(2) See (a) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962. (b) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1970, Supplement I.
(3) R. S. Klein and J. J. Fox, *J. Org. Chem.*, **37**, 4381 (1972).
(4) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).
(5) (a) T. D. Heys and J. C. Roberts, *J. Chem. Soc.*, 328 (1951); (b) J. C. Roberts, *ibid.*, 3065 (1952).
(6) (a) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965); (b) M. D. Raush and D. J. Ciappenelli, *J. Organometal. Chem.*, **10**, 127 (1967).
(7) (a) W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (b) E. J. Corey and D. Seebach, *ibid.*, **31**, 4097 (1966).
(8) 2,4,6-Trimethylpyrimidine has been shown to undergo metalation with phenyllithium exclusively at the 4-methyl group.[5]
(9) (a) 2-Methyl-4(3*H*)-quinazolinone has been shown to undergo condensation at the methyl group with chloral: P. Y. Kulkarni, *J. Indian Chem. Soc.*, **19**, 180 (1942). (b) The *N*-phenyl derivative also has been reported to undergo similar reactions with other aldehydes: B. D. Singh and D. N. Chaudbury, *ibid.*, **45**, 311 (1968). (c) Alkylation of 2-methyl-4(3*H*)-quinazolinone employing sodium hydride reportedly gives only N- and O-alkylated products: C. Bogentoft, L. Kronberg, and B. Danielsson, *Acta Pharm. Suecica*, **6**, 489 (1969).
(10) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. G. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(11) See R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967), and references cited therein.
(12) Related 1,1-dianions derived from aromatic, primary amines and 1,1-diarylhydrazines have recently been reported: R. West and H. F. Stewart, *J. Amer. Chem. Soc.*, **92**, 853 (1970).

Metallo Aldimines. A Masked Acyl Carbanion[1,2]

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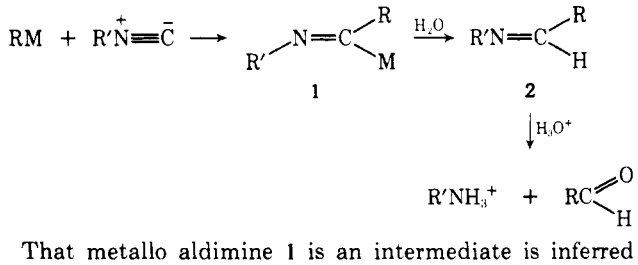
The addition of lithium and Grignard reagents to isocyanides not containing α hydrogens proceeds by an α addition to produce metallo aldimines. The lithium aldimines are versatile reagents which can be used as precursors for the preparation of aldehydes, ketones, α diketones, α-hydroxy ketones, α-keto acids, α- and β-hydroxy acids, and silyl ketones.

There has been a paucity of work on the reaction of organolithium and Grignard reagents with isocyanides. In 1904 Sachs and Loevy[3] added phenylmagnesium bromide to methyl isocyanide and detected benzaldehyde from the steam distillate. Gilman and Heckert[4] 24 years later verified this reaction and reported isolating a 2.5% yield of benzaldehyde; however, the use of ethyl isocyanide or *tert*-butyl isocyanide proved unsuccessful. In 1961, another attempt to use this reaction was made by Ugi,[5] who showed, under a variety of conditions, that the reaction of phenylmagnesium bromide with cyclohexyl isocyanide gave only a 1.5% yield of benzaldehyde.

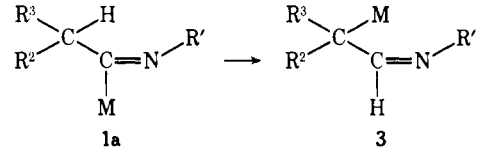
The recent discovery in our laboratory that organolithium reagents added to isocyanides[6] prompted a reinvestigation of this problem. This paper deals with the α addition of organolithium and Grignard reagents to isocyanides to yield metallo aldimines (**1**) and the use of these metallo aldimines as precursors for the synthesis of a variety of functional groups.

Results and Discussion

1-Metallo Aldimines. Metallo aldimines can be most simply prepared by the α addition of an organometallic reagent to an appropriate isocyanide.



That metallo aldimine **1** is an intermediate is inferred from the fact that addition of water to **1** yields the aldimine **2**, which can be isolated. Hydrolysis of **1** or **2** produces the corresponding aldehyde and amine salt. To resolve the question of whether **1** rearranges to give **3**, the metallo aldimine was quenched with D_2O (>99%) and then hydrolyzed. The deuterioaldehyde formed was shown by nmr analysis to have greater than 98% deuterium in the 1 position, which confirms the structural assignment as **1**.



1a **3**

M = Li, MgBr

However, during the deuterolysis of various halomagnesium aldimines, it was observed that less than 100% of the deuterium was incorporated into the C-1 position, and incorporation of some deuterium occurred at the C-2 position (Table III). Several explanations could be conjectured for the presence of deuterium at C-2. First, addition of Grignard reagents to isocyanides requires several hours at room temperature, in contrast to the rapid addition of lithium reagents, and the long reaction time may permit rearrangement of **1a** to the more thermodynamically stable **3**. Secondly, the metallo aldimine **1a** could abstract a proton from the ether solvent and finally a C-2 hydrogen could be abstracted by **1a** during deuterolysis.

To determine if the lithium aldimine was stable to rearrangement, two experiments were conducted. In the first experiment, ethyllithium was added to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) in diethyl ether at 0°. The mixture was stirred for 75 min, then quenched with a fivefold excess of D_2O. The aldimine was distilled, and from the nmr spectrum the relative deuterium content at C-1 and C-2 positions was determined (the methylene protons of the 1,1,3,3-tetramethylbutyl moiety at 1.51 ppm were used as an internal standard). Only 86% incorporation of the deuterium occurred at C-1 while 14% occurred at C-2. The observation that 100% of the deuterium was incorporated into the aldimine suggests[7] that **1a** is not abstracting a proton from the ether solvent, since if this were the case less than 100% deuterium would be incorporated.

The other experiment that was performed involved the addition of ethyllithium to TMBI in ether followed by stirring the reaction mixture at 0° for 6 hr. An inverse ad-

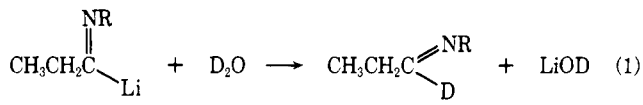
Table I
Synthesis of Aldimines and Aldehydes from the α Addition of Organolithiums to Isocyanides

Registry no.	RLi	Solvent	Isonitrile (registry no.)	% aldimine (registry no.)	Overall % aldehyde[c] (purity, %) (registry no.)
109-72-8	*n*-Butyl	Pentane	TMBI (14542-93-9)	100[a] (49707-47-3)	
59830-1	*sec*-Butyl	Pentane	TMBI	100[a] (49707-48-4)	
	n-Butyl	Ether	TMBI		93[b] (92) (110-62-3)
	sec-Butyl	Ether	TMBI		96[b] (94) (96-17-3)
594-19-4	*tert*-Butyl	Ether	TMBI	93 (49707-49-5)	92 (630-19-3)
	n-Butyl	Ether	TBI[d] (7188-38-7)	92[e] (49707-50-8)	
811-49-4	Ethyl	Ether	DMPI[f] (2769-71-3)	50[g] (49707-51-9)	
591-51-5	Phenyl	Ether	TMBI	45–67[g] (49707-52-0)	55[b] (87) (100-52-7)
917-57-7	Vinyl	Ether	TMBI	0	
	Phenylethynyl	Ether	TMBI	0	
	sec-Butyl	Ether	TMBI	93[h,i] (34668-70-7)	92[b,i] (98.6) (25132-57-4)

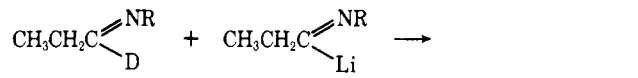
[a] Analytically pure crude product. [b] Purities were determined by vpc analysis. [c] Beilstein, "Handbuch der organische Chemie, Dritte Teil," Friedrich Richter, Springer-Verlag, Berlin, 1959. [d] *tert*-Butyl isocyanide. [e] Crude yield, 90% pure. [f] 2,6-Dimethylphenyl isocyanide. [g] Yields based on nmr analysis of crude product. [h] Yield recovered after distillation. [i] *1-d* compound.

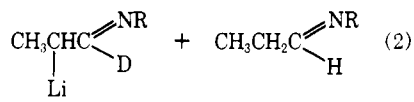
dition was carried out in which the reaction mixture was transferred under anhydrous conditions to a stirred flask containing a fivefold excess of D_2O in THF at −15°. The deuterium analysis showed 97% deuterium incorporation at C-1 and only 3% at C-2.

From the analysis it was clear that **1a** was not being converted to **3** to any appreciable extent, since only 3% was converted in this manner over a 6-hr period (usually the reaction is run for 15–30 min). It is concluded that deuterolysis at C-2 is occurring during the addition of D_2O to the lithium aldimine as shown in eq 1–3. It is suggested



(1)





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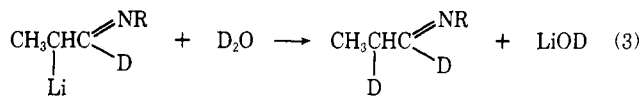
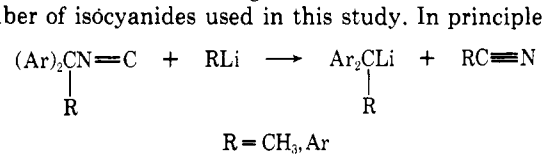


(3)

that to avoid this side reaction, reactions of metallo aldimines should be performed by the addition of the metallo aldimine to the substrate.

In summary, it can be stated that the 1-lithio aldimine is stable in solution and exists as structure **1a**. It should be noted that in contrast to the above, the reaction of *sec*-butyllithium with TMBI followed by the addition of D_2O to the reaction mixture resulted in incorporation of 97% deuterium at C-1. This result is not necessarily unexpected, since the hydrogen atom at C-2 is now markedly reduced in acidity. Table I summarizes the results of the α addition of lithium reagents to various isocyanides.

Choice of Isocyanide. A convenient synthesis of isocyanides has recently been published.[8] The selection of the isocyanide for the preparation of metallo aldimines is important. Since the α-hydrogen atoms of the isocyanide can readily react with organolithium reagents,[9] it is necessary for the α carbon to be trisubstituted. This may account, in part, for the lack of success by the earlier workers to achieve a simple 1:1 α addition to isocyanides in which the alkyl groups were methyl and ethyl.[3,4] A further limitation on the choice of isocyanide is that the α carbon cannot contain two or more aromatic groups, since the addition of lithium reagents to these isocyanides results in a isocyanide–lithium exchange reaction.[10] Table I lists a number of isocyanides used in this study. In principle any



R = CH_3, Ar

aryl or *tert*-alkyl isocyanide can be used, but the aryl isocyanides tend to oligomerize. The most convenient isocyanide to use is TMBI, owing to its ease of preparation[11] and the fact that it is not offensively malodorous.

Effect of Organometallic Reagent. As can be seen from Table I, primary, secondary, and tertiary aliphatic lithium reagents react very readily with TMBI to produce excellent yields of lithium aldimines or their hydrolysis product, aldehydes. Attempts to improve the yield (45–50%) of the phenylithium adduct, by varying the reaction temperature and solvent, failed. However, it was noted that by adding a 50% excess of phenyllithium a higher yield of aldimine (70%) was obtained. Vinyllithium and 2-propenyllithium did not give a simple α addition to TMBI. The reaction resulted in a complex mixture of products presumably due to further reaction of the initially formed aldimine.

Based on the results with phenyllithium it appears that the lithium aldimine **1** is in equilibrium with the starting materials, phenyllithium and TMBI. An unfavorable equilibrium is probably also involved in the case of sodium diethylmalonate and lithium phenylacetylide, both of which failed to add to TMBI. If the McEwen-Streitwieser-Applequist-Dessy pK_a scale[12] is related to the results obtained (Table II), one concludes that the conjugate bases of acids with $pK_a < 37$ will not add appreciably to TMBI. This is consistent with the observations by An-

Table II
Relation of Some Entries from the McEwen–Streitwieser–Applequist–Dessy pK_a Scale to the Result When the Organolithium Reagent Is Added to TMBI in a 1:1 Ratio

RLi	pK_a of RH	Results in ether
$(EtOOC)_2CH$	13	No adduct[a]
$PhC{\equiv}C$	18.5	No adduct
Ph	37	50% adduct
Et	42	100% after 45–60 min
n-C_4H_9		100% after 10–20 min
$(CH_3)_2CH$	44	
$EtCH(CH_3)$		100% after 0–5 min
t-C_4H_9	44	100% after 0–5 min

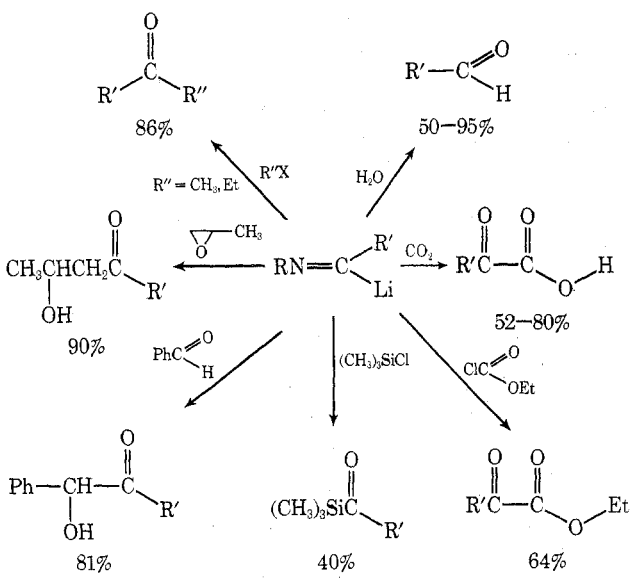
[a] Sodium malonate in THF was treated with TMBI.

selme[13] as well as Meyers[14] and Schöllkopf[15] on the reaction of alkoxide (ROH, $pK_a \cong 18$) with certain isocyanides. In the latter cases[14,15] an equilibrium is established owing to the intramolecular nature of the reaction.

As can be seen from Table III, Grignard reagents do not react as well as lithium reagents. Moreover, phenylmagnesium bromide does not add to any appreciable extent. This observation provides another reason for the lack of success that the earlier workers[3-5] experienced in their attempts to obtain a simple 1:1 α addition to isocyanides. Again, this result may in part be due to an unfavorable equilibrium which, in the case of phenylmagnesium bromide, lies more to the side of the starting reagents.

Reactions of Lithium Aldimines. The lithium aldimine reagents may be viewed as masked acyl carbanions[16] similar in principle to those devised by Corey and Selbach[16] (lithiodiathiane), Stork[17] (magnesium enamines), and Meyers[18] (dihydro-1,3-oxazine system). Thus deuterolysis of 1 provides a simple and inexpensive synthesis of 1-deuterioaldehydes (Table I). Carbonation of 1 yields the corresponding α-keto acid in good yields and treatment of 1 with ethyl chlorocarbonate provides the corresponding ethyl ester.

Chart I
Reactions of Lithium Aldimine[a]



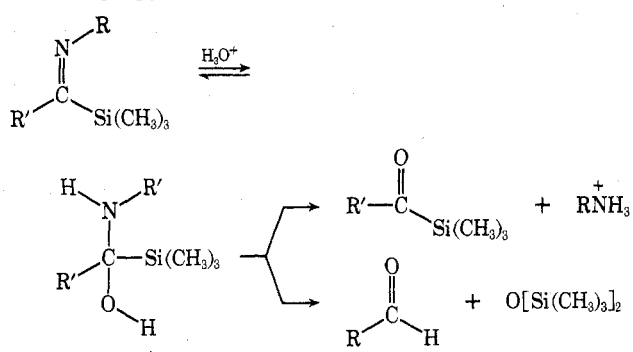
[a] R = 1,1,3,3,-tetramethylbutyl and R′ = n-butyl, ethyl, *sec*-butyl, or phenyl; see Experimental Section.

Chart I shows the different types of reactions that have been carried out using lithium aldimines. Alkylation with ethyl and methyl halides proceeds in good yields to give upon hydrolysis the corresponding ketones. Isopropyl iodide did not alkylate; presumably elimination occurred. However, trimethylsilyl chloride reacted quite well but hydrolysis of the intermediate imine proved difficult. Various attempts (steam distillation from ammonium chloride, sat. hydrochloric acid at 0°, pyruvic acid or dil. hydrochloric acid in methanol at room temperature) resulted in approximately 50% yields of silyl ketone and 50% yield of aldehyde and hexamethylsiloxane. Reaction of 1 with benzaldehyde leads to the formation of α-hydroxy ketones and with propylene oxide to isolable β-hydroxy ketones.

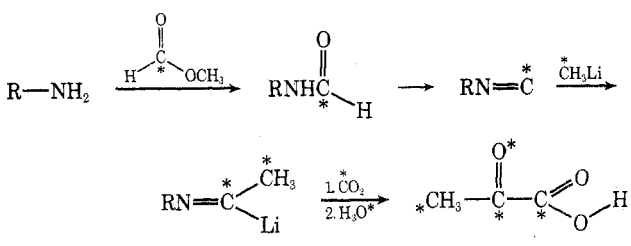
Table III
Aldehydes and α-Keto Acids from Alkyl Grignard Reagents and TMBI

RMgBr[a]	Solvent	Time, hr	% aldehyde (registry no.)	% α-keto acid (registry no.)
sec-Butyl	Ether	3	67 (96)[b]	47 (1460-34-0)
tert-Butyl	THF	24	48	
n-Hexyl	THF	1.5	62 (111-71-7)	26 (328-51-8)
n-Butyl	THF	1.5		34 (2492-75-3)
2-Phenylethyl	THF	1.5	63 (80)[b] (104-53-0)	
Cyclopentyl	THF	1.5	66 (89)[b] (872-53-7)	
Phenyl	THF	18	2	

[a] Concentration of Grignard reagents was *ca.* 0.1 *M*. [b] Per cent deuterium at C-1 as determined by nmr.



It should also be recognized that this system has great potential for the syntheses of labeled compounds. For example, pyruvic acid may be conveniently labeled on four atoms by the following route.



Experimental Section[19]

Bulk solvents were distilled before use. Reagent grade diethyl ether, tetrahydrofuran (THF), and dimethoxyethane were distilled from lithium aluminum hydride prior to use. Infrared spectra were taken neat or in solution (0.5-mm sodium chloride cell) on a Perkin-Elmer Model 247. Nmr spectra were obtained on Varian Associates A-60 and Brucker 90 spectrometers using TMS as internal standard.

Vapor phase chromatography was conducted on an F & M Model 500 programmed temperature gas chromatograph with a thermistor detector. All melting points were taken with a Mel-Temp apparatus. The partial immersion thermometer was calibrated over the range of 81–235°. The addition reactions to *tert*-butyl isocyanide (TBI) and 2,6-dimethylphenyl isocyanide

(DMPI) were carried out in a manner identical with that described for TMBI.

2-(*N*-2-Methylbutylideneamino)-2,4,4-trimethylpentane. A solution of 0.982 g (0.00704 mol) of 1,1,3,3-tetramethylbutyl isocyanide (TMBI) in 70 ml of pentane was treated with 0.00711 mol of *sec*-butyllithium in hexane while stirring at 25°. After 10 min, 0.38 ml of water was added, and the mixture was stirred for 15 min to yield 1.4 g (quantitative yield) of the aldimine after filtering and evaporating off the solvent. The product needed no further purification: bp 85.5° (10 mm); ir (neat) 1667 (m), 1464, 1366, 1223 cm^{-1}; nmr (CCl_4) δ 0.85-1.75 (m, 25), 2.18 (m, 1, CH), 7.50 (d, 1, J = 4.6 Hz, -N=CH).

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79. Found: C, 79.38; H, 13.68.

2-(*N*-Pentylideneamino)-2,4,4-trimethylpentane. In like manner, 0.5 g (0.00359 mol) of TMBI in pentane was treated with 0.00369 mol of a hexane solution of *n*-butyllithium. A quantitative yield, 0.71 g, of the aldimine was obtained which needed no further purification: bp 89.5° (10 mm); ir (neat) 1667 (m), 1469, 1367, 1223 cm^{-1}; nmr (CCl_4) δ 0.88-1.75 (m, 24), 2.23 (m, 2, CH_2), 7.65 (t, 3, J = 4.5 Hz, -N=CH).

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79. Found: C, 79.3; H, 13.7.

2-(*N*-1-*d*-2-Methylbutylideneamino)-2,4,4-trimethylpentane. The reaction was carried out as above. However, D_2O (>99%) was used to quench the lithium aldimine, and 1.4 g of the 1-*d*-aldimine was obtained: bp 85.5° (10 mm); nmr (CCl_4) δ 0.85-1.75 (m, 25), 2.23 (m, 1), 7.50 (d, <0.02).

1-*d*-2-Methylbutanal. To 35.1 ml (0.2 mol) of TMBI in 300 ml of ether under nitrogen was added, with mechanical stirring at 0° (ice-salt bath), 0.2 mol of *sec*-butyllithium (in hexane) at a rate such that the temperature never exceeded 5°. After an additional 15 min of stirring, 8 ml (0.4 mol) of D_2O (<99%) was injected into the reaction mixture. Filtration of the mixture followed by evaporation of the solvent gave the aldimine, which was distilled, bp 52.5-54° (1.5 mm), to give 36.9 g (0.186 mol). Steam distillation from 200 ml of an oxalic acid solution (2 *M*) gave 16.0 g (0.184 mol) of the 1-*d*-aldehyde: yield 92% overall; $n^{30}D$ 1.3896; purity 98.6% by vpc analysis (LS-40); isotopic purity 97.9% by nmr analysis; nmr (neat) δ 9.79 (d, 0.021, J = 1.8 Hz); bp 92°; 2,4-DNP mp 128.5-130° (lit.[20] mp 129-130°).

1-*d*-2,2-Dimethylpropanal. Similarly, to 35.1 ml (0.2 mol) of TMBI in 400 ml of ether under nitrogen was added, with mechanical stirring at −15°, 0.2 mol of *tert*-butyllithium (in pentane). D_2O (>99%, 8 ml, 0.4 mol) was injected into the reaction mixtures with continued external cooling. Filtration of the mixture, followed by evaporation of the solvent, gave the aldimine, which was distilled, bp 48-50° (3.2 mm), to give 37.2 g (0.186 mol, 93%). Steam distillation afforded 16.0 g (0.184 mol, 92% yield) of the 1-*d*-aldehyde: chemical purity 99% by vpc analysis (LS-40); isotopic purity 98% by nmr analysis, nmr (neat) δ 9.33 (s, 0.018); bp 75°; 2,4-DNP mp 211-213° (lit.[20] mp 209-211°).

2-Oxo-3-methylpentanoic Acid. To a stirred solution of 3.76 g (0.027 mol) of TMBI dissolved in 27 ml of ether at 0° under a nitrogen atmosphere was added 0.026 mol of *sec*-butyllithium (in hexane). After 10 min, the solution was added dropwise to an ether slurry of Dry Ice. The solvent was evaporated and the carbonated imine was refluxed in an oxalic acid solution for 15 min. Extraction with methylene chloride, followed by evaporation of solvent, gave 2.8 g (0.021 mol, 80%) of the keto acid: ir (CCl_4) 3410 (m), 1785 (s), 1715 cm^{-1} (s, broad); nmr (CCl_4) δ 11.79 (s, 1); purity 95% by vpc analysis; 2,4-DNP mp 169-170° (lit.[20] mp 171°).

3-Heptanone. To a stirred solution of 20.9 g (0.15 mol) of TMBI dissolved in 150 mol of the THF at −10° under a nitrogen atmosphere was added 0.15 mol of *n*-butyllithium (in hexane). After 30 min the solution was cooled to −75°, and 17 g (0.155 mol) of ethyl bromide in 50 ml of THF was added dropwise. The solution was warmed to 0°, taken up in pentane, washed with water, dried (sodium sulfate), and evaporated to yield an oil which was distilled, bp 68° (0.25 mm). The ketimine, 30.2 g (0.134 mol), was hydrolyzed by steam distillation from an oxalic acid solution (2 *M*) to yield 13.6 g (0.131 mol, 87%): bp 149.5°; ir (neat) 1711 cm^{-1} (s); semicarbazone mp 99.5-101° (lit.[21] mp 99-110°).

1-Hydroxy-1-phenylbutanone. To a stirred solution of 6.95 g (0.05 mol) of TMBI in 50 ml of THF at −10° under a nitrogen atmosphere was added 0.05 mol of ethyllithium (in benzene). After 1 hr, 5.3 g (0.05 mol) of benzaldehyde in 25 ml of THF was added at −50 to −60° (Dry Ice-acetone). The solution was stirred for 1 hr, after which 1.5 ml of water was added. The solvent was filtered and evaporated and the hydroxyl imine was then hydrolyzed with dilute hydrochloric acid and methanol (2 hr) to yield 7.5 g of the crude hydroxy ketone. Distillation gave 6.7 g (0.041 mol, 81%), bp 69° (0.2 mm) [lit.[20] bp 124-128° (11 mm)].

2-Hydroxy-4-octanone. To a stirred solution of 13.9 g (0.1 mol) of TMBI dissolved in 100 ml of THF at −10° under a nitrogen atmosphere was added 0.1 mol of *n*-butyllithium (in hexane). After 30 min 6.85 ml (0.105 mol) of propylene oxide in 25 ml of THF was added dropwise. After continued stirring for 30 min, the solution was taken up in pentane, washed with water, and evaporated to yield the hydroxy ketimine. Hydrolysis to the hydroxy ketone was accomplished by refluxing the imine in a solution of 75 ml of THF, 25 ml of ether, 10 ml of H_2O, 10.5 g (0.2 mol) of ammonium chloride, and 0.1 ml of concentrated hydrochloric acid for 16 hr. Extraction with methylene chloride gave, after drying (sodium sulfate) and evaporating the solvent, 9 g (0.09 mol, 90%) of the hydroxy ketone: bp 61-62° (1 mm) [lit.[22] bp 86-87° (5 mm)]; ir (neat) 3420 (broad), 1703 cm^{-1} (s); nmr (CCl_4) δ 0.7-1.7 (m, 7, $CH_3CH_2CH_2$-), 1.10 (d, 3, J = 6 Hz, CH_3), 2.44 (d, 2, J = 6.3 Hz, CH_2), 2.38 (t, 2, J = 7 Hz, CH_2), 4.03 (s, 1, OH), 4.06 (sextet, 1, J = 6 Hz, CH); *N*-phenylcarbamate mp 55-56°, ir (CCl_4) 3452, 1741, 1718 cm^{-1}.

Anal. (carbamate) Calcd for $C_{15}H_{21}NO$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.19; N, 5.24.

2-(*N*-1-Trimethylsilylpropylideneamino)-2,4,4-trimethylpentane. To a stirred solution of 10.5 g (0.075 mol) of TMBI dissolved in 150 ml of THF at −5° under a nitrogen atmosphere was added 0.075 mol of ethyllithium (in benzene). After 45 min the solution was cooled to −75°, and 8.1 g (0.075 mol) of trimethylchlorosilane in 25 ml of THF was added dropwise. The solution was warmed to 0°, and 1.5 ml of saturated sodium carbonate solution was added. The solvent was evaporated to dryness, the residue was triturated with pentane (leaving behind the insoluble salts), and the pentane was evaporated, yielding 17.0 g of the crude imine. Distillation afforded 14.5 g (0.6 mol, 80%) of the product: bp 44.5-45° (0.005 mm); ir (neat) 1601 (m), 1245 (s), 834 cm^{-1} (s); nmr (CCl_4-$CHCl_3$) δ 0.21 [s, 9, $Si(CH_3)_3$], 1.09 [s, 9, $C(CH_3)_3$], 1.14 (t, 3, J = 7.5 Hz, CH_3), 1.39 [s, 6, $C(CH_3)_2$], 1.74 (s, 2, CH_2), 2.50 [q, 2, J = 7.5 Hz, CH_2].

Anal. Calcd for $C_{14}H_{31}NSi$: C, 69.62; H, 12.94; N, 5.80. Found: C, 69.75; H, 12.95; N, 5.81.

Ethyl 2-[*N*-(2-Phenyl-2-butyl)]imino-3-methylpentanoate. To a stirred solution of 4.35 g (27.3 mmol) of 2-phenyl-2-butyl isocyanide dissolved in 50 ml of ether at 0° under nitrogen was added 29.6 ml of 0.97 *M* *sec*-butyllithium solution in cyclohexane and the mixture was stirred for 30 min. After cooling to −20° the reaction mixture was added dropwise to a stirred solution of 15 g (0.138 mol) of ethyl chlorocarbonate in 80 ml of THF at −78° and then stirred overnight at ambient temperature. Filtration and distillation of the product at reduced pressure gave 5.07 g (64%) of ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate: bp 100-102° (0.25 mm); ir (CCl_4) 1735 (s), 1665 (m, broad), 699 cm^{-1} (m); mass spectrum *m/e* (measured mass) 289.2032 (calcd for $C_{18}H_{27}NO_2$, 289.2041).

Grignard Addition to TMBI. The addition of Grignard reagents was performed in an identical manner with that of the lithium reagents. The results are recorded in Table III. Two typical experiments are given.

3-Methyl-2-oxopentanoic Acid. The Grignard reagent of 2-bromobutane was prepared in the usual manner from 3.62 g (0.150 mol) of magnesium and 20.6 g (0.150 mol) of 2-bromobutane in 150 ml of tetrahydrofuran. To this solution was added 10.4 g (0.75 mol) of TMBI and the mixture was stirred for 4 hr. This solution was transferred under a nitrogen atmosphere to an addition funnel and then added to an ether solution which had been cooled to −78° and saturated with carbon dioxide. After the solution had warmed to room temperature, the mixture was hydrolyzed with dilute hydrochloric acid by refluxing for 15 min. The solution was then extracted with sodium bicarbonate solution, and after acidification of the aqueous layer and extraction with ether, the organic layer was dried over sodium sulfate. Evaporation of the ether gave an oil (7.5 g) which on analysis by nmr gave a yield of 48% 3-methyl-2-oxopentanoic acid and 32% 2-methylbutyric acid. The α-keto acid gave ir (neat) 3410, 2970, 2930, 2870, 1785, 1715, 1510, 1460, 1381, 1340, 1165, 1040, 980, 950 cm^{-1}; nmr (CCl_4) 1.1 (m, 6 H), 1.58 (m, 2 H), 3.28 (m, 1 H), 11.62 (s, 1 H).

1-*d*-2-Methylbutyraldehyde. The Grignard reagent of *sec*-butyl bromide was prepared in the usual manner from 3.62 g (0.150 mol) of magnesium and 20.6 g (0.150 mol) of *sec*-butyl bromide in 150 ml of tetrahydrofuran. To the Grignard solution was added, by means of a syringe, 14.2 g (0.102 mol) of 1,1,3,3-tetramethylbutyl isocyanide and the mixture was stirred at room tempera-

ture for 4 hr. To the solution cooled at 0° was added 6.1 g (0.306 mol) of D_2O followed by an additional 100 ml of water. After extraction with 2 × 100 ml of diethyl ether, the organic layer was washed with a saturated sodium chloride solution and dried over sodium sulfate. After evaporation of the ether the aldimine was distilled, yielding 13.65 g (0.0695 mol, 67.75%), bp 52-54° (1.5 mm).

Steam distillation of the aldimine from 17.2 g (0.14 mol) of aqueous oxalic acid gave 5.85 g (0.069 mol, 67%) yield of *l-d*-2-methylbutyraldehyde. The per cent deuterium incorporation was determined by nmr at δ 9.54 to be 96%.

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Registry No.—*sec*-BuBr, 78-76-2; *t*-BuBr, 507-19-7; $CH_3(CH_2)_5Br$, 111-25-1; BuBr, 109-65-9; $PhCH_2CH_2Br$, 103-63-9; cyclopentyl bromide, 137-43-9; *l-d*-2,2-dimethylpropanal, 41162-98-5; 3-heptanone, 106-35-4; 1-hydroxy-1-phenylbutanone, 16183-45-2; 2-hydroxy-4-octanone, 49707-56-4; 2-hydroxy-4-octanone *N*-phenylcarbanilate, 49707-57-5; 2-(*N*-1-trimethylsilylpropylideneamino)-2,4,4-trimethylpentane, 49707-58-6; ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate, 49707-59-7; 2-phenyl-2-butyl isocyanide, 49707-54-2.

References and Notes

(1) This support of this work by a Public Health Service Grant No. 04065 from the National Cancer Institute and, in part, by the National Science Foundation is gratefully acknowledged.
(2) For a preliminary report see H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970).
(3) F. Sachs and H. Loevy, *Chem. Ber.*, **37**, 874 (1904).
(4) H. Gilman and L. C. Heckert, *Bull. Soc. Chim. Fr.*, **43**, 224 (1928).
(5) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 2239 (1961).
(6) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(7) This result also argues against the formation of a dimetallo aldimine RN=C(Li) CH(Li)R, since this would yield greater than 100% incorporation. However, it should be pointed out that under certain conditions lithium aldimine **1** can undergo a cleavage reaction. See M. P. Periasamy and H. M. Walborsky, *J. Org. Chem.*, **39**, 611 (1974).
(8) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).
(9) U. Schöllkopf and R. Jentsch, *Angew. Chem.*, **85**, 355 (1973), and earlier references cited therein.
(10) H. M. Walborsky, G. E. Niznik, and M. P. Periasamy, *Tetrahedron Lett.*, 4965 (1971).
(11) For a convenient synthesis see G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, *Org. Syn.*, **51**, 31 (1971).
(12) D. C. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 19.
(13) N. Koga, G. Koga, and J. P. Anselme, *Tetrahedron Lett.*, 3309 (1970).
(14) A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).
(15) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
(16) For interesting reviews see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); *Synthesis*, **1**, 17 (1969); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).
(17) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).
(18) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portney, *J. Org. Chem.*, **38**, 36 (1973), and earlier references cited therein.
(19) Mass spectral analyses were conducted under the supervision of Professor R. C. Dougherty, The Florida State University. Elemental analyses were performed by Beller Laboratories, Gottingen, Germany.
(20) Beilstein, "Handbuch der organische Chemie," Vol. 3, Friedrich Richter, Springer-Verlag, Berlin, 1959.
(21) H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 353 (1963).
(22) R. Luft, *Ann. Chim. (Paris)*, **4**, 745 (1959).

Partial Asymmetric Syntheses of Amino Acids Using Lithium Aldimine Precursors[1]

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Carboxylation or carbethoxylation of the lithium aldimines formed by the α addition of ethyllithium, *sec*-butyllithium, and isopropyllithium to (±)- or (*R*)-(+)-2-phenyl-2-butylisonitrile produced the corresponding α-imino acid or ester. Optically active α-amino acids were synthesized by the reduction, under a variety of conditions, of the α-imino acids and esters.

The use of lithium aldimines as useful synthetic intermediates for the preparation of aldehydes, α-keto acids, ketones, acyloins, α-diketones, and silyl ketones has previously been reported.[2,3] The use of lithium aldimines as precursors for the syntheses of optically active α-amino acids is the subject of this paper.

Results and Discussion

Chart I outlines the procedure used for the preparation of α-amino acids.

The α addition of *sec*-butyllithium, isopropyllithium, and ethyllithium to 2-phenyl-2-butylisonitrile (**1**) proceeds quite readily to yield the corresponding lithium aldimines (**2**). Treatment of **2** with carbon dioxide or ethyl chloroformate produced lithium imino carboxylate salt **3** and ethyl α-imino carboxylate (**5**), respectively. In contrast to the case of imines produced from α-keto acids and α-alkylbenzylamine,[4] attempted concomitant hydrogenation and hydrogenolysis of **3** by the use of palladium hydroxide[5] did not give good results. However, the direct reduction of the corresponding ester **5** did proceed, although in poor yields, to give α-amino acids. Most of the reductions in our studies were carried out in a stepwise fashion using **3** or **3*** as substrate. The double bond was first reduced with either lithium or sodium borohydride, diborane, diisopinocampheylborane, or triisopinocampheylborane and the resulting amine hydrochlorides were debenzylated by catalytic hydrogenolysis to produce the α-amino acids. These results are summarized in Table I.

The α-amino acids isolated using standard procedures[6] contained slight impurities[7] which were difficult to remove. Therefore, all optically active α-amino acids were converted into their 2,4-dinitrophenyl derivatives[8] and purified, without attempted resolution, by use of a Celite column.[9] The diastereomeric ratio of racemic isoleucine to alloisoleucine (R = *sec*-butyl) was determined by nmr based upon the α-methine proton absorptions.[10] Catalytic reduction of **5** gave a mixture (ratio 1.3) in which isoleucine predominated, whereas stepwise reduction gave a mixture (ratio 0.7) richer in alloisoleucine. As can also be seen (Table I) the direct hydrogenation and hydrogenolysis of the imino ester **5** or **5*** is not a very satisfactory method, since one obtains a low overall yield and a very small optical induction. The stepwise reduction of **3** or **3*** is the preferred method since the optical yields are reasonably good. It should be recognized that since lithium borohydride and diborane exhibit similar stereoselectivities in the reduction of **3***, the former is obviously the re-