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Invited Review

Reduction with lithium dialkylamides

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1. Introduction

A reaction in which a lithium dialkylamide transfers a hydride ion to another species (Fig. 1(c)) and thus functions as a reducing agent is an easy-to-imagine analogy to the Meerwein–Ponndorf–Verley reduction [1] (Fig. 1(b), where E^+ is a ketone). Similar hydride transfer processes (Fig. 1(a)), involving Grignard reagents and other organometallics, are also well known [2]. Organometallic compounds and lithium amides can also transfer an electron to another species and thus initiate a single-electron transfer (SET) pathway leading to reduction [3,4]. Cases of reduction with lithium amides proceeding via both SET and hydride transfer mechanisms were, in fact, observed in the past: however, they did not attract a lot of attention from organic chemists. Lithium amides are amongst the most often used reagents in synthetic laboratories, and all practitioners of enolate chemistry should be aware of these reagents' potential for reducing organic compounds.

Lithium dialkylamide bases were first synthesized about 60 years ago [5] and were subsequently developed as reagents for enolization of carbonyl compounds [6,7]. The most popular of these amides is lithium diisopropylamide (LDA), which is truly an indispensable reagent in modern organic synthesis [6–9]. The importance of lithium amides is underscored by extensive literature spanning topics as diverse as their formation [9], selective enolization of carbonyl compounds [10], theoretical and experimental studies of their structure in the gas phase and in solution [11], and use of chiral lithium amides in enantiotopic group selective reactions [12].

Despite all this wealth of information, some facets of generation of organolithium compounds via deprotonation of CH acids with lithium amides remain poorly understood. While LDA is the most often used lithium amide, a check of pertinent literature would frequently reveal a procedure involving use of a relatively less common reagent, *e.g.* lithium isopropylcyclohexylamide (LICA) or lithium hexamethyldisilazide (LHMDS) for a seemingly typical deprotonation. Reasons why a more "exotic" amide was used instead of cheap and readily available LDA are rarely given, but one can guess that undesirable side reactions were less of a problem. One such side reaction involves the lithium amide behaving as a reducing agent. Another important side reaction, which was recognized very early [8] but is surprisingly often neglected, is addition of lithium amides to carbon–heteroatom double bonds [13].

First reported cases of reduction with lithium amides can be traced to Gilman's work and involved aromatic halides [14]. Ever since, a number of reports describing LDA, and other lithium amides, reducing aromatic and aliphatic halides and triflates, aldehydes and ketones,

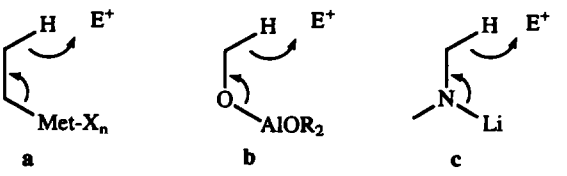

Fig. 1. Schematic representation of hydride transfer reactions from organometallic species (**a**, Met = Mg, Zn, Al, B; X = ligand), metal alkoxides (**b**) and metal amides (**c**).

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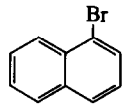
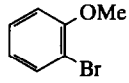
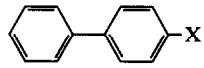
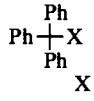
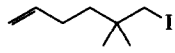
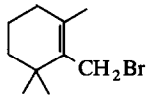
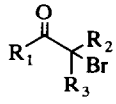
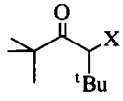
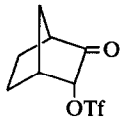
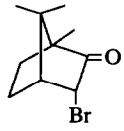
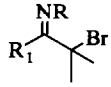
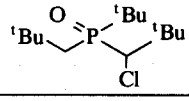
oxaziridines, tetrazines, aromatic and heteroaromatic hydrocarbons and activated olefins were published. In several cases the reduction was mentioned as a harmful process interfering with a total synthesis [15,16].

The aim of this review is to bring to the attention of organic chemists the potential of LDA and other lithium amides for reducing diverse compounds. The full synthetic scope of this reaction has never been exploited.

2. Reduction of alkyl and aryl halides and triflates

Reduction of aryl halides with lithium amides was observed shortly after lithium amides were developed

TABLE 1. Reduction of alkyl and aryl halides and triflates with lithium amides

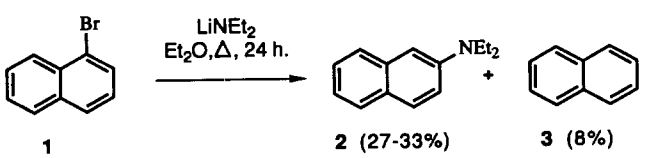
Entry	Substrate	Amide	Product (% yield)	Ref.
1.		$LiNEt_2$	naphthalene (9)	[14]
2.		$LiN(CH_2Ph)_2$ $LiNMe_2$ $LiN(CH_2{}^tBu)_2$	anisole (36) (16) (32)	[17,18]
3.	 X = Cl, OTf	LDA	biphenyl (57)	[19,20]
4.	 X = Br, Cl	LDA LiNet^{t}Bu	triphenylmethane (92) + dimer (8)	[21,22]
5.		LDA LiTMP $LiN(C_6H_{11})_2$	R–H + cyclic products	[22,23]
6.		LDA	R–R (12)	[24]
7.		LDA	R–H (97)	[25,26]
8.	 X = Br, OTf	LiTMP	R–H (81)	[27]
9.		LDA	R–H (31) + R–R (trace)	[28]
10.		LiTMP	R–H (30)	[29]
11.		LDA	R–R (89)	[30]
12.		LiTMP LDEA	R–H (42)	[31]

as a new class of compounds [5]. In 1945, Gilman reported that when 1-bromonaphthalene (**1**) was treated with lithium diethylamide (LDEA), two new compounds (Scheme 1) were produced in low yield [14]:

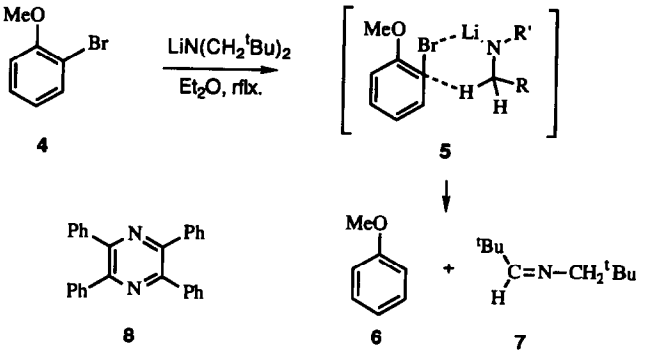
Formation of 2-diethylaminonaphthalene (**2**) could be rationalized in terms of a benzyne mechanism. The small amount of naphthalene could originate either via reduction or via lithium–halogen exchange. Gilman proposed that the former was true. This proposal was later supported by work of Benkeser and De Boer, who investigated reactions of *ortho*-bromoanisole (**4**) with several lithium amides [17]. In these reactions *ortho*-bromoanisole was reduced to anisole (**6**) in up to 36% yield. It was determined that, in order for the reduction to proceed, the lithium amide had to have hydrogen atoms connected to the carbon bonded to the nitrogen atom (β-carbon). Accordingly, lithium *N,N*-diphenylamide gave no reduction. The authors proposed a hydride transfer mechanism, involving a cyclic transition state **5**, to rationalize these observations. A side product in a hydride transfer reaction should be the imine corresponding to the lithium amide used. The authors did not observe any imine in the reaction products; however, 2,3,5,6-tetramethylpyrazine (**8**) was isolated and it was proposed that this compound originated from lithium dibenzylamide via the corresponding imine. Mosher, knowing that 2,2-dimethylpropylidene-2′2′-dimethylpropylamine (**7**) was an exceptionally stable imine, used lithium dineopentylamide in a reaction with *ortho*-bromoanisole and isolated imine **7** from the reaction products (Scheme 2) [18].

More reports on reduction of alkyl and aryl halides and trifluoromethanesulfonates (triflates) with lithium amides were published subsequently (Table 1). Typically, these compounds of general formula R–X are reduced to the parent hydrocarbons (R–H) and/or dimeric species (R–R, Scheme 3). Some authors were of the opinion that the reaction proceeds via a single-electron transfer process (SET), while others favored the hydride transfer mechanism.

Ashby proposed that alkyl halides are reduced by LDA to hydrocarbons via a SET mechanism [22]. He based this proposal on the observation that, at room temperature, LDA reacted rapidly with trityl chloride and yielded an orange-red solution, the EPR spectrum

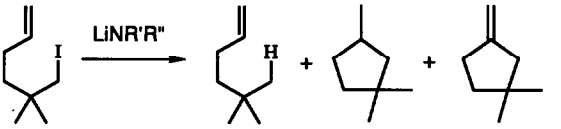


Scheme 1.

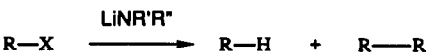


Scheme 2.

of which was consistent with the presence of the trityl radical. To bolster his arguments, Ashby used 6-iodo-5,5-dimethyl-1-hexene (**9**) as a cyclizable probe [22]. Initially, reaction of this compound with LDA afforded substantial amounts of cyclic products (**11** and **12**) [22] which was interpreted as the evidence for the SET mechanism. Recently, a thorough investigation of the reaction mechanism using this probe has been described by Ashby's group [23] (*cf.* Section 7). It has been concluded that LDA reacts with compound **9** via a combination of three mechanisms: SET, carbanion pathway and carbene pathway.



Bromoketones were found to undergo facile dehalogenation upon treatment with LDA and other lithium amides (Table 1, entries 7, 8) [25–27]. In the presence of trimethylsilyl chloride this reaction led to formation of silyl enol ethers of the corresponding dehalogenated ketones in high yield. It is noteworthy that dehalogenation was preferred over the reduction of the ketone functionality to the corresponding alcohol (*cf.* the following section) and was also faster than proton abstraction, at least in cases where the α-proton was sterically hindered. Pivaloin bromide and triflate (Table 1, entry 8) [27] and *endo*-3-bromocamphor (entry 10) [29] were readily reduced to the non-halogenated ketones by lithium 2,2,6,6-tetramethylpiperidide (LiTMP). Since the LiTMP molecule does not have hydrogen atoms connected to the β-carbons, and is not capable of hydride donation, the reaction was thought



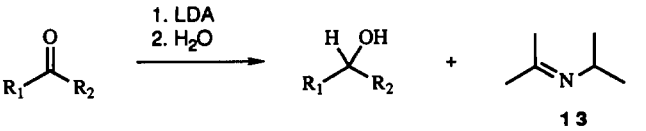
Scheme 3.

to proceed via a SET mechanism. By using α-deuteropivaloin as the starting material it was established that the ketone was not deprotonated by LiTMP [27].

Clearly, lithium amides can reduce alkyl and aryl halides and triflates to the parent hydrocarbons and other products (dimers). The reaction is often efficient and could be used in synthesis for removal of halogens. Lithium amides are often not compatible with aryl halides, a practical consideration when working in the area of enolate chemistry.

3. Reduction of ketones

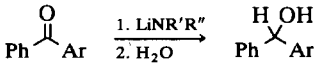
Non-enolizable ketones react with LDA and other lithium amides to give the corresponding alcohols according to the general equation shown in Scheme 4.

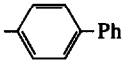
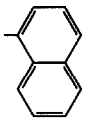


Scheme 4.

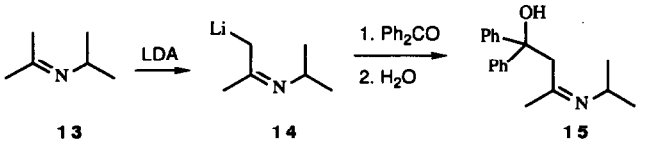
Reduction of benzophenone with lithium diethylamide was first observed by Wittig [32]. During the last three decades this ketone was subjected to treatment with various lithium amides [33–38] and its reduction has become an important model reaction against which other processes of this type were often discussed. Reactions of benzophenone and other bis-aryl ketones with various lithium amides are summarized in Table 2. Development of a deep color (blue, violet or dark red) upon mixing of the amide and the ketone was observed in most cases, indicating the possible intermediacy of charge transfer complexes or radical ions. The mechanism of reduction of benzophenone was studied extensively by Wittig [39,41], Ashby [33] and Newcomb [35–38], and important conclusions as to the nature of lithium amide reduction in general were drawn (*cf.* Section 7). It seems well established now, that benzophenone (and, implicitly, other ketones as well) is reduced by LDA and other lithium amides via a hydride transfer mechanism analogous to the Meerwein–Ponndorf–Verley reaction. The amide has to have at least one hydrogen atom at the β-carbon;

TABLE 2. Reduction of phenyl aryl ketones with lithium amides



Entry	Ar	Amide	Yield (%)	Ref.
1.	Ph	LDA	66–92	[33–38]
2.	Ph	$LiNEt_2$	37	[32]
3.	Ph	$LiNPhCH_2Ph$	64–94	[34,39]
4.	Ph	LiNPhEt	37	[34]
5.	Ph	LiPhMe	91	[34]
6.	Ph	**20**	87 [a]	[40]
7.		$LiNPhCH_2Ph$	70	[40]
8.		$LiNPhCH_2Ph$	20	[40]
9.		**20**	81	[40]
10.		**20**	77	[40]
11.		**20**	83 [b]	[40]
12.		$LiNPhCH_2Ph$	83 [c]	[40]
13.		LiNPhCH(Me)Ph	25 [d]	[40]

[a] Rxn. time 12 min. [b] Rxn. time 1 h. [c] Rxn. time 3 days. [d] Rxn. time 20 days.



13 14 15

Scheme 5.

accordingly LiTMP and LHMDS do not reduce ketones.

During the reaction, the lithium amide is oxidized to the corresponding imine (*e.g.* **13**). The imine can be further deprotonated with the amide acting as a base, and the resulting anion (*e.g.* **14**) can attack benzophenone yielding an adduct (*e.g.* **15**) as observed by Wittig [32] (a similar product of the reaction between the lithiated imine **14** and an electrophile was also observed during the reaction of β-cyclogeraniol with LDA [24]). Consequently, two equivalents (or more) of the amide are needed for the reduction to proceed efficiently. The addition reaction can be utilized practically for synthesis of higher aldehydes; phenylcinnamaldehyde was synthesized by this method in 53% yield by Woo and Mak from benzophenone and lithium ethylanilide [34].

In order to be reasonably efficient as the reducing agent, the lithium amide should yield a stable imine and the hydride transfer should not be hindered sterically. It is also advantageous if the imine originating from the amide cannot be further deprotonated. The dependence of the efficiency of reduction of bis-aryl ketones on the amide structure is clearly visible in the data presented in Table 2 (entries 6,11–13).

Reductions of aromatic, aliphatic, cyclic and polycyclic (fused and bridged) ketones with LDA are summarized in Table 3. Both the enolizable and non-enolizable ketones undergo reduction. The yields are usually modest. In evaluating the efficiency of the reduction, it should be noted that almost no kinetic data are available, yields were often not reported and in many cases a competition between enolization and reduction takes place. Because of that, the efficiency of reduction can usually be discussed only in relative terms *vs.* efficiency of deprotonation, and the yields (and not reaction rates) must be used as measures. Any generalizations should be treated with caution.

Reduction seems to be promoted over enolization by higher temperatures. During an investigation of lithiation reactions of chromones, Costa [49] observed a reduction of the aryl t-butyl ketone derived from chromone with LDA at 0°C; this reduction did not occur at lower temperature.

Solvent polarity is also important, as indicated in

TABLE 3. Reduction of ketones with LDA

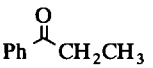
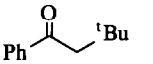
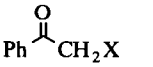
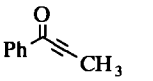
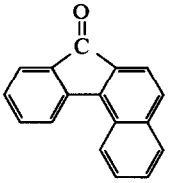
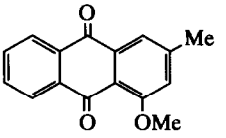
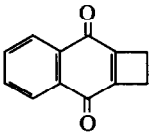
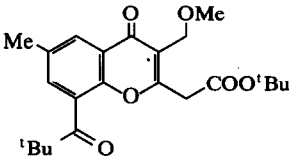
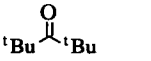
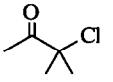
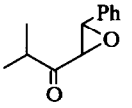
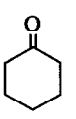
Entry	Substrate	Yield (%)	Ref.
1.		35 [a]	[42]
2.		40	[43]
3.	 **a** X = Cl; **b** X = Br	50	[44]
4.		71	[45]
5.		[b]	[46]
6.		53	[47]
7.		[b]	[48]
8.		[b]	[49]
9.		57	[50]
10.		47	[51]
11.		23	[52]
12.	 **a** R = Me **b** R = ^{n}Pr **c** R = Cl(CH$_2$)$_3$	22 69 33	[53]
13.		34	[44]

TABLE 3 (continued)

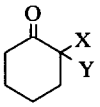
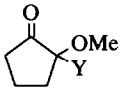
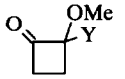
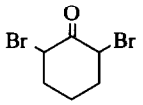
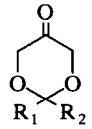
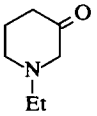
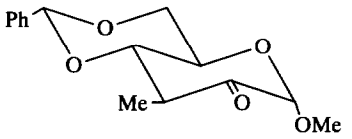
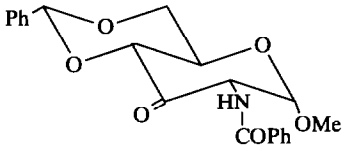
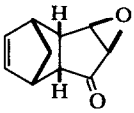
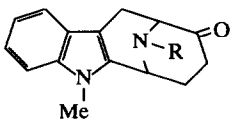
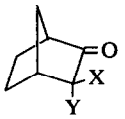
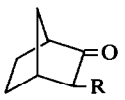
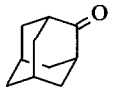
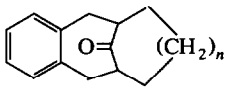
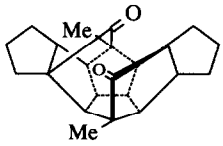
Entry	Substrate		Yield (%)	Ref.
14.		**a** X = Br Y = H **b** X = Cl Y = h **c** X = OMe Y = H **d** X = Y = OMe	26 24 0 80	[44]
15.		**a** Y = H **b** Y = OMe	10 0	[44]
16.		**a** Y = H **b** Y = OMe	0 30	[44]
17.			77	[25]
18.		**a** R_1 = Ph, R_2 = H **b** R_1 = ^{t}Bu, R_2 = H **c** R_1 = R_2 = Me	90 80 20	[54]
19.			[b]	[55]
20.			[b]	[56]
21.			23	[57]
22.			80	[59]
23.			[b]	[16]
24.		**a** X = H, Y = Cl **b** X = Cl, Y = H **c** X = H, Y = OMe **d** X = OMe, Y = H **e** X = Y = OMe **f** X = Y = Me	15 5 65 79 63 40	[44]
25.		**a** R = H **b** R = Me **c** R = C_5H_{11}	0 10 40	[60]

TABLE 3 (continued)

Entry	Substrate		Yield (%)	Ref.
26.			14	[61]
27.		**a** n = 3 **b** n = 2 **c** n = 1	[b]	[34]
28.			97	[62]

[a] In PhMe at −78°C; no reduction in THF. [b] Yield not reported.

several papers [42,44,54]. A study on enantioselective hydroxylation of propiophenone enolate with oxaziridines indicated that use of non-polar solvents (*e.g.* toluene) resulted in higher enantioselectivity of oxidation [42]. Unfortunately, when toluene was used as solvent, the reduction competed with enolization (Table 3, entry 1). It is noteworthy that no reduction was observed in THF.

Deprotonation of 1,3-dioxa-5-ones attempted by our group [54] was initially unsuccessful owing to large amounts of the reduction products. Reduction was especially efficient in ether, where alcohols were the only products in some cases (Table 3, entry 18). In THF, yields of the alcohols (usually trapped as silyl ethers) were around 50% and partial enolization occured. Kowalski observed significant reduction of cyclohexanone by LDA (Table 3, entry 13) in ether [44]; in THF enolization seems to be the only reaction proceeding. Clearly, the lower the solvent polarity, the faster the reduction.

Lithium halides (*e.g.* LiBr) which might be produced in the reaction mixture during alkylation, or might result from using alkyllithium-containing LiBr to generate the amide, also increase the amount of reduction [44].

The structure of the ketone is an important factor. Several non-enolizable ketones (*e.g.* benzophenone, bis-aryl ketones, hexamethylacetone) were reported to undergo a facile reduction. As far as enolizable ketones are concerned, the presence of a heteroatom substituent at the α position clearly makes the ketone more susceptible to reduction with LDA. Table 3 includes examples of α-halo-, α-epoxy-, α-methoxy-, α-aminoketones and α-ketoesters. The "heteroatom effect" seems to be additive; when two heteroatoms are

present, the ketone is even more prone to reduction [25,44]. An exception here seems to be 1,1-dimethoxyacetone, which was cleanly deprotonated with LDA without any evidence of the reduction taking place [63]. The "heteroatom effect" might be electronic in nature, *i.e.* the electron-withdrawing substituent decreases the electron density of the C=O group which makes hydride transfer more facile. The known attenuation of the enolization rate by methoxy and fluoro substituents at the α-position [64] might also make reduction more pronounced.

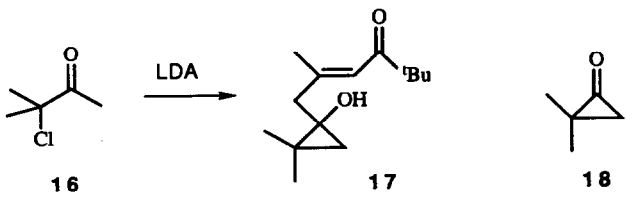
In reactions of α-bromoketones with lithium amides, the reduction of the carbonyl group and debromination might compete (*cf.* the preceding section). Acyclic α-bromoketones undergo debromination very readily (Table 1, entries 6 and 7). On the other hand, 2,6-dibromocyclohexanone is reduced by LDA to the corresponding cyclohexanol [25] (Table 3, entry 17). Monobromocyclohexanone has been reduced to the bromocyclohexanol [44] (Table 3, entry 14a), but the total yield of products derived from both the reduction and the enolization (enolate was trapped with acetic anhydride) was only 50%, which might have been caused by debromination and loss of produced cyclohexanone on work-up.

In cases where the speed of enolization is lower owing to steric or other effects (*e.g.* when the α-proton is at the bridgehead position), reduction occurs predominantly (*cf.* Table 3, entries 22,25,27).

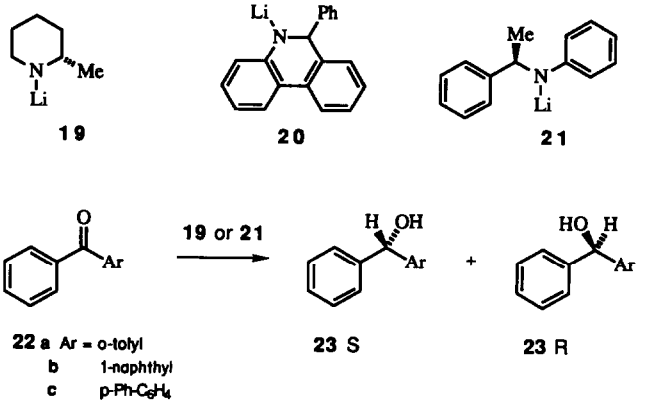
Occasionally the combination of deprotonation and reduction gave rise to unusual products. De Kimpe isolated enone **17** from the reaction between 3-chloro-3-methyl-2-butanone (**16**) with 2 equivalents of LDA (Scheme 6) [51].

Formation of compound **17** was rationalized as the combination of two equivalents of cyclopropanone **18**, which was formed in a Favorskii rearrangement, with the lithiated imine **14**.

Reduction of a diketone by LDA, which was used by Paquette during synthesis of dodecahedrane [62], deserves special mention. Starting material in this reaction (Table 3, entry 28) was unusual — two carbonyl groups were held together in close proximity by the rigid polycyclic framework. The reaction yielded pina-



Scheme 6.



Scheme 7.

col, a bond being created between two carbonyl carbon atoms. This was quite unprecedented and was probably a result of enforced proximity of the two carbonyl groups. The reaction was very efficient but not especially fast (6 h at 25°C).

3.1. Stereoselectivity of LDA reduction

In an early fundamental study on reduction of α-substituted cyclic ketones with LDA, Kowalski and coworkers found the reaction to proceed with excellent diastereoselectivity; delivery of the hydride ion occurred exclusively from the face opposite to the substituent (Table 3, entries 14–16 and 24) [44]. It was concluded that LDA reductions show the same trend as mixed hydride reductions but are more stereoselective [44].

Reductions of dioxanones are also highly stereoselective; delivery of the hydride occurs exclusively from the axial direction [54] to give trans alcohols (Table 3, entries 18a and 18b). Similar selectivity was also noted in reactions involving ketones derived from carbohydrates (Table 3, entries 20 and 21) [56,57].

Enantioselective reduction of ketones using chiral lithium amides was tried with little success [40,65]. Cervinka used amide **14** in reactions with prochiral aryl ketones (Scheme 7) [65]. The yields of alcohols were very low (5%); the enantiomeric excess was never measured but, judging from the optical rotation data, was also very low.

Lithiated phenanthridine **20** was chosen after some experimentation by Wittig as a potential chiral reducing agent [40]. It proved to be efficient: reductions proceeded in about 80% yield. Because the imine formed from **20** via hydride transfer could not be deprotonated (it is devoid of β-hydrogens), no complications due to formation of lithiated imine, followed by its attack on the ketone, were encountered. Unfortunately the phenanthridine **20** was not available in opti-

cally pure form. Naphthyl phenyl ketone was then selected as the primary model for investigating enantioselective reduction with lithium *R*-(−)-α-phenylethylanilide (**21**). The reaction was very slow; after 32 days, 25% of the (+) isomer of phenyl naphthyl carbinol **23b** were produced (in ether). The optical purity of this product was not measured by Wittig but, since the specific rotation of optically pure **23** is known [66], the optical rotation data reported indicate that the enantiomeric excess in Wittig's experiment was not greater than 60%. The enantioselectivity was solvent-dependent and was much lower in THF.

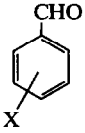
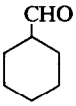
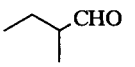
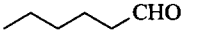
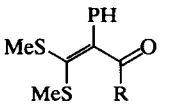
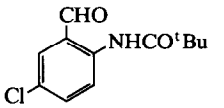
3.2. Avoiding LDA reduction

Reduction of ketones with LDA occurs quite often as an undesirable side-reaction during attempted enolization, which in turn is usually a preamble to alkylation or hydroxyalkylation. In most cases the reduction could be successfully avoided by using lithium amides which do not have β-hydrogens which could be transferred to the ketone molecule. Lithium hexamethyldisilazide (LHMDS) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) were often employed and were found to give clean enolization in cases where use of LDA resulted in reduction [16,43,44,52,54,56,60]. However, under forcing conditions, LiTMP can enter into other side-reactions with ketones and aldehydes: a methyl group can be transferred from LiTMP to the ketone [67], deprotonation at a "remote" center leading to a homoenolate anion might occur [67], and non-enolizable aldehydes can be deprotonated to yield acyllithiums [67]. In the case of 1,3-dioxanones (Table 3, entry 18) it was established that Corey's internal quench method [68] resulted in suppressing the reduction (only about 5% of the alcohols were obtained *vs.* 50% under "external quench" conditions) [54].

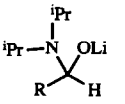
4. Reduction of aldehydes

Aldehydes can be reduced to the corresponding alcohols by LDA; examples are given in Table 4 [69–72]. Aromatic aldehydes undergo clean reduction but, interestingly, the reaction never seems to go to completion and some parent aldehyde (up to 80%) is always recovered [69]. Apparently the addition of LDA to the carbonyl group competes, resulting in the intermediate **24** analogous to the product of reduction of an amide with a metal hydride. These intermediates can be trapped as silyl ethers **25**, and were also used practically for *in situ* protection of the aldehyde functional group in directed metallation reactions [13]. Similar addition of LDA to carbonyl group has never been

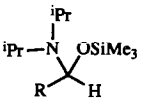
TABLE 4. Reduction of aldehydes with LDA

Entry	Substrate		Conv. (%)	Ref.
1.		**a** X = H **b** X = (ip-CF_3 **c** X = *m*-CF_3 **d** X = *p*-CL **e** X = *p*-Me **f** X = *p*-OMe	36 69 60 46 24 18	[69,70]
2.			42	[69]
3.			22	[69]
4.	^{t}Bu–CHO		58	[69]
5.			7	[69]
6.		**a** R = H **b** R = Ph	20 0	[71]
7.			8	[72]

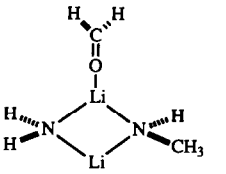
demonstrated in ketones, although it was speculated that it plays a part in some cases [44].



24



25



26

Substituents on the aromatic ring of aryl aldehydes have a profound effect on the competition between the reduction and the addition reactions. Electron-withdrawing groups promote the reduction, and electron-donating ones attenuate it; the conversion rate of aldehydes to alcohols correlates well with the value of the Hammett σ constant of the substituent [69] (Fig. 2). As a result, aromatic aldehydes which are electron-rich (*e.g.* 2,4-dimethoxybenzaldehyde) do not undergo reduction at all [73].

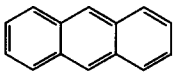
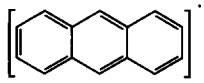
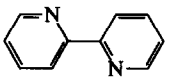
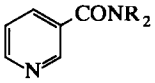
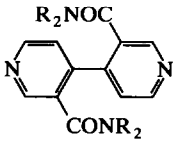
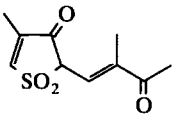
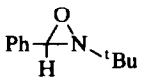
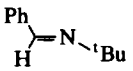
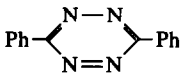
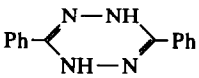
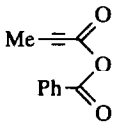
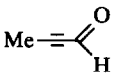
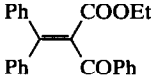
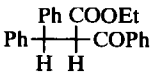
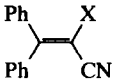
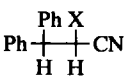
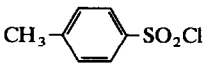
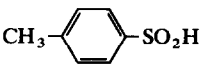
Enolizable aldehydes also undergo a combination of reduction and LDA addition reactions (Table 4, entries 2,3,5) [69], and the amount of enolization is small, as evidenced by a small amount of self-aldol products. Aldehydes seem to be more prone to reduction with LDA than ketones, as demonstrated by Marino [71] (Table 4, entry 6).

An interesting theoretical study addressed the reduction of formaldehyde to methanol by lithium methylamide [74]. Calculations (MNDO and *ab initio*) indicated that the reaction should involve the amide dimer (modelled as **26**), which complexes first to formaldehyde through one lithium and then undergoes an internal hydride transfer.

5. Other hydride transfer reactions

Occasionally, when aldol-type reactions between aldehydes and enolates are conducted, reduced products which did not originate from a reaction involving the lithium amide are observed. In some such cases the presence of an alcohol in the reaction products might

TABLE 5. Reduction of miscellaneous compounds with LDA

Entry	Substrate	Product	Yield (%)	Ref.
1.			60	[22]
2.			–	[76]
3.			59	[77]
4.			69	[78]
5.			89	[35,79,80]
6.	O_2	$R_2NO^{\cdot}$	–	[81]
7.			35	[82]
8.			–	[45]
9.			77	[83]
10.	 a X = COOEt b X = CN		80	[83]
11.			–	[84]
12.			90	[85]

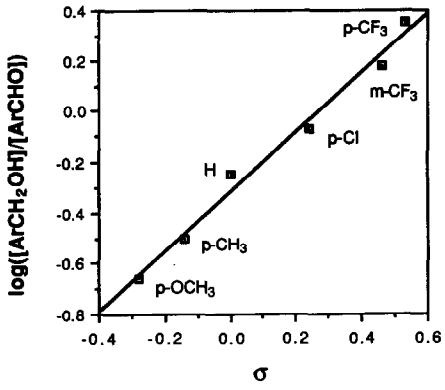
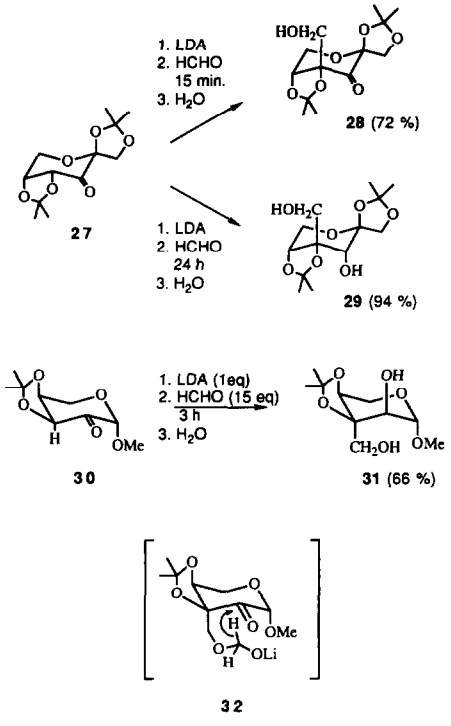


Fig. 2. Efficiency of reduction of aromatic aldehydes with LDA as a function of electronic effect of the substituent (Hammett σ constant) [69].



Scheme 8.

be due not to LDA reduction but instead to a hydride transfer from an aldolate anion to aldehyde, resulting in formation of the 1,3-dicarbonyl compound [75].

In a study of lithium enolates of ketones derived from carbohydrates, Klemer encountered reductions **27** → **29** and **30** → **31** [57,58] (Scheme 8). These reactions were attributed to hydride transfer from LDA to the ketones. Considering that one equivalent of LDA and a large excess of formaldehyde were used in each case, and that the reactions, when run for a shorter time, gave the expected aldol product **28**, this rationalization seems unlikely. Instead, an intermediate **32** involving two molecules of aldehyde can be postulated. This intermediate can then undergo intramolecular hydride transfer which resembles the Cannizzarro mechanism and converts the lithium aldolate to the 1,3-diol. Analogous reaction has been observed recently in a different system [52].

Thus, when unexpected products of reduction or oxidation are observed during a reaction involving a lithium enolate, the lithium amide (which was used to generate the enolate) is not necessarily the culprit.

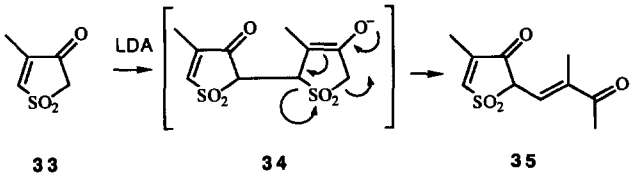
6. Reduction of other compounds

In addition to halides, triflates, ketones and aldehydes, a number of diverse organic compounds were also reduced by LDA in THF or ether (Table 5). Aromatic hydrocarbons (perylene, 2,3-benzanthracene, benzo[α]pyrene, phenanthrene, chrysene, anthracene) gave colorful radical anions (*e.g.* Table 5, entry 1) [22]. Pyridine and derivatives also are readily reduced (Table 5, entries 2,3), and the solutions show strong EPR signals due to diisopropylaminyl radicals during the reaction [76,77]. The pyridinyl radical was initially not observed, however; it is known to dimerize rapidly. Since HMPA stabilizes the pyridinyl radical, Newkome was able to observe this species by EPR at 0°C in HMPA [76]. Attempted directed ortho lithiation of nicotinamides failed due to competing reduction with LDA [77].

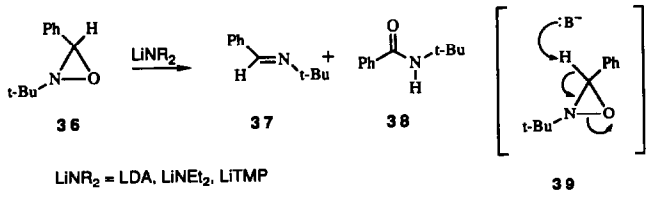
An unusual reaction was reported by Motherwell [78] (Table 5, entry 4; Scheme 9): cyclic keto-sulfone (**33**) when treated with LDA afforded the product **35**, which was rationalized by an initial SET process, leading to the dimeric enolate **34** which then fragmented, expelling the SO_2 molecule.

Newcomb's group studied reactions of (*E*)-2-tert-butyl-3-phenyloxaziridine **36** (Table 5, entry 5) with various lithium amide bases. Two competing reactions were observed (Scheme 10): reduction of the oxaziridine to *N*-tert-butylbenzaldimine **37** and rearrangement of the oxaziridine to give *N*-tert-butylbenzamide **38** (via **39**) [35,79,80]. LiTMP gave the highest yield of reduction, and it was concluded that this reaction proceeds via a SET process which consumes two equivalents of the base.

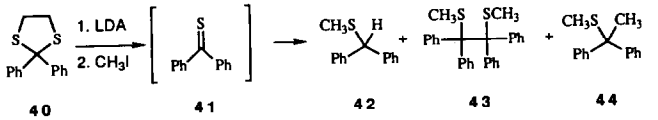
Molecular oxygen reacts with LDA via a SET process to give nitroxide radicals [81] (Table 5, entry 6).



Scheme 9.



Scheme 10.



Scheme 11.

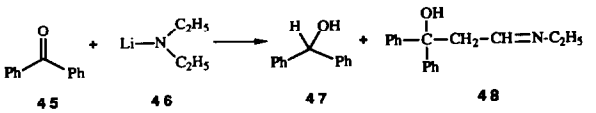
Alkene functional groups in certain alkylidene derivatives of α-benzoyl- and α-cyanoacetate esters were reduced by LDA to the corresponding alkanes [83] (Table 5, entries 9 and 10). The presence of two electron-withdrawing substituents on the same vinyl carbon seems to be crucial, since α,β-unsaturated ketones might be expected to be reduced to alcohols (*cf.* Table 3, entry 4).

During a study on base-induced fragmentation of dithioacetals (**40**), some unexpected products (**42–44**) were observed [84]. These products were believed to originate from a SET reduction of thioketones (**41**) which were the intermediates (not isolated) in the reaction (Scheme 11).

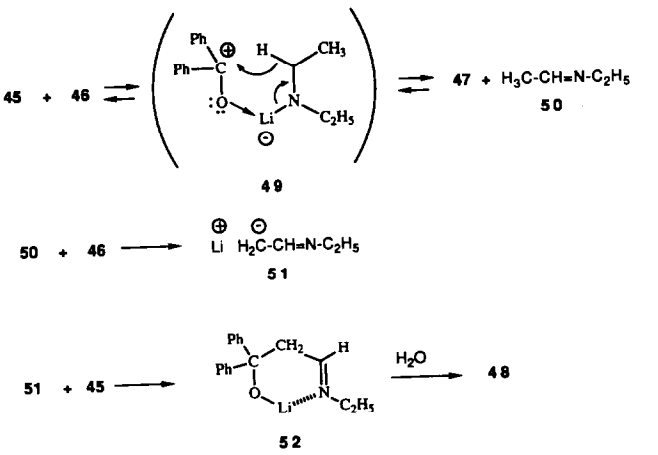
7. Mechanistic studies

Gilman's paper on reduction of bromoanisole during a reaction with lithium diethylamide (LDEA) [14] apparently piqued the curiosity of Wittig, who investigated reductive behaviour of lithium amides and observed that this amide also reduced benzophenone to the corresponding secondary alcohol [32]. A by-product of this reaction was identified as *N*-(3-hydroxy-3,3-diphenylpropylidene)-*N*-ethylamine (**48**, Scheme 12).

The mechanism of this particular reaction, which was proposed by Wittig [39], is given in Scheme 13. In the first, reversible, step benzophenone (**45**) interacts with LDEA (**46**) and forms the "ate" complex **49**. Transfer of a hydride ion within this complex results in reduction of the ketone and oxidation of the amide to the corresponding imine **50**. In the second step this



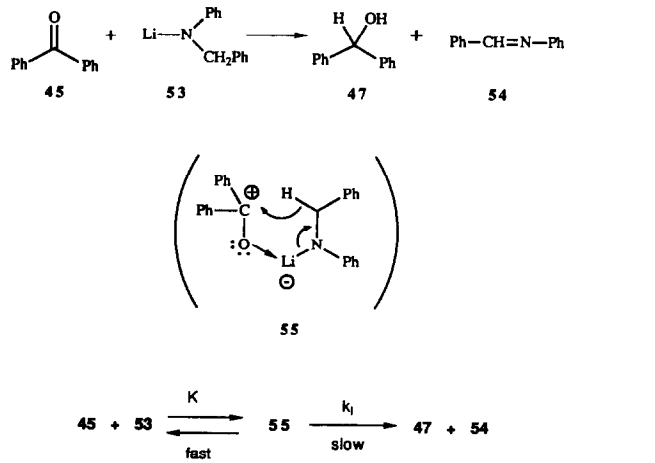
Scheme 12.



Scheme 13.

imine is deprotonated with LDEA, and the resulting lithiated imine **51** adds to benzophenone (that is why no imine was initially observed in the reaction products) in the third step, producing the adduct **52**, which is stabilized by coordination of lithium by both oxygen and nitrogen. Wittig recognized the importance of this stabilizing effect and realized that the formation of stable adducts of this type should make controlling the aldol reaction possible, which was one of the important synthetic problems at the time. Thus the concept of "directed aldol reaction" was born [86].

During the next several years, Wittig and colleagues conducted reactions in which Li amides acted as hydride donors, using several different reagents of the general formula LiNR′R″ (where R′ and/or R″ were ethyl, phenyl, benzyl and *n*-butyl) [40,41,50]. Predictably, when the amide did not have β-hydrogen atoms, as in the case of lithium benzylphenylamide, the corresponding imine **54** could not be deprotonated and was isolated from the products (Scheme 14).



Scheme 14.

Wittig proposed that all reductions with lithium amides proceed via "ate" complexes (*e.g.* **49**, **55**); this hypothesis was largely based on the observation that when benzophenone was treated with lithium benzylphenylamide (**53**) the reaction mixture acquired a dark red colour (a new absorption band appeared in the visible region $\lambda_{max} = 475$ nm) [41]. The reaction, after quenching with water, produced benzhydrol (**47**) and the imine **54** in quantitative yield. The complex resulting from the reaction of lithium diphenylamide ($LiNPh_2$) with benzophenone (note that in this case reduction via a hydride transfer is not possible owing to the lack of the necessary hydrogen atom in the amide) was isolated and purified by crystallization. The infrared spectrum of this complex shows the band attributed to the C=O stretch at 1652 cm^{-1}.

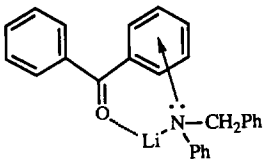
Trying to gain more insight into the mechanism of the reaction, Wittig's group turned to kinetic studies [41]. In a preliminary investigation it was established that the reduction of benzophenone with LiN(Ph)-CH_2Ph was not reversible, and that, under the reaction conditions, the lithium salt of benzhydrol did not appreciably reduce benzophenone via the Meerwein–Ponndorf–Verley mechanism. The isotopic effect in the reduction ($k_H/k_D = 3.4$) was interpreted as an indication that C–H bond formation proceeds in the rate-controlling step. The possibility of a mechanism involving free radicals was ruled out on the basis of EPR and CINDP experiments. It was also established, by osmometry, that lithium *N*-benzylanilide, at concentrations lower than about 0.05 M in ether, is monomeric (but aggregation of the amide occurs at higher concentrations); consequently most of the kinetic measurements were carried out below this concentration. Data obtained from these kinetic studies, and from analyzing the effect of different solvents on reaction rate and on the equilibrium of the complex formation, supported the mechanism shown in Scheme 14. A series of experiments in ether, at 20°C, led to determination of the following values [41]:

$$K = 1.90(\text{L mol}^{-1})$$

$$k_1 = 1.84 \times 10^{-2}(\text{min}^{-1})$$

Activation parameters for the reaction were also determined. It was found that the formation of the complex **55** was slightly endothermic (ΔH, 2.7 kcal mol^{-1}); stability of this complex was due to entropic effect; the positive value of entropy (ΔS, +10.6 cal mol^{-1} K^{-1}) indicated that solvent molecules were released during formation of the complex.

When the reaction was performed with *para*-chlorobenzophenone and *para*-methylbenzophenone as substrates, a measurable substituent effect on the complex formation was observed. Apparently electron-withdrawing substituents (*e.g.* chlorine) increase the complex concentration, whereas electron-donating substituents (the methyl group) decrease it. On the basis of these substituent effects, Wittig proposed that the complex has a charge-transfer character; an interaction is present between the lone electron pair on nitrogen and the π system of the ketone as described by structure **56**.

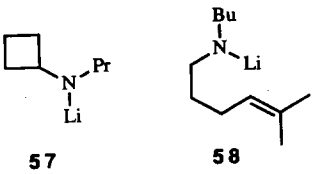


56

Wittig's proposals were not universally accepted, and a single-electron transfer (SET) mechanism for reduction with lithium amides was also thought to be important, especially since a report published by Scott and coworkers which, without giving any quantitative data, described formation of tetraphenyloxirane during the reaction of benzophenone with LDA [87].

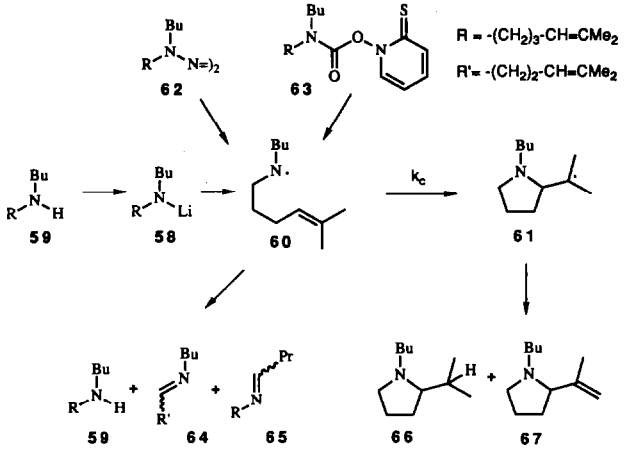
Intrigued by the possibility that lithium dialkylamides might reduce organic molecules via a SET pathway, Newcomb and colleagues undertook a systematic and thoughtful investigation of this reaction using (*E*)-2-tert-butyl-3-phenyloxaziridine (**36**, *cf.* Scheme 10) and benzophenone as two model oxidants [21,35–38,79,80].

To address the question of a possible free-radical mechanism, Newcomb's group synthesized two lithium dialkylamide probes (**57** and **58**); compounds which were designed to rearrange upon being converted to corresponding aminyl radicals [35,38,80]. Thus, if lithium butyl-5-methyl-4-hexenylamide (**58**, Scheme 15) is oxidized by a SET process to the aminyl radical (**60**), the radical would be expected to cyclize to the carbon-centered radical (**61**). Both radicals should react further to yield amine **59**, imines **64** and **65** and pyrrolidine(s) **66** and/or **67**. While non-cyclic products **59**, **64**, **65** could also result from reactions which have nothing to do with a single-electron transfer from the lithium amide, the presence of cyclic products (**66** and/or **67**) would testify to the intermediacy of the aminyl radical **60** and indicate a SET pathway.



57 **58**

In order to establish if the lithium amide **58** is a viable probe, the aminyl radical **60** was generated by

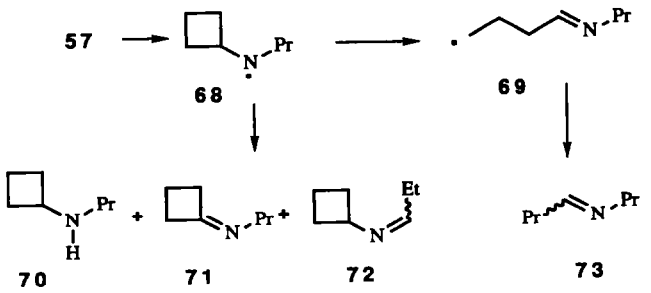


Scheme 15.

known methods from the appropriate tetrazone **62** and from the carbamate **63**. In both cases the pyrrolidines **66** and **67** were detected in the products.

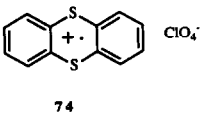
Lithium cyclobutylpropylamide **57** was similarly evaluated as a potential probe. The corresponding radical in this case is **68** (Scheme 16), which rearranges to the acyclic radical **69**. The presence of the acyclic imine **73** in the products would indicate that the reaction proceeded via the aminyl radical **68** and would suggest a SET pathway.

The oxaziridine **36** reacted with lithium dialkylamides (LiTMP, LDA, LDEA) to give two products: the imine **37** and the amide **38** (Scheme 10) [35,79,80]. After studying the kinetics and the kinetic isotope effect of this reaction, Newcomb concluded that the amide was produced by a simultaneous deprotonation and ring-opening as shown in structure **39**, and that the imine was most likely formed via a SET process. When the oxaziridine **36** was allowed to react with probes **57** and **58**, the products indicating the SET pathway (**66**, **67**, **73**) were observed and it was concluded that this reduction proceeds via transfer of a single electron from lithium amide to oxaziridine. A similar experiment with thianthrene radical cation perchlorate **74** also indicated the intermediacy of aminyl radicals. However, probe **58** tested negative in reactions with



Scheme 16.

weaker organic oxidants: diaryl ketones (benzophenone, dimesityl ketone), pyridine, iodomethane, *p*-dicyanobenzene, perylene, 2,4,6-tri-tert-butylnitrobenzene, benzil and *p*-dinitrobenzene.



The authors concluded that lithium dialkylamides are not especially strong one-electron reducing agents. Apparently, several earlier reports suggesting electron transfer between $LiNR_2$ and weak organic oxidants should be treated with caution.

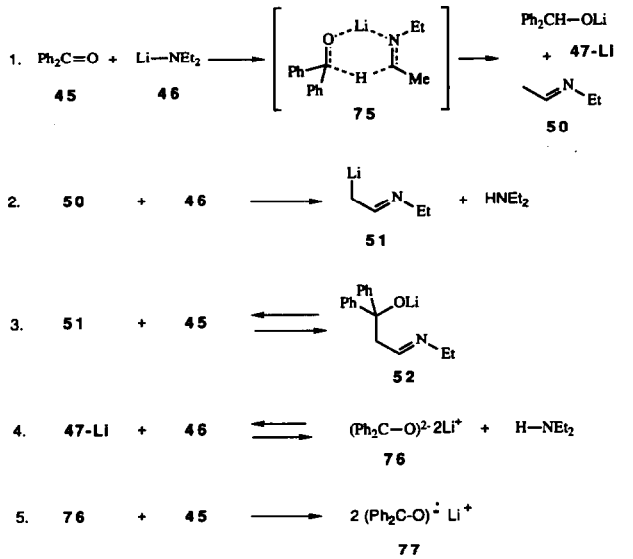
Two questions arose:

i. What is the origin of benzophenone ketyl, which was observed during reaction of benzophenone with lithium amides by others?

ii. What is the mechanism of reduction of benzophenone with Li amides?

Newcomb and coworkers hypothesized that benzophenone ketyl is produced in a secondary reaction and *not* during the reduction of benzophenone to diphenylcarbinol. They postulated that five different reactions occur, in a system comprising benzophenone and a lithium dialkylamide [36] (for convenience these reactions are shown with LDEA, Scheme 17):

i. Reaction 1 is a concerted β-hydride transfer from the amide to the ketone, which proceeds via a cyclic transition state **75** and is analogous to the well-known Meerwein–Ponndorf–Verley reduction (similarities and differences with Wittig's proposal are noteworthy).



Scheme 17.

ii. In reaction 2 the imine **50** produced in reaction 1 is deprotonated by LDEA, and in reaction 3 the resulting lithiated imine (**51**) adds, in a reversible aldol-type reaction, to benzophenone. These reactions are well precedented in Wittig's work, which resulted in isolation of the alcohol corresponding to the adduct **52**; thus reactions 2 and 3 must compete with reaction 1. The reversibility of aldol-type reactions is well established. Newcomb's group measured the rate of the retro-aldol process by looking of the rate of isotopic label equilibration in a reaction between the lithium aldolate adduct **52** and $Ph_2^{13}C{=}O$, and concluded that the cleavage of the adduct **52** is significantly faster than the overall rate of ketyl formation.

iii. Lithium amide deprotonates another compound produced in the first step (reaction 4). This is, perhaps, the most unusual step in the proposed sequence. The authors proved that this deprotonation occurs: when diphenylcarbinol (**47**) was added to a solution of LDEA or LDA, the mixture slowly turned a deep red color which was attributed to the dianion **76**. The reaction is slow and the rate constant k_2 for the (assumed) second-order deprotonation of **47-Li** with LDA was measured to be 4×10^{-5} M^{-1} s^{-1} (at 22°C, in THF). This reaction is the rate-limiting step for the ketyl formation.

iv. In the disproportionation step 5, the dianion **76** reacts with benzophenone, and two molecules of benzophenone ketyl **77** are produced.

It is known [41,44] that lithium amides reduce benzophenone rapidly; the reduction is usually over in a few minutes at −78°C. It is also known that these reactions do not go to completion, and a substantial amount of benzophenone is always recovered after the reaction, even when alkyl lithium is added to the reaction mixture to trap the unreacted benzophenone [44]. Newcomb speculated [36] that benzophenone is trapped as the aldol-type adduct **52** which hydrolyzes on work-up and also decomposes on GC. The detection of benzophenone by GC might have suggested to some researchers that reduction was slow.

The authors also observed that, when benzophenone was added to a solution of LDA or LDEA under argon, the characteristic blue color of benzophenone ketyl **77** developed over a period of a few hours (note that the reduction should be over in a matter of minutes, *vide supra*). The amount of ketyl reached a maximum after about 35 h and then began to decrease. The rate constants for deprotonation of **47-Li** were found to be essentially equal to one-half of the rate constants for ketyl formation as predicted by the mechanism summarized in Scheme 17.

The proposed set of reactions explains the formation of benzophenone ketyl and, at the same time, provides a pathway where no free-radical intermediates are formed in the actual reduction of benzophenone with lithium bases. This is in agreement with the study involving cyclizable probes and with Wittig's original proposal of the β-hydride transfer mechanism [39]. It was suggested that some previous observations could be rationalized by this scheme:

i. Wittig observed no EPR signals when investigating the reaction of benzophenone with $LiNEt_2$ [41] because he used 1 equiv. of base and short reaction times.

ii. Kowalski noticed only partial reduction of benzophenone because a substantial portion of the ketone was trapped as the adduct **52** [44].

iii. Products derived from coupling of ketyl radical anion and EPR signals observed previously [33,87] were due to excess base and extended reaction times.

The mechanism of radical anion formation described above on the example of benzophenone ketyl might be more general. It was proposed [36] that reactions between negatively charged nucleophiles and weak organic oxidants (*e.g.* aromatic hydrocarbons) can often proceed by a two-electron pathway to yield one-electron products according to the following set of equations:

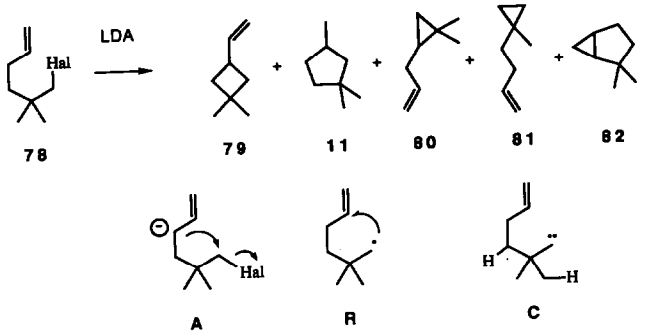
$$(B{-}H)^- + Ox \rightarrow (Ox{-}H)^- + B \qquad (i)$$

$$(Ox{-}H)^- + (B{-}H)^- \rightarrow (Ox)^{2-} + H{-}B{-}H \qquad (ii)$$

$$(Ox)^{2-} + Ox \rightarrow 2(Ox)^{-\cdot} \qquad (iii)$$

In a recent study, Newcomb *et al.* established (by measuring kinetics and kinetic isotope effects) that LDA and lithium tert-butylethylamide reduce trityl chloride and trityl bromide (weak oxidants) to triphenylmethane via a mechanism involving the rapid predissociation of the halide to form an ion pair containing the trityl-THF oxonium ion [21]. The base then transfers an electron to the cation, and the resulting radical pair exchanges a hydrogen atom from the aminyl radical to the trityl radical. The kinetic data also indicated that LDA reacts as a monomer in this process.

The work of Newcomb's group, described above, indicated that electron transfer from lithium dialkylamides is only apparent when relatively strong oxidants are involved (reduction potential of the oxidant must be greater than 0.0 V *vs.* Standard Hydrogen Electrode). A crude reduction potential for the $R_2N^-/R_2N^{\cdot}$ couple was calculated to be no less than −0.1 V *vs.* SHE. This was in good agreement with the value reported at the same time by Fox [88]. It was concluded that reductions of weak oxidants, *e.g.* diarylketones, aromatic hydrocarbons, occur via β-hydride transfer from the amide.



Scheme 18.

A recent exhaustive study from Ashby's group shed some light on the mechanism of reduction of alkyl halides with lithium amides [23]. Thus when 6-halo-5,5-dimethyl-1-hexene (**78**, Hal = I, Br, Cl or OTs) was treated with LDA, up to five products (**11**, **79–82**) were observed. Product **11** originates from a cyclization involving free radical **R** formed from the halide in a SET process. Compound **79** can originate from the carbanion **A**, which could be formed by deprotonation of the halide at the allylic position, or from a carbene **C**. Compounds **80–82** are produced from the carbene **C** (via an insertion into one of the indicated C–H bonds or via addition to C=C): this carbene intermediate could be a result of lithiation at the carbon atom adjacent to the halogen, followed by elimination of LiHal from the carbenoid species. Effects of solvents, halides, stoichiometry, temperature and different radical traps on the product distribution and yields were studied. Iodide gave the most of the cyclic product **11**, whereas chloride and tosylate did not afford **11** at all. Other lithium dialkylamides (LiTMP, lithium pyrrolidide and lithium dicyclohexylamide) were also studied; all of them gave the cyclic product **11** in variable amounts. The reaction of 6-iodo-5,5-dimethyl-1-hexene with LDA was demonstrated to involve a competition of SET and carbene pathways and (possibly) also the carbanion **A**. The corresponding bromide, which has lower reduction potential, reacted mainly via the carbene pathway.

While the mechanisms of some reductions have been reasonably well established, care should be taken in attempts to generalize these observations. The mechanism could change from, for example, SET to hydride transfer with the change in either the oxidant or the base. Bases like LiTMP do not have any β-hydrogen atoms and, therefore, cannot enter into the β-hydride transfer process. The potential products of the nucleophilic addition of the lithium amide to the C=O group [13] should not be forgotten in the analysis of reductions involving benzophenone and other ketones.

8. Conclusions

Lithium dialkylamides, reagents normally thought of as strong bases, useful in kinetic deprotonation of C–H acids, can enter into several different reactions. Among other possibilities the amides can transfer a hydride atom to carbonyl compounds, transfer a single electron to alkyl or aryl halides, aromatic hydrocarbons, oxaziridines and other compounds and thus precipitate a free-radical pathway, generate carbenes from alkyl halides or add to carbonyl groups. Some of these reactions can be useful in organic synthesis, while the others constitute undesirable side-reactions and the chemists' goal will be to avoid them. These reactions can only be avoided or minimized succesfully if they are reasonably well understood. Several studies contributed to the present level of understanding of these reactions; one of the aims of this review is to bring these studies to the attention of synthetic chemists who frequently encounter "unexpected" products during reactions involving lithium amides. It should also be pointed out that greater synthetic utility can be gained by exploiting reactions of dialkylamides of metals other than lithium; magnesium diisopropylamide seems to be a promising reducing agent [89].

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