Anal. Calcd for $C_{14}H_8F_6S$: C, 52.17; H, 2.51; S, 9.94; mol wt, 322.2. Found: C, 52.15; H, 2.55; S, 9.81; mol wt, 324.6.

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Registry No.—4-Nitrobenzophenone, 1144-74-7; ethyl *p*-nitrobenzoate, 99-77-4; methyl *p*-nitrobenzoate, 619-50-1; *p*-nitrobenzonitrile, 619-72-7; *o*-dinitrobenzene, 528-29-0; *m*-dinitrobenzene, 99-65-0; *p*-dinitrobenzene, 100-25-4; 4-nitrophenyl phenyl sulfone, 1146-39-0; 3,5-bis(trifluoromethyl)nitrobenzene, 328-75-6; 2-nitropropane Li salt, 12281-72-0; sodium phenoxide, 139-02-6; benzylmercaptan Na salt, 3492-64-6; sodium ethoxide, 141-52-6; sodium benzenesulfinate, 873-55-2; sodium thiophenoxide, 930-69-8; sodium methoxide, 124-41-4; 2-nitrobutane Li salt, 35818-95-2; sodium methylmercaptide, 5188-07-8; *p*-nitrophenyl methyl sulfide, 701-57-5.

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Substitution Reactions of Specifically Ortho-Metalated Piperonal Cyclohexylimine

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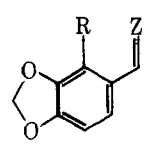
The specific ortho metalation of piperonal and 6-bromopiperonal cyclohexylimine is discussed. Typical reactions of the lithio and cuprous organometallics are explored.

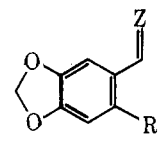
Since the observations of Hauser[2] concerning the stabilizing effect of a neighboring tertiary amine on the stability of ortho-lithiated aryls, this type of reaction has been applied to monosubstituted amides,[3] oxazolines,[4] and imines.[5]. Reiff has observed[5] that when acetophenone cyclohexylimine is treated with *n*-butyllithium (*n*-BuLi) in ether at −78 °C, addition to the imine is the major reaction pathway with minor quantities of dilithioimine derived from metalation at both the methyl group and the ortho position.

We have observed in the instance of piperonal cyclohexylime (**1a**) that reaction with *n*-BuLi in tetrahydrofuran (THF) at 0 °C afforded products of imine addition. When the temperature was lowered to −78 °C, only lithiation at the 2 position (**1b**) was observed, since low-temperature deuteration provided 2-deuteriopiperonal cyclohexylimine (**1d**) with a characteristic ortho-coupling pattern in its NMR spectrum.[6] When 6-bromopiperonal cyclohexylimine (**2e**) was lithiated at −78 °C, the NMR spectrum of the deuterium oxide quenched product indicated that deuteration had occurred exclusively at the 6 position (**2d**). However, when the 6-lithiated imine was allowed to warm to ambient temperature and then quenched with iodine at the same temperature or at −78 °C, only the 2-iodoimine **1f** was observed. Thus, the 2 position of imine **1a** is the site of kinetic and thermodynamic lithiation due to the electron-withdrawing effect of the adjacent oxygen atom. In the latter case, metal–halogen exchange is the kinetic process rather than C-2 deprotonation.[7] The equilibration is thought to be promoted by piperonal cyclohexylimine acting as a proton source. Although a sufficient excess of butyllithium was used in control runs to ensure the metalation of all of the piperonalimine, exchange still occurred. This may imply a disproportionation in which 2 mol of 6-lithiated imine affords 2,6-dilithiated imine and piperonalimine, thereby generating the necessary exchange medium. Alternatively, decomposition (i.e., oxidation and hydrogen abstraction from THF) would also generate piperonalimine.



1

a, R = H; Z = NC_6H_{11}
b, R = Li; Z = NC_6H_{11}
c, R = CuI; Z = NC_6H_{11}
d, R = D; Z = NC_6H_{11}
e, R = Br; Z = NC_6H_{11}
f, R = I; Z = NC_6H_{11}



2

g, R = I; Z = O
h, R = CH_3; Z = O
i, R = $CH_2CH{=}CH_2$; Z = O
j, R = CO_2H; Z = O
k, R = CO_2CH_3; Z = O

Both ortho-lithiated imines were subjected to alkylation with allyl bromide and methyl iodide. The data in Table I under entries A and B indicate that methylation is virtually

Table I

Conditions	Yields,[a] % (% piperonal) 1h	2h	1i	2i
A	61 (0)	79 (1)	61 (12)	57 (31)
B	69 (9)	66 (2)	11 (59)	56 (18)
C	94 (4)[b]	86 (5)	71 (1)[c]	53 (1)[d]
D	61 (15)	66 (9)	62 (5)	61 (3)

A: BuLi (−78 °C); RX (−78 °C, 3 h); warm to room temperature; H_2O; H_3O^+
B: BuLi (−78 °C); RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H_3O^+
C: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); warm to room temperature; H_2O; H_3O^+
D: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H_3O^+

[a] Yields are absolute and unless specified are determined by GLC and corrected for differences in thermal conductivity. [b] Sublimed. [c] Distilled. [d] Identified as its semicarbazone.

Table II

Electrophile	Yield, % From 1b	From 2b
D_2O	100[a]	100[a]
I_2	60[b]	64[b]
CO_2	54[b]	43[b]
$ClCO_2Me$	68[b]	6[b,c]

[a] NMR analysis, percent conversion. [b] Isolated. [c] Complex reaction mixture.

complete at −78 °C, while in the allyl bromide alkylation the conversion is not as effective. In the particular case of 2-allylpiperonal (**1i**), the reaction (condition B) is only 11% complete.

When the ortho-lithiated imines were treated with CuI[8] at −78 °C, a green suspension was formed which showed a more pronounced effect on the allyl bromide alkylation yield than in the absence of copper. Although a change in mechanism for the methyl iodide alkylations cannot be inferred from these data, the copper(I)–allyl bromide alkylations suggest oxidative addition[9] as the mode of alkylation. It was observed that upon allowing the cuprous imine **2c** to warm to room temperature followed by treatment with allyl bromide, only a minor amount of the 2-allyl product was obtained, indicating that **2c** is less prone to rearrange than its lithium counterpart, **2b.**

In addition to the alkylation reactions, the lithiated imines could be iodinated, carboxylated, and carbomethoxylated as outlined in Table II.

The direct formation of the 2-lithiated imine **1b** is not a general reaction. Metalation of *m*-methoxybenzaldehyde cyclohexylimine with BuLi at −78 °C gave only addition to the imine. The freely rotating methoxyl group provides sufficient steric inhibition to deprotonation, allowing the imine addition to be the preferred reaction pathway. This difficulty is avoided in the case of piperonalimine since the ether functions are constrained from rotation. Direct metalation of 3,4,5-trimethoxybenzaldehyde failed to result in ortho metalation as was expected, but the lithiated imine could be successfully generated by metal–halogen exchange of the corresponding bromoimine.

Myristicinaldehyde (5-methoxypiperonal) cyclohexylimine, which has both the attributes of piperonal and *m*-methoxybenzaldehyde imines, was metalated to the extent of 60% (deuterium quench) at only one of the two ortho positions. Although the chemical shifts of the two signals could not be assigned with certainty, the selectivity could be observed by internal calibration with the methylenedioxy function and was inferred from the prior results to be the 2 position (adjacent to the methylenedioxy group) as opposed to the 6 position which was metalated.

Experimental Section

Melting points (corrected) were determined on a Fisher-Johns apparatus. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. NMR spectra were determined on a Joelco Minimar 100-MHz or Perkin-Elmer R-32 90-MHz spectrometer, using Me_4Si (δ) as an internal standard. Gas chromatographic analyses were performed on a Varian 90-P instrument (TC) using a 6 ft × 0.25 in. 20% SE-30 on Anakrom 60/70 SD column. Tetrahydrofuran was distilled from sodium benzophenone ketyl. All glassware was flame dried under N_2. Solutions and solvents were transferred via syringe through serum caps.

Preparation of Cyclohexylimines. The imines were prepared from the aldehydes (1.0 equiv) and cyclohexylamine (1.2 equiv, distilled) in benzene solution by azeotropic removal of water. Recrystallization from methanol or distillation provided the imines in 80–90% yield.

Piperonal Cyclohexylimine (1a): mp 62.5–63.5 °C (lit.[10] 65–66 °C); NMR ($CDCl_3$) δ 1.15–2.0 (10 H, m), 3.15 (1 H, br s, =NCH), 5.92 (2 H, s, OCH_2O), 6.80 (1 H, d, J = 8 Hz, H-5), 7.10 (1 H, dd, J = 1.5, 8 Hz, H-6), 7.38 (1 H, d, J = 1.5 Hz, H-2), and 8.19 (1 H, s, –CH=N–).

6-Bromopiperonal Cyclohexylimine (2e): white needles, mp 127.5–128.5 °C (85% yield); NMR ($CDCl_3$) δ 1.23–1.84 (10 H, m), 3.25 (1 H, br s), 5.97 (2 H, s), 6.97 (1 H, s), 7.52 (1 H, s), and 8.54 (1 H, s).

Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.20; H, 5.20; Br, 25.76; N, 4.52. Found: C, 54.08; H, 5.26; Br, 25.67; N, 4.58.

***m*-Methoxybenzaldehyde Cyclohexylimine:** bp 120–123 °C (0.01 mm); NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.15 (1 H, br s), 3.81 (3 H, s), 6.85–7.05 (1 H, m, aryl), 7.20–7.38 (3 H, m, aryl), and 8.27 (1 H, s).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.28; H, 8.80; N, 6.50.

Myristicinaldehyde Cyclohexylimine: mp 72–73 °C; NMR ($CDCl_3$) δ 1.21–1.93 (10 H, m), 3.15 (1 H, br s), 3.93 (3 H, s), 5.99 (2 H, s), 6.94 (2 H, s), and 8.15 (1 H, s).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.85; H, 7.39; N, 5.34.

Typical Metalation Procedure. In a flame-dried flask equipped with a serum cap was placed 2 mmol of imine in 15 ml of THF and the mixture was cooled to −78 °C with a CO_2–acetone bath. To the stirred solution was added a solution of 2.1 mmol of *n*-BuLi–hexane (Alfa-Ventron) over 1 min via syringe through the serum cap. A yellow color appeared upon introduction of the *n*-BuLi. After stirring for 15 min at −78 °C the ortho-metalated imine was ready for further reactions.

2-Deuteriopiperonal Cyclohexylimine (1d). Imine **1b** was treated with 0.2 ml of D_2O and allowed to warm to room temperature. The solution was poured into water, extracted with ether, dried over $MgSO_4$, filtered, and evaporated, providing a crystalline solid **1d.** The NMR spectrum showed the complete disappearance of the δ 7.38 resonance and the loss of meta coupling in the δ 7.10 doublet, indicating quantitative deuteration at C-2.

In a similar fashion **2b** provided **2d** which showed no resonance at δ 7.10 and singlets at δ 6.80 and 7.38 in its NMR spectrum.

2-Iodopiperonal Cyclohexylimine (1f). Iodination. To a solution of the metalated imine **1b** at −78 °C was added dropwise a solution of 762 mg (3.0 mmol) of iodine in 5 ml of THF. The iodine color was immediately discharged upon contact with the solution. The addition was continued until the iodine color persisted. The solution was warmed to room temperature, poured into water, extracted with ether, washed with saturated aqueous Na_2SO_3, dried ($MgSO_4$), filtered, and concentrated. Two crystallizations of the residue from ether–petroleum ether afforded 432 mg (60%) of **1f** as colorless prisims: mp 167–168.5 °C; NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.26 (1 H, br s), 6.04 (2 H, s), 6.75 (1 H, d, J = 8 Hz), 7.55 (1 H, d, J = 8 Hz), and 8.34 (1 H, s).

Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.07; H, 4.52; I, 35.53; N, 3.92. Found: C, 46.85; H, 4.59; I, 35.38; N, 3.97.

Hydrolysis was effected by vigorously stirring 245 mg (0.69 mmol) of imine **1f** in 15 ml of CH_2Cl_2 and 15 ml of 10% aqueous HCl for 2 days. The organic layer was washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated, providing 150 mg of solid. Recrystallization from methanol afforded 93 mg (48%) of **1g** as white needles: mp 135–136 °C; NMR ($CDCl_3$) δ 6.15 (2 H, s), 6.84 (1 H, d, J = 9 Hz), 7.62 (1 H, d, J = 9 Hz), and 9.89 (1 H, s).

Anal. Calcd for $C_8H_5IO_3$: C, 34.81; H, 1.83; I, 45.98. Found: C, 34.84; H, 1.87; I, 45.86.

The 6-lithiated imine **2b** afforded 459 mg (64%) of **2f** as white needles from MeOH: mp 157–157.5 °C; NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.25 (1 H, br s), 5.99 (2 H, s), 7.26 (1 H, s), 7.53 (1 H, s), and 8.38 (1 H, s).

Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.07; H, 4.52; I, 35.53; N, 3.92. Found: C, 47.01; H, 4.54; I, 35.44; N, 3.89.

Aldehyde **2g** was formed (vide supra) in 46% yield from imine **2f**: mp 108.5–110.5 °C (MeOH) (lit.[11] 111 °C); NMR ($CDCl_3$) δ 6.08 (2 H, s), 7.31 (1 H, s), 7.34 (1 H, s), and 9.86 (1 H, s).

2-Methylpiperonal (1h) (Method A). To a stirred solution of imine **1b** at −78 °C was added dropwise over 1 min 454 mg (3.2 mmol) of distilled methyl iodide dissolved in 3 ml of THF. The solution was stirred for 3 h at −78 °C and then allowed to warm to room temperature. The reaction mixture was worked up (vide supra) to afford 491 mg of light yellow solid. Hydrolysis provided, upon recrystallization from hexane, aldehyde **1h** in 61% overall yield: mp 73–74.5 °C (lit.[12] 74–75 °C); NMR ($CDCl_3$) δ 2.55 (3 H, s, CH_3), 6.08 (2 H, s), 6.82 (1 H, d, J = 8 Hz), 7.39 (1 H, d, J = 8 Hz), and 10.03 (1 H, s).

Method C. To a stirred solution of metalated imine **2b** at −78 °C was added 381 mg (2.0 mmol) of cuprous iodide (as CuI, Alfa-Ventron) producing after 1 h a gray-green suspension.

After methylation as in method A, the reaction mixture was poured into H_2O, ether was added, and the mixture was shaken and filtered in vacuo through a Celite pad to remove suspended copper salts. The layers were separated and the organic layer extracted twice with ether. The combined organic extracts were washed with 5% NH_4OH, dried ($MgSO_4$), filtered, and concentrated. Hydrolysis afforded a solid which upon sublimation (60 °C, 1 mm) provided a 98% recovery of material (94% **1h**, 4% piperonal by GLC).

The lithiated imine **2b** provided (via method A) **2h** contaminated with piperonal; recrystallization (petroleum ether) afforded product in two crops (79%). Sublimation (55 °C, 1 mm) of the first crop (147 mg) gave 132 mg of pure 6-methylpiperonal (**2h**): mp 86–87.5 °C (lit.[13] 86–87 °C); NMR ($CDCl_3$) δ 2.61 (3 H, s), 6.01 (2 H, s), 6.69 (1 H, s), 7.29 (1 H, s), and 10.18 (1 H, s).

2-Allylpiperonal (1i) (Method C). To the copper reagent **1c** (vide supra) at −78 °C was added 411 mg (3.4 mmol) of allyl bromide and the mixture was stirred for 3 h at −78 °C. After warming to room temperature and workup an oil was obtained. Distillation (bulb to bulb) provided 271 mg (72%) of 2-allylpiperonal (**1i**): bp 122 °C (3 mm); NMR ($CDCl_3$) δ 3.76 (2 H, d, J = 6 Hz), 5.07 (1 H, m, $=CH_2$), 4.94 (1 H, m, $=CH_2$), 6.03 (1 H, m), 6.03 (2 H, s), 6.77 (1 H, d, J = 8 Hz), 7.36 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.21; H, 5.36.

In a similar fashion 6-allylpiperonal (**2i**) was prepared as a crude oil: NMR ($CDCl_3$, FT) δ 6.02 (2 H, s), 6.71 (1 H, s), 7.31 (2 H, s), and 10.11 (1 H, s). Semicarbazone, mp 193–195 °C (lit.[14] mp 195 °C).

Anal. Calcd for $C_{12}H_{13}N_3O_3$ (semicarbazone): C, 58.29; H, 5.30; N, 16.99. Found: C, 58.34; H, 5.32; N, 17.00.

Methyl 2-Formyl-5,6-methylenedioxybenzoate (1k). To the lithiated imine **1b** at −78 °C was added dropwise 368 mg (3.9 mmol) of freshly distilled methyl chloroformate (from $CaCO_3$) dissolved in 3 ml of THF. The yellow color of the solution was discharged. Upon warming to room temperature, the solution was poured into water, extracted with ether, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The residual oil (644 mg) was preabsorbed on silica gel and eluted from a silica gel column (30/1) with 300 ml of benzene saturated with water, affording 54 mg of oil containing piperonal (GLC). The 5% ether–wet benzene eluent (100 ml) gave 338 mg of solid. Recrystallization from ether–petroleum ether provided the ester **1k** (68%): mp 105.5–106.5 °C; NMR ($CDCl_3$) δ 3.97 (3 H, s), 6.15 (2 H, s), 6.97 (1 H, d, J = 9 Hz), 7.50 (1 H, d, J = 9 Hz), and 10.09 (1 H, s).

Anal. Calcd for $C_{10}H_8O_5$: C, 57.50; H, 3.87. Found: C, 57.76; H, 3.86.

2-Formyl-5,6-methylenedioxybenzoic Acid (1j). To 2 mmol of lithiated imine **1b** was added several chunks of dry ice, the yellow color of the solution being immediately discharged. After warming to room temperature, 15 ml of 10% HCl and 15 ml of ether were added and the mixture stirred overnight. The organic layers were separated, extracted with 10% aqueous KOH, acidified with concentrated HCl in the cold, and thoroughly extracted with ethyl acetate, dried, filtered, and concentrated, providing 211 mg (54%) of acid upon recrystallization from water: mp 164.5–165.5 °C (lit.[15] 155 °C); ir ($CHCl_3$) 1763 cm^{-1} (lactol); NMR (acetone-d_6) δ 3.8 (1 H, br s, lactol –OH, D_2O exchange), 6.22 (2 H, s) 7.1–7.3 (2 H, m, aryl). Methylation with CH_2N_2 provided ester **1k**, mp 103.5–105.5 °C.

In a similar fashion, 2-formyl-4,5-methylenedioxybenzoic acid (**2j**) was prepared from **2b** (43%): mp 165–165.5 °C (lit.[16] 167 °C); ir ($CHCl_3$) 1775 cm^{-1} (lactol); NMR (acetone-d_6) δ 2.9 (1 H, br s, lactol OH, D_2O exchange), 6.21 (2 H, s), 6.60 (1 H, br s, methine), and 7.19 (1 H, s, aryl).

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Registry No.—**1a**, 58343-42-3; **1b**, 58384-27-3; **1c**, 58384-28-4; **1d**, 58343-43-4; **1f**, 58343-44-5; **1g**, 58343-45-6; **1h**, 58343-46-7; **1i**, 58343-47-8; **1j**, 58343-48-9; **1k**, 58343-49-0; **2b**, 58384-29-5; **2d**, 58343-50-3; **2e**, 58343-51-4; **2f**, 58343-52-5; **2g**, 58343-53-6; **2h**, 58343-54-7; **2i**, 58343-55-8; **2i** semicarbazone, 4518-37-0; **2j**, 51877-66-8; cyclohexylamine, 108-91-8; piperonal, 120-57-0; 6-bromopiperonal, 15930-53-7; *m*-methoxybenzaldehyde, 591-31-1; *m*-methoxybenzaldehyde cyclohexylimine, 58343-56-9; myristicinaldehyde, 5780-07-4; myristicinaldehyde cyclohexylimine, 58343-57-0; allyl bromide, 106-95-6; methyl chloroformate, 79-22-1.

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