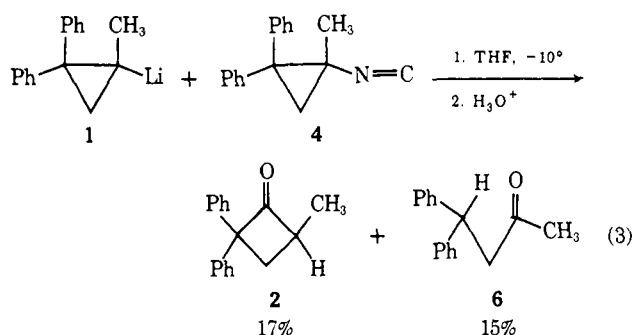
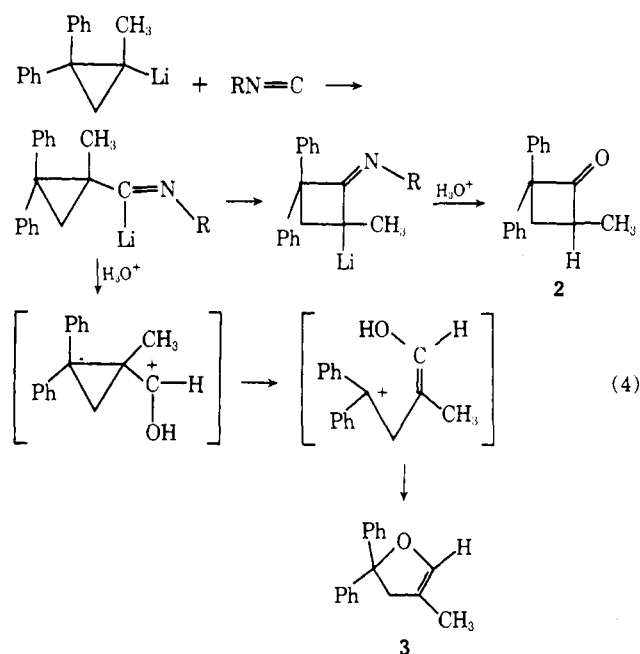


gested that they both may have originated from a common intermediate. The hypothesis, which was adopted, is illustrated in Chart I.

The intermediate 9 is a logical precursor of 2 and 6 and the anionic addition to the ketenimine 8 to form 9 is reasonable. Protonated 9 could not be isolated and purified; however, the spectral data of the crude mixture (see Experimental Section) showed the presence of a compound of mass 441 whose nmr spectrum contained the characteristic benzhydryl triplet at δ 4.44 and the adjacent methylene doublet at δ 2.94, imitating the pattern found in the nmr spectrum of 6. To test the validity of the hypothesis that 1 added to 4 *via* an α addition, the cyclopropyllithium compound was prepared from 1-bromo-1-methyl-2,2-diphenylcyclopropane in ether. This solution was added to the cyclopropyl isocyanide 4 to give, after hydrolysis, the two ketones 2 and 6 (eq 3).

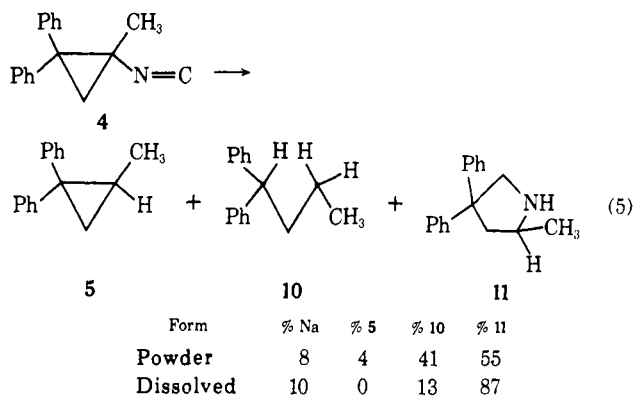


The results represented in eq 1 can be rationalized in the following way (eq 4).



The cyclopropyllithium 1 adds to form the lithium aldime intermediate, which undergoes ring enlargement to form the lithiocyclobutanone imine. The formation of 3 probably results from hydrolysis of a small amount of the lithium aldimes as shown. This pathway to 3 was verified by treating 2,2-diphenyl-1-methylcyclopropanecarboxaldehyde with acid to give 3. The results illustrated in eq 1 together with 3 indicate that 1 is the origin of 2 and that 4 is the precursor to 6.

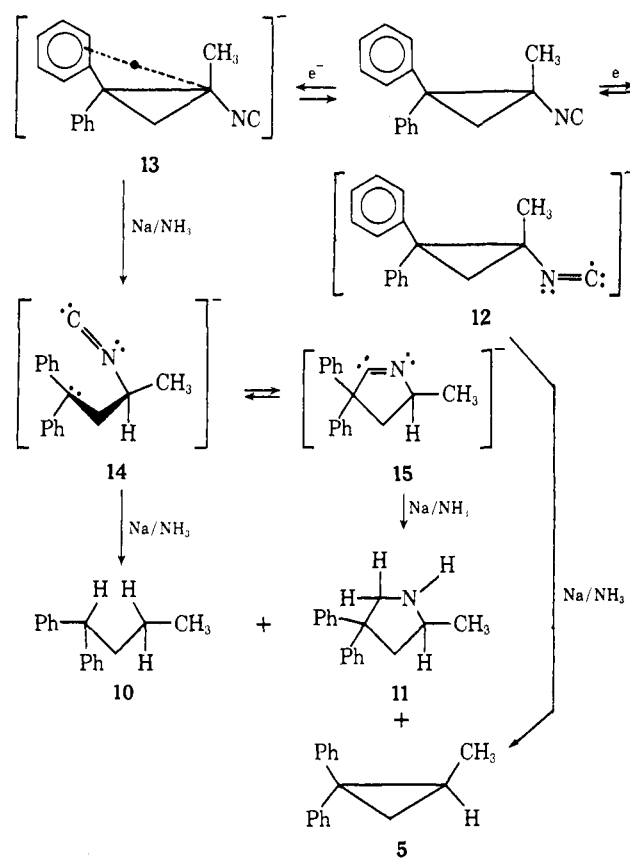
Another novel ring expansion was observed when the cyclopropyl isocyanide 4 was reduced with sodium in liquid ammonia (eq 5). Again the principal product was not the expected cyclopropane 5. Instead, 1,1-diphenylbutane (10) and 3,3-diphenyl-5-methylpyrrolidine (11) were ob-



tained as the major products. One can rule out the fact that 10 may have arisen as a result of Birch reduction of the cyclopropane 5, for it had already been shown that under the conditions used in this experiment (8–10% Na) no ring-opened products are produced.^{5b}

To explain the product mixture it is proposed (Chart II) that two radical anions are produced as primary interme-

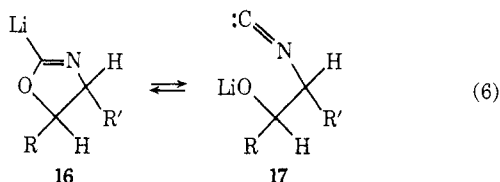
Chart II
Reduction of 2,2-Diphenyl-1-methylcyclopropyl Isocyanide



diates, 12 and 13. In ether solvents an electron transfer occurs at the isocyanide site to give the expected radical anion, 12. Further reduction gives the expected cyclopropane 5. However, in the liquid ammonia system, we feel that solvation at the isocyanide site raises the potential of the system so that the preferred site for the electron transfer is at one of the aromatic phenyl groups to produce the radical anion 13. A similar occurrence was also observed during the study of the reduction of 1-fluoro-2,2-diphenyl-1-methylcyclopropane.⁶

Reductive cleavage of 13 yields 14, the ring-opened carbanion, which is in equilibrium with the cyclic imino carbanion 15. This assumption of a reversible α addition of the diphenyl carbanion to the isocyanide function is

supported by the work of Gerhart and Schöllkopf,⁷ who found that the lithium oxazoline 16 is in equilibrium with the ring-opened 17 (eq 6). This reversibility was also ob-



served by Meyers and Collington.⁸ Further reduction of 14 and 15 would give the observed products 1,1-diphenylbutane (10) and the pyrrolidine 11. The small amount of the cyclopropane 5 could be accounted for by the alternate pathway through the radical anion 12. It should be noted that in Chart II the α -addition step serves as a means of trapping the intermediate 14, which could not have otherwise been identified.

Experimental Section⁹

Reaction of 2,2-Diphenyl-1-methylcyclopropyllithium with 1,1,3,3-Tetramethylbutyl Isocyanide (TMBI). To a stirred solution of 1.22 g (0.0043 mol) of 2,2-diphenyl-1-methylcyclopropyl bromide in 40 ml of ether was added 0.0049 mol of *sec*-butyllithium (in hexane) at 0°. After stirring for an additional 15 min, the temperature was lowered to -10° and 0.68 g (0.0049 mol) of TMBI¹⁰ was added. The reaction mixture was stirred for 18 hr, followed by addition of 0.5 ml of methanol. The mixture was taken up in ether, extracted with water, and dried over sodium sulfate. Evaporation yielded in oil (1.52 g) which was hydrolyzed in dilute hydrochloric acid-tetrahydrofuran. The mixture was then taken up in ether and washed with water and sodium carbonate solution, and vpc analysis (SE-33) of this solution showed four components, corresponding to 1,1-diphenyl-2-methylcyclopropane (44%), 2,2-diphenyl-4-methylcyclobutanone (46%), 2,2-diphenyl-1-methylcyclopropyl bromide (6%), and 3-methyl-5,5-diphenyldihydrofuran (4%), which were identified by peak enhancement with authentic materials.

Lithium Metal Reduction of (*R*)-(-)-2,2-Diphenyl-1-methylcyclopropyl Isocyanide. A mixture of 2.5 g of lithium dispersion (30% in wax, fine mesh) was washed with hexane and then with portions of THF under argon¹¹ so that only fine particles of clean lithium remained floating over the clear solvent. The solvent was drained and the lithium was washed into the reaction vessel (containing ground glass and a polyethylene-coated magnetic bar) with 30 ml of DME. The surface of the lithium particles was polished by stirring the suspension vigorously at 25° for 2 hr; then at a temperature of -10°, 0.395 g of the optically pure cyclopropyl isocyanide (powder) was added. After 10 min the deep red solution was decanted from the unused lithium to a flask of cold methanol. The reaction mixture was taken up into ether and washed several times with water. The ether layer was dried (sodium sulfate) and then concentrated to an orange paste: ir (neat) 1720-1620 (w, broad) 1374 (w), 1355 (w), 692 (s), 671 cm⁻¹ (s); nmr (CCl₄) δ 0.8-1.4 (m, broad), 1.83 (s), 2.6 (m), 2.94 (d, $J = 7$ Hz, CH₂CH), 4.44 (t, $J = 7$ Hz, CH₂CH), 7.03 (s, aromatic), 7.16 (s, aromatic); mass spectrum m/e 441 (parent). The orange paste was hydrolyzed with dilute hydrochloric acid in tetrahydrofuran, and the products were extracted into ether, dried over anhydrous sodium sulfate, and evaporated to yield 0.381 g of an oil. Vpc analysis (15% SE-33 on 80/100 Chromosorb P, AW) showed three major products: 2, 5 [(*R*)-(+)-2,2-diphenyl-1-methylcyclopropane], and 6. The hydrocarbon 5 was identified by comparison with the ir and nmr spectra of the authentic material and by vpc peak enhancement (20% EGIP on 80/100 Chromosorb P, AW), $[\alpha]_D^{25} +18.0 \pm 0.5^\circ$. The ketone 6 showed the following properties: ir (CCl₄) 1720 cm⁻¹ (s) (lit.¹¹ 1715 cm⁻¹); nmr (CDCl₃) δ 2.06 (s, 3, CH₃), 3.20 (d, $J = 7.5$ Hz, CH₂), 4.71 (t, $J = 7.5$ Hz, CH), 7.42 (s, 10, aromatic); 2,4-DNP mp 173-175° (lit.¹² mp 174-175°). The cyclobutane 2 showed the following properties: ir (CCl₄) 1783 (s), 1494 (m), 1450 (m), 692 cm⁻¹ (s); nmr (CDCl₃) δ 1.32 (d, 3, $J = 7$ Hz, CH₃), 2.37 (m, 1, $J_{AB} = 10.5$, $J_{AX} = 8$ Hz, HCH), 3.09 (m, 1, $J_{AB} = 10.5$, $J_{BX} = 10.5$ Hz, HCH), 3.32 (m, 1, CH), 7.0-7.5 (m, 10, aromatic); ir irradiation at δ 1.32, 3.32 (m, $J_{AX} = 8$, $J_{BX} = 10.5$ Hz); irradiation at δ 3.32, 2.37 (d, $J_{AB} = 10.5$ Hz); mass spectrum m/e (calcd mass) 235.1199 (calcd for C₁₇H₁₆O, 236.1200),

237.1219 (calcd for C₁₆¹³CH₁₆O, 237.1234), 208.1274 (calcd for C₁₆H₁₆, 208.1292), 181.1020 (calcd for C₁₄H₁₃, 181.1017), 166.0778 (calcd for C₁₃H₁₀, 166.0782); 2,4-DNP mp 207-208°.

Addition of 2,2-Diphenyl-1-methylcyclopropyllithium to 2,2-Diphenyl-1-methylcyclopropyl Isocyanide. From 1.2 g (0.0042 mol) of 1-bromo-2,2-diphenyl-1-methylcyclopropane a solution of the cyclopropyllithium was prepared in 30 ml of ether¹³ under an argon atmosphere. The cyclopropyllithium solution was then filtered into a 60-ml THF solution (-10°) of 0.671 g (0.0028 mol) of 2,2-diphenyl-1-methylcyclopropyl isocyanide. The mixture was stirred for 1 hr, quenched with methanol, and washed with water. The organic layer was dried (sodium sulfate) and evaporated to a viscous oil. The oil was dissolved into 80 ml of hexane with heating. Upon cooling, the unreacted isocyanide separated as crystals. The hexane solution was decanted, and the crystals were dried, 0.56 g, mp 115-123°, ir (CHCl₃) 2240 cm⁻¹ (s). The hexane solution was evaporated, the concentrate was hydrolyzed in dilute hydrochloric acid-tetrahydrofuran solution for 20 min and taken up in ether, and the ether was washed several times with water. After drying (sodium sulfate), the ether solution was concentrated yielding 0.246 g of an oil. Vpc analysis of the oil (SE-33, silastic LS-40) gave the following composition: 2,2-diphenyl-4-methylcyclobutanone (17%), 4,4-diphenylbutanone (15%), 1-bromo-2,2-diphenyl-1-methylcyclopropane (47% together with some 2,2-diphenyl-1-methylenecyclopropane as impurity).

Acidic Rearrangement of 2,2-Diphenyl-1-methylcyclopropanecarboxaldehyde. To a solution of 0.82 g of 2,2-diphenyl-1-methylcyclopropanecarboxaldehyde¹⁴ in 20 ml of tetrahydrofuran was added 0.5 ml of concentrated sulfuric acid at 25°. The mixture was swirled and left to stand overnight in a stoppered vessel. The contents were then poured into water (0°) and extracted. The ether layer was dried over sodium sulfate and then concentrated to give 0.81 g of a viscous oil: ir (neat) 2930 (m), 1487 (m), 1444 (m), 1378 (m), 1004 (s), 1694 cm⁻¹ (s); nmr (CCl₄) δ 1.53 (s, 3, CH₃), 3.16 (s, 2, CH₂), 6.14 (s, 1, C=CH), 7.0-7.4 (m, 10, aromatic); mass spectrum m/e (calcd mass) 236.1208 (calcd for C₁₇H₁₆, 226.1200).

Sodium Metal Reduction of 2,2-Diphenyl-1-methylcyclopropyl Isocyanide in Liquid Ammonia. An 8% sodium in liquid ammonia solution (45 ml) was prepared according to the procedure of Pierce and Walborsky.¹⁵ To this solution was added 0.2 g of the isocyanide with stirring. The mixture was then cooled with a Dry Ice-acetone bath as 20 ml of saturated ammonium chloride solution was added dropwise. After addition of hexane, the ammonia was evaporated. The contents of the reaction vessel were separated, and the hexane layer was washed with dilute hydrochloric acid and dried over magnesium sulfate. Evaporation of the solvent gave 0.076 g of a hydrocarbon mixture which, from vpc analysis (20% EGIP on 80/100 Chromosorb P, AW) by peak enhancement with authentic materials was composed of 1,1-diphenyl-2-methylpropane (0.4%). The acidic layer was neutralized with sodium hydroxide solution (0°) yielding an amine which was taken up in ether and dried over sodium sulfate. Evaporation gave 3,3-diphenyl-5-methylpyrrolidine (0.015 g): ir (neat) 3320 (broad), 1491 (s), 1444 (s), 1370 (m), 1028 (m), 689 cm⁻¹ (s); nmr (CCl₄) δ 1.04 (d, 3, $J = 6$ Hz, CH₃CH), 1.59 (s, 1, NH), 1.86 (q, 1, $J_{ab} = 12$, $J_{ax} = 9$ Hz, HCHCH), 2.50 (q, 1, $J_{ab} = 12$, $J_{bx} = 6$ Hz, HCHCH), 2.80-3.65 (m, 3), 6.99 (s, 10, aromatic); nmr (addition of D₂O) δ 1.59 (disappearance of singlet NH), irradiation at 1.04, 3.32 (q, $J_{ax} = 9$, $J_{bx} = 6$ Hz, HCHCHCH₃), 3.41 (d, $J_{a'b'} = 11.5$ Hz, H'CH'), 3.66 (d, $J_{a'b'} = 11.5$ Hz, H'CH'); mass spectrum m/e (calcd mass) 238.1571 (calcd for C₁₆¹³CH₁₉N, 238.1550), 237.1517 (calcd for C₁₇H₁₉N, 237.1517), 193.1026 (calcd for C₁₅H₁₃, 193.1017), 167.0868 (calcd for C₁₃H₁₁, 167.1860), 133.0898 (calcd for C₉H₁₁N, 133.0890).

1-(*p*-Nitrobenzoyl)-3,3-diphenyl-5-methylpyrrolidine. The above 3,3-diphenyl-5-methylpyrrolidine was treated with *p*-nitrobenzoyl chloride in the usual manner: mp 146.5-148°; ir (CHCl₃) 2995 (m), 1361 (s), 1600 (s), 1524 (s), 1494 (m), 1351 cm⁻¹ (s); nmr (CHCl₃) δ 0.99 (d, 0.25, $J = 6$ Hz, CH₃CH) and 1.48 (d, 0.75, $J = 6$ Hz, CH₃CH), 2.30 (q, 1, $J_{ab} = 13$, $J_{ax} = 10$ Hz, HCHCH), 3.07 (q, 1, $J_{ab} = 13$, $J_{bx} = 7$ Hz, HCHCH), 3.5-4.5 (m, 3), 6.9-7.5 (m, 10, Ph₂C), 7.65 (d, 2, $J = 8.6$ Hz, 2,6-H), 8.24 (d, 2, $J = 8.6$ Hz, 3,5-H).

Anal. Calcd for C₂₄H₂₂N₂O₃: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.63; H, 5.77; N, 7.25.

Registry No.—1, 50259-68-2; 2, 50259-69-3; 2, 2,4-dinitrophenylhydrazones, 50259-70-6; 3, 50259-71-7; 4, 32528-88-4; 5, 17413-48-8; 6, 5409-60-9; 11, 50259-75-1; 1-(*p*-nitrobenzoyl)-3,3-diphenyl-5-methylpyrrolidine, 50259-76-2.

References and Notes

- (1) The support of this work by grants from the National Science Foundation, a Public Health Service Grant No. 04065 from the National Cancer Institute, is gratefully acknowledged.
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Isocyanides. Dissociation of Metallo Aldimines

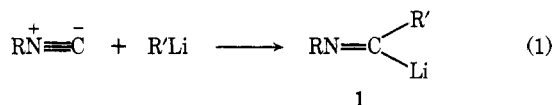
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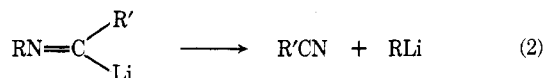
Metallo aldimines were prepared by the addition of organolithium reagents to *tert*-butyl isocyanide, 1,1,3,3-tetramethylbutyl isocyanide, 2-phenyl-2-butyl isocyanide, and triphenylmethyl isocyanide. The reactions of organolithium reagents, Grignard reagents, and organocopper reagents with triphenylmethyl isocyanide are discussed in detail. A new synthetic route for the formation of secondary and tertiary nitriles is described as is a simple and convenient method for the preparation of ketones. The lithium aldimines were converted to copper aldimines by treatment with cuprous iodide. Studies on the dissociative nature of metallo aldimines indicated that both relief of steric crowding (steric effect) and formation of stable intermediates (electronic effect) are the driving forces for the dissociation.

Recent reports on the reaction of isocyanides with organometallic reagents have shown that the chemistry of isocyanides can provide new synthetic pathways to a variety of molecules. It has recently been reported¹ that the α addition of an organolithium reagent to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) yields lithium aldimine (1), which can be used for the preparation of aldehydes, ketones, α -keto acids, and α - and β -hydroxy ketones (eq 1).



The reactions of α -metalated isocyanides are being investigated by Schöllkopf and others.^{2,3} In addition, the synthetic applications of copper-isocyanide complex catalyzed reactions for the preparation of a variety of compounds have been explored by Saegusa.⁴

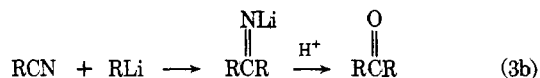
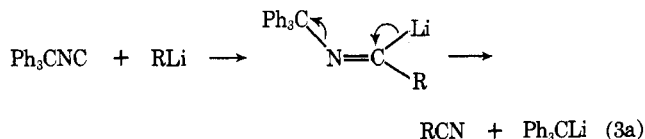
During the course of investigating the synthetic utility of lithium aldimines it was discovered that certain aldimines dissociated to produce nitriles in very good yields⁵ (eq 2). Preliminary investigations indicated that an 88%



yield of *tert*-butyl cyanide could be achieved by the addition of the *tert*-butyllithium to triphenylmethyl isocyanide (TPMI). However, the use of other lithium reagents produced the corresponding symmetrical ketones which apparently results from the addition of RLi to the nitrile formed (eq 3b).

A detailed study, with an aim of establishing the scope and limitations of this "isocyanide-metal exchange" reaction⁵ was undertaken and is the subject of this paper.

Isocyanide-Metal Exchange Reaction. The isocyanide-metal exchange reaction (eq 3a) showed promise as a new method for the preparation of nitriles and ketones. An investigation of the scope and limitation of this reac-



tion was undertaken. The results obtained in Table IV clearly point to triphenylmethyl isocyanide (TPMI) as the isocyanide of choice, and it was therefore selected for our studies.

Reactions with Organolithium Reagents. The results of the reactions of a representative set of organolithium reagents with TPMI are given in Table I.⁵ It is evident that this reaction provides a convenient method for the preparation of symmetrical ketones and hindered nitriles such as *tert*-butyl cyanide in high yield. Unsymmetrical ketones can also be prepared by the simple expediency of first adding 1 equiv of the more hindered lithium reagent to permit the exchange reaction (eq 3a) to occur, followed by the addition of the less hindered lithium reagent. Using this procedure, *tert*-butyl *sec*-butyl ketone was prepared in 83% yield. It is worth mentioning that by careful work-up of the reaction mixture (see Experimental Section) one can isolate the precursor ketimine in excellent yields. For example, di-*tert*-butyl ketimine was obtained in 77% yield.⁶ Lithium phenylacetylide, owing to an unfavorable equilibrium, did not add to TPMI.

The associated nature of organolithium reagents^{7,8} may increase the probability of the immediate availability of lithium reagents for further addition to the nitrile as it is formed in the reaction. The observation that the yield of nitrile increased on going from primary to tertiary lithium reagent indicates that steric hindrance also becomes an important factor so that α addition of *tert*-butyllithium to TPMI is favored over its addition to the nitrile formed in