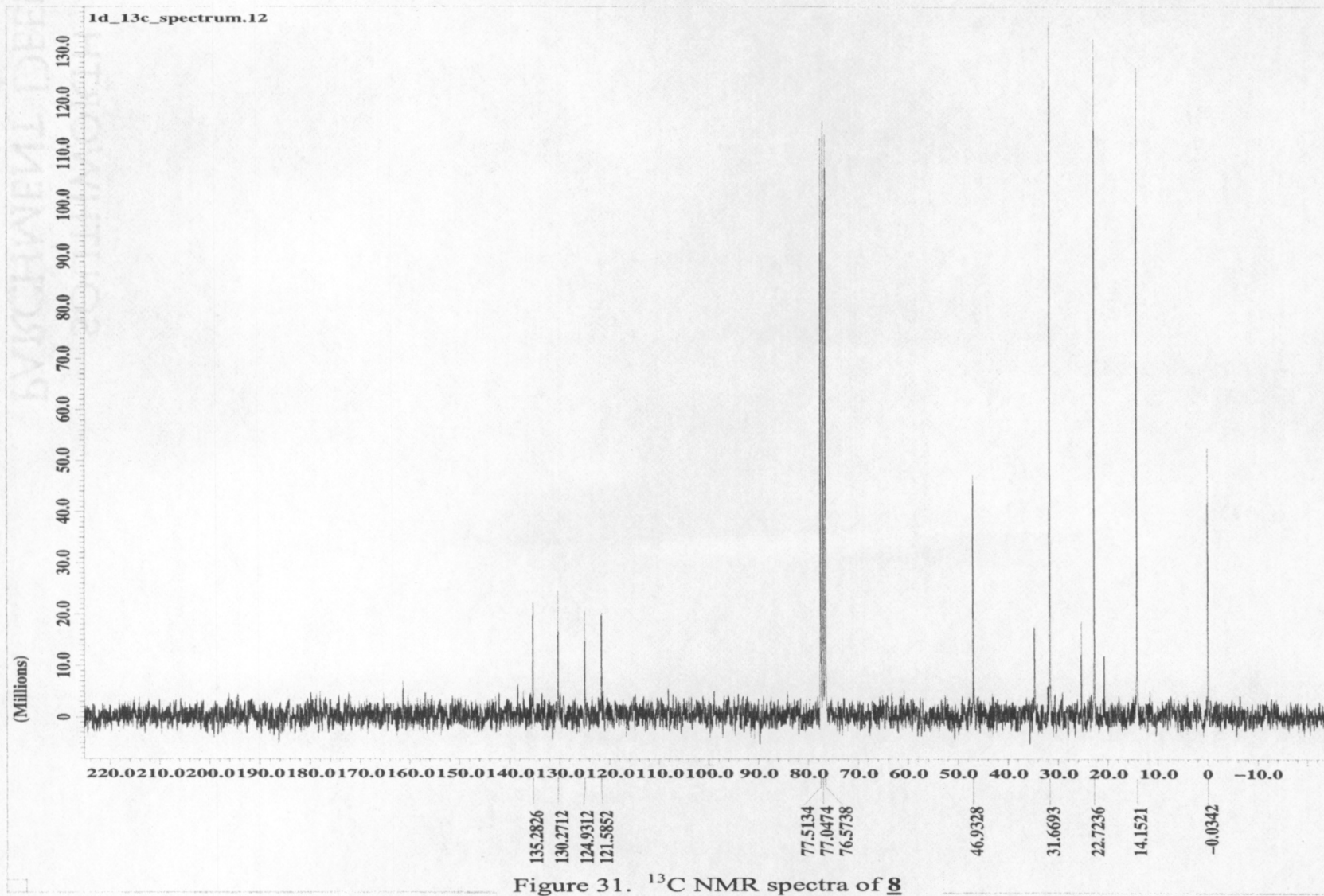
## APPENDIX A

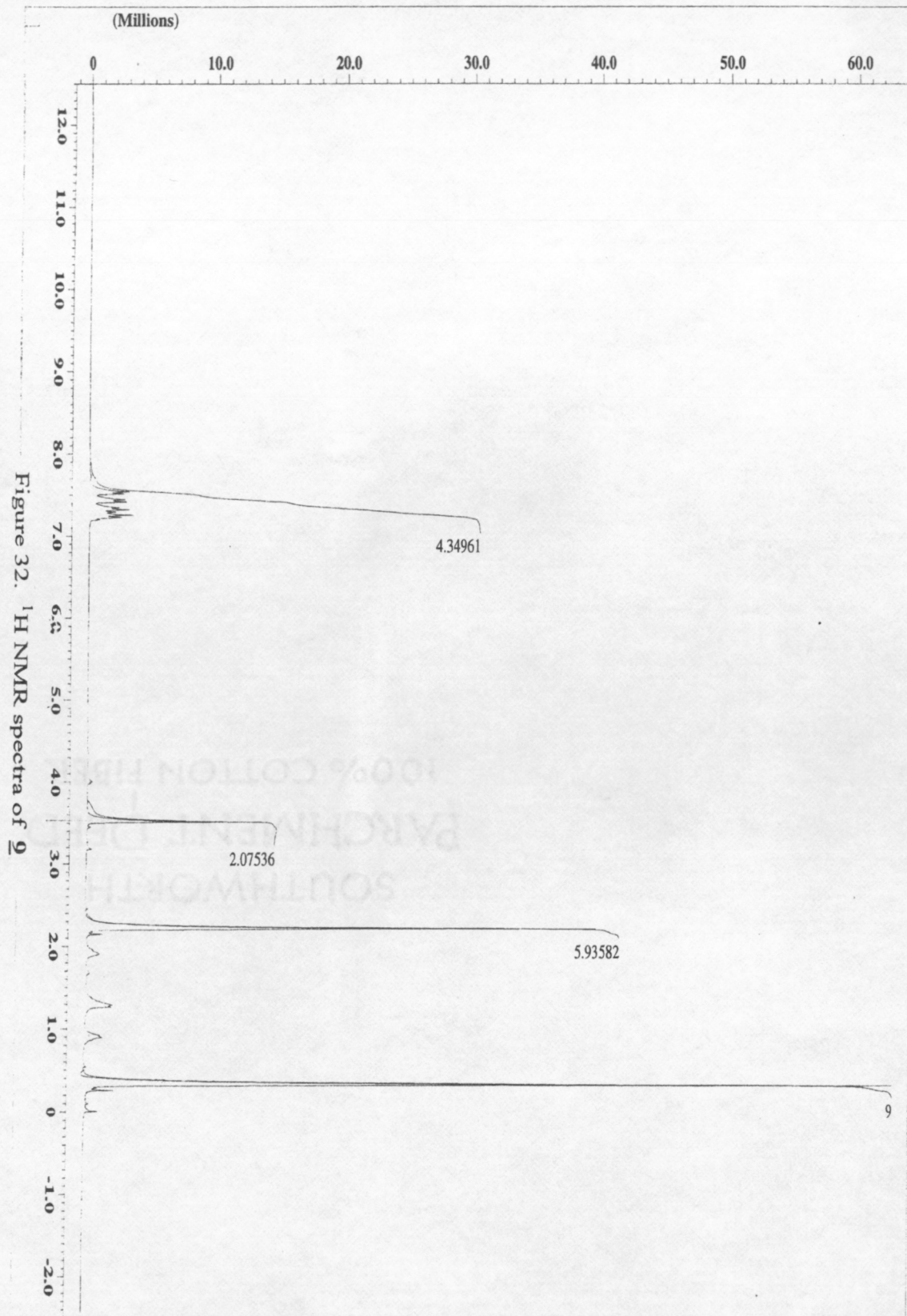
Table 20: List of Abbreviations

Abbreviation	Description
DoM	Directed ortho-Metalation
EAS	Electrophilic Aromatic Substitution
n-BuLi	n-Butyllithium
CIPE	Complex Induced Proximity Effect
DMBA	N,N-Dimethylbenzylamine
DMA	N,N-Dimethylaniline
1,4-TMPDA	N,N,N',N'-Tetramethyl-1,4-phenylenediamine
3-MDMBA	3-Methoxy-N,N-Dimethylbenzylamine
3-MDMA	3-Methoxy-N,N-Dimethylaniline
CITMS	Chlorotrimethylsilane
TMS	Trimethylsilyl (trapping/derivatizing agent)
o-	ortho-
m-	meta-
p-	para-
GC	Gas Chromatography
GC/MS	Gas Chromatograph/Mass Spectrometer
NMR	Nuclear Magnetic Resonance
eq.	Equivalents











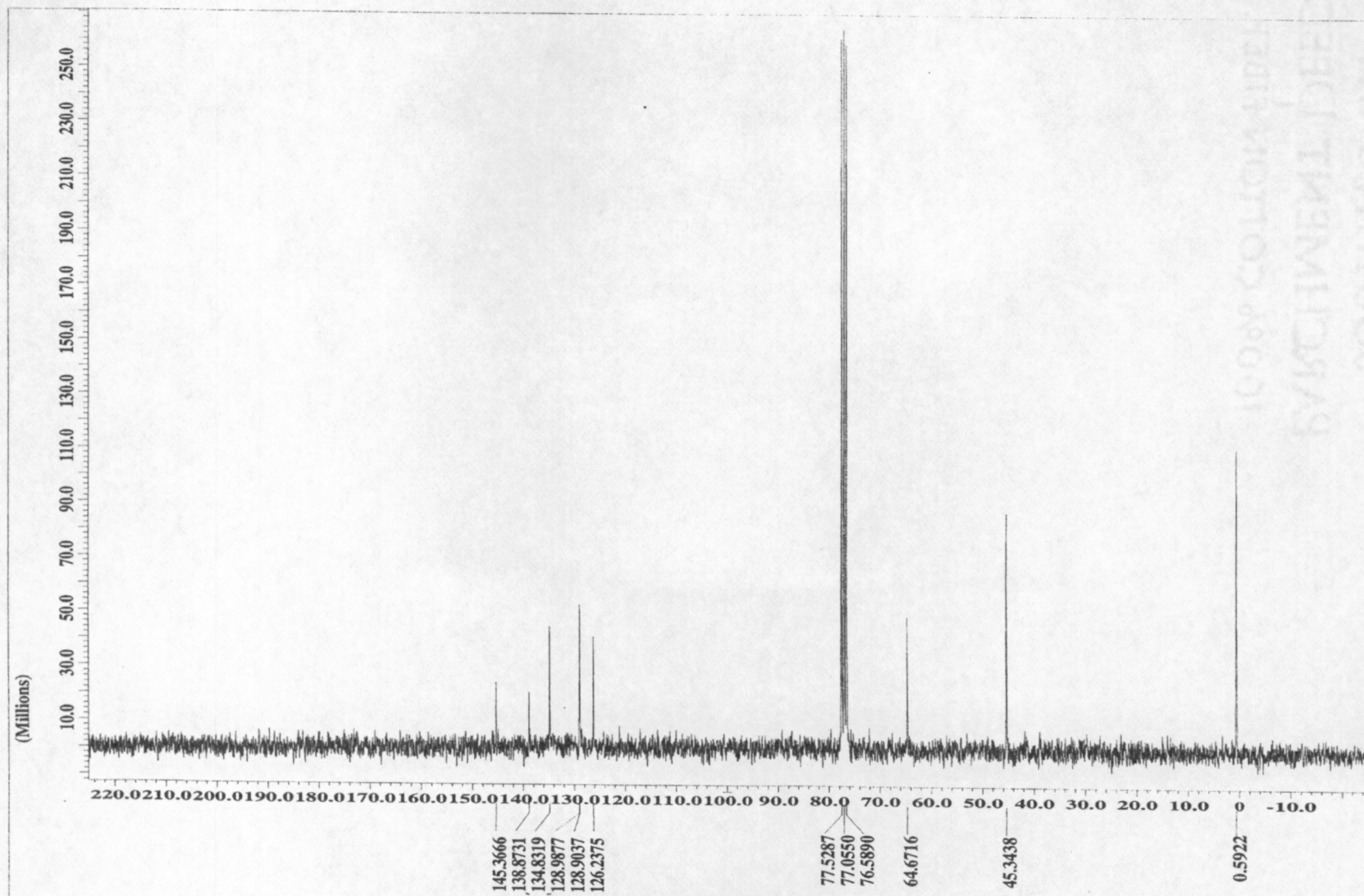


Figure 33.  $^{13}\text{C}$  NMR spectra of **9**

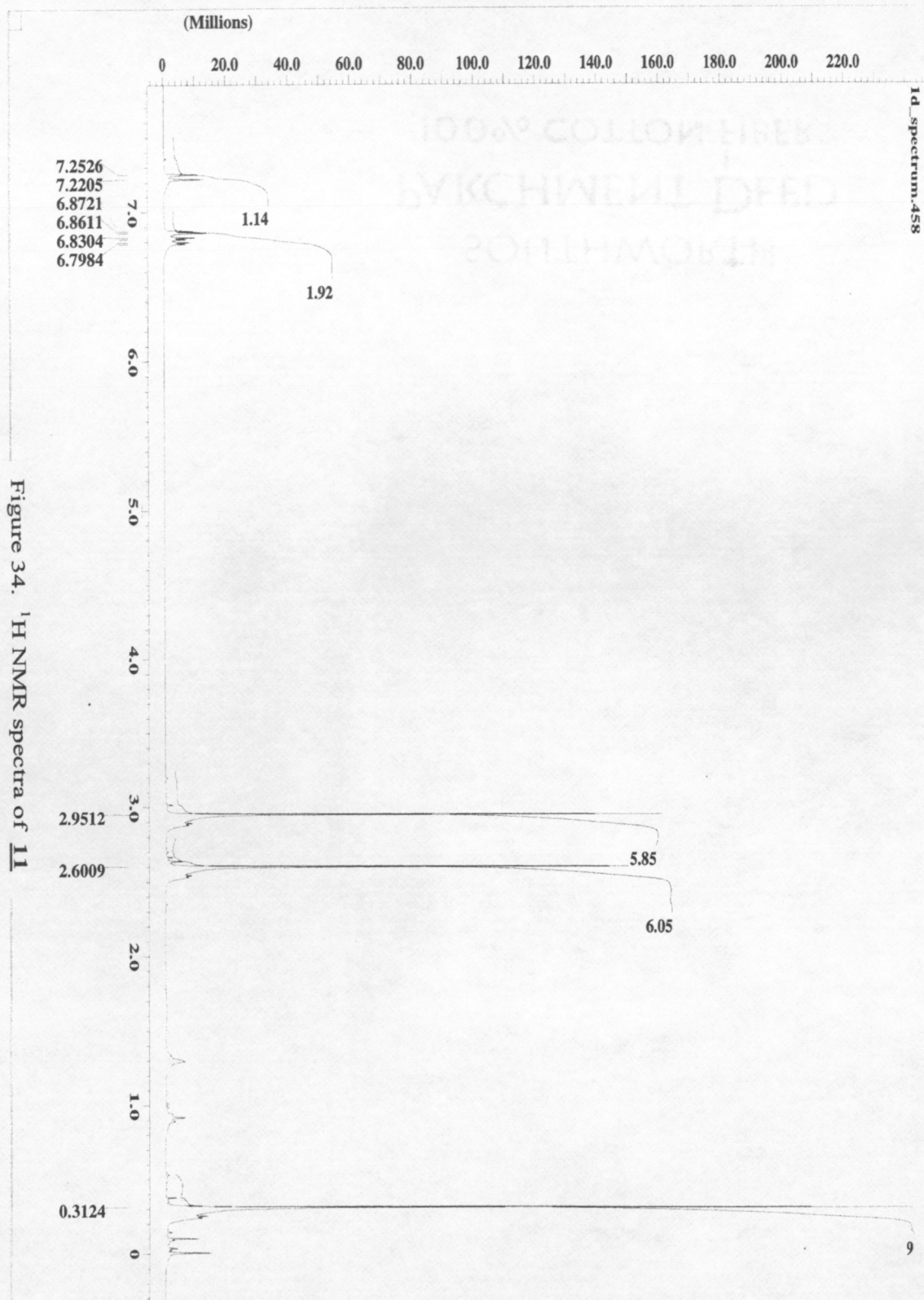


Figure 34.  $^1\text{H}$  NMR spectra of **11**

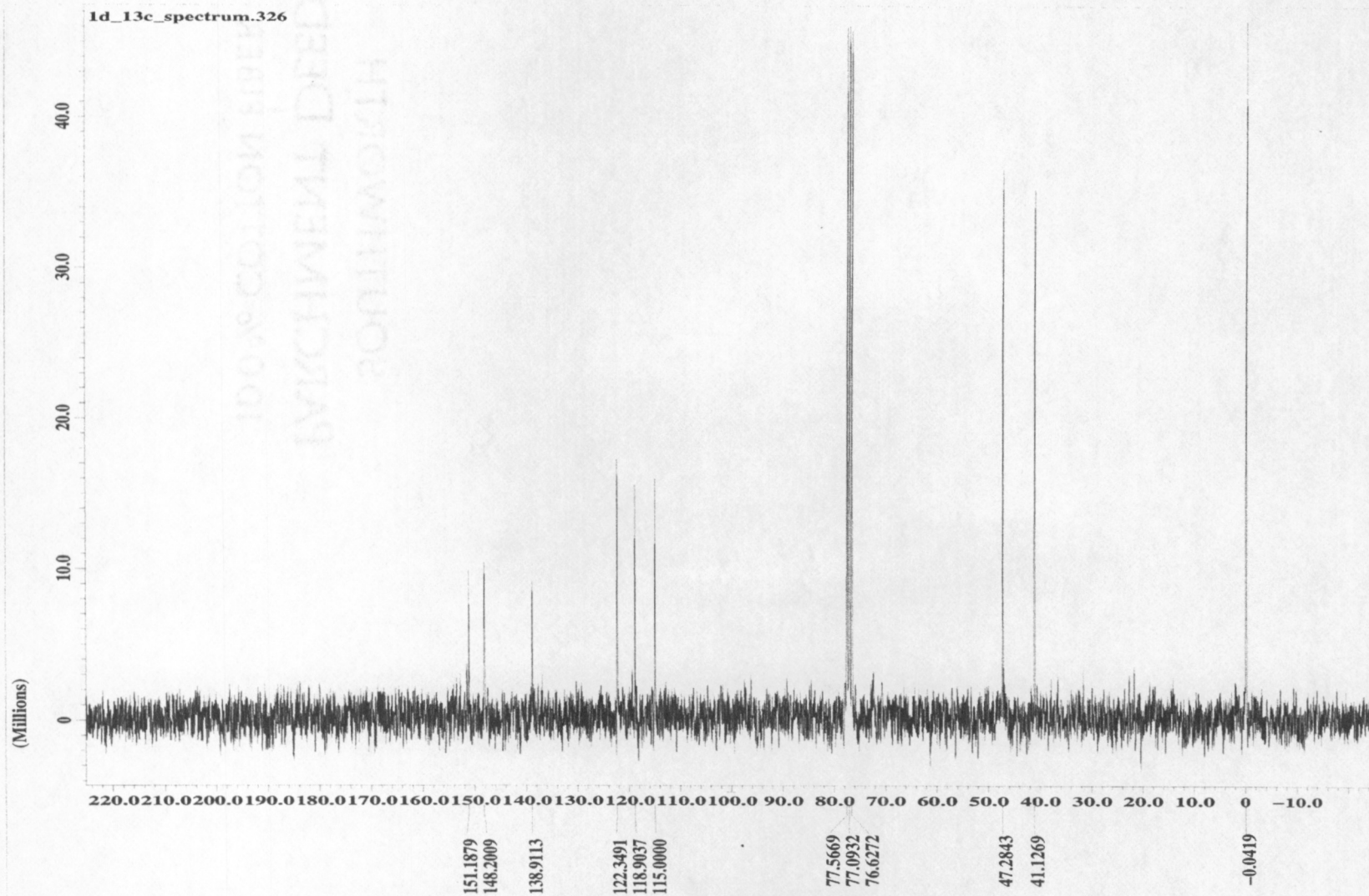


Figure 35.  $^{13}\text{C}$  NMR spectra of **11**