form the corresponding diarylmethanes in relatively low yields (40–51%).[4]
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The Ortho Lithiation of Tertiary Benzamides

Summary: It is shown that tertiary benzamides can be metalated at the ortho position with *sec*-butyllithium–tetramethylethylenediamine at −78 °C in tetrahydrofuran; subsequent trapping of *o*-lithio-*N,N*-diethylbenzamide with deuterium oxide, methyl iodide, trimethylsilyl chloride, and benzophenone is reported.

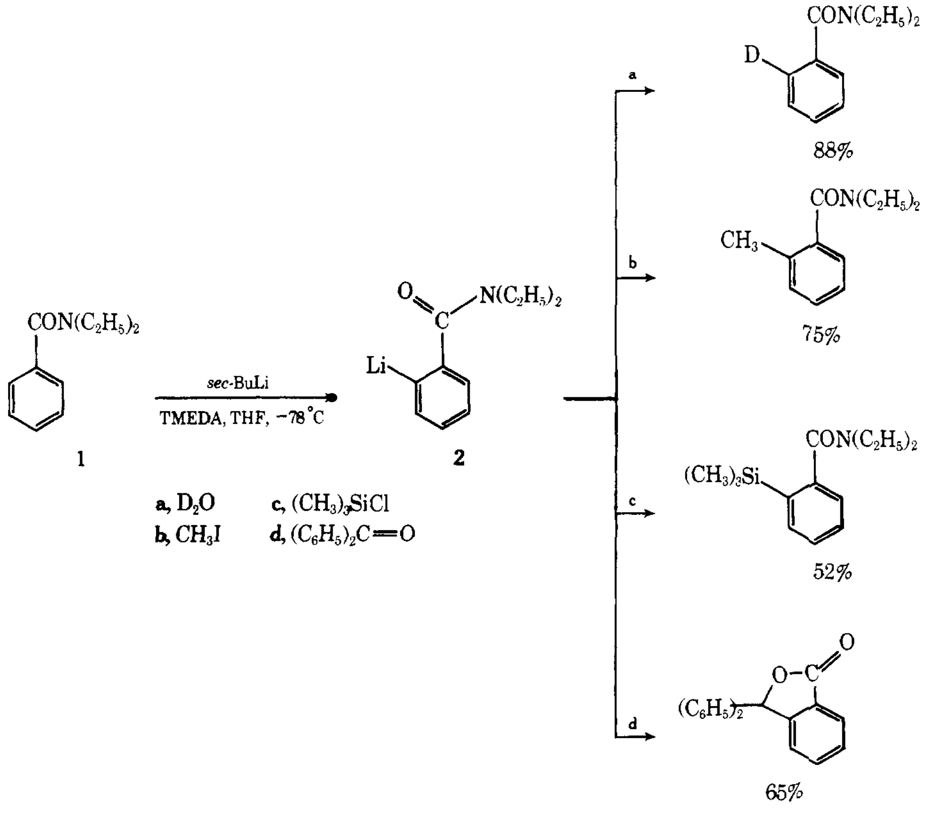
Sir: For some time it appeared that ortho lithiations of aromatic rings would be restricted to control by substituent groups which either are not susceptible to nucleophilic addition or are deactivated toward nucleophilic attack by proton removal or initial addition.[1–4] However, within the last 2 years it has been shown that oxazolines,[5] certain piperonal cyclohexyl imines,[6] and pyrazoles[7] can retain their structural integrity and provide synthetically useful ortho lithiated intermediates. We have earlier demonstrated that the carbonyl function of a tertiary amide, an ester, or a ketone can activate the ortho hydrogen of a phenyl ring toward lithiation, but under the conditions previously used the intermediates are transient and subsequently react with starting material to give self-substituted ortho derivatives.[8–10] We now wish to report that persistent ortho lithiated species can be produced directly from tertiary benzamides and to demonstrate that these species are synthetically useful.

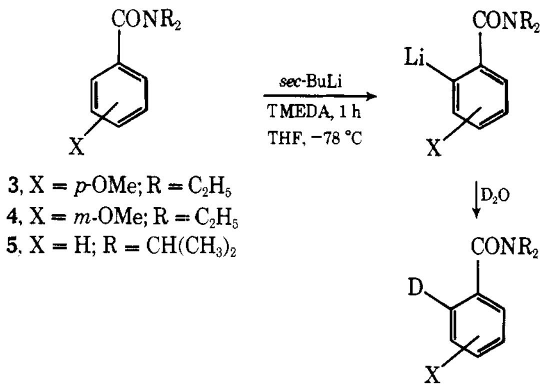
Reaction of *N,N*-diethylbenzamide (1) with *sec*-butyllithium–tetramethylethylenediamine (TMEDA) in tetrahydrofuran at −78 °C for 1 h, followed by addition of deuterium oxide, methyl iodide, trimethylsilyl chloride, or benzophenone, provides the products shown in Scheme I in the isolated yields indicated. The location of the 95 at. % of deuterium was established by ^{1}H and ^{13}C NMR spectroscopy and the location of the other substitutents was established by analytical and spectral criteria and by comparison with the properties of previously reported materials.[11] The formation of 3,3-diphenylphthalide from **2** and benzophenone provides a chemical proof of the structure of **2**. The intermediacy of **2** has extensive analogy.[1–10] The contrast between these reactions and the nucleophilic addition of *n*-butyllithium to *N,N*-dimethylbenzamide to give valerophenone[2,3,5] again points out the superiority of *sec*-butyllithium as a base.[1,12,13]

The fact that this metalation is not unduly sensitive to other substituents is demonstrated by the metalation and deuteration of **3–5** in yields of 89–95%. The case of **3** shows that under these conditions the tertiary benzamide function is more strongly activating for ortho lithiation than is the methoxy function.[2] The reaction of **4** to give a single product in which the deuterium is located between the substituents, as established by ^{13}C NMR spectroscopy,[11a] demonstrates the substituent effects can be supplementary.

These results suggest that the scope of synthetically useful ortho metalations may be wider than previously suspected. In any case, the facile formation of **2** and the ready conversions of tertiary amides to other functions offer some convenience over alternative approaches.[5,14–16] This work complements the recent report of Gschwend et al. that tertiary benzamides undergo nucleophilic addition of alkyllithiums to the amide to give species which can be ortho lithiated and allowed to

Scheme I





3, X = *p*-OMe; R = C_2H_5
4, X = *m*-OMe; R = C_2H_5
5, X = H; R = $CH(CH_3)_2$

react with electrophiles to provide ortho substituted ketones after hydrolysis.[4] The present results also extend the well-known metalation reaction of secondary benzamides, first reported by Hauser,[3,14] and are consistent with the reports by Parham et al. and Meyers et al. that nitriles, acids, esters, halides, and oxazolines can be stable to carbon–metal bonds at low temperatures.[15,16] The recent report by Schmidt and Berger that amide and nitrile substituted dihydropyridines undergo vinylic metalation suggests the scope of such reactions may extend beyond aromatic species.[17] Further efforts to define the scope and utility of ortho metalation should be useful.

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