attraction leads to conformations possessing sandwiched structures.

The observation of intramolecular $\pi-\pi$ complexing in these simple systems lends support to a proposed mechanism of action of anthraquinone during the pulping of wood. This proposal, which was arrived at simultaneously by several investigators, including this author, is that anthraquinone and/or its reduced form may promote pulping by complexing with wood constituents, followed by electron transfer between structures.

Experimental Section

The equipment used, procedures, and source of compounds studied can be found in the previous publication.[1]

Registry No. 1, 79769-65-6; 2, 79769-66-7; 3, 79769-67-8; 4, 79769-68-9; 5, 79769-69-0; 6, 79769-70-3; 7, 79769-71-4; 8, 79769-72-5; 9, 79769-73-6; 10, 69544-83-8; 11, 79769-74-7; 12, 79769-75-8; 13, 78787-97-0; 14, 79769-76-9; 15, 79769-77-0.

The Tertiary Amide as an Effective Director of Ortho Lithiation

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The tertiary amides *N,N*-diethylbenzamide (1) and *N,N*-diisopropylbenzamide (3) give the ortho-lithiated species 2 on treatment with *sec*-BuLi/TMEDA or *n*-BuLi/TMEDA, respectively, at −78 °C. Lithiation of 1 followed by reaction with either methyl iodide, ethyl iodide, benzophenone, acetone, benzaldehyde, or trimethoxyborane–hydrogen peroxide gives the expected ortho substituted product. Intramolecular competition between the diethylamido and chloro, methoxyl, sulfonamido, (dimethylamino)methyl, or oxazolino functions in ortho- and para-substituted benzamides establishes the tertiary amido group to be more effective in directing metalation than any noncarboxamide functional group under the prescribed conditions. Complimentarity of directing effects is observed with the chloro and methoxyl groups in the meta-substituted diethylbenzamides but not with the methyl group. The secondary amide is found to have a directing ability comparable to the tertiary amide with *sec*-BuLi/TMEDA at −78 °C in THF although the yields are low. ^{13}C NMR chemical shifts are particularly useful for the structural assignments which are confirmed chemically by lactonization of some products. A labeling study with *N,N*-diisopropyl-2,6-dideuteriobenzamide suggests that lithiation of the ortho position of 3 is direct and not the result of rearrangement of an initially formed α-aza anion. Control of metalation at the ortho or benzylic position by proper selection of the organolithium base is illustrated for *N,N*-diisopropyl-*p*-toluamide. The value of the tertiary amide for control of ortho lithiations and regiospecific aromatic substitutions is noted.

The formation of regiospecifically ortho metalated aromatics by deprotonation, illustrated for substituted benzenes in Scheme I, is a reaction of synthetic value and mechanistic interest. A classic and seminal case is the reaction of anisole with *n*-butyllithium to give 2-lithioanisole reported by Gilman and by Wittig over 40 years ago.[1] Early developments, initially by Gilman and Hauser with subsequent contributions from many other laboratories, expanded the scope of these metalations to a variety of substituted aromatic and olefinic systems.[1,2]

In a recent, excellent review of this area, Gschwend and Rodriguez suggested a hierarchical order of substituent directing abilities which corresponds to the order shown in Scheme I with the more activating group to the left in the series. This order was defined for coordinatively unsaturated metalating agents and, as Gschwend and Rodriguez point out, the relative ability of a substituent to direct a metalation can generally be interpreted in terms of an interplay of inductive and complexation effects.[2]

Until a few years ago the substituents which were regarded as useful directors for ortho metalations were those which would sensibly be considered to be inert to the strong organometallic bases used for deprotonation. Recently, however, it has been reported that groups which might be thought to be susceptible to nucleophilic addition by the organolithium bases can retain their structural integrity and function as effective ortho directors. Discoveries that oxazolines[3] and tertiary amides[4] are capable of directing lithiation to positions adjacent to these substituents have been reported and quickly adopted for synthetic purposes.[5-7] The oxazoline has been placed between the sulfonamide and secondary carboxamide in the directing order of Gschwend and Rodriguez.[2] Recently we[8] and Meyers and Lutomski[9] have communicated ob-

(1) H. Gilman and R. L. Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939); H. Gilman and F. J. Webb, *ibid.*, **62**, 987 (1940); G. Wittig and G. Fuhrmann, *Chem. Ber.*, **73**, 1197 (1940); see H. Gilman and J. W. Morton, Jr., *Org. React.*, **8**, 258 (1954), for a review of the early literature.

(2) H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1–360 (1979).

(3) H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975); A. I. Meyers and E. D. Mihelich, *ibid.*, **40**, 3158 (1975).

(4) P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).

(5) For cases involving the oxazoline, see A. Padwa, A. Ku, A. Mazzu, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **98**, 1048 (1976); M. S. Newman and S. Kumar, *J. Org. Chem.*, **43**, 370 (1978); T. D. Harris, B. Neuschwander, and V. Boekelheide, *ibid.*, **43**, 727 (1978); L. D. Vecchia and I. Vlattas, *ibid.*, **42**, 2649 (1977); A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978); A. I. Meyers and R. A. Gabel, *Tetrahedron Lett.*, 227 (1978); C. R. Ellefson, *J. Org. Chem.*, **44**, 1533 (1979); S. Djuric, T. Sarkar, and P. Magnus, *J. Am. Chem. Soc.*, **102**, 6885 (1980), and references cited therein.

(6) For cases involving the tertiary amide: (a) S. O. deSilva, J. N. Reed, and V. Snieckus, *Tetrahedron Lett.*, 5099 (1978); (b) S. O. deSilva and V. Snieckus, *ibid.*, 5103 (1978); (c) S. O. deSilva, I. Ahmad, and V. Snieckus, *ibid.*, 5107 (1978); (d) S. O. deSilva, M. Watanabe, and V. Snieckus, *J. Org. Chem.*, **44**, 4802 (1979); (e) S. O. deSilva, I. Ahmad, and V. Snieckus, *Can. J. Chem.*, **57**, 1598 (1979); (f) M. Watanabe and V. Snieckus, *J. Am. Chem. Soc.*, **102**, 1457 (1980).

(7) Other groups which might be susceptible to nucleophilic substitution but retain their identity and direct ortho lithiation in the presence of a second activating group include (a) the meta alkoxy substituted imine [F. E. Ziegler and K. W. Fowler, *J. Org. Chem.*, *41*, 1564 (1976)] and (b) *m*-chloro nitrile (ref 2).

(8) P. Beak and R. A. Brown, *J. Org. Chem.*, **44**, 4463 (1979).

(9) A. I. Meyers and K. Lutomski, *J. Org. Chem.*, **44**, 4464 (1979).

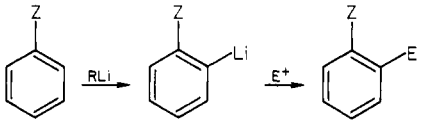
0022-3263/82/1947-0034$01.25/0

Table I. Reaction of Ortho-Lithiated Benzamides 2 from *N,N*-Diethylbenzamide (1) and *N,N*-Diisopropylbenzamide (3) with Electrophiles[a]

amide	base	amide concn[b]	metalation time	electrophile[c]	product	% yield
1	*d*	0.15 M	20 min	20 D_2O	8, E = D	88 (95% d_1)
1	*d*	85 mM	1 h	2.5 CH_3I	8, E = CH_3	77
1	*e*	0.13 M	15 min	2.0 C_2H_5I	8, E = C_2H_5	70
1	*d*	40 mM	5 min	1.1 $B(OCH_3)_3$; H_2O_2	8, E = OH	56
1	*f*	52 mM	5 min	1.0 $(CH_3)_2CO$	9, R = CH_3	54
1	*d*	87 mM	1 h	1.1 $(C_6H_5)_2CO$	9, R = C_6H_5	65
1	*d*	50 mM	20 min	1.1 C_6H_5CHO	9, R = C_6H_5, H	56
3	*g*	0.11 M	20 min	1.2 C_6H_5CHO	9, R = C_6H_5, H	79
3	*d*	68 mM	1 h	16 D_2O	8, E = D	90 (97% d_1)
3	*d*	0.33 M	15 min	2.1 CH_2=$CHCH_2Br$	8, E = Br	60

[a] The reaction procedure is addition of a THF solution of amide dropwise to a cold (−78 °C) THF solution of the base, followed, after the metalation time, by addition of the electrophile. [b] Concentration after addition to the base. [c] The number of equivalents of electrophile is also given. [d] 1.1 equiv of *sec*-BuLi/TMEDA. [e] 1.0 equiv of *sec*-BuLi/TMEDA. [f] 1.0 equiv of *sec*-BuLi. [g] 1.1 equiv of *n*-BuLi/TMEDA.

Scheme I

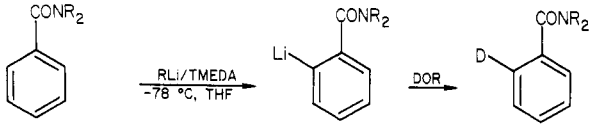


Z = SO_2Y, CONHR, CH_2NR_2, OR, OAr, NHAr, NRAr, NR_2

servations which suggest that with organolithium/tetramethylethylenediamine (TMEDA) bases the tertiary carboxamide is generally more effective as a director of ortho lithiation than any of the noncarboxamido directing groups previously studied. We now report the details of our work.[10]

Results and Discussion

Directed Lithiation of Unsubstituted Benzamides. The efficiency of ortho lithiation of tertiary benzamides is a function of the reaction solvent, organolithium, complexing agent, temperature, order of addition, and substituents on the amide nitrogen.[10] The optimum conditions which we have found for metalation of *N,N*-diethylbenzamide (1) are slow addition of the amide in dry tetrahydrofuran (THF) to a slight excess of a 1:1 *sec*-butyllithium (*sec*-BuLi)/TMEDA complex in THF at −78 °C.[11a] Lithiation appears to be complete after 5 min, but the ortho lithio species 2 is stable for up to 1 h if its concentration is less than 0.2 M. In the case of *N,N*-diisopropylbenzamide (3) lithiation can be achieved under the same conditions or with *n*-butyllithium and 2 is stable at concentrations up to 0.46 M.[11b]



1, R = CH_2CH_3
3, R = $CH(CH_3)_2$

2 4

Under the above conditions, the extent of lithiation of 1 and 3 is greater than 90% as determined by yields of the 2-deuterio amides 4. The extent of deuteration was established by comparison of the intensities of the acylium ions in the electron-impact mass spectrum because the molecular ions show large M − 1 peaks.[12] The reliability of this analysis was corroborated by the results obtained under field-ionization conditions, where no M − 1 ion is observed and direct comparison of the protio and deuterio molecular ions is possible. The site of lithiation, as revealed by the location of the deuterium, was usually determined from the ^{13}C NMR spectra which show the expected reduction in intensity of the signal for the deuterated carbon on comparison with starting material.[13] The assignments of chemical shifts for the carbons in 1 and 3 were made by comparison with the assignments for *N,N*-dimethylbenzamide[14] and confirmed by gated decoupling which showed the multiplets for the ortho carbons to be narrower than those for the meta carbons.[15] In the case of substituted benzamides (vide infra) assignments made on the basis of the established additivity of the substituent shifts, either from accepted compilations or as determined in this work, gave clear distinctions between the alternatives.[10,13] The mass spectra and ^{13}C NMR assignments were also confirmed by ^1H NMR spectroscopy in cases where sufficient separation of the signals allowed assignments to be made.[10,16]

The effect of the nitrogen substituent on the course of the lithiation may be seen by comparison of the products resulting from exposure of *N,N*-dimethylbenzamide (5) and *N,N*-diethylbenzamide (1) to *sec*-BuLi/TMEDA. While 1 undergoes efficient lithiation under these conditions, 5 gives a mixture of α-methylbutyrophenone (6) and *N,N*-dimethyl-*o*-benzoylbenzamide (7) along with unidentified material.[17,18] The ketone 6 results from nucleophilic addition of *sec*-BuLi to 5 while 7 arises from

(10) For details, see: R. A. Brown, Ph.D. Thesis, University of Illinois, 1981; available from University Microfilms, Ann Arbor, MI 48106.

(11) (a) If the order of addition is reversed and *sec*-BuLi/TMEDA is added to 1, then *N,N*-diethyl-*o*-benzoylbenzamide is produced in high yield presumably by reaction of 1 with 2 as it is generated. (b) While small amounts of valerophenone are observed under the latter conditions, its formation can be reduced to undetectable levels by use of *n*-BuLi/TMEDA.

(12) J. F. Biellman and C. G. Hirth, *Org. Mass Spectrom.*, **2**, 723 (1969); A. M. Duffield, G. deMartino, and C. Djerassi, *ibid.*, **9**, 137 (1974). The M − 1 ion appears to involve loss of an ortho proton.

(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972.

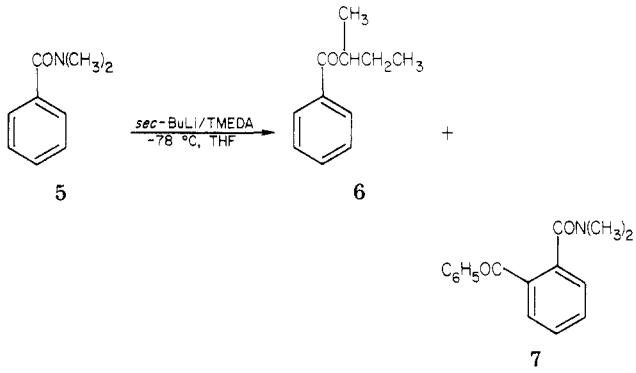
(14) D. Liebfritz, *Chem. Ber.*, **108**, 3014 (1975).

(15) R. Freeman and H. D. W. Hill, *J. Magn. Reson.*, **5**, 278 (1971); O. A. Gansow and W. Schittenhelm, *J. Am. Chem. Soc.*, **93**, 4294 (1971); F. J. Weigert and J. D. Roberts, *ibid.*, **89**, 2967 (1967).

(16) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", International Series of Monographs in Organic Chemistry, Vol. 5, 2nd ed, Pergamon Press, Oxford, 1969, p 202.

(17) These products, which comprise less than 50% of the reaction mixture, were identified by ^1H NMR spectral comparison of the mixture with the authentic materials.

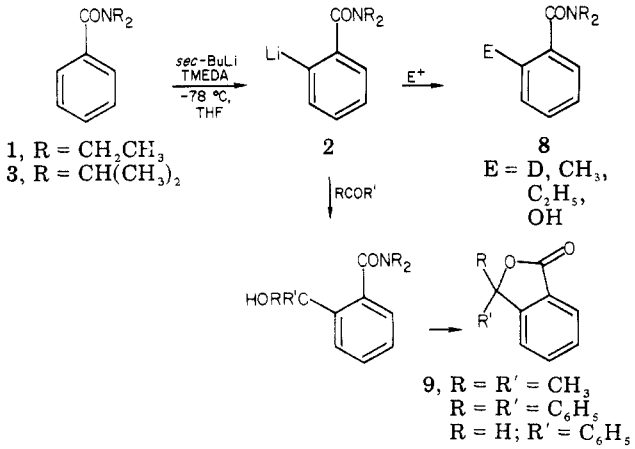
(18) The use of the dimethyl carboxamido group as a substituent which undergoes nucleophilic addition prior to ortho direction of lithiation has been reported; see L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, *J. Org. Chem.*, **41**, 3651 (1976), and references cited therein.



5 6 7

ortho lithiation of **5** followed by nucleophilic addition of that organolithium to **5**.[19] The fact that the diisopropyl amide **3** is still less susceptible to nucleophilic addition than the diethyl amide **1** follows from the observation that *n*-BuLi is effective in converting **3** to **2**, whereas attempted lithiation of **1** with *n*-BuLi gives valerophenone. The later reaction is precedented by the reaction of **5** with *n*-butyllithium to give the same ketone.[20] We also have found that lithiation of **1** with *sec*-BuLi in the absence of TMEDA results in a partial conversion of **2** to the ortho benzoyl product. Metalation of **1** in diethyl ether with *sec*-BuLi/TMEDA at −78 °C gives mainly **2**, but 14% **6** is also obtained.

Reaction of Ortho-Lithiated Benzamides 2 with Electrophiles. The ortho-lithiated *N,N*-diethylbenzamide (**2**) from **1** adds to electrophiles to give the expected substituted products. Deuteration, methylation, ethylation and boration–oxidation give **8**, and additions to acetone, benzophenone, and benzaldehyde give **9**, in acceptable yields as shown in Table I. The lithiated benzamide **2** from the diisopropyl amide **3** undergoes deuteration and addition to benzaldehyde in acceptable fashion, but attempted alkylation with allylbromide provided *N,N*-diisopropyl-2-bromobenzamide. The additions to aldehydes and ketones ultimately produce the phthalides **9** as the isolated reaction products. These lactones provide chemical confirmation of the site of lithiation. Attempted reactions of **2** from **1** with ethyl bromide, *n*-propyl bromide, and triphenylvinylphosphonium bromide and of **2** from **3** with ethylene oxide, benzonitrile, and heptanal were not successful.



1, R = CH_2CH_3
3, R = $CH(CH_3)_2$

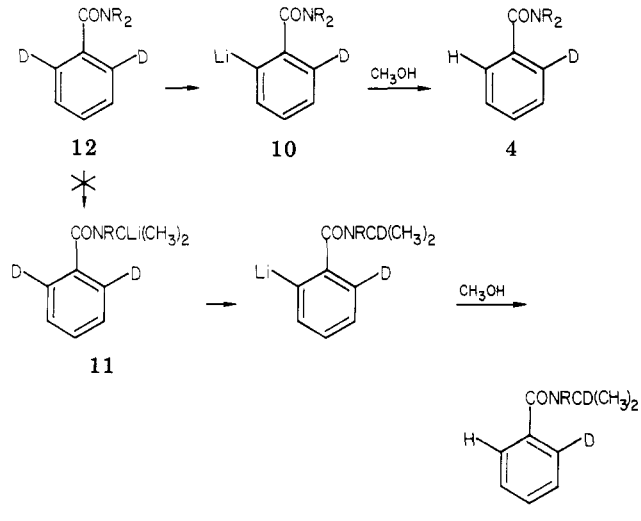
2

8
E = D, CH_3, C_2H_5, OH

9, R = R′ = CH_3
R = R′ = C_6H_5
R = H; R′ = C_6H_5

Possible Role of an α-Azalithio Species in the Ortho Lithiations of the Tertiary Benzamides. The most straightforward sequence for the metalation of tertiary benzamides is direct proton removal from an ortho position to give the organolithium as illustrated for the formation of **10** in Scheme II. However, it is known that ethylbenzamides can undergo lithiation adjacent to nitrogen to give a dipole-stabilized carbanion.[21] Accordingly, another possibility is that the *o*-lithio anion **2** arises by rearrangement of an initially formed α-aza anion **11** as shown in Scheme II. To distinguish between these possibilities, *N,N*-diisopropyl-2,6-dideuteriobenzamide (**12**) was prepared, allowed to react with *sec*-BuLi/TMEDA at −78 °C in THF for 15 min, and treated with methanol. If the reaction proceeds by **10**, then the recovered amide **4** would contain a single ortho deuteron, while reaction via **11** would provide dideuterated material **13** which would have a deuteron transferred from an ortho position to an isopropyl group.

Scheme II[a]



12 10 4

11

13

[a] R = $CH(CH_3)_2$.

Product analysis was carried out by mass spectrometric comparison of the starting material and product. The molecular ion ($M^+\cdot$), observed with field ionization, provided the total deuterium content, while the acylium ion ($ArCO^+$), observed with electron-impact ionization indicated the deuterium content of the ring. The starting amide **12** gave for $M^+\cdot$, 98% d_2, 2% d_1, and for $ArCO^+$, 96% d_2, 4% d_1. The product of the reaction gave for $M^+\cdot$, 5% d_2, 94% d_1, 1% d_0 and for $ArCO^+$, 7% d_2, 92% d_1, 1% d_0. Accordingly, the product from this sequence has lost 46 ± 4% deuterium, a result consistent with direct reaction via **10**.

Attempts to carry out a similar experiment with *N,N*-diethyl-2,6-dideuteriobenzamide suggest the same pathway is followed although the analysis is less definitive because substantial formation of α-methylbutyrophenone occurs and only about 15% lithiation is observed.[10] In this case the large isotope effect at −78 °C is sufficient to allow addition to be competitive with metalation.

Intramolecular Competition by Different Directing Groups. Since the ability of the tertiary amide to direct and activate ortho lithiation has been recognized only recently, its ranking with respect to the other directing groups needs to be established.[4,8,9] We have carried out intramolecular competitions between the tertiary amido group and previously known directing groups by investigation of the position of lithiation of the substituted *N,N*-diethylbenzamides **14–26** with *sec*-BuLi/TMEDA. The

(19) The self-condensation to give **7** is precedented for **5** and for **1** if **2** is allowed to stand at room temperature. P. Beak, G. R. Brubaker, and R. F. Farney, *J. Am. Chem. Soc.*, **98**, 3621 (1976), and ref 6f.

(20) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

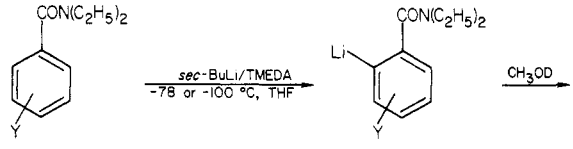
(21) P. Beak and D. B. Reitz, *Chem. Rev.*, 78 275 (1978).

Table II. Regiospecific and Regioselective Metalations of Substituted *N,N*-Diethylbenzamides[a]

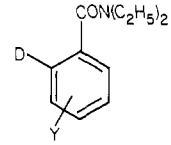
amide	base	amide concn[b]	temp, °C	metalation time	electrophile[c]	product	% yield[d]
14	*e*	49 mM	−100	20 min	10 CH_3OD	27	87 (79% d_1)
14	*e*	48 mM	−100	0 min[f]	10 CH_3OD	27	80 (86% d_1)
15	*g*	51 mM	−100	0 min[f]	9 CH_3OD	28	80 (83% d_1)
16	*g*	50 mM	−100	0 min[f]	9 CH_3OD	28	85 (99% d_1)
16	*g*	45 mM	−78	0 min[f]	1.0 $(C_6H_5)_2CO$	47	60
17	*e*	49 mM	−78	35 min	10 CH_3OD	30	83 (89% d_1)
18	*e*	67 mM	−78	1 h	16 D_2O	31	88 (90% d_1)
19	*g*	0.12 M	−78	70 min	10 D_2O	32	101 (94% d_1)[h]
20	*e*	49 mM	−100	20 min	10 CH_3OD	33[i]	84 (90% d_1)
21	*e*	49 mM	−100	20 min	10 CH_3OD	34	75 (98% d_1)
22	*e*	40 mM	−100	20 min	40 CH_3OD	35	74 (43% d_1, 1% d_2)
22	*j*	29 mM	−78	5 min	1.0 $(C_6H_5)_2CO$	44	21
23	*k*	44 mM	−100	20 min	40 CH_3OD	36	60 (74% d_1, 1% d_2)
23	*l*	24 mM	−100	1 h	1.4 $(C_6H_5)_2CO$	45	41
24	*e*	58 mM	−100	20 min	20 CH_3OD	37	84 (67% d_1)
25	*e*	25 mM	−78	15 min	20 CH_3OD	38	59 (96% d_1, 1% d_2)
25	*e*	48 mM	−78	2 min	1.1 $(C_6H_5)_2CO$	46	46
26	*l*	14 mM	−100	20 min	40 CH_3OD	39	56 (82% d_1)
40	*e*	51 mM	−78	15 min	excess CH_3OD	41	68 (91% d_1)
42	*e*	48 mM	−100	2 min	10 CH_3OD	43[m]	
50	*k*	12 mM	−78	20 min	40 CH_3OD	51	83 (~60% d_1)[n]
50	*k*	24 mM	−100	1 h	1.3 $(C_6H_5)_2CO$	52, 53	20,[h] 7

[a] The reaction procedure is addition of a THF solution of the amide dropwise to a cold THF solution of the base, followed after the metalation time by addition of the electrophile. [b] Concentration after mixing with the base. [c] The number of equivalents of electrophile is also given. [d] Unless otherwise specified, yields are of material which has been fully characterized by spectral and analytical means. [e] 1.1 equiv of *sec*-BuLi/TMEDA. [f] Electrophile added immediately upon completion of the addition of the amide. [g] 1.0 equiv of *sec*-BuLi/TMEDA. [h] Analytical sample was not obtained. [i] Ratio of 33a/33b of 2:1 approximated from ^{13}C NMR peak heights for C-2 and C-6. [j] 1.0 equiv of *t*-BuLi/TMEDA. [k] 2.1 equiv of *sec*-BuLi/TMEDA. [l] 2.0 equiv of *sec*-BuLi/TMEDA. [m] Characterized by ^1H NMR to bear $ArCH_2D$. [n] Deuterium of content estimated from ^1H NMR spectrum.

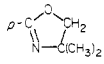
extent and site of metalation was evaluated by treatment of solutions of lithiated amide with deuteriomethanol, followed by mass spectrometric and nuclear magnetic resonance determination of the amount and location of deuterium in products **27–39**. The results, summarized in Table II, show that lithiation occurs preferentially adjacent to the amide. Apparently the tertiary amide is more effective than any noncarboxamide as a director of ortho lithiation under the specified conditions. Puterbaugh and Hauser have shown that the secondary amide is also an effective ortho director.[20,22,23]



14–26

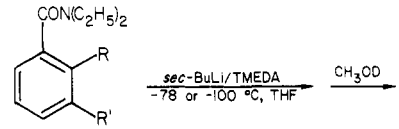


27–39

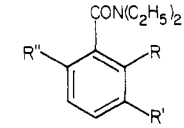
14, 27, *o*-Cl; **15**, **28**, *m*-Cl; **16**, **29**, *p*-Cl; **17**, **30**, *o*-OCH_3; **18**, **31**, *m*-OCH_3; **19**, **32**, *p*-OCH_3; **20**, **33**, *m*-CH_3; **21**, **34**, *p*-CH_3; **22**, **35**, *p*-$SO_2N(C_2H_5)_2$; **23**, **36**, *p*-SO_2NHCH_3; **24**, **37**, *p*-$CH_2N(CH_3)_2$; **25**, **38**,  ; **26**, **39**, *p*-CO_2H

The lithiations of **14–19** provide competition between the diethyl amide and the weakly directing chloro or the moderately directing methoxyl group.[2,23] Complimentarity is observed with lithiation occurring between the two groups in the meta isomers **15** and **18**. Retention of the ortho chloro and methoxyl functions in **14** and **17** stands in contrast to the replacement of ortho fluoro and ortho methoxyl groups of 2-aryloxazolines by Grignard and organolithium reagents.[24]

Lithiations of *N,N*-diethyl-*m*- and *p*-toluamides **20** and **21** occur adjacent to the amide. In the case of **20** lithiation appears to take place at both ortho positions; the product is a 2:1 mixture of 6-deuterio and 2-deuterio isomers as characterized by ^{13}C NMR. The stability of a meta methyl group toward metalation is confirmed by lithiation of *N,N*-diethyl-3-methyl-*o*-anisamide (**40**) to provide, after deuteration, the 6-deuterated product **41**.[25] In the case



40, R = OCH_3; R′ = CH_3
42, R = CH_3; R′ = H



41, R = OCH_3; R′ = CH_3; R″ = D
43, R = CH_2D; R′ = R″ = H

(22) For recent cases of direction by a secondary amide, see N. S. Narasimhan and R. S. Mali, *Synthesis*, 797 (1975); A. Marxer, H. R. Rodriguez, J. M. McKenna, and H. M. Tsai, *J. Org. Chem.*, **40**, 1427 (1975); J. E. Baldwin and K. W. Bair, *Tetrahedron Lett.*, 2559 (1978), and references cited therein; for secondary thioamides, see J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, **41**, 4029 (1976).

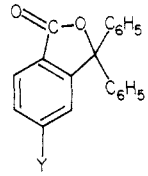
(23) D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976).

(24) A. I. Meyers, M. Reuman, and R. A. Gabel, *J. Org. Chem.*, **46**, 783 (1981), and references cited therein.

(25) Benzylic lithiation is competitive with ortho lithiation in the case of the methyl ether of *o*-cresol [T. E. Harmon and D. A. Shirley, *J. Org. Chem.*, **39**, 3164 (1974)] but not in the case of the corresponding methoxymethyl ether [H. Christensen, *Synth. Commun.*, **5**, 65 (1975)].

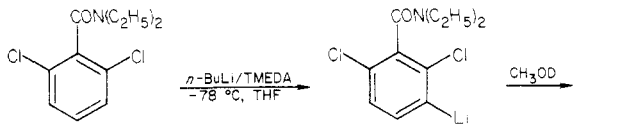
of *N,N*-diethyl-*o*-toluamide (**42**), however, a benzylic proton is removed to give **43** after deuteration, a result which is well-precedented.[2,6c,26]

Lithiations of the *N,N*-diethylbenzamides **22–25** in which the para substituents are either diethylsulfonamido, methylsulfonamido, (dimethylamino)methyl, or (4,4-dimethyl)oxazolino, place the tertiary amido group in competition against groups which in previous studies were found to be the most effective in directing ortho lithiation.[2,23] As shown in Table II, the position of deuterium in the products **35–38** indicates in all cases that metalation occurs preferentially adjacent to the amide. For **22**, **23**, and **25** the position of lithiation is confirmed by trapping with benzophenone and cyclization to give the phthalides **44–46** in 21–46% yields. Although those yields are not high, no evidence could be found for lithiation ortho to the competing group. The phthalide **47** was also prepared from **16** in 60% yield.

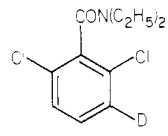


44, Y = $SO_2N(C_2H_5)_2$
45, Y = SO_2NHCH_3
46, Y = $C{=}NC(CH_3)_2CH_2O$
47, Y = Cl

The lithiation of *N,N*-diethylterephthalamic acid (**26**) was undertaken to establish the possibility of ortho lithiation on a ring bearing an anionic group. Lithiation proceeds ortho to the amide to give the deuterated product **39** in 56% yield. In a test of a system containing no ortho hydrogens, *N,N*-diethyl-2,6-dichlorobenzamide **48** was found to undergo lithiation with *n*-BuLi/TMEDA to give *N,N*-diethyl-3-deuterio-2,6-dichlorobenzamide **49** in 81% (99% d_1) yield.



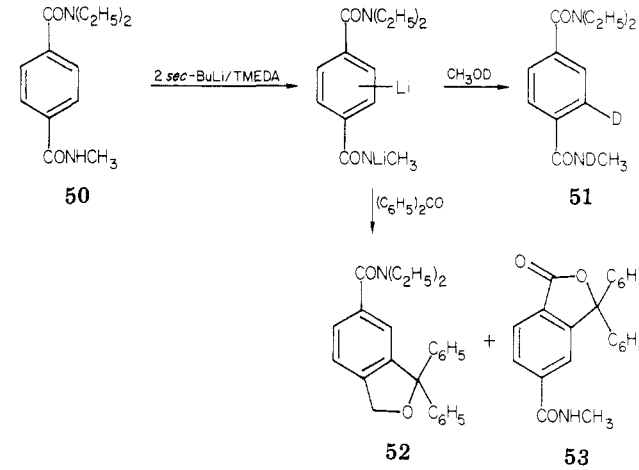
48



49

The only group which we have found to be competitive with the tertiary amide in directing ortho lithiation under the present conditions is the secondary amide. The lithiation of *N,N*-diethyl-*N'*-methylterphthalamide (**50**) with 2 equiv of *sec*-BuLi leads to **51** which, by ^1H NMR spectroscopy, shows incorporation of deuterium adjacent to the secondary amide. Moreover addition of benzophenone to the lithiated terephthalamide gave 20% of **52** and 7% of **53**. Although these yields are low and an analytical sample of **52** was not obtained, these results do indicate that under these conditions the tertiary and secondary amides have comparable directing ability. However, further studies will be required to more adequately compare these groups.

Closely related work also shows the tertiary amide to be



50 51 52 53

a very good ortho director. Thus the intramolecular competitions which we reported[8] agree with the intermolecular competitions reported by Meyers and Lutomski, with two exceptions.[8,9] The latter workers found the oxazoline to be a better director than the secondary carboxamide with *n*-BuLi in the presence of 2 equiv of hexamethylphosphortriamide, whereas in our experiments the secondary carboxamide is comparable to the tertiary amide and the latter is a more effective director than the oxazoline. The intermolecular competitions also show the dimethylsulfonamide to be a better director than the diisopropylcarboxamide with *n*-BuLi at −45 °C in contrast with the above result for the corresponding intramolecular case of **22** at −78 °C with *sec*-BuLi/TMEDA. The possibility that the differences between the intramolecular and intermolecular cases lie in the different inductive effects of the meta substituents cannot be discounted, but before any explanation is offered direct comparison under the same conditions is needed.

Consistent with our comparison, Meyers and Avila have recently reported that *N,N*-diethyl-3,5-dimethoxybenzamide undergoes lithiation adjacent to the tertiary amide with *n*-BuLi in THF, whereas the corresponding oxazoline gives isomers in which lithiation has occurred adjacent to the oxazoline or between the methoxyl groups under the same conditions.[27] While this experiment involves a coordinatively unsaturated base, the ratio of the metalation at different sites was shown to depend on the reaction conditions. That result, as the authors note, suggests both that a wide range of conditions should be explored for the synthetic use of metalations and that caution should be exercised in interpreting the course of metalations.

The limitations of the present and related studies in providing information about the factors which influence ortho lithiations must be clearly recognized. While equilibration of the lithiated species is probably slow relative to deuteration,[9,28] we estimate that as much as 15% of an isomeric deuterated species could be undetected. Moreover, it is well-known that the site of lithiation can be affected by solvent and complexing agents[2,23,27] and the present work was carried out only with *sec*-BuLi/TMEDA in THF.

Attempts to understand the regiochemistry of directed lithiations are further hindered by a lack of information about whether the site of metalation is kinetically or thermodynamically controlled. Ziegler and Fowler have shown that the *N*-cyclohexylimine of 2-lithiopiperonal is produced either upon direct metalation of the imine at −78

(26) R. E. Ludt, J. S. Griffiths, K. N. McGrath, and C. R. Hauser, *J. Org. Chem.*, 38, 1668 (1973).

(27) A. I. Meyers and W. B. Avila, *Tetrahedron Lett.*, 3335 (1980).
(28) P. Beak and A. Tse, unpublished results, 1980.

°C or by allowing the 6-lithio isomer, which is stable at −78 °C, to warm to room temperature.[7a] In another study we have shown that dimeric *o*-lithioanisole is 8 kcal/mol more stable than the isomeric and dimeric meta and para compounds in di-*n*-butyl ether, a result which parallels the well-established ortho lithiation of anisole.[1,2,29] In these cases kinetic and thermodynamic effects appear to be congruent.

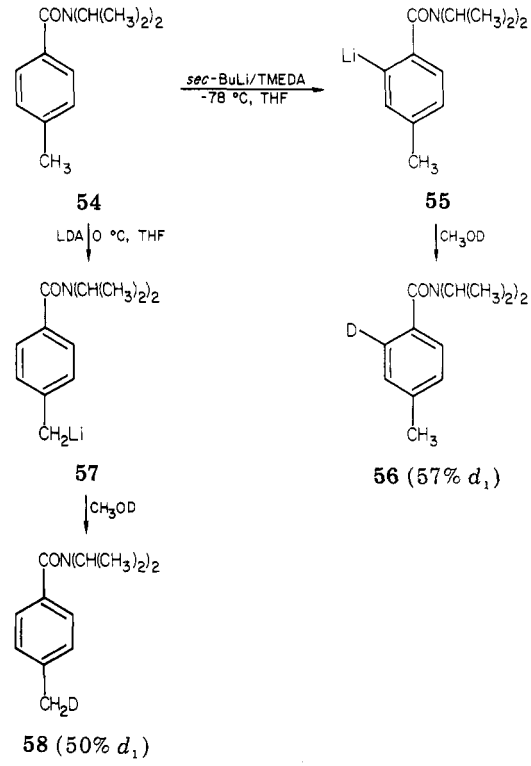
Whether the present results are attributed to kinetic and/or thermodynamic control, the effect of complexation provides a rationale.[2,23] Thus the amide is a strong binder of lithium and a preequilibrium association between the tertiary amide and the organolithium base should be favorable.[30] If this is the case, kinetic control would result from intramolecular delivery of the organolithium base to the acidic proton. Thermodynamic control could be attributed to intramolecular association of the lithium with the amide in the ortho metalated compound. The observation that the para methyl group in **21** is not deprotonated while the ortho methyl group in **42** is lithiated could be taken to indicate that complexation of the base to the amide is product controlling. A similar conclusion follows from the apparent kinetic and thermodynamic lithiations of *N,N*-diisopropyl-*p*-toluamide (**54**) (vide infra).

The dominance of the amides as ortho directors as reported herein does not appear to correspond to relative σ_I values,[31] but complexation with lithium should increase the inductive effect of both the tertiary amide and the lithiated secondary amide. If this complexation effect is important with *sec*-BuLi/TMEDA, it might be expected to be favored with coordinatively unsaturated metalating agents,[2] provided that competing nucleophilic addition does not become a favored path.

Control of the Site of Lithiation. Control of the site of lithiation in systems containing different potentially acidic protons would be useful. We have found that lithiation of *N,N*-diisopropyl-*p*-toluamide (**54**) with *sec*-BuLi/TMEDA at −78 °C occurs ortho to the amide to give **55**, as judged by isolation of **56** in 85% yield. On the other hand, reaction of **54** with lithium diisopropyl amide (LDA) at 0 °C gives **57** in which the methyl group has been metalated, as judged by isolation of **58** in 93% yield. These results are precedented by the report of Hauser et al. that **57** undergoes reaction with benzophenone and *n*-butylbromide to give the expected products in 80% and 93% yields.[26]

Although there is a temperature difference, a plausible interpretation of these results is that **55** is a product of kinetic lithiation, while **57** is the thermodynamic product. This interpretation is consistent with the above suggestions about the importance of complexation. Presumably in the metalation with LDA, the energetic advantage of complexation to the amide is greatly reduced. This result shows that for synthetic purposes, the site of lithiation and subsequent substitution can be selected by proper choice of the base.

In another attempt to control the position of metalation we have investigated the lithiation of *N,N*-diethyl-*p*-bromobenzamide.[32] Our goal was to achieve ortho lithiation in the presence of a reactive bromine to provide a compliment to the very useful halogen–metal exchanges developed by Parham and co-workers for systems which have reactive functional groups in aromatic rings. In the case of *o*-bromobenzoic acid the Parham approach provides lithium *o*-lithiobenzoate, a species which is synthetically equivalent to **2** for many purposes.[33] However, with *N,N*-diethyl-*p*-bromobenzamide we observed only halogen–metal interchange with *sec*-butyllithium and *p*-bromobenzophenone formation with phenyllithium.[10]



Value of Tertiary Carboxamides as Directors of Ortho Lithiations. The present results suggest the tertiary amide is a more powerful directing group for ortho lithiation with *sec*-BuLi/TMEDA at −78 °C in THF than all other known directing groups except possibly the secondary amide. The tertiary amide thus provides an ortho directing group which is readily prepared, is useful under mild conditions where other substituents are stable, resists attack by nucleophiles both at the carbonyl and at potentially displaceable ortho substituents, and can be converted to other functionalities at the same or different oxidation levels after a lithiation–substitution sequence. In addition, control over the site of metalation appears to be possible by the choice of the base. A disadvantage of the tertiary amide is that its hydrolysis can require severe reaction conditions, although for some cases this may be mitigated by efficient intramolecular substitution of the amide as demonstrated in the anthraquinone syntheses of Snieckus and co-workers.[6] While the high priority of the tertiary amide in these reactions is interpretable in terms of complexation effects, more information about kinetic and thermodynamic stabilities is clearly needed before this can be considered established. Regardless of the uncer-

(29) P. Beak and B. Siegel, *J. Am. Chem. Soc.*, **96**, 6803 (1974). The fact that dimeric *m*- and *p*-lithioanisole are each 8 kcal/mol less stable than dimeric *o*-lithioanisole is evidence for the operation of a complexation effect in controlling these relative thermodynamic stabilities. Extrapolation to the transition states for the lithiation step is clearly speculative.

(30) U. Olsher, G. A. Elgavish, and J. Jagur-Grodzinski, *J. Am. Chem. Soc.*, **102**, 3338 (1980); K. G. Rao, E. D. Becker, and C. N. R. Rao, *J. Chem. Soc., Chem. Commun.*, 350 (1977), and references cited therein.

(31) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley, New York, 1975, p 98.

(32) Reaction of *p*-bromophenyl ethers with phenyllithium in diethyl ether has been reported to result in lithiation ortho to the ether without significant exchange of bromine; R. G. Jones and H. Gilman, *Org. React.*, **6**, 339–366 (1951); K. Yamada, H. Yazawa, D. Uemura, M. Toda, and Y. Hirata, *Tetrahedron*, **25**, 3509 (1969); R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975).

(33) C. K. Bradsher and D. C. Reames, *J. Org. Chem.*, **43**, 3800 (1978); W. E. Parham, L. D. Jones, and Y. Sayed, *ibid.*, **40**, 2394 (1975); W. E. Parham, C. K. Bradsher, and K. J. Edgar, *ibid.*, **46**, 1057 (1981), and references cited therein.

tainties in any current interpretations, the present results should be useful in making choices in synthetic studies and for guidance in probing the factors which determine the directing priorities. For many cases, the tertiary amide appears to be the functional group of choice for directing lithiation to an adjacent position on an aromatic ring.

Experimental Section

General Procedures. Mass spectral data were obtained by Mr. C. Cook and associates on Varian MAT-CH5 and 731 mass spectrometers. Isotope ratio mass spectral data were obtained from oscillographic traces of the molecular or acylium ion region by measurement of peak heights. Field-ionization and field-desorption mass spectra were obtained in part under a grant from the National Institute of General Medical Sciences (GM 27029).

Melting points and boiling points are uncorrected. The temperatures given for micro- or Kugelrohr distillations are of those of the oil or hot air bath and not necessarily an accurate measure of the boiling points.

Materials. Tetrahydrofuran (THF) was dried by distillation of Aldrich Gold Label material under nitrogen atmosphere from sodium/benzophenone ketyl radical. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried by distillation under nitrogen from CaH_2 or $LiAlH_4$ and was stored in a nitrogen atmosphere. The titer of commercially obtained (Ventron and Aldrich) *n*-butyllithium (*n*-BuLi) and *sec*-BuLi solutions were determined by the Watson–Eastham titration procedure.[34] Solutions of *n*-BuLi were stored in serum-capped bottles in a nitrogen atmosphere, whereas solutions of *sec*-BuLi were stored at −10 °C in serum-capped bottles inside plastic bags containing indicating Drierite.

Preparation of Amides. Several amides were prepared from the acid chloride and excess amine and purified by conventional procedures. Unless otherwise noted the amides had IR, ^1H NMR and analytical properties consistent with the structure assignments.

***N,N*-Diethylbenzamide (1)**: Kugelrohr distillation 90–95 °C (0.6 mm) [lit.[35] bp 150–151 °C (15 mm)]. ***N,N*-Diisopropylbenzamide (3)**: mp 69–72 °C (lit.[36] mp 69–71 °C). ***N,N*-Dimethylbenzamide (5)**: mp 44–45 °C (lit.[37] mp 42–43 °C). ***N,N*-Diethyl-*o*-chlorobenzamide (14)**: Kugelrohr distillation 100–105 °C (0.15 mm) [lit.[38] bp 125–128 °C (0.4 mm)]. ***N,N*-Diethyl-*m*-chlorobenzamide (15)**: Kugelrohr distillation 96–97 °C (0.2 mm) [lit.[39] bp 106–108 °C (0.6 mm)]. ***N,N*-Diethyl-*p*-chlorobenzamide (16)**: bp 128–130.5 °C (1 mm) [lit.[40] bp 115 °C (0.2 mm)]. ***N,N*-Diethyl-*o*-anisamide (17)**: Kugelrohr distillation 117 °C (0.3 mm) [lit.[40] bp 100–104 °C (1 mm)]. ***N,N*-Diethyl-*m*-anisamide (18)**: lit.[41] bp 177 °C (14 mm). ***N,N*-Diethyl-*p*-anisamide (19)**: mp 42.5–43 °C (lit.[40] mp 48°). ***N,N*-Diethyl-*m*-toluamide (20)**: Kugelrohr distillation 88–90 °C (0.25 mm) [lit.[40] bp 111 °C (1 mm)]. ***N,N*-Diethyl-*p*-toluamide (21)**: mp 46–48 °C (lig.[40] mp 53.5–55.5 °C). ***N,N*-Diethyl-*o*-toluamide (42)**: bp 105 °C (0.6 mm) [lit.[40] bp 105 °C (1 mm)]. ***N,N*-Diethyl-2,6-dichlorobenzamide (48)**: mp 92–93 °C (lit.[42] mp 94–95 °C). ***N,N*-Diisopropyl-*p*-toluamide (54)**: mp 85–87.5 °C (lit.[26] mp 85–86 °C).

***N,N*-Diethyl-4-[(diethylamino)sulfonyl]benzamide (22).** *p*-Toluenesulfonic acid was oxidized by reaction with aqueous $KMnO_4$ to *p*-carboxybenzenesulfonic acid, which was treated with PCl_5 in $POCl_3$ to yield *p*-(chlorosulfonyl)benzoyl chloride. This material was treated with $HNEt_2$ and the resulting solid recrystallized from aqueous EtOH to yield **22** as white crystals: mp 96.5–97.0 °C; ^1H NMR ($CDCl_3$) δ 1.13 (t, 12 H, J = 7 Hz, CH_3), 3.2 (br s, 2 H, $CONCH_2$), 3.21 (q, 4 H, J = 7 Hz, SO_2NCH_2), 3.4 (br s, 2 H, $CONCH_2$), 7.43 (BB′, 2 H, line spacing = 8 Hz, C_2-H and C_6-H), 7.81 (AA′, 2 H, line spacing = 8 Hz, C_3-H and C_5-H); IR (Nujol) 1626 (s, C=O), 1425 (m), 1360 (m), 1342 (s, SO_2N), 1300 (m), 1290 (m), 1203 (m), 1160 (s, SO_2N), 1099 (m), 1085 (m), 1015 (m), 935 (m), 751 (m), 728 (m), 685 cm^{-1} (m); mass spectrum (70 eV), *m/e* (relative intensity) 314 (4), 313 (13), 312 (59, $M^{+\cdot}$), 311 (62), 299 (4), 298 (10), 297 (62), 242 (8), 241 (15), 240 (100, $ArC{\equiv}O^+$ and/or $ArSO_2^+$), 177 (6), 176 (28), 175 (14), 148 (11), 105 (11), 104 (29), 76 (21), 72 (11), isotope ratio (70 eV) 243 (0.991), 242 (7.298), 241 (15.2), 240 (100, $ArC{\equiv}O^+$ and/or $ArSO_2^+$), 239 (0.812).

Anal. ($C_{15}H_{24}N_2O_3S$) C, H, N, S.

***N,N*-Diethyl-4-[(methylamino)sulfonyl]benzamide (23).** Reaction of *p*-[(methylamino)sulfonyl]benzoic acid[43] with $SOCl_2$ gave a yellow oil which was added in Et_2O solution to excess aqueous diethylamine. Addition of $CHCl_3$ effected dissolution and extractive workup gave an off-white solid which was recrystallized from $CHCl_3$–EtOAc to yield a white solid which was purified by MPLC on silica, using 1:19 (v/v) EtOH–$CHCl_3$ as eluent. Recrystallization of the recovered material from CH_2Cl_2–Et_2O afforded pure **23** in 36% yield as white crystals: mp 141–142 °C; ^1H NMR ($CDCl_3$) δ 1.22 (br s, 6 H, CH_2CH_3), 2.65 (d, 3 H, J = 6 Hz, $NHCH_3$), 3.27 (br s, 2 H, CH_2), 3.52 (br s, 2 H, CH_2), 5.23 (br m, 1 H, NH), 7.48 (BB′, 2 H, line spacing = 8 Hz, C_2-H and C_6-H), 7.89 (AA′, 2 H, line spacing = 8 Hz, C_3-H and C_5-H); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.1 (br, 13, CH_2CH_3), 14.1 (br, 11, CH_2CH_3), 29.3 (31, NCH_3), 39.4 (br, 12, CH_2), 43.5 (br, 12, CH_2), 127.0 (100, C-2 and C-6), 127.5 (98, C-3 and C-5), 139.9 (25, C-4), 141.3 (24, C-1), 169.8 (19, CO); IR (KBr) 3155 (m, NH), 1610 (s, C=O), 1480 (m), 1464 (m), 1422 (m), 1330 (s, SO_2N), 1315 (m), 1295 (m), 1167 (s, SO_2N), 1102 (m), 1090 (m), 1070 (m), 849 (m), 766 (m), 728 (m), 600 (m), 588 cm^{-1} (m).

Anal. ($C_{12}H_{18}N_2O_3S$) C, H, N, S.

***N,N*-Diethyl-*p*-[(dimethylamino)methyl]benzamide (24).** To a solution of 8.84 g (38.8 mmol) of *N,N*-dimethyl-*p*-bromobenzamide in 50 mL of dry THF at 0 °C was added 66 mL of a BH_3-THF solution (0.98 M, 65 mmol) over the course of 30 min. The solution was then heated at reflux for 29 h. The solution was treated at ambient temperature with 60 mL of 6 N HCl and stirred for 30 min. After removal of THF in vacuo and basification of the residue, the basic aqueous phase was extracted with Et_2O. Drying over Na_2CO_3 and removal of solvent in vacuo left a white solid which was heated in 150 mL of 3% aqueous HCl and 25 mL of MeOH at reflux for 2 days. The cooled mixture was washed with Et_2O to remove a small amount of undissolved solid, then basified by addition of 10% NaOH, and extracted with Et_2O. Drying of the organic phase ($MgSO_4$) and removal of solvent in vacuo afforded 6.3 g of a clear liquid which was distilled, bp 112–115 °C (11–13 mm) [lit.[44] 120–121 °C (20 mm)], to give 5.44 g (76%) of *N,N*-dimethyl-*p*-bromobenzylamine as a clear, colorless liquid: ^1H NMR ($CDCl_3$) δ 2.23 (s, 6 H, CH_3), 3.34 (s, 2 H, CH_2), 7.29 (AA′BB′, 4 H, ArH); IR (film) 2976 (s), 2941 (s), 2865 (m), 2817 (s), 2777 (s), 1495 (s), 1488 (s), 1404 (m), 1362 (m), 1174 (m), 1159 (m), 1099 (m), 1070 (s), 1032 (s), 1011 (s), 856 (s), 833 (m), 795 (s), 675 cm^{-1} (m).

Anal. ($C_9H_{12}BrN$) C, H, N; Br, calcd 37.32, found 37.92.

To a solution of 5.0 g (23 mmol) of *N,N*-dimethyl-*p*-bromobenzylamine in 300 mL dry THF was added 8.7 mL (2.8 M in hexane, 24 mmol) of an *n*-BuLi solution over 30 min. The solution was stirred for 1 h, then 4.0 mL (31 mmol) of *N,N*-diethylcarbamoyl chloride was added quickly and the bath was removed after 5 min. After the solution had been allowed to warm to ambient temperature, the THF was removed in vacuo and the residue was treated with 10% aqueous HCl. The mixture was washed with Et_2O, then basified with 10% aqueous NaOH, and extracted with Et_2O. Drying ($MgSO_4$) of the extract and removal of solvent in vacuo left 6.2 g of a yellow liquid which was distilled, bp 109–111 °C (0.05 mm), to yield 3.6 g (65%) of **24** as a clear,

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(35) C. R. Hauser and H. G. Walker, Jr., *J. Am. Chem. Soc.*, **69**, 295 (1969).
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(37) L. M. Jackman, T. E. Kavanagh, and R. C. Haddon, *Org. Magn. Reson.*, **1**, 109 (1969).
(38) J. R. Geigy-A.G., Swiss Patent 268783 (1950) [*Chem. Abstr.*, **45**, 6659i (1951)].
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colorless liquid. Analytically pure **24** was obtained from a second distillation: bp 104–106.5 °C (0.04 mm); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 6 H, J = 7 Hz, CH_2CH_3), 2.24 (s, 6 H, NCH_3), 3.35 (br s, 4 H, CH_2CH_3), 3.39 (s, 2 H, NCH_2), 7.30 (s, 4 H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.6 (br, 23, CH_2CH_3), 39.7 (br, 9, CH_2CH_3), 42.3 (br, 12, CH_2CH_3), 45.4 (67, NCH_3), 64.0 (45, NCH_2), 126.3 (100, C-2 and C-6), 129.0 (98, C-3 and C-5), 136.0 (21, C-1), 140.1 (37, C-4), 171.2 (15, CO); IR (film) 2976 (m), 2865 (m), 2833 (m), 2790 (m), 1639 (s, C=O), 1456 (s), 1429 (s), 1385 (m), 1366 (m), 1316 (m), 1289 (m), 1098 (m), 1035 (m), 1022 (m), 864 cm^{-1} (m); mass spectrum (70 eV), m/e (relative intensity) 235 (8), 234 (47, $M^{+\cdot}$), 233 (25), 163 (4), 162 (33, $C{=}O^+$), 132 (10), 118 (16), 105 (16), 91 (17), 90 (21), 89 (12), 58 (100, $Me_2N{=}CH_2^+$), 42 (11), isotope ratio (70 eV) 165 (0.919), 164 (1.16), 163 (13.7), 162 (100, $C{\equiv}O^+$), 161 (4.31), 160 (6.95).

Anal. ($C_{14}H_{22}N_2O$) C, H, N.

***N,N*-Diethyl-*p*-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-benzamide (25).** To a solution of 6.33 g (24.9 mmol) of 4,4-dimethyl-2-*p*-bromophenyl-2-oxazoline[45] in 500 mL of dry THF at −78 °C was added dropwise 19 mL (1.42 M in hexane, 27.0 mmol) of an *n*-BuLi solution over a 30-min period. The solution was then stirred for 15 min before 4.25 g (313 mmol) of *N,N*-diethylcarbamoyl chloride was added dropwise over a 1-min period. The bath was removed and the reaction mixture allowed to warm to ambient temperature and aqueous KOH was added. Most of the THF was removed in vacuo and an Et_2O solution of the residue was washed with aqueous base and then dried ($MgSO_4$). Removal of solvent in vacuo afforded 8.02 g of a bright yellow oil which was subjected to Kugelrohr distillation. Purified **25** was collected at 145–150 °C (0.4 mm) as a thick, slightly yellow oil which was recrystallized from hexane to give pure **25** as a white solid: mp 99–101 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 6 H, J = 7 Hz, CH_2CH_3), 1.38 (s, 6 H, $C(CH_3)_2$), 3.37 (br s, 4 H, CH_2CH_3), 4.09 (s, 2 H, OCH_2CMe_2), 7.38 (BB′, 2 H, line spacing = 8 Hz, C_2-H and C_6-H), 7.95 (AA′, 2 H, line spacing = 8 Hz, C_3-H and C_5-H); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.3 (br, 17, CH_2CH_3), 28.4 (51, $C(CH_3)_2$), 39.2 (br, 11, NCH_2), 43.1 (br, 12, NCH_2), 67.7 (36, OCH_2), 79.2 (13, CMe_2), 126.2 (97, C-3 and C-5), 128.3 (100, C-2 and C-6), 128.7 (20, C-1), 139.9 (23, C-4), 161.4 (23, OC=N), 170.5 (18, C=O); IR (Nujol) 1647 (s, C=N), 1626 (s, C=O), 1439 (m), 1420 (m), 1356 (m), 1316 (m), 1289 (m), 1099 (m), 1067 (s), 1020 (m), 962 (m), 964 (m), 855 cm^{-1} (m); mass spectrum (70 eV), m/e (relative intensity) 275 (7), 274 (44, $M^{+\cdot}$), 273 (63), 260 (6), 259 (30), 231 (12), 204(4), 203 (27), 202 (100, $ArC{\equiv}O^+$), 201 (2), 194 (11), 160 (3), 159 (25), 158 (4), 130 (20), 105 (4), 104 (11), 103 (20), 102 (10), 101 (4), 76 (11), isotope ratio (70 eV) 205 (0.461), 204 (4.09), 203 (26.1), 202 (100, $ArC{\equiv}O^+$), 201 (2.18), 200 (0.430).

Anal. ($C_{16}H_{22}N_2O_2$) C, H, N.

***N,N*-Diethylterephtalamic Acid (26).** To a solution of 5.20 g (20.3 mmol) of *N,N*-diethyl-*p*-bromobenzamide in 200 mL of dry THF at −100 °C was added dropwise over a 3-min period 22.5 mL (1.85 M in pentane, 41.6 mmol) of *t*-BuLi solution. The solution was stirred for 40 min and gaseous CO_2 added over 15 min as the reaction mixture warmed. After aqueous NaOH was added and the THF was removed in vacuo, the residue was washed with Et_2O, acidified, and extracted with Et_2O, and the extract was dried ($MgSO_4$). Removal of solvent in vacuo left a yellow gummy solid which was dissolved in hot aqueous EtOH. Concentration and acidification with 3% aqueous HCl with cooling yielded a brown oil which was taken up in CH_2Cl_2 and dried ($MgSO_4$). Removal of solvent in vacuo afforded an off-white solid which was recrystallized from CH_2Cl_2–hexane to give **26** as 964 mg (21%) of a white solid: mp 154–157 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (br s, 6 H, CH_3), 3.27 (br s, 2 H, CH_2), 3.53 (br s, 2 H, CH_2), 7.45 (BB′, 2 H, line spacing = 9 Hz, C_2-H and C_6-H), 8.12 (AA′, 2 H, line spacing = 9 Hz, C_3-H and C_5-H); ^{13}C NMR ($CDCl_3$) δ 13.0 (br, 13, CH_3), 14.2 (br, 15, CH_3), 39.6 (br, 13, CH_2), 43.3 (br, 14, CH_2), 126.4 (88, C-2 and C-6), 130.4 (100, C-3, C-4, and C-5), 141.9 (23, C-1), 170.4 (49, CO_2H and $CONEt_2$); IR (KBr) 2980 (s), 2950 (br s, CO_2H), 2770 (m), 2605 (m), 2500 (m), 1720 (vs, HO*C*=*O*), 1630 (s), 1597 (vs, N*C*=*O*), 1570 (v s), 1515 (s), 1468 (s), 1452 (s), 1409 (m), 1387 (m), 1367 (m), 1315 (m), 1250 (v s), 1192 (m), 1176 (s), 1122 (s), 1110 (s), 1101 (s), 1020 (m), 947 (m), 869 (m), 803 (m), 793 (m), 741 (s), 710 (m), 688 cm^{-1} (m); mass spectrum (70 eV), m/e (relative intensity) 222 (2), 221 (18, $M^{+\cdot}$), 220 (31), 150 (8), 149 (100, $HO_2CC_6H_4C{\equiv}O^+$), 121 (14), 65 (24), isotope ratio (70 eV) 151 (1.18), 150 (9.746), 149 (100.0), $HO_2CC_6H_4C{\equiv}O^+$), 148 (1.00).

Anal. ($C_{12}H_{15}NO_3$) C, H, N.

***N,N*-Diethyl-2-methoxy-3-methylbenzamide (40).** The crude amide was prepared from the acid via the acid chloride and was Kugelrohr distilled [110 °C (0.45 mm)] to give a liquid which was subjected to MPLC on silica, using 1:5 (v/v) THF–hexane as eluent and Kugelrohr distillation [110 °C (0.45 mm)]. Repetition of the chromatography with 3:7 (v/v) EtOAc–hexane, followed by careful Kugelrohr distillation [95 °C (0.4 mm)], a forerun being discarded, gave **40** as a clear colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.25 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.28 (s, 3 H, $ArCH_3$), 3.15 (q, 2 H, J = 7 Hz, CH_2), 3.5 (br m, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 7.10 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.8 (70, CH_2CH_3), 13.9 (69, CH_2CH_3), 15.9 (51, $ArCH_3$), 38.9 (83, CH_2), 43.0 (81, CH_2), 61.3 (51, OCH_3), 124.0 (84, C-3 and C-5), 125.2 (92, C-6), 131.4 (57, C-1), 131.6 (100, C-4), 154.1 (17, C-2), 169.1 (17, CO); IR (film) 2967 (m), 2941 (m), 1626 (s, C=O), 1462 (s), 1422 (s), 1376 (m), 1359 (m), 1342 (m), 1309 (m), 1289 (s), 1255 (m), 1220 (s), 1120 (m), 1083 (m), 1006 (s), 841 (m), 794 (m), 767 (m) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 221 (6, $M^{+\cdot}$), 220 (13), 190 (5), 150 (10), 149 (100, $C{\equiv}O^+$), 148 (2), 91 (23), 73 (26), 58 (16), isotope ratio (70 eV) 151 (1.00), 150 (11.03), 149 (100, $C{\equiv}O^+$), 148 (3.11), 147 (0.88).

Anal. ($C_{13}H_{19}NO_2$) C, H, N.

***N,N*-Diethyl-*N*′-methylterephthalamide (50).** To a solution of 5.00 g (23.4 mmol) of *N*-methyl-*p*-bromobenzamide in 150 mL of dry THF at −78 °C was added 17.0 mL (2.80 M in hexane, 47.6 mmol) of an *n*-BuLi solution over a 20-min period. Stirring was continued for 1 h, and then 3.1 mL (24 mmol) of *N,N*-diethylcarbamoyl chloride was added quickly, the bath was removed, and the reaction mixture was stirred under ambient conditions for 40 min and then in a 50 °C bath for 30 min. The THF was removed in vacuo and an ether solution of the residue was washed with aqueous HCl and then saturated brine. After drying ($MgSO_4$), removal of solvent in vacuo left 4.35 g (80%) of a yellow oil which was filtered through basic alumina and then silica gel and separated by MPLC on silica, using 2:3 (v/v) EtOAc–$CHCl_3$ as eluent. Fractions containing the desired material were combined and subjected to MPLC on silica, using 1:19 (v/v) EtOH–$CHCl_3$ as eluent. The white solid which was thus obtained was recrystallized from $CHCl_3$–Et_2O to give **50** as 718 mg (13%) of a white solid: mp 137.0–137.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (br s, 6 H, CH_2CH_3), 3.00 (d, 3 H, J = 5 Hz, $NHCH_3$), 3.4 (br s, 4 H, CH_2CH_3), 6.80 (br s, 1 H, NH), 7.32 (BB′, 2 H, line spacing = 7.5 Hz, C_2-H and C_6-H), 7.73 (AA′, 2 H, line spacing = 7.5 Hz, C_3-H and C_5-H).

***N,N*-Diethyl-*p*-bromobenzamide.** The crude amide was prepared from the acid via the acid chloride and purified by recrystallization to give **60** as a white solid: mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 6 H, J = 7 Hz, CH_3), 3.4 (br s, 4 H, CH_2), 7.21 (BB′, 2 H, line spacing = 9 Hz, C_2-H and C_6-H), 7.50 (AA′, 2 H, line spacing = 9 Hz, C_3-H and C_5-H); IR (KBr) 2985 (w), 1630 (s, C=O), 1592 (m), 1475 (m), 1460 (m), 1440 (m), 1435 (m), 1390 (m), 1368 (m), 1316 (m), 1292 (m), 1094 (m), 1081 (m), 1069 (m), 1014 (m), 849 (m), 831 (m), 755 cm^{-1} (m).

Anal. ($C_{11}H_{14}BrNO$) C, H, Br, N.

Lithiation of Amides. Unless otherwise specified, all reactions were performed in oven-dried glassware under a nitrogen atmosphere, by addition of a solution of the amide in dry THF dropwise to a cold stirred solution of a 1:1 alkyllithium–TMEDA complex in dry THF at −78 °C. After a reaction period, the mixture was treated with an electrophilic reagent at −78 °C. After the reaction mixture had been allowed to warm to ambient temperature, water was added and the THF was removed in vacuo. An Et_2O solution of the residue was washed with aqueous base and aqeous acid and dried ($MgSO_4$). Removal of solvent in vacuo gave the crude product. Products were purified by recrystallization, distillation, or chromatography, as indicated. For deuterated products, the position and extent of deuteration was determined by ^{13}C NMR and ^{1}H NMR spectroscopy and mass spectrometry.

Assignment of Position of Deuteration. We used the es-

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Table III. ^{13}C NMR Substituent Shifts ($\Delta\delta$) of Monosubstituted Benzenes in $CDCl_3$[a]

substituent	carbon Δδ values ipso	ortho	meta	para	source
$CONMe_2$	+8.1	−1.4	−0.2	+1.0	*b*
$CONEt_2$	+8.8	−2.2	−0.1	+0.6	*c, d*
$CON(i\text{-}Pr)_2$	+10.5	−3.0	−0.1	0.0	*c, d*
OMe	+31.1	−14.6	+1.0	−7.8	*c*
	+31.4	−14.4	+1.0	−7.7	*e*
Me	+9.4	+0.6	−0.3	−3.2	*c*
	+8.9	+0.7	−0.1	−2.9	*e*
Cl	+6.0	+0.3	+1.4	−1.9	*c*
	+6.2	+0.4	+1.3	−1.9	*e*
Br	−6.0	+3.1	+1.5	−1.7	*c*
	−5.5	+3.4	+1.7	−1.6	*e*
CH_2NMe_2	+10.4	+0.6	−0.3	−1.5	*c*
	+11.0	+0.6	0.0	−1.3	*f*
	0.0	0.0	0.0	+2.9	*c*
	+0.4	−0.2	0.0	+3.3	*g*
SO_2NEt_2	+12.1	−1.5	+0.5	+3.7	*c*
	+12.3	−1.1	+0.5	+5.1	*h*
SO_2NMe	+10.1	−1.4	+0.6	+4.3	*c*
CO_2H	+2.1	+1.5	0.0	+5.1	*e*
	+1.3	+2.0	+0.1	+4.6	*f*

[a] Shifts are reported in terms of parts per million (δ) relative to the benzene resonance at δ 128.5. Positive values correspond to downfield shifts. [b] Reference 14. [c] Experimental values, obtained in $CDCl_3$. [d] Meta and ortho carbons are assigned by analogy to values reported[14] for $PhCONMe_2$. [e] Reference 13. [f] Calculated from the spectrum of the *p*-$CONEt_2$. [g] Calculated from the spectrum of the *p*-Br derivative. [h] Calculated from the spectrum of the *p*-Me derivative.

tablished additivity of individual ^{13}C NMR substituent shifts, which are shown in Table III and which were determined from the ^{13}C NMR spectra of mono- and disubstituted benzenes.[13] The position of each signal is presented in terms of a substituent shift, which expresses the direction and magnitude of that carbon's chemical shift difference from 128.5 ppm, the reported chemical shift of benzene.[13] Assignments for the benzyl amine, oxazoline, and tertiary sulfonamide were made following examination of the ^{13}C NMR spectra of para-substituted *N,N*-diethylbenzamide derivatives. In each case, subtraction of the known substituent shifts for the para substituent gave approximate values for the desired substituent shifts and indicated the correct assignments in the parent compound.[10]

The additive nature of substituent shifts in ^1H NMR spectra provides an alternative method of determination of the site of deuteration. Furthermore, the extent of deuteration can be estimated from the ^1H NMR integration values. Shown in Table IV are the ^1H NMR substituent shifts for the various functional groups involved in this study. The values for the functionalities in the first five entries of Table IV were taken from the literature.[16] The values for all the other functional groups in Table IV were calculated from para-substituted derivatives.[10]

The location of the deuterium in **27–39** was determined by analysis of the ^{13}C NMR (Table V) and ^1H NMR (Table VI) spectra of the starting amides and deuterated products (vide supra). Listed in Table V are the observed chemical shifts and relative intensities of the signals for the aromatic carbons of the substituted benzamides listed in Table II, along with the predicted chemical shifts, which were calculated with the substituent shifts given in Table III. For the para- and meta-substituted benzamides, the experimental and calculated values agree within 0.9 ppm, while 92% of the values agree within 0.6 ppm, a value which is smaller, in most cases, than the difference in chemical shifts of potentially acidic carbons. For the ortho-substituted and 2,3- and 2,6-disubstituted benzamides, the errors are larger than for the above cases but still smaller than the chemical shift differences between potentially competitive lithiation sites. Thus, the close

Table IV. Ortho and Meta ^1H NMR Substituent Shifts ($\Delta\delta$) of Substituted Benzenes[a]

substituent	Δδ ortho	meta	source
Me	−0.17	−0.09	*b*
OMe	−0.43	−0.09	*b*
Cl	+0.02	−0.06	*b*
Br	+0.22	−0.13	*b*
CO_2H	+0.80	+0.14	*b*
$CONEt_2$	+0.10	+0.04	*c*
CH_2NMe_2	−0.01	−0.07	*d*
CH_2NMe_2	+0.02	−0.06	*e*
	+0.64	+0.01	*d*
	+0.64	−0.01	*e*
SO_2NEt_2	+0.50	+0.06	*d*
SO_2NMe_2	+0.47	+0.11	*d*
SO_2NHMe	+0.58	+0.11	*d*
SO_2NHMe	+0.58	+0.10	*e*
$CONHMe$	+0.42	−0.05	*d*
$CONHMe$	+0.50	+0.03	*e*
$CONHEt$	+0.45	−0.06	*d*
$CONHEt$	+0.44	−0.05	*e*
$CONMe_2$	+0.11	0	*e*

[a] Spectra were obtained in $CDCl_3$. Substituent shifts are reported in terms of δ relative to the benzene resonance at δ 7.27; positive values correspond to downfield shifts. [b] Reference 16. [c] Average of values calculated from spectra of para-substituted *N,N*-diethylbenzamides. [d] Calculated from the spectrum of the *p*-$CONEt_2$ derivative. [e] Calculated from the spectrum of the *p*-Br derivative.

agreement between calculated and experimental chemical shifts allows unambiguous assignment of the aromatic signals, except for the competitions with the *p*-sulfonamide groups. In this case, comparison of the signal intensities in the spectra of starting material and product reveals the site of deuterium incorporation by a reduction in the intensity of that carbon's signal.

Confirmation, both of the extent and position of deuterium incorporation, is provided by the ^1H NMR spectra of the amide starting materials and products, as listed in Table VI.

For each of the following lithiations, the details of the metalation procedure are summarized in parentheses. The following format is used: number of molar equivalents and identity of the alkyllithium reagent used, molarity of the amide after mixing with base, reaction temperature, lithiation time, number of molar equivalents and identity of the electrophile used, variations in the procedure for isolation of the crude product from the general procedure described above.

***N,N*-Diethyl-2-deuteriobenzamide (4, R = C_2H_5).** From 860 mg of *N,N*-diethylbenzamide (1.0 *sec*-BuLi–TMEDA, 0.15 M, −78 °C, 20 min, 20 D_2O) 0.90 g of crude benzamide was isolated. Column chromatography on silica, using EtOAc as eluent, gave 756 mg (88%) of a slightly yellow viscous liquid: ^1H NMR ($CDCl_3$) δ 1.16 (t, 6 H, J = 7 Hz, CH_3), 3.41 (q, 4 H, J = 7 Hz, CH_2), 7.38 (s, 4 H, ArH). Samples for spectral and elemental analyses were obtained by gas chromatography (9 ft × 0.25 in. SF 96); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 13.5 (br, 29, CH_3), 39.5 (br, 10, CH_2), 42.8 (br, 9, CH_2), 126.3 (67, C-6), 128.3 (100, C-3 or C-5), 128.4 (92, C-3 or C-5), 129.1 (65, C-4), 137.3 (25, C-1), 171.3 (15, CO); IR (film) 2960 (m, CH), 2925 (m, CH), 2240 (w, CD), 1640 (s, CO), 1490 (m), 1465 (m), 1430 (s), 1387 (m), 1370 (m), 1320 (m), 1290 (s), 1224 (m), 1097 (m), 780 (m), 730 cm^{-1} (s); mass spectrum, *m/e* (relative intensity) isotope ratio (field ionization) 180 (0.96), 179 (12.52), 178 (100, $M^{+\cdot}$), 177 (13.71), 176 (3.40), (70 eV) 108 (0.62), 107 (8.60), 106 (100, $C{\equiv}O^+$), 105 (5.69), 104 (0.28).

Anal. $C_{11}H_{14}DNO$: C, N, calcd for D(H) 9.04, found H, 8.70.

Reaction of *N,N*-Dimethylbenzamide (5) with *sec*-BuLi–TMEDA To Yield α-Methylbutyrophenone (6) and *N,N*-Dimethyl-*o*-benzoylbenzamide (7). From 530 mg of **5** (1.1 *sec*-BuLi–TMEDA, amide solution added quickly rather than dropwise, 68 mM, −78 °C, 1 h, 15 D_2O), the crude product was obtained and separated by column chromatography on silica, using first $CHCl_3$ and then 3:7 (v/v) Et_2O–$CHCl_3$ as eluent. With $CHCl_3$, 69 mg of a yellow oil was collected. The ^1H NMR of the

Table V. Calculated and Experimental Aromatic ^{13}C NMR Shifts for Substituted Benzamides

compd, H (D)	carbon[a]	δ calcd	δ H exptl (rel int)	δ D exptl (rel int)	compd, H (D)	carbon[a]	δ calcd	δ H exptl (rel int)	δ D exptl (rel int)
1 (2)	1		137.3 (13)	137.3 (25)	21 (34)	1	134.1	134.7 (16)	134.3 (16)
	2, 6		126.3 (100)	126.3 (65)		2, 6	126.0	126.6 (100)	126.4 (58)
	3, 5		128.4 (85)	128.3 (100)		3, 5	129.0	129.2 (95)	129.0 (100)
				128.4 (92)		4	138.5	139.3 (25)	139.0 (19)
	4		129.1 (46)	129.1 (65)					
					22 (35)	1	141.0	141.1 (49)	
3 (4)	1		139.0 (12)	138.9 (11)		2, 6	126.8	127.0 (100)[b]	
	2, 6		125.5 (100)	125.6 (50)		3, 5	126.9	127.4 (95)[b]	
	3, 5		128.4 (98)	128.3 (86)		4	141.2	141.1 (49)	
				128.4 (100)					
	4		128.5 (71)	128.5 (79)	24 (37)	1	135.8	136.0 (21)	136.0 (21)
						2, 6	126.0	126.3 (100)	126.4 (73)
14 (27)	1	137.6	137.0 (23)	136.9 (14)		3, 5	129.0	129.0 (98)	129.0 (100)
	2	132.3	130.4 (26)	130.1 (89)		4	129.5	140.1 (37)	140.0 (31)
	3	128.7	129.8 (100)	129.8 (100)					
	4	130.5	130.1 (99)	130.1 (89)	23 (36)	1	141.6	141.3 (24)	
	5	126.5	127.3 (95)	127.1 (80)		2, 6	126.9	127.0 (100)[c]	
	6	127.7	127.7 (91)	127.7 (17)		3, 5	127.0	127.5 (98)[c]	
						4	139.2	139.9 (25)	
15 (28)	1	138.7	139.3 (23)	139.1 (17)					
	2	126.6	126.8 (84)	126.8 (17)	25 (38)	1	140.2	139.9 (23)	139.8 (29)
	3	134.4	134.7 (36)	134.6 (15)		2, 6	126.3	126.2 (97)	126.2 (63)
	4	129.4	129.5 (100)	129.5 (100)		3, 5	128.4	128.3 (100)	128.2 (100)
	5	129.8	130.1 (89)	130.1 (98)		4	128.1	128.7 (20)	128.7 (20)
	6	124.4	124.6 (88)	124.6 (91)					
					26 (39)	1	142.4	141.9 (23)	141.8 (29)
16 (29)	1	135.4	135.6 (12)	135.6 (45)		2, 6	126.3	126.4 (88)	126.4 (67)
	2, 6	127.7	127.8 (78)	128.0 (63)		3, 5	129.9	130.4 (100)	130.3 (100)
	3, 5	128.7	128.6 (100)	128.7 (100)		4	131.2	130.4 (100)	130.3 (100)
	4	135.1	135.1 (13)	135.2 (78)					
					40 (41)[d]	1	127.6	131.4 (57)	131.6 (89)
17 (30)	1	122.7	127.3 (34)	127.6 (18)		2	156.1	154.1 (17)	154.1 (15)
	2	157.4	155.5 (34)	155.5 (18)		3	120.6	124.0 (84)	123.9 (100)
	3	113.8	111.2 (92)	111.2 (97)		4	130.7	131.6 (100)	131.6 (89)
	4	130.1	130.1 (100)	130.1 (99)		5	120.7	124.0 (84)	123.9 (100)
	5	120.6	121.0 (84)	120.8 (100)		6	124.5	125.2 (92)	
	6	127.3	127.7 (92)	127.6 (18)					
18 (31)	1	138.3	138.6 (14)	138.6 (19)	42	1	137.9	137.2 (20)	
	2	111.7	111.8 (82)			2	135.7	133.9 (27)	
	3	159.8	159.6 (20)	159.5 (17)		3	129.0	130.3 (92)	
	4	114.5	114.9 (100)	115.0 (89)		4	128.8	128.5 (99)	
	5	129.4	129.5 (82)	129.5 (100)		5	125.2	125.5 (86)	
	6	118.5	118.3 (89)	118.4 (76)		6	126.0	125.8 (100)	
19 (32)	1	129.5	129.6 (15)	129.3 (30)	48 (49)[e]	1	137.3	135.9 (13)	135.9 (14)
	2, 6	127.3	128.2 (98)	128.1 (55)		2, 6	132.8	131.8 (34)	131.8 (37)
	3, 5	113.8	113.6 (100)	113.4 (100)		3, 5	127.8	128.1 (100)	128.1 (81)
				113.5 (87)		4	131.5	130.0 (55)	129.9 (100)
	4	160.2	160.3 (13)	160.2 (13)					
20 (33)	1	137.0	137.3 (33)	137.2 (20)					
	2	126.9	126.9 (100)	127.0 (65)					
	3	137.8	138.1 (34)	138.3 (23)					
	4	129.7	129.7 (98)	129.8 (100)					
	5	128.1	128.2 (96)	128.1 (91)					
	6	123.1	123.1 (98)	123.2 (35)					

[a] Carbon 1 bears the amide function. [b,c] These assignments may be reversed. [d] The calculated values were obtained by adding the substituent shifts for CH_3 to the carbon chemical shifts of *N,N*-diethyl-*o*-anisamide, 17. [e] The calculated values were obtained by adding the substituent shifts for Cl to the carbon chemical shifts of *N,N*-diethyl-*o*-chlorobenzamide, 14.

material revealed it to be α-methylbutyrophenone, 6 (14%) [lit.[46] bp 109 °C (13 mm)]. With 30% $Et_2O/CHCl_3$ as eluent, 116 mg (26%) of *N,N*-dimethyl-*o*-benzoylbenzamide (7) was obtained, spectrally identical with authentic material, prepared from *o*-benzoylbenzoic acid: Kugelrohr distillation 165 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 2.80 (s, 6 H, CH_3), 6.9–7.6 (m, 9 H, ArH); IR (KBr) 3050 (m), 1660, 1630 (s, C=O).

Anal. ($C_{16}H_{15}O_2N$) C, H, N.

Reaction of *N,N*-Diethylbenzamide (1) in Diethyl Ether. From 415 mg 1 (1.1 *sec*-BuLi–TMEDA, 45 mM in Et_2O, −78 °C, 5 min, 10 CH_3OD), the crude product was isolated as 390 mg of a pale yellow viscous liquid. Microdistillation [120 °C (0.5 mm)] gave 280 mg (67%) of a clear colorless liquid which, by ^1H NMR and IR spectral characteristics, was a mixture of starting material (presumably partially deuterated) and α-methylbutyrophenone. Separation was accomplished by column chromatography on silica, using 3:7 (v/v) EtOAc–hexane as eluent, giving 53 mg (14%) of α-methylbutyrophenone: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.17 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.66 (m, 2 H, CH_2), 3.36 (sextet, 1 H, J = 7 Hz, CH), 7.4 (m, 3 H, C_3-H, C_4-H, and C_5-H), 7.9 (m, 2 H, C_2-H and C_6-H); IR (film) 2950 (s), 2850 (m), 1685 (s, C=O), 1590 (m), 1570 (m), 1455 (s), 1440 (s), 1370 (m), 1290 (m), 1260 (m), 1220 (s), 1215 (s), 1160 (m), 1003 (m), 975 (s), 957 (m), 793 (m), 735 (m), 703 cm^{-1} (s).

Reaction of *N,N*-Diethylbenzamide (1) with *n*-BuLi To Yield Valerophenone. A 1.2-mL portion of *n*-BuLi solution (2.8

(46) J.-P. Guetté and A. Horeau, *Bull. Soc. Chim. Fr.*, 1747 (1965).

Table VI. ^{1}H NMR Data of Substituted *N,N*-Diethylbenzamides[a]

para substituent	hydrogens	protio (intensity)[b]	deuterio (intensity)[b]	% d ^{1}H NMR	% d MS
Me	2, 6	7.22 (~2)	7.2 (3.0)	100	98
	3, 5	7.11 (~2)			
OMe	2, 6	7.34 (2.1)	7.33 (0.99)	100	94
	3, 5	6.89 (2.0)	6.88 (2.1)		
Cl	2, 3, 5, 6	7.38 (4.3)	7.32 (2.9)	110	99
CO_2H	2, 6	7.45 (2.0)	7.45 (1.3)	70	82
	3, 5	8.12 (1.8)	8.08 (2.6)		
CH_2NMe_2	2, 3, 5, 6	7.30 (3.9)	7.30 (3.1)	90	67
	2, 6	7.38 (1.9)	7.40 (0.9)	110	98
	3, 5	7.95 (1.8)	7.98 (2.2)		
SO_2NEt_2	2,6	7.43 (2.1)	7.44 (1.4)	60	45
	3, 5	7.81 (1.9)	7.80 (2.3)		
SO_2NHMe	2, 6	7.48 (2.0)	7.48 (1.2)	80	76
	3, 5	7.89 (2.0)	7.66 (1.8)		
CONHMe	2, 6	7.32 (2.3)	7.23 (2.0)		
	3, 5	7.73 (1.9)	7.75 (1.4)	60	
CONHEt	2, 6	7.31 (2.2)	7.23 (2.0)		
	3, 5	7.76 (1.9)	7.75 (1.3)	70	

[a] Spectra obtained in $CDCl_3$ solution. Chemical shifts are reported in parts per million (δ) downfield from Me_4Si. [b] Integrated area vs. 4.0 for the two methylenes of the amide function.

M in hexane, 3.36 mmol) was dissolved in 5 mL of dry THF and then added dropwise to a cold (−78 °C) stirred solution of 600 mg (3.37 mmol) of **1** in 20 mL of dry THF over 2.5 min. After 30 min, 2 mL (16 mmol) of chlorotrimethylsilane was added and the bath was removed. Extractive workup with CH_2Cl_2 and drying of the organic phase ($MgSO_4$) led to the isolation of an oil. Column chromatography using 3:7 (v/v) EtOAc–hexane as eluent gave 170 mg of a liquid whose ^{1}H NMR and IR spectra are identical with published spectra of valerophenone (31% yield):[47] ^{1}H NMR ($CDCl_3$, CH_2Cl_2 internal reference at δ 5.28) δ 0.97 (t, 3 H, J = 10.5 Hz, CH_3), 1.1–2.0 (m, 4 H, $PhCOCH_2CH_2CH_2CH_3$), 2.88 (t, 2 H, J = 10.5 Hz, $PhCOCH_2$), 7.2–7.6 (m, 3 H, C_3-H, C_4-H, and C_5-H), 7.8–8.1 (m, 2 H, C_2-H and C_6-H); IR (film) 2920 (s), 2850 (m), 1685 (s, C=O), 1600 (m), 1550 (w), 1455 (m), 1440 (m), 1260 (m), 1210 (m), 753 (m), 690 cm^{-1} (m).

***N,N*-Diisopropyl-*o*-deuteriobenzamide (4, R = $CH(CH_3)_2$).** From 729 mg of *N,N*-diisopropylbenzamide (1.1 *sec*-BuLi/TMEDA, 68 mM, −78 °C, 1 h, 16 D_2O), the crude product was obtained as 793 mg of a clear oil, which was sublimed [70 °C (0.25 mm)] to give 657 mg (90%) of **4** (R = $CH(CH_3)_2$) as a white solid: mp 67–71 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 12 H, J = 6.5 Hz, CH_3), 3.70 (septet, 2 H, J = 6.5 Hz, CH), 7.37 (s, 4 H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 20.7 (207, CH_3), 48.2 (17, CH), 125.6 (50, C-6), 128.3 (86, C-3 or C-5), 128.4 (100, C-3 or C-5), 128.5 (79, C-4), 138.9 (11, C-1), 171.0 (7, CO); IR (Nujol) 1630 (s, C=O), 1600 (m), 1342 (s), 1214 (m), 1160 (m), 1035 (m), 790 cm^{-1} (m); mass spectrum, *m/e* (relative intensity) isotope ratio (field ionization) 207 (16), 206 (100, $M^{+\cdot}$), 205 (5.9), (70 eV) 108 (0.623), 107 (8.82), 106 (100, $C{\equiv}O^+$), 105 (2.04), 104 (0.324), 103 (0.0584).

In another experiment, reaction of 292 mg of *N,N*-diisopropylbenzamide (1.1 *n*-BuLi–TMEDA, 0.44 M, −78 °C, 30 min, 9 CH_3OD) gave 286 mg (98%) of an off-white solid. MPLC using 1:9 (v/v) THF–hexane as eluent, followed by MPLC using 1:9 (v/v) EtOAc–hexane as eluent gave **4** (R = $CH(CH_3)_2$) as 257 mg (88%) of a white solid: mp 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 12 H, J = 7 Hz, CH_3), 3.67 (septet, 2 H, J = 7 Hz, CH), 7.33 (s, 4 H, ArH); mass spectrum, *m/e* (relative intensity) isotope ratio (70 eV) 108 (0.61), 107 (8.52), 106 (100, $C{\equiv}O^+$), 105 (4.91), 104 (0.31).

(47) "Sadtler Standard Spectra", Sadtler Research Laboratories, Philadelphia, PA; ^{1}H NMR No. 8673; IR No. 11920.

***N,N*-Diethyl-*o*-toluamide (8, E = CH_3).** From 570 mg of *N,N*-diethylbenzamide (1.1 *sec*-BuLi–TMEDA, 85 mM, −78 °C, 1 h, 2.5 CH_3I), the crude product was obtained as 1.10 g of a dark yellow oil. Column chromatography on silica, using EtOAc as eluent, gave 813 mg (95%) of a yellow liquid, microdistillation of which [90 °C (0.7 mm), lit.[40] bp 105 °C (1 mm)] gave 664 mg (77%) of **8** (E = CH_3) as a clear colorless viscous liquid: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 6.5 Hz, CH_3), 1.23 (t, 3 H, J = 6.5 Hz, CH_3), 2.29 (s, 3 H, $ArCH_3$), 3.11 (q, 2 H, J = 6.5 Hz, CH_2), 3.57 (q, 2 H, J = 6.5 Hz, CH_2), 7.30 (m, 4 H, ArH), plus 1.90 (s, 0.2 H, impurity).

***N,N,o*-Triethylbenzamide (8, E = C_2H_5).** From 224 mg of *N,N*-diethylbenzamide (1.0 *sec*-BuLi–TMEDA, 0.13 M, −78 °C, 15 min, 2.0 EtI), the crude product (**8**, E = C_2H_5) was obtained as 181 mg (70%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, $ArCH_2CH_3$), 1.23 (t, 3 H, J = 7 Hz, NCH_2CH_3), 1.26 (t, 3 H, J = 7 Hz, NCH_2CH_3), 2.62 (q, 2 H, J = 7 Hz, $ArCH_2$), 3.10 (q, 2 H, J = 7 Hz, NCH_2), 3.53 (br s, 2 H, NCH_2), 7.50 (m, 4 H, ArH).

***N,N*-Diethylsalicylamide (8, E = OH).** The procedure of Kidwell et al. was followed.[48] To 0.40 mL of TMEDA (2.6 mmol) in 40 mL of dry THF at −78 °C was added dropwise 2.0 mL (1.3 M in cyclohexane, 2.6 mmol) of a *sec*-BuLi solution. After several minutes, a solution of 0.41 g (2.3 mmol) of *N,N*-diethylbenzamide in 15 mL of dry THF was added dropwise over a 10-min period. After another 5 min, the solution was cannulated over a 20-min period into another flask containing a cold (−78 °C) solution of 0.30 mL (2.6 mmol) of trimethyl borate in 25 mL of dry THF. After completion of the transfer, the bath was replaced by an ice bath and the solution was maintained at 0 °C for 1 h. Addition of 200 μL of glacial HOAc in one quantity, followed immediately by the dropwise addition of 500 μL of 30% H_2O_2, gave a solution which was allowed to stir overnight at ambient temperature. Some Et_2O and H_2O were added, and the reaction mixture was washed 3 times with a 10% (w/v) aqueous solution of $Fe(NH_4)_2(SO_4)_2$ saturated with $(NH_4)_2SO_4$ and once with a saturated brine solution. The organic phase was then extracted with 5% KOH. The aqueous phase was acidified and extracted twice with ether, and the combined ether extracts were dried ($MgSO_4$). Removal of solvent in vacuo afforded 580 mg of a thick yellow liquid which was separated by preparative TLC (two plates, 3:7 (v/v) EtOAc–hexane as eluent, four elutions). Trituration of the silica in hot methanol, filtration through a Celite bed, and removal of solvent in vacuo gave 253 mg (56%) of **8** (E = OH) as a thick yellow oil [lit. bp.[49] 146–148 °C (14 mm), lit. mp[50] 103–104 °C]; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 6 H, J = 7 Hz, CH_3), 3.48 (q, 4 H, J = 7 Hz, CH_2), 6.84 (m, 2 H, ArH), 7.22 (m, 2 H, ArH), 9.37 (br s, 1 H, OH).

3,3-Dimethyl-1(3*H*)-isobenzofuranone (9, R = R′ = CH_3). From 240 mg of *N,N*-diethylbenzamide (1.0 *sec*-BuLi, 52 mM, −78 °C, 5 min, 1.0 $(CH_3)_2CO$), the crude product was isolated as 194 mg (88%) of a yellow oil. Chromatography by preparative TLC involved three elutions with 1:4 (v/v) EtOAc–hexane, trituration of the silica with hot methanol, filtration, removal of methanol in vacuo, trituration of the residue with CH_2Cl_2, filtration, and removal of solvent in vacuo. This procedure gave 119 mg (54%) of **9** (R = R′ = CH_3): mp 68–69.5 °C (lit.[51] 67–68 °C); ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6 H, CH_3), 7.67 (m, 4 H, ArH); IR (KBr) 2997 (m), 1765 (s, C=O), 1619 (m), 1474 (m), 1369 (m), 1340 (m), 1292 (s), 1237 (m), 1133 (m), 1094 (m), 1046 (s), 950 (m), 905 (m), 765 (m), 699 (m), 620 (m), 556 cm^{-1} (m).

3,3-Diphenyl-1(3*H*)-isobenzofuranone (9, R = R′ = C_6H_5). From 0.60 g of *N,N*-diethylbenzamide (1.1 *sec*-BuLi/TMEDA, 87 mM, −78 °C, 1 h, 1.1 Ph_2CO), the crude product was isolated as 1.55 g of a yellow viscous oil which was recrystallized from Et_2O–hexane to give 854 mg (65%) of **9** (R = R′ = C_6H_5) as a slightly yellow solid: mp 118–121 °C (lit.[52] mp 118–120 °C); ^{1}H NMR ($CDCl_3$) δ 7.10–7.95 (ArH); IR (Nujol) 1767 (s, C=O), 1295 (m), 1265 (m), 1115 (m), 1076 (m), 965 (m), 947 (m), 932 (m), 770 (m), 762 (m), 705 cm^{-1} (m).

(48) R. L. Kidwell, M. Murphy, and S. Darling, *Organic Synthesis*", Vol. 5, Wiley-Interscience, New York, 1973, p 918.
(49) J. A. van Allen, *J. Am. Chem. Soc.*, **69**, 2913 (1947).
(50) M. P. Couturier, *Ann. Chem.*, **10**, 566 (1938).
(51) H. Bauer, *Chem. Ber.*, **37**, 735 (1904).
(52) F. Rottering, *Jahr. Fortschr. Chem.*, 596 (1875).

3-Phenyl-1(3*H*)-isobenzofuranone (9, R, R′ = C_6H_5, H). From 230 mg of *N,N*-diethylbenzamide (1.1 *sec*-BuLi/TMEDA, 50 mM, −78 °C, 20 min, 1.1 PhCHO), the crude product was isolated as 330 mg of a yellow solid, which was heated in toluene at reflux for 3 h. Removal of solvent in vacuo gave 325 mg of a dark yellow solid, recrystallization of which from Et_2O–hexane, accompanied by treatment with activated charcoal, gave 153 mg (56%) of 9 (R, R′ = C_6H_5, H) as a yellowish solid: mp 115–115.5 °C (lit.[52] mp 115 °C); ^1H NMR ($CDCl_3$) δ 6.40 (s, 1 H, OCH), 7.42 (m, 8 H, C_6H_5, C_4-H, C_5-H, and C_6-H), 8.00 (m, 1 H, C_7-H); IR (KBr) 1760 (s, C=O), 1470 (m), 1461 (m), 1340 (m), 1311 (m), 1302 (m), 1292 (s), 1215 (m), 1104 (m), 1075 (s), 1018 (m), 970 (s), 765 (m), 745 (s), 713 (m), 702 (s), 691 (m), 625 cm^{-1} (m).

From 233 mg of *N,N*-diisopropylbenzamide (1.1 *n*-BuLi/TMEDA, 0.11 M, −78 °C, 20 min, 1.2 PhCHO), 445 mg of a yellow oil was isolated and then heated in toluene at reflux for 3 h. Solvent removal in vacuo left 328 mg of a slightly yellow solid which was recrystallized from Et_2O–hexane to give 189 mg (79%) of a white solid: mp 115.5–116 °C; ^1H NMR ($CDCl_3$) δ 6.38 (s, 1 H, OCH), 7.40 (m, 8 H, C_6H_5, C_4-H, C_5-H, and C_6-H), 7.93 (m, 1 H, C_7-H). The IR spectrum was identical with that of the material isolated from the above reaction.

***N,N*-Diisopropyl-*o*-bromobenzamide (8, E = Br).** From 290 mg of *N,N*-diisopropylbenzamide (1.1 *sec*-BuLi/TMEDA, 0.33 M, −78 °C, 15 min, 2.1 CH_2=$CHCH_2Br$), the crude product was obtained and purified by preparative TLC, using 2:3 (v/v) EtOAc–hexane as eluent to give 240 mg (60%) of an off-white solid which was sublimed [110 °C (0.05 mm)] and then recrystallized from Et_2O–hexane to give 52 mg (13%) of a white solid: mp 141–145 °C; ^1H NMR ($CDCl_3$) δ 1.06 (t, 3 H, J = 7 Hz, CH_3), 1.25 (t, 3 H, J = 7 Hz, CH_3), 1.57 (t, 3 H, J = 7 Hz, CH_3), 1.59 (t, 3 H, J = 7 Hz, CH_3), 3.52 (septet, 1 H, J = 7 Hz, CH), 3.59 (septet, 1 H, J = 7 Hz, CH), 7.0–7.6 (m, 4 H, ArH); mass spectrum (70 eV), *m/e* (relative intensity) 285 (8), 284 (6), 283 (8, $M^{+\cdot}$), 282 (4), 242 (26), 240 (23), 204 (10), 185 (100), 183 (98, $C{\equiv}O^+$), 157 (21), 155 (19), 105 (22), 84 (11), 77 (24), 76 (20), 75 (15), 70 (12); IR (KBr) 2987 (m), 1636 (s, C=O), 1592 (m), 1563 (m), 1477 (m), 1443 (s), 1428 (m), 1373 (s), 1345 (s), 1213 (m), 1033 (m), 773 cm^{-1} (s).

Anal. ($C_{13}H_{18}BrNO$) C, H, Br, N.

***N,N*-Diisopropyl-2,6-dideuteriobenzamide (12).** To a solution of 977 mg (4.76 mmol) of *N,N*-diisopropylbenzamide and 270 μL (4.77 mmol) of TMEDA in 10 mL of dry THF at −78 °C was added dropwise 2.0 mL (2.38 M in hexane, 4.76 mmol) of an *n*-BuLi solution. After 10 min, 200 μL (4.92 mmol) of CH_3OD was injected, followed by the dropwise addition of 2.1 mL (5.00 mmol) of the *n*-BuLi solution. After 10 min, 500 μL (12 mmol) of CH_3OD was added and the bath was removed. After the solution had warmed to ambient temperature, some Et_2O was added, and the solution was extracted with 10% aqueous HCl and then dried ($MgSO_4$). Removal of solvent in vacuo left 1.14 g of a yellowish liquid. Flash chromatography on silica, using 3:17 (v/v) EtOAc–hexane, Kugelrohr distillation, and recrystallization from hexane gave 513 mg (52%) of a white solid: mp 69.5–70 °C; ^1H NMR ($CDCl_3$) δ 1.34 (d, 12 H, J = 7 Hz, CH_3), 3.67 (septet, 2 H, J = 7 Hz, CH), 7.32 (s, 3 H, ArH); mass spectrum, *m/e* (relative intensity) isotope ratio (70 eV) 109 (0.58), 108 (8.66), 107 (100, $C{\equiv}O^+$), 106 (38.2), 105 (2.99), 104 (0.31).

To a solution of 470 mg (2.27 mmol) of the above amide and 125 μL (0.83 mmol) of TMEDA in 20 mL of dry THF at −78 °C was added dropwise 0.60 mL (1.36 M in cyclohexane, 0.82 mmol) of an *n*-BuLi solution. After 10 min, 0.5 mL (10 mmol) of CH_3OD was added and the bath was removed. As the solution warmed to ambient temperature, nitrogen was allowed to flow through the flask so that the solvent was removed. To the residue was added some Et_2O and this solution was washed with 10% aqueous HCl and then dried ($MgSO_4$). Removal of solvent in vacuo left 466 mg (99%) of an off-white solid. Kugelrohr distillation [93 °C (0.35 mm)] gave 437 mg (93%) of **12** as a white solid: mp 69–70.5 °C; ^1H NMR ($CDCl_3$) δ 1.30 (d, 12 H, J = 6.5 Hz, CH_3), 3.63 (septet, 2 H, J = 6.5 Hz CH), 7.27 (s, 3 H, ArH); mass spectrum, *m/e* (relative intensity) isotope ratio (field ionization) 209 (1.3), 208 (14.5), 207 (100, $M^{+\cdot}$), 206 (2.49), 205 (0.12), (70 eV) 109 (0.66), 108 (8.78), 107 (100, $ArC{\equiv}O^+$), 106 (5.41), 105 (0.76).

Reaction of *N,N*-Diisopropyl-2,6-dideuteriobenzamide (12) with *sec*-BuLi/TMEDA To Yield *N,N*-Diisopropyl-*o*-deuteriobenzamide (4). From 200 mg of **12** (1.0 *sec*-BuLi/TMEDA, 89 mM, −78 °C, 15 min, 30 CH_3OH), the crude product was isolated as 178 mg (89%) of a yellowish solid. Kugelrohr distillation (115–120 °C (0.3 mm)] gave 175 mg (88%) of a white solid, mp 65–70 °C, which was recrystallized from hexane to give 94 mg (47%) of **4** (R = $CH(CH_3)_2$) as a white solid: mp 68–71 °C; mass spectrum, *m/e* (relative intensity) isotope ratio (field ionization) 208 (2.47), 207 (21.1), 206 (100, $M^{+\cdot}$), 205 (0.63), (70 eV) 108 (1.30), 107 (16.2), 106 (100, $C{\equiv}O^+$), 105 (1.97), 104 (1.28).

5-Chloro-3,3-diphenyl-1(3*H*)-isobenzofuranone (47). From 535 mg of *N,N*-diethyl-*p*-chlorobenzamide (1.0 *sec*-BuLi/TMEDA, 45 mM, −78 °C, 0 min, 1.0 Ph_2CO, 0.5 M in THF), the crude product was isolated as 930 mg of a gummy yellow solid. MPLC on silica, using $CHCl_3$ as eluent, gave 530 mg (65%) of a white solid which was recrystallized from CH_2Cl_2–hexane to give 485 mg (60%) of **47** as a white solid: mp 156–157.5 °C; ^1H NMR ($CDCl_3$) δ 7.34 (s, 10 H, C_6H_5), 7.49 (d, 1 H, J = 9 Hz, C_6-H), 7.53 (s, 1 H, C_4-H), 7.85 (d, 1 H, J = 9 Hz, C_7-H); IR (KBr) 1776 (s, C=O), 1609 (m), 1593 (m), 1451 (m), 1270 (m), 1243 (m), 1160 (m), 1123 (m), 1096 (m), 1079 (m), 973 (m), 960 (m), 782 (m), 775 (m), 759 (m), 707 (s), 685 cm^{-1} (m); mass spectrum (70 eV), *m/e* (relative intensity) 323 (3), 322 (15), 321 (10), 320 (44, $M^{+\cdot}$), 246 (5), 245 (34), 244 (16), 243 (100), 242 (12), 241 (61), 240 (5), 239 (19), 218 (1), 217 (10), 216 (4), 215 (29), 152 (33), 105 (13), 77 (23).

5-(4,5-Dihydro-4,4-dimethyl-2-oxazolyl)-3,3-diphenyl-1-(3*H*)-isobenzofuranone (46). From 690 mg of *N,N*-diethyl-4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)benzamide (1.1 *sec*-BuLi/TMEDA, 48 mM, −78 °C, 2 min, 1.1 Ph_2CO in minimum amount of THF, extraction of the Et_2O layer with aqueous base only, drying over K_2CO_3), the crude product was isolated as 1.08 g of a white solid. The sample was passed through a short silica column with EtOAc and separation of the resulting yellow oil by MPLC on silica, using 3:7 (v/v) EtOAc–petroleum ether as eluent, gave a solid which was recrystallized from hexane to give 440 mg (46%) of **46** as a white solid: mp 160.5–161 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H, CH_3), 4.08 (s, 2 H, CH_2), 7.28 (s, 10 H, C_6H_5), 7.98 (m, 3 H, C_4-H, C_6-H, and C_7-H); IR (Nujol) 1763 (s, C=O), 1650 (m), 1275 (m), 1126 (m), 1098 (m), 1080 (m), 1066 (m), 972 (m), 954 (m), 930 (m), 910 (m), 774 (m), 756 (m), 716 (m), 699 cm^{-1} (m); mass spectrum (70 eV), *m/e* (relative intensity) 383 (18, $M^{+\cdot}$), 368 (100), 353 (11), 340 (8), 324 (10), 312 (9), 306 (49), 278 (20).

***N,N*-Diethyl-1,3-dihydro-1-oxo-3,3-diphenyl-5-isobenzofuransulfonamide (44).** To a solution of 470 mg (1.5 mmol) of *N,N*-diethyl-4-[(diethylamino)sulfonyl]benzamide and 0.23 mL (1.5 mmol) of TMEDA in 50 mL of dry THF at −78 °C was added dropwise 1.0 mL (1.5 M in pentane, 1.5 mmol) of a *t*-BuLi solution. After 5 min, 279 mg (1.5 mmol) of Ph_2CO in 5 mL of dry THF (0.3 M) was added quickly and the bath was removed. Normal extractive workup afforded a light yellow oil which was purified by column chromatography using 3:7 (v/v) EtOAc–hexane as eluent. Recrystallization from 95% EtOH gave 130 mg (21%) of **44** as a white solid: mp 129.5–131.5 °C; ^1H NMR ($CDCl_3$) δ 1.02 (t, 6 H, J = 7 Hz, CH_3), 3.21 (q, 4 H, J = 7 Hz, CH_2), 7.30 (s, 10 H, C_6H_5), 7.98 (s, 3 H, C_4-H, C_6-H, and C_7-H); IR (Nujol) 1767 (s, C=O), 1470 (m), 1405 (m), 1345 (s, SO_2N), 1320 (m), 1305 (m), 1270 (m), 1256 (m), 1222 (m), 1206 (m), 1172 (s, SO_2N), 1152 (m), 1127 (m), 1100 (m), 1021 (m), 974 (m), 964 (m), 930 (m), 769 (m), 760 (m), 715 (m), 691 cm^{-1} (s); mass spectrum (70 e/v), *m/e* (relative intensity) 421 (12, $M^{+\cdot}$), 406 (100), 349 (10), 344 (7), 285 (31), 241 (11), 239 (14), 180 (5), 152 (8), 105 (6), 103 (79).

Anal. ($C_{24}H_{23}NO_4S$) C, H, N, S.

***N*-Methyl-1,3-dihydro-1-oxo-3,3-diphenyl-5-isobenzofuransulfonamide (45).** To a solution of 200 μL (1.33 mmol) of TMEDA in 10 mL of dry THF at −100 °C was added 1.0 mL (1.3 M in cyclohexane, 1.3 mmol) of a *sec*-BuLi solution dropwise. A solution of 173 mg (0.640 mmol) of *N,N*-diethyl-4-[(methylamino)sulfonyl]benzamide in 15 mL of dry THF was then added over a 10-min period. The reaction mixture was stirred for 1 h, at which time a solution of 158 mg (0.867 mmol) of Ph_2CO in 5 mL of dry THF (0.2 m) was added quickly. The bath was not removed, so that slow warming to ambient temperature was achieved. Stirring at ambient temperature was continued for 2 h before the addition of some water and 30 mL of toluene. The THF was removed by distillation and the residue was heated at reflux for 30 min, cooled, and washed with 10% aqueous HCl and saturated brine, and then dried ($MgSO_4$). Removal of solvent

in vacuo left 323 mg of a yellow oil which was purified by MPLC on silica, using 1% EtOH in $CHCl_3$ as eluent to give 203 mg (84%) of **45** as a yellowish solid, which was recrystallized from benzene–cyclohexane to give 99 mg (41%) of tan crystals: mp 160–162.5 °C; ^1H NMR ($CDCl_3$) δ 2.69 (d, 3 H, J = 5.5 Hz, CH_3), 4.63 (br m, 1 H, NH), 7.37 (s, 10 H, C_6H_5), 8.06 (s, 3 H, C_4-H, C_6-H, and C_7-H); IR (KBr) 3302 (m, NH), 1780 (s, C=O), 1451 (m), 1418 (m), 1335 (m), 1324 (m, SO_2N), 1276 (m), 1254 (m), 1173 (s, SO_2N), 1158 (s), 1132 (m), 1100 (m), 1080 (m), 965 (m), 770 (m), 700 (s), 624 (m), 563 cm^{-1} (m); mass spectrum (70 eV), m/e (relative intensity) 379 (38, $M^{+\cdot}$), 302 (100), 274 (32), 241 (77), 207 (32).

Anal. Calcd for $C_{21}H_{17}NO_4S$: H; S; C, 66.48; N, 3.69. Found: H, 64.81; N, 3.33.

***N,N*-Diethyl-2,6-dichloro-3-deuteriobenzamide (49).** From 176 mg of *N,N*-diethyl-2,6-dichlorobenzamide (1.1 *n*-BuLi/TMEDA, 88 mM, −78 °C, 2 h; excess CH_3OD), the crude product was obtained as 164 mg (93%) of a white solid. MPLC on silica, using 1:9 (v/v) THF-hexane as eluent, followed by MPLC on silica, using 1:9 (v/v) EtOAc-hexane as eluent, gave 143 mg (81%) of **49** as a white solid: mp 88–92.5 °C (lit.[42] mp 94–95 °C); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7 Hz, CH_3), 1.27 (t, 3 H, J = 7 Hz, CH_3), 3.15 (q, 2 H, J = 7 Hz, CH_2), 3.61 (q, 2 H, J = 7 Hz, CH_2), 7.25 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ (relative intensity) 12.4 (60, CH_3), 13.7 (58, CH_3), 38.9 (87, CH_2), 42.7 (78, CH_2), 128.1 (81, C-3 and C-5), 129.9 (100, C-4), 131.8 (37, C-2 and C-6), 135.9 (14, C-1), 164.5 (20, CO); mass spectrum (70 eV), m/e (relative intensity) 248 (9), 247 (2), 246 (13, $M^{+\cdot}$), 213 (22), 212 (9), 211 (69), 210 (1), 178 (10), 177 (5), 176 (64), 175 (9), 174 (100, $C{\equiv}O^+$), 173 (2), 148 (12), 147 (12), 146 (18), 145 (1), isotope ratio (70 eV) 250 (11.9), 249 (9.95), 248 (65.8), 247 (15.3), 246 (100, $M^{+\cdot}$), 245 (2.14), 179 (1.0), 178 (11.2), 177 (6.17), 176 (65.6), 175 (10.5), 174 (100, $C{\equiv}O^+$), 173 (2.74).

***N,N*-Diethyl-1,3-dihydro-1-oxo-3,3-diphenyl-5-isobenzofurancarboxamide (52) and *N*-Methyl-1,3-dihydro-1-oxo-3,3-diphenyl-5-isobenzofurancarboxamide (53).** From 150 mg of *N,N*-diethyl-*N'*-methylterephthalamide [2.1 *sec*-BuLi/TMEDA, 24 mM, −100 °C, 1 h, 1.3 Ph_2CO, 0.2 M in THF; after slow warming of the reaction mixture toluene was added, the THF was removed by distillation, and the residue was heated at reflux for 30 min, washed with 10% aqueous HCl, and dried ($MgSO_4$)], the crude product was obtained and separated by MPLC on silica, using 1–10% EtOH in $CHCl_3$ as eluent. The diethyl amide **52** was eluted first as 50 mg (20%) of an oil which was distilled by using a Kugelrohr apparatus to give 12 mg (5%) of **52** as a yellow gum: ^1H NMR ($CDCl_3$) δ 1.13 (br s, 6 H, CH_3), 3.17 (br s, 2 H, CH_2), 3.45 (br s, 2 H, CH_2), 7.30 (s, 10 H, C_6H_5), 7.50 (m, 2 H, C_4-H and C_6-H), 7.93 (d, 1 H, J = 7 Hz, C_7-H); mass spectrum (field desorption), m/e (relative intensity) 387 (5), 386 (43), 385 (100, $M^{+\cdot}$), 384 (7).

Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 68.63; H, 5.39; N, 3.18.

The methyl amide **53** was eluted next, giving 15 mg (7%) of a solid which was recrystallized from benzene–cyclohexane to give 10 mg (5%) of **53** as a light tan solid: mp 219.5–220 °C; ^1H NMR ($CDCl_3$) δ 3.00 (d, 3 H, J = 5 Hz, CH_3), 6.25 (br s, 1 H, NH), 7.30 (s, 10 H, C_6H_5), 7.95 (m, 3 H, C_4-H, C_6-H, and C_7-H); mass spectrum (70 eV), m/e (relative intensity), 345 (2), 344 (11), 343 (43, $M^{+\cdot}$), 342 (1), 300 (4), 299 (17), 270 (2), 269 (10), 268 (3), 267 (19), 266 (100), 243 (5), 242 (24), 241 (20), 240 (10), 239 (29), 238 (38), 237 (5), 236 (4), 235 (20), 210 (2), 209 (12), 208 (5), 207 (12), 161 (11), 152 (12), 151 (10), 105 (14), 78 (15), 77 (20), 58 (25). An analytical sample was obtained by recrystallization from benzene.

Anal. ($C_{22}H_{17}NO_3$) C, H, N.

***N,N*-Diisopropyl-2-deuterio-4-toluamide (56).** From 467 mg of *N,N*-diisopropylbenzamide (1.1 *n*-BuLi, 89 mM, −78 °C, 30 min, 6 MeOD), the crude product was obtained as 446 mg (95%) of a white solid. Purification by MPLC on silica, using 1:9 (v/v) EtOAc-hexane as eluent, followed by Kugelrohr distillation [105 °C (0.4 mm)] gave **56** as 399 mg (85%) of a white solid: mp 85–87 °C (lit.[26] mp 85–86 °C); ^1H NMR ($CDCl_3$) δ 1.32 (d, 12 H, J = 7 Hz, CH_2CH_3), 2.33 (s, 3 H, $ArCH_3$), 3.68 (septet, 2 H, J = 6.8 Hz, CH_2), 7.16 (s, 3.6 H, ArH); mass spectrum (70 eV), m/e (relative intensity) 221 (1), 220 (8, $M^{+\cdot}$), 219 (5), 218 (1), 177 (16), 176 (10), 121 (8), 120 (100, $C{\equiv}O^+$), 119 (68), 92 (26), 91 (20), 66 (7), 65 (10), isotope ratio (70 eV) 122 (0.57), 121 (8.97), 120 (100, $C{\equiv}O^+$), 119 (73.0), 118 (1.25).

***N,N*-Diisopropyl-α-deuterio-*p*-toluamide (58).** From 473 mg of *N,N*-diisopropyl-*p*-toluamide (1.1 LDA, 0.13 M, 0 °C, 30 min, 6 MeOD), the crude product was obtained as 473 mg (100%) of a white solid. Kugelrohr distillation [130 °C (0.6 mm)] gave **58** as 444 mg (93%) of a white solid: mp 81–87 °C (lit.[26] mp 85–86 °C); ^1H NMR ($CDCl_3$) δ 1.31 (d, 12 H, J = 7 Hz, CH_2CH_3), 2.30 (s, 2.5 H, $ArCH_2D$), 3.66 (septet, 2 H, J = 7 Hz, NCH_2), 7.13 (s, 4 H, ArH); mass spectrum (70 eV), m/e (relative intensity) 221 (1), 220 (7, $M^{+\cdot}$), 219 (8), 218 (1), 177 (17), 176 (15), 121 (9), 120 (100, $C{\equiv}O^+$), 119 (89), 92 (23), 91 (23), 66 (6), 65 (10), isotope ratio 122 (0.61), 121 (8.982), 120 (100, $C{\equiv}O^+$), 119 (91.28), 118 (1.4), 117 (0.35).

Deuterations of 14–26, 40, 42, and 50. These procedures follow essentially that described above for **1** and **3**. The experimental descriptions are available as supplemental data.

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Registry No. **1**, 1696-17-9; **3**, 20383-28-2; **4** (R = C_2H_5), 62924-91-8; **4** (R = $CH(CH_3)_2$, 62924-99-6; **5**, 611-74-5; **6**, 938-87-4; **7**, 6158-53-8; **8** (E = CH_3; R = Et), 2728-04-3; **8** (E = C_2H_5; R = Et), 5434-08-2; **8** (E = OH; R = Et), 19311-91-2; **8** (E = Br; R = Pr-*i*), 79839-66-0; **9** (R = R^1 = CH_3), 1689-09-4; **9** (R = R^1 = C_6H_5), 596-29-2; **9** (R = H; R^1 = C_6H_5), 5398-11-8; **12** (R = Pr-*i*), 79839-67-1; **14**, 10345-79-6; **15**, 15952-65-5; **16**, 7461-38-3; **17**, 51674-10-3; **18**, 62924-93-0; **19**, 7465-86-3; **20**, 134-62-3; **21**, 2728-05-4; **22**, 71888-22-7; **23**, 71888-23-8; **24**, 71888-25-0; **25**, 71888-21-6; **26**, 71888-24-9; **27**, 71888-41-0; **28**, 71888-42-1; **29**, 71888-43-2; **30**, 71902-00-6; **31**, 79839-68-2; **32**, 62924-97-4; **33a**, 71888-38-5; **33b**, 71888-39-6; **34**, 71888-40-9; **35**, 71888-34-1; **36**, 71888-35-2; **37**, 71888-37-4; **38**, 71888-33-0; **39**, 71888-36-3; **40**, 72003-94-2; **41**, 79839-69-3; **43**, 79839-70-6; **44**, 71901-99-0; **45**, 71888-27-2; **46**, 71888-26-1; **47**, 71888-28-3; **48**, 10345-78-5; **49**, 79839-71-7; **50**, 71888-29-4; **51**, 79839-72-8; **52**, 71888-31-8; **53**, 71888-32-9; **54**, 6937-52-6; **56**, 79839-73-9; **58**, 79839-74-0; **60**, 5892-99-9; *p*-toluenesulfonic acid, 104-15-4; *p*-carboxybenzenesulfonic acid, 636-78-2; *p*-(chlorosulfonyl)benzoyl chloride, 7516-60-1; *p*-[(methylamino)sulfonyl]benzoic acid, 10252-63-8; *N,N*-dimethyl-*p*-bromobenzylamine, 6274-57-3; *N,N*-diethylcarbamoyl chloride, 88-10-8; 4,4-dimethyl-2-*p*-bromophenyl-2-oxazoline, 32664-14-5; 2-methoxy-3-methylbenzoic acid, 26507-91-5; 2-methoxy-3-methylbenzoyl chloride, 22256-43-5; *N*-methyl-*p*-bromobenzamide, 27466-83-7; *p*-bromobenzoic acid, 586-76-5; *p*-bromobenzoyl chloride, 586-75-4; valerophenone, 1009-14-9; D_2O, 7789-20-0; CH_3I, 74-88-4; C_2H_5I, 75-03-6; $B(OCH_3)_3$–H_2O_2, 79872-81-4; $(CH_3)_2CO$, 67-64-1; $(C_6H_5)_2CO$, 119-61-9; C_6H_5CHO, 100-52-7; $CH_2{=}CHCH_2Br$, 106-95-6; C_6H_5OMe, 100-66-3; C_6H_5Me, 108-88-3; C_6H_5Cl, 108-90-7; C_6H_5Br, 108-86-1; $C_6H_5CH_2NMe_2$, 103-83-3; Et_2NCO-*p*-$C_6H_9CONHEt$, 79839-75-1; $C_6H_5SO_2NEt_2$, 1709-50-8; $C_6H_5SO_2NHMe$, 5183-78-8; $C_6H_5CO_2H$, 65-85-0; $C_6H_5SO_2NMe_2$, 14417-01-7; $C_6H_5CONHMe$, 613-93-4; $C_6H_5CONHEt$, 614-17-5; 4,4-dimethyl-2-phenyl-2-oxazoline, 19312-06-2; *N,N*-dimethyl-3-deuterio-4(*N*-methyl-*N*-deuteriocarboxamide)benzamide, 79839-76-2.

Supplementary Material Available: Experimental descriptions for the deuterations of **14–26, 40, 42,** and **50** (8 pages). Ordering information is given on any current masthead page.