Activation of the Carbon–Nitrogen Double Bond by Copper(I)

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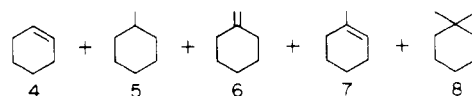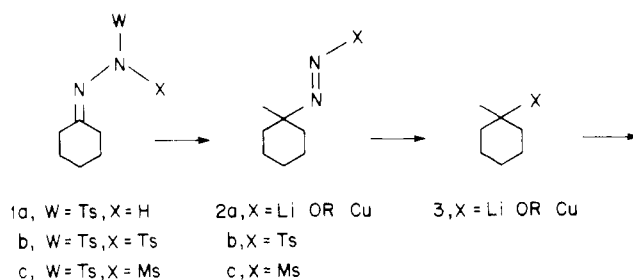
Ketone tosylhydrazones are converted to olefins by the action of lithium reagents in the well-known Shapiro reaction.[1] However, variable amounts of addition products have been observed, and in special cases the addition reaction predominates.[2] In a study intended to find general experimental conditions which favor this addition, it has been discovered that Cu(I) activates the CN double bond toward the nucleophilic addition of a lithium reagent.
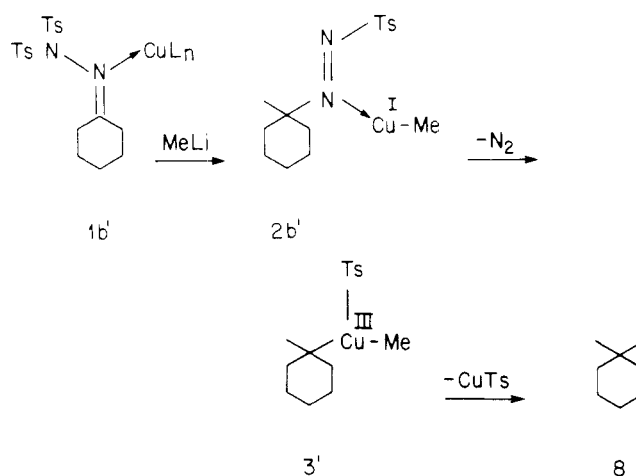
The methylation of **1a–c** by dilithium trimethylcuprate[3] in diethyl ether vividly illustrates this effect (Scheme I). The combined yield of products generated by addition to the CN double bond of these compounds is 2–3 times greater when Cu(I) is present (Table I, entries 5, 9, and 14) than when only MeLi (as a LiBr complex) is the reagent (entries 1, 7, and 13). The presence of extra LiI does not increase the percentage of addition (entries 2, 3, and 8) nor does the use of salt-free reagent decrease it (entry 6). This behavior stands in contrast to that of the carbon–oxygen double bond, the activation of which by the Macdonald–Still reagent is due to complexation by lithium,[4] an effect which is disrupted by tetrahydrofuran (THF). In the present case, the effect of Cu(I) also disappears upon the addition of THF, presumably because THF preferentially complexes the Cu(I). Stable transition metal–hydrazone complexes are known[5] in which the bonding (to the lone pair on the N of the CN double bond) is analogous to that which is postulated here for the Cu-(I)–hydrazone interaction (Scheme II). Only traces of **4–8** are observed when Me₂CuLi alone is present, and the amount of Me₃CuLi₂ can be reduced to 1 equiv, provided that an additional equivalent of MeLi is added. With a threefold excess of MeLi, the yield of reductive alkylation product (**5**) obtained upon quenching with acid is 46%, which is comparable to those of Herz[2a] and Vedejs.[2c] When the same reaction mixture is quenched with MeI, only 23% of **8** is produced, the difference being due to proton abstraction by **3** (X = Li) from the medium. Sixty percent of the **5** produced when the reaction of **1b** with Me₃CuLi₂ is performed in ether-d_{10} is labeled with deuterium at the 1 position.[6]

The fact that a mixture of products is formed precludes synthetic utility in the case of the ditosyl- and mesyltosylhydrazones; however, a number of novel mechanistic observations can be made. The formation of **8** represents the first observation of a gem-dialkylated product directly from the reaction of a lithium reagent with a tosyl- or ditosylhydrazone derivative.[7] In the case of **1b**, **8** cannot be formed as a result of the thermal decomposition of a

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(2) (a) J. E. Herz and C. V. Ortiz, *J. Chem. Soc. C*, 2294 (1971); (b) R. H. Shapiro and T. Gadek, *J. Org. Chem.*, **39**, 3418 (1974); (c) E. Vedejs and W. T. Stolle, *Tetrahedron Lett.*, 135 (1977); (d) E. Vedejs, J. M. Dolphin, and W. T. Stolle, *J. Am. Chem. Soc.*, **101**, 249 (1979).
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(6) Determined by ¹³C NMR in the presence of Cr(acac)₃.
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Scheme I

1a, W = Ts, X = H	2a, X = Li OR Cu	3, X = Li OR Cu
b, W = Ts, X = Ts	b, X = Ts	
c, W = Ts, X = Ms	c, X = Ms	

Scheme II

mixed Cu(I) intermediate containing methyl and 1-methylcyclohexyl groups, since the yield of **8** from **1a** under the same conditions is much lower. The product conceivably arises by reductive elimination from a Cu(III) species analogous to those implicated in the coupling of cuprates with alkyl halides[8] (Scheme II). The intervention of free radicals[9] is excluded by the generation of the 1-methylcyclohexyl radical in the presence of Me₃CuLi₂ by the photolysis (350 nm) of bis(1-methylcyclohexyl)diazene (**9**), which yields <1% of **8**. Decomposition of the cuprate does not occur upon irradiation at long wavelengths of light.[10] Of the volatile products **4–8**, only **4** was detected using diazocyclohexane as the substrate. A copper carbenoid is therefore not an intermediate in the formation of **5–8**.

The olefins **6** and **7** may be attributed in part to β-hydride elimination[11] from a 1-methylcyclohexylcuprate, **3** (the Cu of which undoubtedly bears other ligands), but other phenomena such as a base-induced elimination of Ts⁻ (and N₂) from **2**(**b** or **c**) or the reductive elimination of **7** from a (cyclohexenyl)methylcuprate also must be operating to account for the observed variations in regioselectivity in the formation of **6** and **7**. When such a mixed cuprate is prepared from 1-cyclohexenyllithium, the

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Table I. Reaction of Hydrazones (1) with MeLi and Me₃CuLi₂

entry no.	substrate	reagent, conditions[a]	yield[b] of product,[c] %					sum 4–8	sum addn[d]
			4	5	6	7	8		
1	1a	4MeLi[e]	38	17	<1	5	<1	60	22
2	1a	4MeLi + 3LiI	43	10	<1	2	<1	55	12
3	1a	4MeLi + 8LiI	39	9	<1	3	<1	51	12
4	1a	4Me₃CuLi₂[f]	24	33	2	5	3	67	38
5	1a	1Me₃CuLi₂ + 1MeLi[g]	36	41	<1	3	2	82	43
6	1a	1Me₃CuLi₂ + 1MeLi, salt free	46	39	6	7	1	99	46
7	1b	3MeLi	<1	5	9	4	<1	18	18
8	1b	3MeLi + 3LiI	<1	2	2	12	<1	16	16
9	1b	3Me₃CuLi₂	31	29	5	9	15	89	49
10	1b	3Me₃CuLi₂, 0 °C	19	15	4	8	26	72	45
11	1b	3Me₃CuLi₂, −40 °C	1	6	4	2	24	37	34
12	1b	3Me₃CuLi₂, −70 °C	<1	10	3	1	13	27	26
13	1c	3MeLi	44	8	4	1	<1	57	13
14	1c	3Me₃CuLi₂	34	22	15	6	6	83	43

[a] All experiments were run for 20 h at 25 °C, unless otherwise noted. [b] Determined by GLC calibrated with an internal standard. [c] Confirmed by GC-MS comparison with authentic samples. [d] 5 + 6 + 7 + 8; except when Cu is present, 5 + 6 + 8. [e] MeLi contains equimolar LiBr, unless otherwise stated. [f] Me₃CuLi₂ contains 1 equiv of LiI and 3 equiv of LiBr, unless otherwise stated. [g] Reagent added to lithium salt generated in situ (1a + MeLi).

amount of coupling after 20 h is 26%; therefore, virtually all of the **7** observed in the presence of Cu is due to this reaction. Control experiments preclude the equilibration of **6** and **7** under the reaction conditions.

Compound **4** is simply the product of the Shapiro reaction. The formation of **4** from **1b** and **1c** indicates that the cleavage of a tosyl group to give **1a** is competing with the addition reaction and effectively limiting the yield of **8** even at low temperatures. For this reason, the yield of **8** at −40 °C (entry 11) did not improve with longer reaction times. No 3-methylcyclohexene or 2-methylcyclohexanone tosylhydrazone can be detected in any reaction mixture, nor is any **4** detected when 1-tosylazocyclohexene decomposes at 25 °C in the presence or absence of CuI. Azoene intermediates are therefore not important in the chemistry of **1a–c**, as they apparently are in that of cyclododecanone ditosylhydrazone.[7]

This study indicates that the low yields or lack of specificity observed in a number of cases[12] of addition of lithium reagents to CN double bonds might be improved by the inclusion of copper(I). Considering the abundant variety of organic compounds which contain carbon–nitrogen double bonds, the activation of this functional group by copper(I) to nucleophilic addition should find many synthetic applications, especially in view of the rapid development of organocuprate chemistry.

Experimental Section

A Varian T60 or Bruker WH90 spectrometer was used to measure NMR spectra; Me₄Si was the internal standard. Melting points were measured with a Mettler FP5 and are uncorrected. GLC analyses were performed on a Varian Aerograph 1520 with a Model 475 integrator. Photolysis was done in a Rayonet Reactor. Low temperatures were maintained with a Neslab CryoCool II refrigerator.

Cyclohexanone tosylhydrazone,[13] cyclohexanone azine,[14] diazocyclohexane,[15] 1-tosylazocyclohexane,[16] and 1-cyclohexenyllithium[17] were prepared by the literature methods.

Cyclohexanone Ditosylhydrazone.[7] A 2.8-g (58 mmol) quantity of 50% NaH in mineral oil was weighed into a 250-mL

three-neck flask, which was flushed with N₂ and fitted with a N₂ inlet and two rubber septa. The NaH was washed free of mineral oil with 20 mL of dry THF, used in three portions, and suspended in 50 mL of N-methylpyrolidinone (Aldrich, dried over 5A molecular sieves). The magnetically stirred suspension was cooled to 0 °C, and 13.3 g (50 mmol) of **1a** was added in six portions over a period of 30 min. The ice bath was removed for 30 min and then replaced before 10.0 g (52 mmol) of p-toluenesulfonyl chloride was added during 1 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The slow addition of water to the rapidly stirred solution gave a tan precipitate which was filtered off, washed with water, and dried in a vacuum desiccator over P₂O₅ to give 16.9 g of crude product, recrystallization of which from 300 mL of methanol yielded 14.0 g (67%): mp 153–155 °C; ¹H NMR (CDCl₃) δ 1.40–2.00 (6 H, m), 2.38 (6 H, s), 2.30–2.80 (4 H, m), 7.15 (4 H, d, J = 8 Hz), 7.63 (4 H, d, J = 8 Hz).

Anal. Calcd for C₂₀H₂₄N₂S₂O₄: C, 57.12; H, 5.75; N, 6.66; S, 15.25. Found: C, 57.12; H, 5.86; N, 6.73; S, 15.10.

Cyclohexanone Mesyltosylhydrazone.[18] A 2.66-g (10 mmol) portion of **1a** was dissolved in 10 mL of 1 M NaOH in a 50-mL three-neck flask equipped with two addition funnels, a N₂ inlet, and a magnetic stirring bar. The rapidly stirred solution was treated alternately with 2 mL of 1 M NaOH and 1 mL of a solution of 1.0 mL (13 mmol) of methanesulfonyl chloride (Aldrich) in 5 mL of THF until a total of 10 mL of 1 M NaOH and all of the MsCl solution had been added dropwise over 40 min. The white precipitate which formed was filtered off after an hour of rapid stirring, washed with water, and dried in vacuum to give 2.63 g of crude product, recrystallization of which from 20 mL of methanol yielded 2.39 g (69%): mp 119.6–120.2 °C; ¹H NMR (CDCl₃) δ 1.50–2.00 (6 H, m), 2.47 (3 H, s), 2.33–2.80 (4 H, m), 2.90 (3 H, s), 7.34 (2 H, d, J = 9 Hz), 7.87 (2 H, d, J = 9 Hz).

Anal. Calcd for C₁₄H₂₀N₂S₂O₄: C, 48.82; H, 5.85; N, 8.13; S, 18.62. Found: C, 48.84; H, 5.84; N, 8.07; S, 18.98.

Bis(1-methylcyclohexyl)diazene.[19] Cyclohexanone azine (9.6 g, 50 mmol) dissolved in 200 mL of Al₂O₃-dried CH₂Cl₂ in a 300-mL round-bottom flask was stirred magnetically at dry ice temperature, and Cl₂ was bubbled in until a deep yellow color developed (not the first light yellow coloration) and the rate of escape of the bubbles increased. Rotary evaporation gave a yellow oil which solidified under vacuum. The crude product was dissolved in 100 mL of Al₂O₃-dried hexane and cooled to dry ice temperature under N₂ before adding 50 mL of 25% Me₃Al (hexane solution, Alfa). The reaction mixture was allowed to warm to room temperature and stirred overnight. Ethanol (15 mL) was added dropwise with ice cooling of the reaction mixture, and then 50

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(19) See also J. Hinz and C. Ruechardt, *Justus Liebigs Ann. Chem.*, **765**, 94 (1972); W. Duismann, H.-D. Beckhaus, and C. Ruechardt, *Tetrahedron Lett.*, 265 (1974).

mL of 10% H_2SO_4 was added. The organic layer was separated, and the aqueous layer was extracted with two 100-mL portions of ether. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product, which was chromatographed on 100 g of neutral Al_2O_3. The third and fourth 50-mL fractions yielded 9.03 g (81%) of light yellow liquid upon rotary evaporation and oil pump evacuation: ^1H NMR ($CDCl_3$) δ 0.97 (3 H, s), 1.47 (8 H, s, broad), 1.75–2.25 (2 H, complex m).

Reaction of 1a–c with Me_3CuLi_2. General Procedure. The 25-mL round-bottom flasks used were rinsed with concentrated HNO_3, water, concentrated NH_4OH, water, Alconox solution, distilled water, and acetone. They were dried in an oven (120 °C) and, immediately before use, in a Bunsen burner flame. After the flasks were cooled in a desiccator over P_2O_5, small stirring bars were added to them, they were charged with 0.25–0.50 mmol of substrate and flushed with N_2, and a rubber septum was fastened on with wire. A 30-μL volume of n-nonane was injected (all substances were weighed to the nearest 0.1 mg), and the flask was cooled to dry ice temperature under N_2. Ether (2.5 mL, freshly distilled from sodium benzophenone ketyl) was added by syringe followed after 30 min by 2.5 mL of 0.30 M ethereal Me_3CuLi_2, prepared at –20 °C from 570 mg of CuI (Alfa, ultrapure grade) and 7.2 mL of 1.25 M ethereal MeLi–LiBr diluted to 10.0 mL. After being stirred rapidly for several minutes at –70 °C, the reaction mixtures were warmed to their final temperatures and stirred for 20 h. Quenching with 1 mL of 2 M HCl (deoxygenated with N_2) and drying the ether layer by passing it through a Pasteur pipet plugged with a small wad of cotton and containing a layer of anhydrous Na_2SO_4 over Celite gave the product solution which was analyzed by GLC. With a 30 mL/min flow rate of He, a 10 ft × 0.25 in. 5% OV101 on Chromosorb WHP (80–100 mesh) column at 40 °C gave the following retention times (min) for the products: 4 (3.3), 5 (4.6), 6 (5.2), 7 (6.6), 8 (7.7), and standard (22).

Photolysis of 9. A mixture of 26.5 mg of 9 and 21.1 mg of n-nonane in 2.5 mL of Et_2O was treated with 2.5 mL of 0.30 M Me_3CuLi_2. It was placed in a 0 °C isopropyl alcohol bath and photolyzed using the 350-nm bulbs in a Rayonet reactor. After 24 h, TLC showed some 9 still present. GLC analysis showed <1% 4, 14% 5, 3% 6, 4% 7, and <1% 8. In a companion experiment which contained no cuprate, <1% 4, 25% 5, 14% 6, 15% 7, and <1% 8 were measured. In the absence of light, none of these products were observed when Me_3CuLi_2 and 9 were stirred together.

Control experiments were performed as closely as possible to the "General Procedure". The amounts of LiI required by the stoichiometries in Table I (entries 2, 3, and 8) were added to the flasks containing the substrates in a glove bag under dry N_2, and the experiments were continued in the usual way.

Aliquots (0.25 mL) of a red solution of diazocyclohexane prepared from 176 mg of cyclohexanone hydrazone, 256 mg of Ag_2O, and 74 mg of $MgSO_4$ in 1.0 mL of alumina-dried xylenes were added to the reagents prepared from 140 mg of CuI and 0.6, 1.2, and 1.8 mL of 1.25 M MeLi. The final volumes were adjusted to 4 mL with Et_2O.

To 1.5 mL of 0.38 M 1-cyclohexenyllithium in 10 mL of Et_2O was added 3.0 mL of 0.50 M Me_3CuLi_2. The reaction mixture was stirred at room temperature under Ar; aliquots were removed and quenched with deoxygenated (N_2) water.

A mixture of 34.4 mg of 1-methylcyclohexene and 28.8 mg of n-nonane was treated with 3.0 mL of 0.25 M Me_3CuLi_2. After a day it was quenched with 1 mL of deoxygenated 2.0 M HCl. GLC analysis showed 98% starting material and <1% methylenecyclohexane. Similar treatment of a mixture of 32.3 mg of methylenecyclohexane and 29.6 mg of n-nonane gave 97% starting material and <1% isomeric olefin.
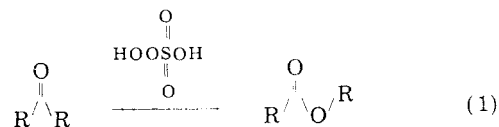
Bis(trimethylsilyl) Monoperoxysulfate: Convenient Baeyer–Villiger Oxidant

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Caro's acid or monoperoxysulfuric acid serves as a common reagent for the conversion of ketones into esters (eq 1), a reaction known as Baeyer–Villiger oxidation.[3] Some

$$R \overset{O}{\underset{}{\overset{\|}{C}}} R \xrightarrow{\underset{O}{\overset{\overset{O}{\|}}{HOOSOH}}} R \overset{O}{\underset{}{\overset{\|}{C}}} O^R \tag{1}$$

of the short comings of this important reagent in preparative applications include (i) the use of aqueous conditions, (ii) the presence of strong acid, and (iii) undesirable side reactions. Since the bis(trimethylsilyl) derivative of Caro's acid is known[4] and conveniently prepared via the reaction of sulfur trioxide with bis(trimethylsilyl) peroxide at –30 °C (eq 2), we explored the potential and utility of

$$Me_3SiOOSiMe_3 \xrightarrow[-30\ °C]{SO_3} Me_3SiO\overset{O}{\underset{O}{\overset{\|}{S}}}OOSiMe_3 \tag{2}$$
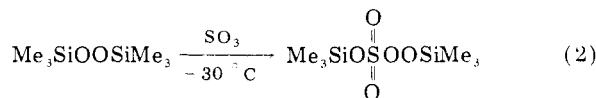
this interesting substance as a Baeyer–Villiger oxidant. The solubility of this reagent in nonprotic and nonpolar media such as methylene chloride and the bis(trimethylsilyl)-buffered sulfuric acid product that is formed after oxygen transfer constitute obvious advantages over the Caro's acid reagent.

Indeed, as the results in Table I confirm, bis(trimethylsilyl) monoperoxysulfate exhibits a great propensity as a Baeyer–Villiger oxidant. From the examples listed in the table, the reagent displays general scope, since aliphatic, aromatic, acyclic, and cyclic ketones are readily oxidized to their corresponding esters in high yield.

Some of the limitations of this novel oxidant are that α,β-unsaturated ketones react sluggishly, that double bonds are oxidized, and that aralkyl ketones such as p-bromoacetophenone are hydrolyzed to the corresponding phenols. Furthermore, as with Caro's acid, the oxidation of cyclohexanone proves problematic, affording the ω-hydroxy acid. However, in general the bis(trimethylsilyl) monoperoxysulfate affords higher yields and purer product than Caro's acid. The preparation of the potentially useful silyl reagent and the general procedure for the Baeyer–Villiger oxidation are described below.

Experimental Section

Melting points are uncorrected. NMR spectra were run on a Hitachi Perkin-Elmer R-24B instrument and IR spectra on a Perkin-Elmer Model 283 infracord. Solvents and reagents were purified according to standard literature procedures.

Bis(trimethylsilyl) Monoperoxysulfate.[4] A 100-mL, three-necked, round-bottomed flask, equipped with a pressure-equalizing addition funnel, Teflon spinbar, rubber septum cap, and a three-way stopcock, was attached to a nitrogen manifold. Under a nitrogen atmosphere, a solution of 1.0 g (5.6 mmol) of bis(trimethylsilyl) peroxide[5] in 20 mL of dry CH_2Cl_2 was syringed

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