**Reaction Mechanisms**

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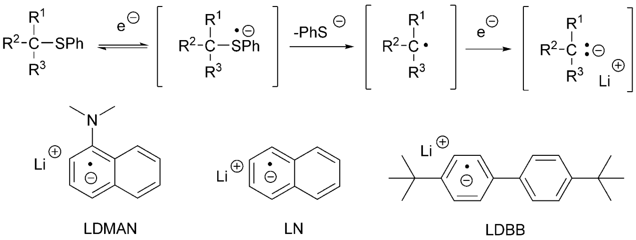
# Fundamental Difference in Reductive Lithiations with Preformed Radical Anions versus Catalytic Aromatic Electron-Transfer Agents: *N*,*N*-Dimethylaniline as an Advantageous Catalyst

*Nicole Kennedy,* Peng Liu, and Theodore Cohen**

***Abstract:*** *The reductive lithiation of phenyl thioethers, or alkyl chlorides, by either preformed aromatic radical anions or by lithium metal and an aromatic electron-transfer catalyst, is commonly used to prepare organolithiums. Revealed herein is that these two methods are fundamentally different. Reductions with radical anions occur in solution, whereas the catalytic reaction occurs on the surface of lithium, which is constantly reactivated by the catalyst, an unconventional catalyst function. The order of relative reactivity is reversed in the two methods as the dominating factor switches from electronic to steric effects of the alkyl substituent. A catalytic amount of N,N-dimethylaniline (DMA) and Li ribbon can achieve reductive lithiation. DMA is significantly cheaper than alternative catalysts, and conveniently, the Li ribbon does not require the removal of the oxide coating when DMA is used as the catalyst.*

The replacement of a C–heteroatom bond with a C−Li bond using aromatic radical anions, known as reductive lithiation, is a practical method for the synthesis of organolithium compounds. Specifically, the reductive lithiation of phenyl thioethers in which aromatic radical anions, including lithium naphthalenide (LN), lithium *p*,*p*′-di-*tert*-butylbiphenylide (LDBB), or lithium 1-(*N*,*N*-dimethylamino)naphthalenide (LDMAN),[1–4] are the source of electrons (Scheme 1).[5]

A catalytic method, which employs a catalytic amount of the aromatic hydrocarbon necessary for the electron transfer from the lithium to the substrate rather than a stoichiometric amount of the aromatic radical anion, was developed in this laboratory[6] to address the decomposition of LDMAN above −45 °C.[7] This widely accepted method was expanded by Yus and co-workers to include 1–5 mol % of *p*,*p*′-di-*tert*-butylbiphenyl (DBB), or naphthalene (Np),[8–11] and a large excess of specially prepared lithium powder[12] for their catalytic reductive lithiation of alkyl chlorides and phenyl sulfides.

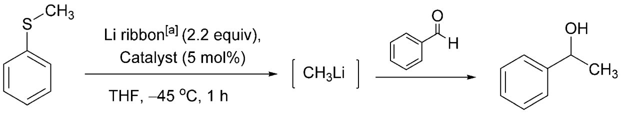


***Scheme 1.*** Reductive lithiation of phenyl thioethers with aromatic radical anions. THF = tetrahydrofuran.

It has been implicitly assumed that the mechanism for both the aromatic radical anion method (Scheme 1) and the catalytic method are the same. However, these mechanisms are very different. This surprising discovery came about while developing a novel type of reductive lithiation catalyst, *N*,*N*-dimethylaniline (DMA), which has been found to be at least as effective as DBB, the most commonly used reductive lithiation catalyst. DMA has significant advantages over DBB, such as an immensely lower cost[13] and the ability to be recycled from the reductive lithiation mixture by a simple aqueous extraction.

DMA was compared to DBB and 1-(*N*,*N*-dimethylamino)naphthalene (DMAN) in the reductive lithiation of methyl phenyl sulfide (**1**) with lithium ribbon[14] (Table 1). The methyl lithium intermediate **2** was trapped with benzaldehyde to produce 1-phenylethanol (**3**). As shown in Table 1, DMA catalyzed the reductive lithiation of **1** almost as well as DMAN and considerably better than DBB (entries 1–3). *N*,*N*-dimethyl-*o*-toluidine (DMOT), which is also commercially available but slightly more expensive,[13] produced a result comparable to that of DMA (entry 4). Isopropyl benzene, which is structurally similar to DMA but lacks a nitrogen atom, did not catalyze the reductive lithiation of **1** (entry 5). Increasing the equivalents of lithium ribbon led to an increase in the yield of **3** (entry 7).

***Table 1:*** Catalytic reductive lithiation of **1**.



**1** **2** **3**

| Entry | Catalyst | Yield [%][b] |
|---|---|---|
| 1 | DBB | 48 |
| 2 | DMAN | 72 |
| 3 | DMA | 68 |
| 4 | DMOT | 65 |
| 5 | isopropyl benzene | 42 |
| 6 | none | 39 |
| 7 | none | 65[c] |

[a] Oxide coating on lithium ribbon was scraped off prior to the reaction. [b] Yield of isolated **3** after chromatographic purification. [c] 5 equiv of lithium ribbon.

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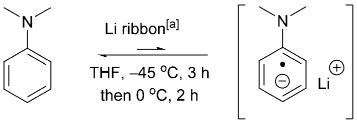
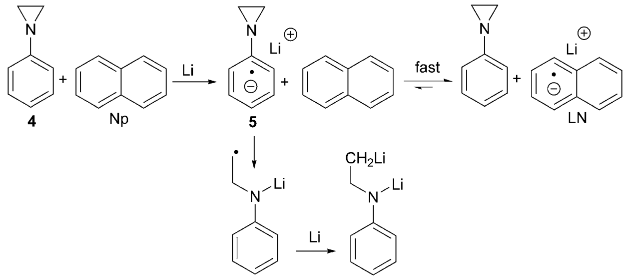
DMA, and by implication DMOT, are novel because all other aromatic electron-transfer agents are converted into their deeply colored radical anions in the presence of lithium (Scheme 1), whereas DMA does not form a perceptible radical anion, lithium *N*,*N*-dimethylanilinide (LDMA), in the presence of lithium. When DMA was treated with lithium ribbon, the mixture remained colorless and DMA was completely recovered (Scheme 2). Unlike DMAN, the equilibrium in the conversion into LDMA may be unfavorable because of reduced electron delocalization, as compared to that for LDMAN.



***Scheme 2.*** Aromatic radical anion LDMA formation. [a] Oxide coating on lithium ribbon was scraped off prior to the reaction.

The discovery that DMA is one of the best catalysts for reductive lithiation occurred while investigating the earlier finding in this laboratory that *N*-phenylaziridine (**4**) failed to reductively lithiate in the presence of LN.[5,15] We proposed that electron transfer from lithium to **4** is more rapid than the transfer of an electron from lithium to Np (Scheme 3).[5]



***Scheme 3.*** Proposed mechanistic explanation for the catalytic method of reductive lithiation of **4**.

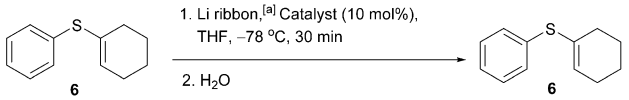
When a catalytic amount of Np is present, the resulting radical anion of *N*-phenylaziridine (**5**) transfers an electron to Np to form LN, which is the more thermodynamically stable radical anion.[5] As a result, **5** becomes the kinetic product of electron transfer from lithium. In this particular case, Np behaves as an inhibitor rather than a catalyst and this was indeed shown experimentally to be the case.[5]

This finding is consistent with LDMAN forming at −45 °C, and is faster than LDBB forms at 0 °C or LN at room temperature. We speculate that the amino group complexes with $Li^+$ on the surface of the metal. As a result, the electrophilicity of the aromatic ring increases while at the same time increasing the electron-donating power of the metal surface such that there is a more rapid electron transfer to the π system.[5]

To further investigate the DMA-catalyzed reductive lithiation of phenyl thioethers, the yields of unreacted starting material of an alternative substrate were compared at a lower temperature and a higher percentage of catalyst. As shown in Table 2, DMA and DBB catalyzed the cleavage of 1-(phenylthio)-1-cyclohexene (**6**) to similar extents (entries 1 and 2).

We wanted to gain an understanding of the relative rates of cleavage in the DMA-catalyzed reductive lithiation of alkyl phenyl sulfides. As shown in Table 3, **7**–**9** cleave considerably slower than **1**, and is in contrast to what would be predicted for the preformed radical anion method.[3a,e,16] The relative reactivity is reversed in going from the radical anion method to the DMA catalytic method. This unique finding results from a steric effect rather than electronic effect. By comparing the relative rates of cleavage of two secondary alkyl phenyl sulfides, **7** and **9**, a sharp increase in unreacted starting material was observed as the bulkiness of the alkyl group increased.

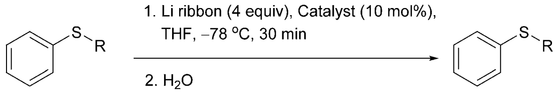
***Table 2:*** Catalytic reductive lithiation of **6**.



| Entry | Catalyst | Yield [%][b] |
|---|---|---|
| 1 | DBB | 76 |
| 2 | DMA | 79 |
| 3 | none | 100 |

[a] Oxide coating on lithium ribbon was scraped off prior to the reaction. [b] The percentage of recovered starting material after chromatographic purification.

***Table 3:*** Catalytic reductive lithiation of alkyl phenyl sulfides.

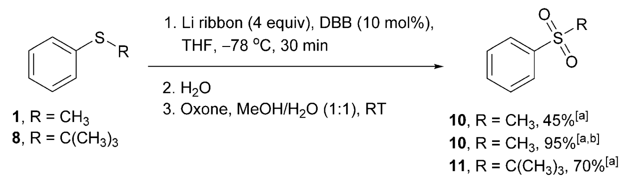


| Entry | SM | R | Catalyst | Yield [%][a] |
|---|---|---|---|---|
| 1 | **1** | $CH_3$ | DMA | 31 |
| 2 | **1** | $CH_3$ | DMA | 30[b] |
| 3 | **1** | $CH_3$ | DMAN | 29[b] |
| 4 | **7** | $CH(CH_3)_2$ | DMA | 62 |
| 5 | **8** | $C(CH_3)_3$ | DMA | 60 |
| 6 | **9** | $c\text{-}C_8H_{15}$ | DMA | 95 |

[a] The percentage of recovered starting material after chromatographic purification. [b] Oxide coating on lithium ribbon was not removed prior to the reaction.

The same relative reactivity was observed for the DBB-catalyzed reductive lithiation, in which **1** cleaved more rapidly than **8** (Scheme 4). To facilitate separation from DBB, the unreacted starting material was oxidized into a sulfone.[17] The catalyzed reductive lithiation of alkyl phenyl sulfides is fundamentally different from the preformed radical anion method.

In our recent publication,[16] we revealed that in the absence of an aromatic electron carrier, the reductive lithiation of phenyl thioethers with lithium dispersion occurs at the surface of the metal and the order of reactivity toward



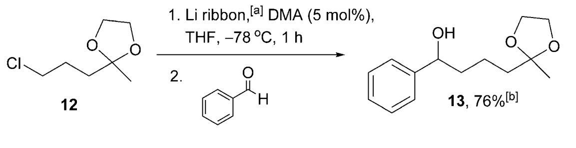
***Scheme 4.*** DBB-catalyzed reductive lithiation of **1** and **8**. [a] Yield of product isolated after purification. [b] Oxide coating on lithium ribbon was not scraped off prior to the reaction.

methyl phenyl sulfide and *tert*-butyl phenyl sulfide is reversed from the preformed radical anion method. Because of smaller steric repulsions between the methyl group and the lithium surface, methyl phenyl sulfide reacts faster than sulfides with bulkier alkyl groups. The results in Table 3 and Scheme 4 indicate that the catalytic method of reductive lithiation has the same selectivity as the lithium dispersion method, in which the cleavage of the C–S bond very likely occurs on the metal surface.

After the aromatic catalyst adsorbs an electron from the lithium metal surface, the resulting radical anion can either transfer the electron to the substrate or back onto the surface of the metal. The latter probably occurs more rapidly since the radical anion is already in contact with that surface. The net result is that the surface is constantly being disrupted and regenerated through dissolution and deposition of Li$^+$. This process is expected to break down the surface films and form a dendritic and thus, more reactive lithium with a large surface area.[18] This effect is especially evident with DMA and DMAN, in which the amino group can complex with Li$^+$ on the surface and promote surface reconstruction. It turns out that the oxide coating does not need to be removed prior to the reaction when DMA or DMAN are employed (Table 3, entries 2 and 3). However, with DBB, the shiny surface, free of the oxide coating, needs to be exposed for successful reductive lithiation (Scheme 4). The type of catalysis revealed here is highly unconventional.

We explored the scope of the DMA-catalyzed reductive lithiation with an alkyl chloride, 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (**12**), which has previously undergone catalyzed reductive lithiation.[19] This substrate was treated with a catalytic amount of DMA and un-scraped lithium ribbon to afford the corresponding alcohol product **13** after the organolithium intermediate was captured with benzaldehyde (Scheme 5).

In conclusion, we have demonstrated that the catalytic method of reductive lithiation is fundamentally different from the preformed radical anion method. Under the catalytic method, the reduction occurs on the lithium surface, which is constantly being reactivated by the catalyst. This process is a highly unconventional type of catalysis. The relative reactivity of the catalyzed reductive lithiation method is just the opposite of that using preformed radical anions. We have also discovered a novel reductive lithiation catalyst, DMA, which was compared to the most common transfer reagents and has been shown to catalyze the reductive lithiation to the same degree, if not better. DMA has a number of advantages over the most commonly used catalysts: DMA is far less expensive,[13] DMA can be removed from the reaction mixture upon workup by a dilute acid wash, and the lithium ribbon does not need to be scraped free of the oxide coating when DMA is the catalyst.



***Scheme 5.*** DMA-catalyzed reductive lithiation of **12**. [a] Oxide coating on lithium ribbon was not scraped off prior to the reaction. [b] Yield of product isolated after purification.

## Acknowledgments

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