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Organolithiums by reductive lithiation: the catalytic aromatic method versus the use of preformed aromatic radical-anions. Naphthalene can behave as a catalyst or an inhibitor☆

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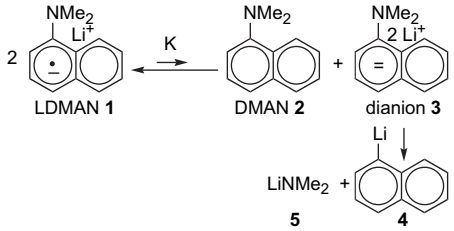
Abstract—Two common modes, using aromatic radical-anions for reductive lithiation, the replacement of a C–heteroatom bond with a C–Li bond, have been compared with regard to yield and the mildness of reaction conditions required. It was found that the use of preformed radical-anions generally resulted in higher yields and milder reaction conditions than the 'catalytic' method in which catalytic amounts of the aromatic compound are used and the radical-anion is generated and used in situ. The one apparent exception is *N*-phenylaziridine, but it is shown that in this case the aromatic compound, naphthalene, is actually an *inhibitor* rather than a *catalyst*. Rational mechanistic explanations are given.

1. Introduction

Since its introduction in 1978,[2,3] reductive lithiation of phenyl thioethers using aromatic radical-anions has been demonstrated to be one of the most versatile methods known for generating organolithiums.[4,5] A number of other leaving groups, such as halides,[6] sulfones,[7] sulfates,[8] nitriles,[9] selenides,[10] allylic and benzylic ethers,[11,12] sulfides,[13] amines,[13] and acetals,[14] have also been used but they have been considerably less versatile than the phenylthio group.[15] An important advantage of reductive lithiation is that unlike the most conventional method of organolithium preparation, removal of an electrophile such as H^+, I^+, R_3Sn^+, etc. by another organolithium, it is often the case that the less stable the organolithium, the greater the ease of its generation by reductive lithiation. The reason is that the mechanism involves the transfer of an electron from the aromatic radical-anion to the substrate followed by a homolytic cleavage of the bond between the organic moiety and the leaving group.[16] Since this step is rate determining, the rate of the reaction is determined largely by the stability of the intermediate radical, rather than that of the carbanion, to which the radical is rapidly reduced. Thus, it is an extremely general method of organolithium production especially since phenyl thioethers are available by a wide variety of synthetic methods, many of them connective. Another considerable advantage is that the aromatic and the thiophenol are recoverable and thus a stoichiometric amount of lithium metal is the only reagent that is destroyed, making this the most economical method available since lithium is far less expensive than any organic form of lithium.

In the earliest reports of the reductive lithiation of phenyl thioethers,[2] a stoichiometric quantity of lithium naphthalenide was used but in several cases, a sub-stoichiometric quantity of naphthalene was used along with a stoichiometric quantity of lithium metal. The latter conditions were successful in reducing the amount of naphthalene that had to be removed from the desired product but the reductive lithiations required higher temperatures and longer reaction times.

In 1980, a report from this laboratory indicated a solution to the problem of removal of the aromatic hydrocarbon.[17] When lithium 1-(dimethylamino)naphthalenide (LDMAN **1**, Scheme 1) was used as the reducing agent, the basic aromatic



Scheme 1.

☆ See Ref. 1.
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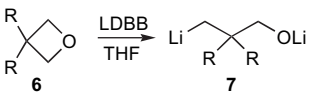
byproduct **2** could be removed and recovered by washing the reaction mixture with dilute acid. An additional advantage of the use of LDMAN is that it can be used in solvents other than THF, the solvent universally used in synthetic procedures involving aromatic lithium radical-anions.[18]

Because LDMAN **1** decomposes to 1-lithionaphthalene **4** above −45 °C,[19] a 'catalytic method' was devised, which allowed reactions with LDMAN to be performed with good results at higher temperatures.[17] Because of the great instability of aryl radicals, it was thought that the decomposition of LDMAN at this low temperature was probably not due to the homolytic cleavage of the bond between the ring carbon atom and the heteroatom, the usual mode in radical-anion decompositions.[20] It was postulated instead that the aromatic dianion **3** was generated in THF in an unfavorable equilibrium[21] with the radical-anion **1** and was decomposing directly to the relatively stable napthyl anion and the dimethylamido anion **5** (Scheme 1).

Since DMAN **2** and Li metal react over a period of hours to produce LDMAN while most reductive lithiations are extremely rapid, it was reasoned that DMAN would act as a conduit for electrons to the substrate undergoing reductive lithiation and that the concentration of the radical-anion **1** would be extremely low until the reductive lithiation is complete. Thus, the equilibrium in Scheme 1 would be driven even further to the left, resulting in a negligible concentration of the unstable dianion **3** and consequently in a very slow decomposition of LDMAN. This reasoning is apparently correct as evidenced by the fact that the green-black color of LDMAN only became evident when all of the substrate thioether had reacted and by the ability, using the catalytic method, of performing reductive lithiations above −45 °C.[17]

The success of the next published use of the catalytic method was more mixed. During a study in this laboratory of the reductive lithiation, using lithium 4,4′-di-*tert*-butylbiphenylide (LDBB), one of the most common aromatic radical-anions,[22] of oxetanes **6** to produce organolithiums **7** bearing an oxyanionic group (Scheme 2), the catalytic aromatic method, as expected from the above results and discussion, took far longer than the method using preformed aromatic radical-anion at the same temperature.[23] However, the result led to just as favorable an outcome with **6** (R=Me) but with **6** (R=H), the production of **7** (R=H) was far less efficient, giving a lower yield of dianion than when preformed aromatic radical-anion was used and leading to the production of considerable 1-propanol. Undoubtedly, the propanol resulted when the intermediate anion **7** (R=H), during the long reaction time required, removed a proton from the 2-position of the sterically unhindered oxetane, a known type of proton loss for oxetanes.[24] The steric hindrance provided by the methyl groups of **6** (R=Me) apparently saved it from this fate.



6 **7**

Scheme 2.

More recently, Yus and his co-workers in Spain introduced the use of the catalytic aromatic method, in a mode somewhat different than that used previously, for the reductive lithiation of some primary alkyl chlorides and two alkyl phenyl sulfides.[25] In their work,[26–28] a solution of the substrate to be reduced in THF is mixed with 1–5 mol % of the aromatic compound, usually naphthalene or 4,4′-di-*tert*-butylbiphenyl (DBB), and a large excess of lithium powder, usually a 4–7-fold molar excess. In their extensive and impressive publications on this topic, they have demonstrated that a large variety of organic compounds can be reductively lithiated, and that this method eases the separation of the aromatic byproduct from the reaction product.[25–28]

In a number of these papers, the claim is made that this version of the catalytic aromatic method (which we abbreviate CA), in which the radical-anion is continually generated and rapidly destroyed by electron transfer to the substrate, is far more powerful than the use of a stoichiometric amount of preformed aromatic radical-anion (PAR).[26,29–32] For example, "above all, the catalytic version is far more reactive, so it is possible to perform new lithiation reactions, which do not work when a lithiation-arene is used as lithiation agent"[29a] and "in the catalytic version, yields are better, reaction times are far shorter, the reactions are very clean."[26a]

This assertion seemed unlikely to us based on the experimental results enumerated above and some other results from our laboratory, heretofore only reported in a thesis (see below). The theoretical basis also appears inconsistent with our experience that radical-anion formation is virtually always slower than the reductive lithiation, as mentioned above. Thus, in most cases the rate-determining step for the reductive lithiation would be the transfer of an electron from the surface of the metal to the aromatic catalyst. The net result would be that, as found in the published work described above, the process of reductive lithiation would be slower at any given temperature than the process using preformed radical-anion. As again indicated above, such longer reaction times can in some cases translate into destruction of some organolithium compounds. Of course, damage is minimized in the Yus protocol in which the radical-anion formation is accelerated by supplying the lithium as a powder instead of larger chunks with less surface area and by the use of a very large excess of lithium. Nonetheless, the rate-determining step is still the electron transfer to the aromatic catalyst as evidenced by the fact that, as in the use of the catalytic method with LDMAN mentioned above,[17] the color of the radical-anion does not appear until all of the reduction substrate has been consumed.[25,29,33]

The mechanistic explanation suggested[30] to account for the purported superiority of the CA method is that there is a greater concentration of aromatic dianion during reduction by the CA method than that by the PAR method and that the dianion is expected to be a more powerful reducing agent. However, it seems to us that there should be a far *lower* concentration of aromatic dianion in the CA method than in the PAR method for the reasons in our earlier paper[17] that are outlined in the discussion above pertaining to Scheme 1.

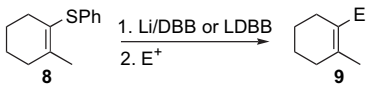
For example, in that scheme, the concentration of dianion **3** is given by the expression: $[\mathbf{3}]=K[\mathbf{1}]^2/[\mathbf{2}]$ where **1** is the radical-anion and **2** is the neutral aromatic. Thus, in the case of preformed aromatic radical-anion, the concentration of dianion is at the maximum since virtually all of the aromatic compound is in the form of the radical-anion and the concentration of neutral aromatic is negligible. On the other hand, in the CA method, the concentration of dianion is minimal since the rapid transfer of an electron from the slowly formed radical-anion to the substrate maintains a negligible concentration of radical-anion and virtually all of the aromatic compound is in the neutral form; this is clearly indicated by the fact that the color of the radical-anion appears only after the substrate has been consumed.[25,29,33]

Presumably, these claims of the greater power of the CA method are at least partly responsible for the choice that most groups now make to adopt it in new work as indicated in recent reviews of Yus.[26,34] On the other hand, if this superiority is found to be unsubstantiated, the choice as to which of the two modes of reductive lithiation is appropriate in a given case should be made on other grounds. The present study was performed to directly compare the PAR and CA methods by conducting reactions using both methods to determine the relative advantages of each.

2. Results and discussion

2.1. Reductive lithiation of 2-methyl-1-(phenylthio)-cyclohexene

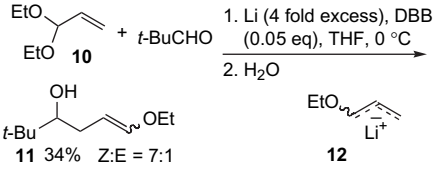
In work that we had performed 15 years ago, but was heretofore only reported in a thesis because its significance was not obvious at the time,[1] evidence for a decreased yield using the catalytic method rather than PAR method was found in the reductive lithiation of 2-methyl-1-(phenylthio)cyclohexene **8** for 8 h at −78 °C (Scheme 3), followed by quenching with various electrophiles. The use of a slightly greater than stoichiometric amount of LDBB gave yields of 80%, 71%, and 71%, respectively, of products **9** when the vinyllithium was quenched with cyclohexanecarboxaldehyde, *n*-hexyl iodide, and allyl bromide. When the same reaction was performed using a slight excess of lithium and only 20% of the stoichiometric amount of DBB, the yields were 54%, 50%, and 52%, respectively. Thus, in this case as in those described in Section 1, preformed aromatic radical-anion gave better yields than the use of the same quantity of Li but a considerably sub-stoichiometric quantity of the aromatic hydrocarbon.



Scheme 3.

2.2. Reductive lithiation of acrolein diethyl acetal

In 1994, a report[32] appeared in which acrolein diethyl acetal **10** was reductively lithiated via the CA method at 0 °C in the presence of various carbonyl compounds that captured the resulting allylic lithioether **12** (the Barbier method[35]) to give 34–40% yields of alcohols. Scheme 4 shows one example. Significantly, it was stated that no reduction occurred at −40 °C and that if the carbonyl compound were added after the reductive lithiation, the yields were greatly reduced due to decomposition of the allyl anionic intermediate.



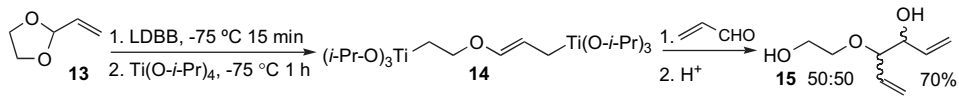
Scheme 4.

This caught our attention for two cogent reasons. First, a previous publication from our laboratory had reported the reductive lithiation of an analogous acrolein acetal **13** at −75 °C using the PRA method to deliver a far higher yield of trapped product **15** (Scheme 5).[12] Second, the anions of allyl ethers such at **12** are known to undergo the Wittig rearrangement, the probable cause of the reported[32] instability of **12**, at temperatures as low as −25 °C,[36] thus making it imperative to work at a lower temperature; a comparison of Schemes 4 and 5 made it appear that this would be possible only by using the PAR method, as discussed above.

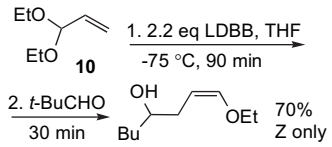
Thus, the substrate **10** was subjected to the PAR conditions. It was found (Scheme 6) that the reductive cleavage occurred smoothly at −50 °C to provide the anion **12**, which was trapped with the same aldehyde to provide a 70% yield of **11** with higher stereoselectivity than that reported using the CA method under the required Barbier conditions and higher temperature.[37] Attempts to cleave **10** with Li powder in the absence of DBB failed, indicating as expected that the aromatic hydrocarbon indeed acts as a catalyst in this reductive lithiation. This case is an excellent demonstration that in cases in which the carbanion being produced by reductive lithiation is unstable, the use of preformed aromatic radical-anion is preferable to the catalytic method even with a large excess of lithium powder (compare Schemes 4 and 6). It seems likely that a more recent reductive lithiation of a related acetal of acrolein[38] using the CA method could have also benefited by the use of a stoichiometric quantity of preformed LDBB.

2.3. Reductive lithiation of 6-chloro-6-methyl-1-heptene

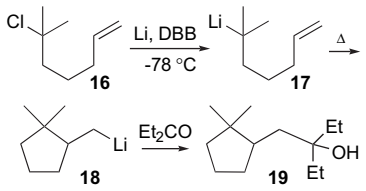
In 2002, a report appeared that the reductive lithiation of 6-chloro-6-methyl-1-heptene **16** using the CA method at −78 °C gave an anion that cyclized at higher temperatures but that the cyclization product could be trapped by 2-pentanone only under very special conditions, namely Barbier mode at 0 °C (76% yield) or in a two-step process at −30 °C (75% yield).[39] The anion **17** was reported to be unstable at −78 °C (Scheme 7).



Scheme 5.

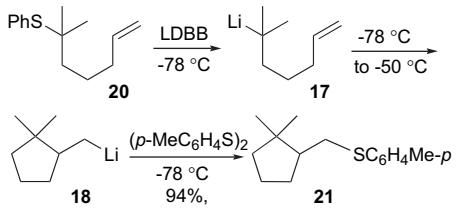


Scheme 6.



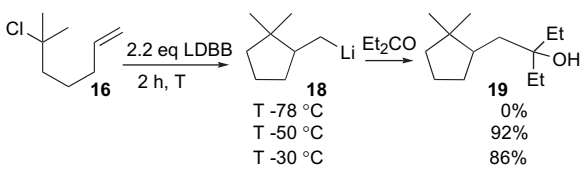
Scheme 7.

This report surprised us since we had performed a reductive lithiation of the phenylthio analogue **20** of **16** at −78 °C and found that the reductive lithiation and cyclization, after warming **17** to −50 °C, occurred smoothly under the usual PAR conditions to provide a 94% yield of trapped product **21**[40] (Scheme 8).



Scheme 8.

In order to make a direct comparison with the published CA method, the tertiary alkyl chloride **16** was treated with LDBB at three temperatures and the cyclized organolithium **18** was treated with 3-pentanone to provide the alcohol **19**. From the results in Scheme 9, it is clear that the reductive lithiation product **17** of **16** does not cyclize rapidly at −78 °C but that it cyclizes smoothly at −50 °C to give an excellent yield of trapped product. In order to test the possibility that higher temperatures would cause destruction of the intermediate organolithiums, the experiment was repeated at −30 °C and the yield was found to drop slightly, indicating that lower temperatures are preferred for reductive lithiations. These are generally better attainable by the PAR mode as discussed above. Once again, the importance of the presence of DBB was tested by performing the reductive lithiation at −30 °C without DBB and the yield merely fell to 53%, thus indicating that in this particular case, the catalyst is not absolutely essential.

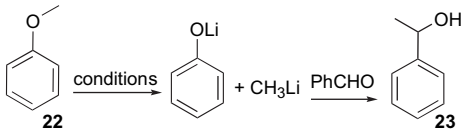


Scheme 9.

Unfortunately, this apparent comparison of the CA and PAR methods became somewhat less meaningful when a more recent paper[41] by the Spanish group revealed that the structure **16** in their preliminary communication,[39] was in error and that the real compound used was 6-chloro-6-ethyl-1-octene (terminal ethyl groups rather than methyls). Nevertheless, the results in Scheme 9 do indicate that tertiary organolithiums can be readily generated by reductive lithiation of the chloride using the PAR method, just as had occurred with the corresponding phenyl thioether at very low temperatures and that this carbanion cyclizes at −50 °C to give an excellent yield of cyclized organolithium. It is also clear (Scheme 8) that the tertiary carbanion is not unstable at −78 °C as the corresponding tertiary carbanion from CA reductive lithiation of 6-chloro-6-ethyl-1-octene is reported to be.[39,41] It seems likely that the latter carbanion does not necessarily remove a proton from the THF at that temperature as suggested, but that the hindered carbanion abstracts an α-proton from the trapping agent, 3-pentanone, instead; the alternative reaction of the carbanion with the carbonyl group would yield a very highly congested di-tertiary C–C bond.

2.4. Reductive cleavage of anisole

A report of the reductive cleavage of anisole **22** at the alkyl C–O bond at room temperature using CA conditions (14-molecular equiv of Li and 0.05 equiv of DBB) yielded 80% of **23**, the product of capture of the methyllithium by benzaldehyde (Scheme 10).[42] This paper indicated that the PAR conditions were somewhat inferior but the conditions of the comparison were somewhat nebulous, particularly because room temperature was apparently used and we have found that LDBB is unstable above 0 °C.[43]



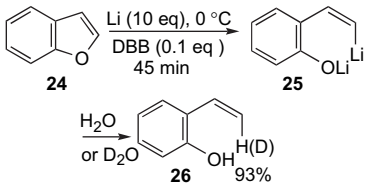
Scheme 10.

We therefore, undertook a comparison of the two methods at 0 °C for 2 h. The results were striking. The CA method (same conditions as above but at 0 °C) yielded 30% of **23** while the PAR method provided 87% of **23**. Using 14 equiv of Li but no DBB gave no product. Thus, the reaction is clearly faster using preformed stoichiometric LDBB than using the catalytic method even with the use of a large excess

of the metal. This is consistent with our preconceived notions as indicated in Section 1.

2.5. Reductive cleavage of 2,3-benzofuran

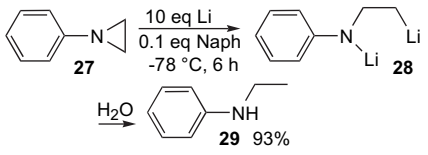
The reductive lithiation of 2,3-benzofuran **24** with an excess of lithium in the presence of DBB was reported to give the result shown in Scheme 11.[44] Other electrophiles were also used. It occurred to us that the LUMO of **24** may be lower in energy than that of DBB and that the electron transfer might occur directly from the metal to **24**, thus obviating the requirement for the purported catalyst, DBB. Indeed, when the reported conditions were duplicated, but in the absence of DBB, a 91% yield of **26** was generated. It is thus doubtful that DBB serves as a catalyst when the CA method is attempted.



Scheme 11.

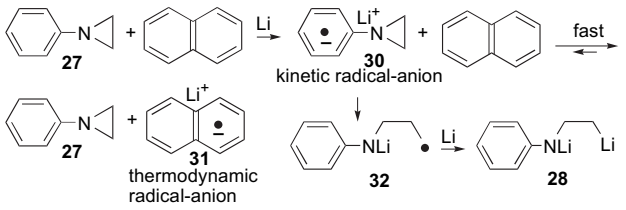
2.6. Reductive cleavage of *N*-phenylaziridine

In some of the papers in which the claim is made that the catalytic method is more powerful than the stoichiometric method, there is a reference to a report of the reductive cleavage of *N*-phenylaziridine by the CA method as shown in Scheme 12.[45] Other electrophiles were used as well. There is a statement in that paper that aziridines do not undergo reductive opening by lithioarenes at low temperature. Since the type of aziridine and the reaction conditions were not included in the paper, we decided to directly compare the CA and PAR methods as applied to the reductive cleavage of *N*-phenylaziridine **27**. To our initial surprise, lithium naphthalenide (LN) did not cause the cleavage of **27** at the temperature and in the time reported in Scheme 12; only the starting material was recovered. A repetition of the literature procedure (Scheme 12)[45] did indeed produce the reported result. This result appeared to support the claim that the CA method is more powerful than the PAR method. However, for the reasons stated in Section 1, it seemed highly unlikely that the method using naphthalene as a catalyst could lead to a faster reductive cleavage than the use of preformed lithium naphthalenide.



Scheme 12.

A possible alternative explanation for these experimental results is illustrated in Scheme 13. The transfer of an electron from the surface of the lithium occurs more rapidly to the *N*-phenylaziridine **27** than to the naphthalene but in the presence of the latter, the resulting radical-anion **30** can rapidly transfer an electron to the naphthalene to generate the more thermodynamically stable naphthalenide radical-anion **31**. In other words, the radical-anion **30** is the kinetic product of electron transfer from the lithium but the naphthalenide ion **31** is the thermodynamic radical-anion as indicated by the inequality of the arrows leading from **30** and naphthalene to **27** and **31**. Since **30** is the immediate precursor of the ring-opened product **32**, its concentration is directly proportional to the rate of ring cleavage. The higher the concentration of naphthalene, the lower is the rate of ring cleavage. By behaving as a sink for electrons, naphthalene reduces the concentration of **30**, and thus inhibits the reductive ring opening. If this reasoning is correct, the aziridine should open at −78 °C even in the absence of the naphthalene 'catalyst.' In fact, naphthalene in this specific case should behave as an inhibitor rather than a catalyst.



Scheme 13.

This hypothesis was tested first by attempting the cleavage of **27** with lithium in the absence of naphthalene. The result was quantitative ring opening within the 6 h test period at −78 °C (entry 2, Table 1). Thus, as predicted, naphthalene is not required and, in fact, the yield in its absence was somewhat higher than the 90% in the presence of 0.1 equiv of naphthalene (entry 3). In order to test the prediction that naphthalene is an inhibitor, reductive cleavages were performed with the usual 5-fold excess (10 equiv) of lithium with 1.0 equiv and 10 equiv of naphthalene. As seen in entries 2–5, the larger the quantity of naphthalene the lower the yield. Thus, naphthalene is indeed an inhibitor. The inability of LN to reductively cleave *N*-phenylaziridine is understandable on the basis of the unfavorable position of the equilibrium in which an electron is transferred from the naphthalenide ion **31** to **27** (Scheme 13).

The reason that *N*-phenylaziridine accepts an electron more rapidly from lithium than naphthalene does is not known but this finding is consistent with our experience that 1-(*N*,*N*-dimethylamino)naphthalene forms a lithium radical-anion *at −45 °C* somewhat faster[46] than naphthalene does[2] *at room temperature*. One can speculate that the amino group complexes with a lithium cation on the surface of the metal

Table 1. Reductive cleavage of *N*-phenylaziridine[a]

Entry	Reagents	Yield%
1	2.2 equiv LN	0
2	10 equiv Li	100
3	10 equiv Li, 0.1 equiv Np	90
4	10 equiv Li, 1.0 equiv Np	76
5	10 equiv Li, 10.1 equiv Np	16

[a] All reactions were performed at −78 °C for 6 h in THF.

thus increasing the electrophilicity of the ring while at the same time increasing the electron donating power of the metal surface, leading to a more rapid transfer of an electron to the pi system of the aromatic. Further studies of this phenomenon and its practical applications are now underway in this laboratory.

3. Conclusions

Yus and his group have made an important contribution to the practice of reductive lithiation using lithium radical-anions as a method of cleavage of bonds between carbon and various heteroatoms to produce organolithiums by developing the version, abbreviated in this paper as the CA method, in which a large excess of finely divided lithium is used in the presence of a catalytic amount of naphthalene or 4,4′-di-*tert*-butylbiphenyl. In extensive publications, they have demonstrated the wide generality of this procedure that can significantly ease the problem of separating the aromatic byproduct of the reductive lithiation from the cleavage product. Another advantage that has to our knowledge only been used once[17] in a different version in which a stoichiometric amount of lithium is used along with a catalytic amount of aromatic in order to maintain a low concentration of the aromatic dianion, when this species can do damage; this is discussed in Section 1.

In the present work, we have demonstrated a major disadvantage of the CA method that should be weighed against its advantages in deciding whether to use that method or the PAR method, involving a stoichiometric quantity of preformed aromatic radical-anion, for performing reductive lithiations. The disadvantage of the CA method is that at any given temperature, the catalytic method is slower than that using a stoichiometric amount of preformed aromatic radical-anion. This is illustrated in all of the cases compared above but most vividly by the large decrease in yield in the reductive cleavage of anisole in going from the PAR to the CA method in experiments with the same limited duration. In some cases this lower rate may not be a highly significant disadvantage, particularly when the organolithium being produced is stable under the reaction conditions and some of the reductive lithiations that the Yus group have performed proceed in good yields. However, in cases in which the organolithium is not entirely stable to the reaction conditions, significant decreases in yield are observed in going from the PAR to the CA method. Examples are the reductive lithiation of acrolein acetals to produce allylic α-lithioethers that are capable of undergoing the Wittig rearrangement and of tertiary alkyl chlorides that can undergo elimination in the presence of the tertiary organolithium products.

Furthermore, some compounds previously believed to undergo catalytic reductive lithiation, such as 2,3-benzofuran **24**, pick up an electron and cleave as fast in the absence as in the presence of the aromatic catalyst. This is not surprising as the radical-anion derived from this substrate has extensive delocalization, probably greater than that in the LDBB that would be the intermediate radical-anion if the catalytic process was indeed occurring.

A far more surprising and significant result is that the reductive cleavage of *N*-phenylaziridine **27** not only does not require naphthalene as a catalyst but the naphthalene is actually an inhibitor of the reductive lithiation. Apparently, this substrate forms a radical-anion **30** by reaction with lithium more rapidly than naphthalene does but the radical-anion **31** from naphthalene is more thermodynamically stable than that of **30** from *N*-phenylaziridine. Thus, the aromatic compound can behave as a catalyst, an unnecessary additive or an inhibitor, depending on the specific substrate.

Finally, one other disadvantage of the CA method should be mentioned. Lithium metal is the most expensive ingredient used in reductive lithiations since the aromatic compound can easily be recovered and recycled. The large excess of lithium used could become an economic liability as well as something of a safely hazard, especially in an industrial setting. The expense is especially onerous considering that the cost of lithium powder from Aldrich is almost six times the cost of the ribbon that we ordinarily use to make preformed radical-anion.

4. Experimental

4.1. General

All reactions were performed under an argon atmosphere in oven-dried (110 °C) flasks and standard precautions against moisture were taken. A dry ice/acetone bath was used to obtain a temperature of −78 °C. An ice bath was used to obtain 0 °C. Silica gel 60 (40–60 μm, Sorbent Technologies) was used for flash column chromatography. Thin-layer chromatography was performed on glass supported 250-μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light, aqueous $KMnO_4$ (1%) with NaOH (0.1%) and K_2CO_3 (6%). Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium benzophenone ketyl. Most reagents were commercially available from Sigma-Aldrich or Acros. Lithium dispersion was commercially available from Alfa, 30% in paraffin. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C at 22 °C unless otherwise noted. Chemical shift data are reported in units of δ (ppm) using $CHCl_3$ as the internal standard: δ=7.27 for ^1H NMR spectra and δ=77.09 for ^{13}C NMR spectra unless indicated otherwise. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hertz.

4.1.1. Reductive lithiation of 1-phenylthio-2-methylcyclohex-1-ene (8).

4.1.1.1. Reductive lithiation of 1-phenylthio-2-methylcyclohex-1-ene (8) with preformed LDBB. To a solution of LDBB[47] (5.25 mL of a 0.40 M solution in THF, 2.1 mmol) at −78 °C, 1-phenylthio-2-methylcyclohex-1-ene (**8**, 0.204 g, 1.00 mmol) in THF (2 mL) was slowly added via syringe pump over a 0.50 h period. The deep blue-green reaction mixture was stirred at −78 °C for 8 h during which time the color slowly changed to red. Cyclohexanecarboxaldehyde (0.133 mL, 0.123 g, 1.10 mmol) (or 1-iodohexane or allyl bromide) in THF (2 mL) was added dropwise until the mixture turned yellow. The reaction was quenched at −78 °C with brine and was allowed to warm to room

temperature. The reaction mixture was extracted with ether (3×20 mL) and the combined extract was washed with 10% NaOH (3×10 mL, or at least until all of the thiophenol was removed) and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. Radial chromatography (4 mm rotor) with hexane was used to recover DBB from the reaction mixture, followed by 20% ethyl acetate in hexane to give the desired product.

9a: E^+=cyclohexanecarboxaldehyde, 80%, ^{1}H NMR ($CDCl_3$) δ 4.23 (d, J=9.2 Hz, 1H), 2.07–2.17 (m, 2H), 1.97 (m, 1H), 1.70–1.87 (m, 2H), 0.75–1.64 (m, 18H). ^{13}C NMR ($CDCl_3$) δ 130.9, 130.0, 75.4, 41.1, 32.4, 30.3, 29.0, 26.6, 26.2, 26.0, 23.1, 22.8, 19.2. MS *m/e* exact mass calculated for $C_{14}H_{24}0$ 208.1827, found 208.1827. IR (thin film) 3378 (s), 2924 (s), 2851 (s), 1449 (s), 1273 (m), 1261 (m), 1076 (m), 999 (m) cm^{-1}.

9b: E^+=iodohexane, 71%, ^{1}H NMR ($CDCl_3$) δ 1.96–2.03 (m, 6H), 1.64 (s, 3H), 1.60–1.62 (m, 4H), 1.31–1.32 (m, 8H), 0.93 (t, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 130.4, 125.7, 33.6, 32.0, 29.7, 29.6, 28.4, 23.7, 23.5, 22.8, 19.1, 14.2. MS *m/e* exact mass calculated for $C_{13}H_{24}$ 180.1878, found 180.1876. IR (thin film) 2924 (s), 1459 (s), 1354 (s), 1141(w) cm^{-1}.

9c: E^+=allyl bromide, 71%, ^{1}H NMR ($CDCl_3$) δ 5.69–5.82 (m, 1H), 4.93–5.02 (m, 2H), 2.73 (d, J=6.28 Hz, 2H), 1.81–1.93 (m, 4H), 1.61 (s, 3H), 1.54 –1.59 (m, 4H). MS exact mass calculated for $C_{10}H_{16}$ 136.1252, found 136.1252. IR (thin film) 3078 (w), 2926 (s), 1638 (m), 1438 (m), 992 (m), 909 (m) cm^{-1}.

4.1.1.2. Reductive lithiation of (8) with lithium in the presence of a deficiency of DBB. To a mixture of DBB (100 mg, 0.40 mmol) and lithium powder (21 mg, 2.4 mmol) in 2 mL of THF at −78 °C, 1-phenylthio-2-methylcyclohex-1-ene (**1**, 0.204 g, 1.00 mmol) in THF (2 mL) were slowly added via syringe pump over a 2 h period. The reaction mixture was stirred for an additional 6 h. Cyclohexanecarboxaldehyde (0.133 mL, 0.123 g, 1.10 mmol) (or iodohexane or allyl bromide) in THF (2 mL) was added dropwise and worked-up as described in the procedure above.

9a: 54%; **9b**: 50%; **9c**: 52%.

4.1.2. Reductive lithiation of acrolein diethyl acetal (10).

4.1.2.1. Reductive lithiation of 10 with preformed LDBB. To a stirred solution of LDBB (4.00 mmol) under argon at −78 °C, acrolein diethyl acetal (**10**, 0.31 mL, 2.1 mmol) was added dropwise over a period of 5 min. Since no new spot except starting material was observed on TLC for the reaction at −78 °C, the reaction mixture was allowed to warm to −50 °C, where it was stirred for 90 min. Pivalaldehyde (180 mg, 0.23 mL, 2.1 mmol) was then added dropwise to the reaction flask and the mixture was allowed to stir at −50 °C for an additional 30 min. Ice-water (10 mL) was added to quench the reaction. The resulting mixture was extracted with ether (3×20 mL), and the combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated by solvent removal by rotary evaporation. Column chromatography, with 10% ethyl acetate in hexanes, afforded the pure product *Z*-1-ethoxy-5,5-dimethylhex-1-ene-4-ol **11** (0.27 g, 70%). ^{1}H NMR ($CDCl_3$): δ 6.20 (dt, J=6.0, 1.5 Hz, 1H), 4.55 (ddd, J=6.9, 6.3, 6.0 Hz, 1H), 3.90 (q, J=7.0 Hz, 2H), 3.31 (1H, m), 2.28 (2H, m), 2.02 (1H, br s), 1.34 (t, J=7.0 Hz, 3H), 1.0 (9H, s). ^{13}C NMR ($CDCl_3$) δ 146.5, 103.4, 78.9, 67.3, 34.4, 26.3, 25.2, 14.9. These spectral data are consistent with those reported in the literature.[32]

4.1.2.2. Reductive lithiation of 10 with lithium in the absence of DBB. Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under argon. THF (10.0 mL) and acrolein dimethyl acetal (**10**, 260 mg, 2.00 mmol) were added under argon at 0 °C. After being stirred for 90 min at that temperature, the mixture was cooled to −78 °C and pivalaldehyde (180 mg, 0.23 mL, 2.10 mmol) was added dropwise to the reaction flask and the mixture was allowed to stir at −50 °C for an additional 30 min. Ice-water (20.0 mL) was slowly added to quench the reaction. The resulting mixture was extracted with ether (3×20 mL) and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was starting material acrolein diethyl acetal by crude NMR analysis.

4.1.3. Reductive lithiation of 6-chloro-6-methyl-1-heptene[48] (16).

4.1.3.1. Reductive lithiation of 16 with preformed LDBB. To a stirred solution of LDBB (4.0 mmol) under argon at −78 °C, 6-chloro-6-methyl-1-heptene (**16**, 0.27 g, 1.9 mmol) was added dropwise over a period of 5 min. The reaction mixture was allowed to warm to −50 °C, where it was stirred for 120 min. 3-Pentanone (180 mg, 2.1 mmol) was added dropwise to the reaction flask and the mixture was allowed to stir at −50 °C for an additional 30 min. Sodium bicarbonate was added to quench the reaction and the reaction vessel was allowed to warm to room temperature. The resulting mixture was extracted with ether (3×20 mL), and the combined extract was dried over anhydrous $MgSO_4$, filtered, and concentrated by solvent removal using rotary evaporation. Column chromatography, with 5% ethyl acetate in hexanes as eluent, afforded pure 3-(2,2-dimethylcyclopentylmethyl)-pentan-3-ol **19** (0.34 g, 92%). ^{1}H NMR ($CDCl_3$) δ 2.0 (m, 1H), 1.30 (m, 12H), 0.96 (s, 3H), 0.85 (2t, J=7.2 Hz, 6H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 74.87, 44.20, 41.59, 41.03, 38.64, 31.95, 31.59, 30.87, 27.36, 21.34, 20.92, 8.03, 7.63. This compound was reported by Yus,[41] but no spectral data were provided.

Under the same conditions but at −30 °C, 0.32 g (86%) of **19** was obtained.

4.1.3.2. Reductive lithiation of 16 with lithium in the absence of DBB. Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under argon. THF (10.0 mL) and 6-chloro-6-methyl-1-heptene (**16**, 293 mg, 2.00 mmol) were added under argon at −30 °C. After 2 h stirring at the same temperature, the mixture was cooled to −78 °C and 3-pentanone (180 mg, 2.10 mmol) was added dropwise to the reaction flask and the mixture was allowed to stir at −78 °C for an additional 30 min. Ice-water (20 mL) was added slowly to quench the reaction and the reaction mixture was allowed to warm to room temperature. The resulting mixture was extracted with ether (3×20 mL) and the organic layer was

dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to afford **19** (0.21 g, 53%).

4.1.4. Reductive lithiation of anisole (22).

4.1.4.1. Reductive lithiation of 22 with preformed LDBB. A solution of freshly prepared LDBB (4.40 mmol) in 10.0 mL of THF was cooled to 0 °C prior to the slow addition of anisole (**22**, 216 mg, 2.00 mmol) under argon over a period of 5 min. The reaction mixture was stirred at the same temperature for 2 h and was then cooled to −40 °C and the reaction was quenched by dropwise addition of benzaldehyde (223 mg, 2.10 mmol). After the reaction mixture had been further stirred for 30 min at −40 °C, the temperature was allowed to rise to room temperature over a period of ca. 3 h and ice-water (20 mL) was added slowly. The resulting mixture was extracted with ether (3×20 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by column chromatography (10% ethyl acetate in hexanes), affording 1-phenylethanol **23** (212 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.5 (q, J=6.5 Hz, 1H), δ 2.10 (s, 1H), 1.47 (d, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 145.75, 128.44, 127.41, 125.34, 70.33, 25.09. These NMR data compared well with those in Ref. 42.

4.1.4.2. Reductive lithiation of 22 with lithium in the presence of DBB. Li (dispersion, 644 mg, 28.0 mmol) was washed with three 10 mL portions of hexane in a 100 mL three-necked flask under argon. THF (10.0 mL), DBB (53.2 mg, 0.20 mmol), and anisole (**22**, 216 mg, 2.00 mmol) were added under argon at 0 °C. The reaction mixture was stirred at that temperature for 2 h before it was cooled to −40 °C and quenched by dropwise addition of benzaldehyde (223 mg, 2.10 mmol). After the reaction mixture had been further stirred for 30 min at −40 °C, the temperature was allowed to rise to room temperature over a period of ca. 3 h and ice-water (20 mL) was added slowly. The resulting mixture was extracted with ether (3×20 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by column chromatography (10% ethyl acetate in hexanes), affording 1-phenylethanol **23** (73.0 mg, 30%).

4.1.4.3. Reductive lithiation of 22 with lithium in the absence of DBB. Under otherwise identical conditions but with no DBB, no 1-phenylethanol **23** was obtained.

4.1.5. Reductive lithiation of 2,3-benzofuran (24).

4.1.5.1. Reductive lithiation of 24 with lithium dispersion. Li (dispersion, 460 mg, 20.0 mmol) was washed with three 10.0 mL portions of hexane in a 100 mL three-necked flask under argon. THF (10.0 mL) and 2,3-benzofuran (**24**, 236 mg, 0.22 mL, 2.00 mmol) were added under argon at 0 °C. After being stirred for 45 min at that temperature, the reaction mixture was cooled to −30 °C and ice-water (20 mL) was added slowly to the resulting mixture. After 15 min, the reaction mixture was neutralized with 1.0 M hydrochloric acid (5 mL). The resulting mixture was extracted with ether (3×20.0 mL), and the organic layer was dried over anhydrous $MgSO_4$ and concentrated by solvent removal. The residue was purified by column chromatography (10% ethyl acetate in hexanes), affording 2-vinylphenol **26** (218 mg, 91%). ^{1}H NMR ($CDCl_3$) δ 7.38 (dd, J=7.7, 1.7 Hz, 1H), 7.14 (td, J=7.7, 1.1 Hz, 1H), 6.92 (m, 2H), 6.78 (dd, J=7.7, 1.1 Hz, 1H), 5.74 (dd, J=17.7, 1.4 Hz, 1H), 5.36 (dd, J=13.2, 1.4 Hz, 1H), 5.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 152.58, 131.31, 128.84, 127.21, 124.79, 120.94, 115.81. These NMR data compared well with those in Ref. 44.

When the above reaction was quenched with D_2O (0.5 mL), after the same workup procedure, 220 mg of deuterated **26** was obtained; yield 92% (30% cis- and 70% trans-isomer), ^{1}H NMR ($CDCl_3$) δ 7.40 (dd, J=7.7, 1.7 Hz, 1H), 7.16 (td, J=7.7, 1.1 Hz, 1H), 6.97 (m, 2H), 6.79 (dd, J=7.7, 1.1 Hz, 1H), 5.75–5.69 (d, J=17.7 Hz, 0.7H), 5.35–5.51 (d, J=11.2 Hz, 0.3H), 5.019 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 152.78, 131.40, 128.86, 127.35, 124.84, 120.93, 115.85, 115.52, 115.20.

4.1.6. Reductive lithiation of *N*-phenylaziridine[49,50] (27).

4.1.6.1. General procedure for reductive lithiation of *N*-phenylaziridine (27) by the PAR method. A solution of freshly prepared lithium naphthalenide (4.40 mmol) in 10 mL of THF was cooled to −78 °C prior to the slow addition of *N*-phenylaziridine (**27**, 238 mg, 2.00 mmol) under argon. The reaction mixture was stirred at that temperature for 6 h and the reaction was quenched by slow addition of ice-water (20 mL). The resulting mixture was extracted with ether (5×20 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated by solvent removal. The residue was purified by column chromatography (5% ethyl acetate in hexanes), affording only starting material **27** and no **29**.

4.1.6.2. General procedure for reductive lithiation of *N*-phenylaziridine (27) by the CA method. Li (dispersion, 460 mg, 20.0 mmol) was washed with four 10 mL portions of hexane in a 100 mL three-necked flask under argon. THF (10 mL) was added and the reaction mixture was cooled to −78 °C. *N*-Phenylaziridine (**27**, 238 mg, 2.00 mmol) and naphthalene (0.05 equiv) were added under argon at the same temperature. After the mixture had been stirred for another 6 h at −78 °C, the reaction was quenched by adding ice-water (20 mL) slowly. The resulting mixture was extracted with ether (5×20 mL) and the organic layer was dried over anhydrous Na_2SO_4 and concentrated by solvent removal. The residue was purified by column chromatography (5% ethyl acetate in hexanes), affording *N*-ethylaniline **29**.

N-Ethylaniline **29**: ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 6.88 (m, 1H), 6.79 (m, 2H), 3.37 (s, 1H), 3.11 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 148.38, 129.15, 117.12, 112.66, 38.37, 14.82. The spectral data are consistent with those reported by Aldrich.

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