# Communications to the Editor

## Metalation of Nonenolizable Ketones and Aldehydes by Lithium Dialkylamide Bases

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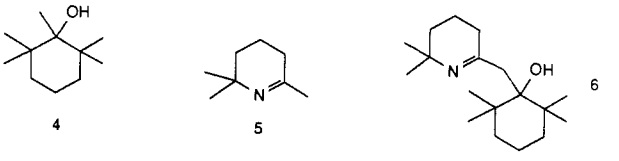
*Received October 5, 1987*

The carbonyl group can promote bridgehead $\alpha$-metalation as well as $\beta$- and even $\gamma$-deprotonations. Upon treatment with base under classical homoenolization[1] conditions (e.g., *t*-BuOK/*t*-BuOH(D), 185–250 °C), many nonenolizable ketones undergo H/D exchange, and in some cases rearrangement, via these pathways.[2] Extensive studies have provided a wealth of mechanistic data, but only a few preparatively useful examples have emerged.[3] More recently, organometallic derivatives of amides and related compounds were generated via low-temperature $\beta$-deprotonations with organolithium bases,[4,5] exploiting the modest reactivity of these substrates toward nucleophiles. Metalations of nonenolizable ketones with strong bases should likewise offer new insights into carbonyl enhancement of acidity, as well as access to synthetically useful organometallic species. An important further objective involves formyl deprotonation of aldehydes, a process heretofore observed only in the gas phase,[6] to furnish acyllithiums. Herein we report that, notwithstanding the constraints imposed by their susceptibility to nucleophilic attack, nonenolizable ketones and aldehydes undergo efficient deprotonations by lithium dialkylamide bases.[7]

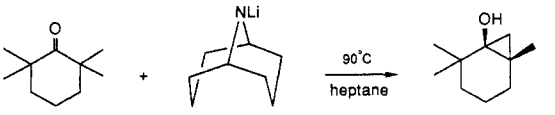
The simplest nonenolizable ketones, exemplified by **1**, merely lack $\alpha$-hydrogens. We envisioned that lithiation of **1** would furnish cyclopropanol **3** via an intermediate or transition structure resembling **2**.[8] Lithium amides bearing transferable $\beta$-hydrides (e.g., lithium diisopropylamide) rapidly reduce nonenolizable ketones,[9] so lithium tetramethylpiperidide (LTMP) was employed in initial experiments. Treatment of **1** with LTMP (5 equiv) in heptane at 80 °C for 24 h did afford **3**[10] in 27% yield. Remarkably, the major pathway involved the transfer of a $\beta$-methyl group from LTMP, furnishing the tertiary alcohol **4**[10] in 33% yield.




4 5

Although the mechanistic details of this apparently unprecedented process remain uncertain, the origin of the carbinol methyl group in **4** was indicated by isolation of the demethylated imine **5**[10] and imino alcohol **6**.[10]

In an effort to suppress both hydride- and alkyl-transfer pathways, we then devised the novel, bridged bicyclic lithium amide, *N*-lithio-9-azabicyclo[3.3.1]nonane (LABN, **7**).[11] $\beta$-




1 LABN (7) 3 (97-100%)

Hydride transfer from LABN would generate an anti-Bredt imine, and plausible transition structures for alkyl group transfer also have anti-Bredt character. In accord with expectations, reaction of **1** with LABN (5 equiv, heptane, 90 °C, 20 h) furnished **3** quantitatively.

Bridgehead ketones comprise the second important group of metalation candidates.[12,13] We have reinvestigated the deprotonation of (−)-camphenilone (**8**),[14] the archetypal substrate for classical homoenolization.[15] High-temperature H/D exchange occurs most rapidly at C(6), with concomitant racemization of the ketone via the symmetrical cyclopropyl alkoxide structure **9**. Prolonged reaction at 250 °C results in incorporation of up to nine


8 9

(1) The term homoenolization is well established, and we refer to high-temperature, *tert*-butoxide-induced deprotonations of nonenolizable ketones as classical homoenolizations. However, we note that enolates and other metalated ketone derivatives contain different functionalities. "Homoenolates" and enolates are not homologous in the usual sense.

(2) Review: Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205–268.

(3) See, for example: Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Ragauskas, A. J.; Stothers, J. B. *Can. J. Chem.* **1984**, *62*, 2521–2525. See, also: ref 13.

(4) Reviews: (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523. (c) Beak, P.; Reitz, D. B. *Ibid.* **1978**, *78*, 275–316. See, also: ref 7. Gas-phase studies: Ingemann, S.; Nibbering, N. M. M. *J. Org. Chem.* **1985**, *50*, 682–689.

(5) Metalated carbonyl compounds and synthetic equivalents thereof have also been prepared from various functionalized precursors; see, for example: Fukuzawa, S.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 475–476. Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1985**, *50*, 2804–2805. Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948. See, also: ref 1.

(6) Peerboom, R.; Ingemann, S.; Nibbering, N. M. M. *Recl. Trav. Chim.* **1985**, *104*, 74–78, and references cited therein.

(7) LTMP/$HgCl_2$ has been employed in metalations of nonenolizable amides: Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948–949.

(8) Methyl deuteriation is the primary pathway in classical homoenolization of **1**: Cheng, A. K.; Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1977**, *55*, 447–453.

(9) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601–2608.

(10) Spectroscopic and analytical data for this compound are provided as Supplementary Material.

(11) Amine precursor: Dupeyre, R. M.; Rassat, A. *Bull. Soc. Chim. Fr.* **1978**, 612–620.

(12) Diaryl ketones, the third class of nonenolizable ketonic structures, are relatively uninteresting in this context because diverse arenes have been metalated without carbonyl activation. Cf., ref 25.

(13) A hindered nonenolizable ketone underwent bridgehead $\alpha$-metalation with *t*-BuLi: Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J. M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139–141. In contrast, *t*-BuLi adds to camphenilone: Peters, E. N.; Brown, H. C. *J. Am. Chem. Soc.* **1975**, *97*, 2892–2895. See, also: Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *Ibid.* **1985**, *107*, 3253–3266.

(14) Preparation: Bailey, P. S. *Chem. Ber.* **1955**, *88*, 795–801. The ketone was resolved via a modification of the Johnson sulfoximine procedure: Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225–1233. Shiner, C. S.; Berks, A. H., manuscript in preparation.

(15) Nickon,, A.; Lambert, J. L.; Williams, R. O.; Werstiuk, N. H. *J. Am. Chem. Soc.* **1966**, *88*, 3354–3358, and references cited therein.

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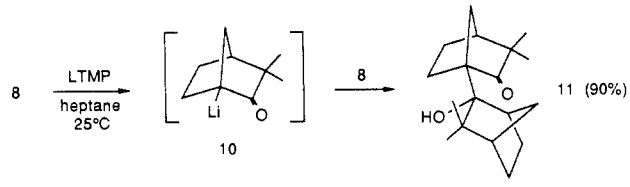
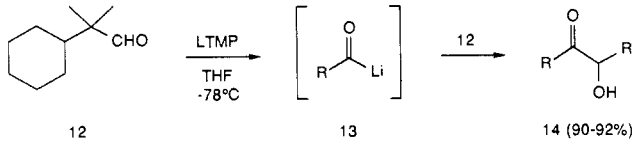
deuteriums, via exchange at C(6), the C(1) bridgehead position, and the two methyl groups. This substance thus afforded an exemplary opportunity to compare the regioselectivity of lithium amide deprotonation with related earlier results. (-)-Camphenilone underwent rapid lithiation by LTMP in heptane at 25 °C (1.1 equiv, 1.5 h), exclusively at the bridgehead position. Exo addition of the α-keto organolithium intermediate **10** to a second molecule of **8** then furnished the formal aldol dimer **11**[10] in 90% yield.[16] Camphenilone did not racemize under these conditions.[17]




Despite long-standing interest, the generation of an acyllithium via deprotonation of the corresponding aldehyde has not previously been achieved. Nonenolizable aldehydes have apparently not been studied under classical homoenolization conditions, but suitable substrates (e.g., trimethylacetaldehyde) do undergo competitive alkyl and formyl deprotonation in the gas phase.[6,18] In solution, acyllithiums have been generated by addition of alkyllithiums to carbon monoxide,[19] and related species are accessible via deprotonation of other formyl derivatives.[20] We now report that the nonenolizable aldehyde **12**[10,21] can be lithiated with remarkable




ease upon exposure to LTMP (1.1 equiv) in THF at -78 °C for 30 min. The acyloin **14**[10] was formed in 90-92% yield, presumably via the intermediacy of acyllithium **13**. A similar reaction of trimethylacetaldehyde at -25 °C for 10 h furnished the expected acyloin **15** in 89% yield.

Dipole and inductive effects[22] should stabilize the metalloketones **2** and **10**, reinforced in the former case by internal complexation.[23] Ab initio studies of formyllithium[24] suggest a preference for ionic $\eta^2$-bonding of lithium to the carbonyl moiety in species such as **13**. Complexation of the lithium bases and carbonyl oxygens presumably accelerates the deprotonation reactions[4a] and also accounts for the regioselectivity of camphenilone metalation. Alternative mechanisms for the conversion of **1** to **3** and the formation of **14** and **15**, involving initial electron transfer from LABN or LTMP to the carbonyl compounds,[25] cannot presently be excluded.

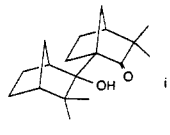
Further studies will address questions of scope and mechanism and will explore the reactivity of acyl and α-keto organolithiums with diverse electrophiles. These efforts, as well as full details of the experiments described herein, will be reported in due course.

**Acknowledgment.** We are grateful for financial support provided by the National Institutes of Health. We also thank R. Curtis Haltiwanger for determination of the crystal structure of **11**.

**Supplementary Material Available:** Spectroscopic and analytical data for **3-6**, **11**, **i**, **12**, **14**, and **15** (2 pages). Ordering information is given on any current masthead page.

(16) The structure of **11** has been confirmed by X-ray analysis. The details of the structure determination will be published separately.

(17) Racemization prior to dimerization would afford mixtures of **11** and the diastereomeric dimer i (ref 10). Dimerization of **8** of low enantiomeric purity afforded greater than statistical quantities of i.



i

(18) Ab initio studies of acyl anions: Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5612-5614. See, also: ref 24.

(19) For leading references, see: Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551-4553. Narayana, C.; Periasamy, M. *Synthesis* **1985**, 253-268.

(20) Metalation of dimethylformamide with LDA in THF at -78 °C furnishes (dimethylcarbamoyl)lithium: Bănhidai, B.; Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 836-837. See, also: Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309-1323.

(21) Prepared by dimethylation of methyl cyclohexylacetate (LDA, $CH_3I$, THF, -78 °C; LDA, $(CH_3)_2SO_4$, THF, -45 °C), LAH reduction, and PCC oxidation.

(22) Ab initio studies: Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108-4110.

(23) Cf., Geurink, P. J. A.; Klumpp, G. W. *J. Am. Chem. Soc.* **1986**, *108*, 538-539. See, also: ref 5.

(24) Kaufmann, E.; Schleyer, P. v. R.; Gronert, S.; Streitwieser, A., Jr.; Halpern, M. *J. Am. Chem. Soc.* **1987**, *109*, 2553-2559.

(25) For discussion of SET from lithium dialkylamides to ketones, see: Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 8276-8282.

## An Asymmetric Intramolecular Michael Reaction. Construction of Chiral Building Blocks for the Synthesis of Several Alkaloids

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*Received September 11, 1987*

An intramolecular Michael reaction is one of the most useful methods for the stereocontrolled assembly of the carbon skeleton in organic synthesis.[1] Although a number of highly enantioselective intermolecular Michael reactions have been reported,[2] few examples are documented of an asymmetric intramolecular Michael reaction that is practically applicable.[3] Here we describe a successful example of the above Michael reaction and its application to the syntheses of several alkaloids. Our study began with the envisaging of asymmetric cyclization **1** → **2** (Scheme I).

The acyclic compound **1** was readily obtained from **3** (Scheme II). Treatment of **3** with 2-(2-bromoethyl)-1,3-dioxolane using sodium hydride as a base followed by partial hydrolysis of the resulting amide afforded the aldehyde **4** in 61% yield. Wittig-type reaction of **4**, followed by the hydrolysis of the resulting product, gave the amine **5**, which was treated with methyl vinyl ketone to furnish **1** in 78% yield.

The key compound **1** was then treated with 1 equiv of (*R*)-(+)-1-phenylethylamine[4] as a chiral base in THF at 5-10 °C to give the optically active cycloadduct **2a** in 80% ee[5] (80% yield) (Scheme III). It should be noted that the use of the 5 Å molecular

(1) Alexakis, A.; Chapdelaine, M. J.; Posner, G. H. *Tetrahedron Lett.* **1978**, 4209. Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. Hirai, Y.; Hagiwara, A.; Yamazaki, T. *Heterocycles* **1986**, *24*, 571.

(2) Leading references for an asymmetric intermolecular Michael reaction: Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250. Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chem. Acta* **1985**, *68*, 212. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. Enders, D.; Papadopoulos, K.; Rendenbach, B. E. M.; Appel, R.; Knoch, F. *Tetrahedron Lett.* **1986**, *27*, 3491.

(3) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087.

(4) Commercial amine, $[\alpha]^{20}D$ +39° (neat) (ee > 99%), was used.

(5) The optical purity of the obtained cycloadducts was determined by obtaining the $^1H$ NMR of the corresponding (+)-MTPA ester[6] of the alcohols **6** and **7**.

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