Directed Lithiations: The Effect of Varying Directing Group Orientation on Competitive Efficiencies for a Series of Tertiary Amide, Secondary Amide, and Alkoxide Directed Ortho Lithiations

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Abstract: Significant differences for competitive efficiencies in directed ortho lithiations for single functional groups in three series, the secondary benzamides **1–4**, the tertiary benzamides **5–11**, and the benzylic alcohols **12–17**, are reported. For both amide series the efficiencies increase as the oxygen and ortho hydrogen in the substrate are more coplanar with the aromatic ring; however, for the alcohol series the opposite order is observed. Rationalizations are offered for these observations.

Introduction

On the basis of their early work on ortho lithiations of heteroatom substituted aromatics, Gilman and Wittig as well as Roberts and Curtin and Hauser suggested, in effect, that association between the lithium of the organolithium reagent and the heteroatom would provide a complex with a favorable location of the carbanion for removal of an adjacent proton.[1] In an encompassing review in 1979, Gschwend and Rodriguez noted that two effects termed "coordination only", for reactions in which complexation is considered to play the major role, and "acid-base", for reactions in which intrinsic acidity is the predominant factor, could be used, separately or in concert, to rationalize most of the available information on ortho lithiations.[1b] These two effects have generally been considered to be dominant factors in directed lithiations.[1] The complex induced proximity effect, which suggested that a complex between a substrate and an organolithium reagent could lead to a kinetically controlled transition structure which would give a novel product, was based, in part, on these earlier precedents.[1d]

The experimental evidence for coordination between lithium and heteroatoms in ground states of organolithium compounds in solution and in the crystalline state is quite convincing.[2] Theoretical support for complexation comes from calculations of transition structures for ortho lithiations which show association between the lithium of the reagent and a heteroatom in the substrate to be energetically favorable.[3]

Nonetheless, there is only inferential experimental evidence that complexes are intermediates on pathways for directed lithiation. Schleyer and co-workers reported NMR studies that reveal agostic interactions between prospectively acidic protons and lithium in a number of aromatic compounds.[3a,b] However, Schleyer and co-workers also showed that the complex between *n*-butyllithium (*n*-BuLi) and anisole, which can be directly observed by NMR, disappears and is replaced by a TMEDA–*n*-BuLi complex on addition of TMEDA under conditions where the formation of the ortho lithioanisole is observed. They noted that the initially observed complex may not be the reactive intermediate and suggested a low concentration of an *n*-BuLi dimer–anisole complex to be an intermediate in the reaction. In their most recent calculation, the Erlangen group suggest complexation and intrinsic acidity to be operative in a directly formed transition structure.[4,5] In somewhat related work on the role of complexes we had suggested earlier, on the basis of a kinetic study of an amide directed α'-lithiation, that the first formed complex between the amide and tetrameric *sec*-butyllithium (*sec*-BuLi) is not the most reactive species, that complexes with more amides on the tetramer are more reactive, and that this pattern also rationalizes the kinetics of the lithiation of which TMEDA is an accelerant and the ligand on the *sec*-BuLi.[6,7] The difficulty of determining the role of a substrate–organolithium reagent complex on a reaction pathway is well recognized.[6-8] Failure to directly observe a possible complex does not rule out it or another complex as a reaction intermediate since they may be kinetically effective but spectroscopically undetectable. On the other hand, observation of a complex does not establish it to be on the reaction pathway as it may be involved in a nonproductive side equilibrium.

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(1) For summarizing reviews, see: (a) Wakefield, B. J. The Chemistry of Organolithium Compounds; Pergamon Press: Oxford, 1974. (b) Gschwend, H. W.; Rodriguez, H. R. *Organic Reactions* **1979**, *26*, 1. (c) Klumpp, G. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1–21. (d) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (e) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(2) For reviews, see: Olsher, L.; Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137. Shambagati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. For recent examples of lithium amide binding, see: Kofron, J. L.; Kuzmic, P.; Kishore, V.; Gemmecker, G.; Fesik, S. W.; Rich, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 2670; Köck, M.; Kessler, H.; Seebach, D.; Tahler, A. *J. Am. Chem. Soc.* **1992**, *114*, 2676.

(3) (a) Bauer, W.; Feigel, M.; Muller, G. and Schleyer, P. v. R. *J. Am. Chem. Soc.* **1986**, *110*, 6033. (b) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (c) Saa, J. M.; Deya, P. M.; Suner, G. A.; Frantera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093. (d) Bachrach, S. M.; Ritchie, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 3134. (e) Stork, G.; Polt, R. C.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 8360. (f) Böche, G.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W.; Thuemmier, C.; Koch, W. *Chem. Ber.* **1992**, *128*, 2265.

(4) Hommes, N. J. R. V. E.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755.

(5) We view the most recent calculations[4] to be consistent with the central point of our explicit suggestion that kinetically controlled reactions are the focus of the complex induced proximity effect, *i.e.*, transition structures are favored which enthalpically and entropically bring the carbanion engaged in removing the proton into a favorable position for that reaction by complexation of the lithium with a heteroatom.[1c]

(6) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.

(7) For a discussion of TMEDA in lithiation reactions, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *10*, 448.

(8) For an analysis of an addition reaction, see: Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2714 and references cited therein.

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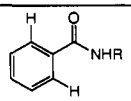
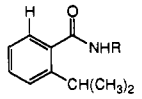
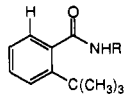
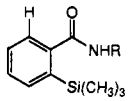
Table I. Competitive Efficiencies of Lithiation and Dihedral Angles and Distances for the Secondary Amides **1–4**

	structure, R = $CH(CH_3)_2$	competitive efficiency	weighted dihedral angle[a] (deg)	weighted av distance[a] (Å)
1		200 (100)[c]	19[b]	2.6
2		17	89[b]	3.2
3		9	91[b]	3.2
4		1	118[b]	3.6

[a] The dihedral angle and distances are the weighted average of conformations calculated to be within 2 kcal/mol of the lowest enregy conformation (see text). [b] The dihedral angles for the lowest energy conformations are **1**, 19°; **2**, 49°; **3**, 57°; **4**, 113°. [c] Corrected for the number of available hydrogens.

Regardless of how a transition structure is achieved, whether from an initially formed complex or directly, complexation between a lithium reagent and a geometrically available heteroatom acting as a directing group is clearly an important factor in transition structures for proton tranfers in directed lithiations.[1-5] We now report an investigation of three series to determine whether relatively small changes in the location of a single directing functional group with respect to the ortho proton can have a significant effect on the efficiency of ortho lithiation. To the best of our knowledge there has not been any study which systematically addresses the role of only one directing group. By comparing a single group we hoped to define the optimal structures for amide and alkoxide directed lithiations. Within each series there should be smaller differences in aggregation, in structures of complexes, and in side reactions than for series which involve comparisons of different ortho directing groups.

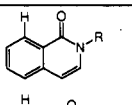
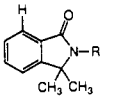
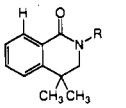
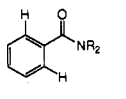
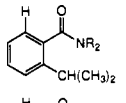
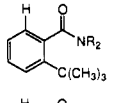
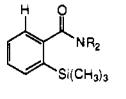
Results

The directing functional groups we have selected for serial investigation are the secondary and tertiary benzamides and the benzyl alcohols. The specific compounds in each series are **1–4**, **5–11**, and **12–17**, respectively, as shown in Tables I–III. In addition the thioamides **18–20** have been studied. The compounds **1–17** were chosen to provide series which have relatively well defined positions of the directing oxygen and the proton to be removed.

Syntheses. Directed lithiation synthetic methodology was used to prepare the benzamides **4** and **8**. The 2-isopropyl benzamides were prepared from 2-iodoisopropylbenzene by iodine lithium exchange followed by reaction with *N,N*-diisopropyl carbonyl chloride to give **6** and reaction with carbon dioxide, thionyl chloride, and isopropyl amine to give **2**. The 2-*tert*-butyl benzamides were obtained by reaction of 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline with *tert*-butyl lithium to give 2-(2-*tert*-butylphenyl)-4,4-dimethyl-2-oxazoline, which was hydrolyzed with triflic anhydride followed by base to provide the 2-*tert*-butylbenzoic acid that, in turn, was converted to **3** and **7** by standard procedures.[9] The cyclic systems **10** and **11** in which benzylic lithiation is blocked by methyl substitution were prepared

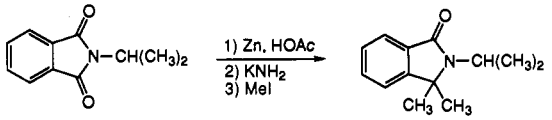
(9) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372–1379. Phillion, D. P.; Pratt, J. K. *Synth. Commun.* **1992**, *22*, 13.

Table II. Competitive Efficiencies of Lithiation, Dihedral Angles, and Distances for the Tertiary Amides **5–11**

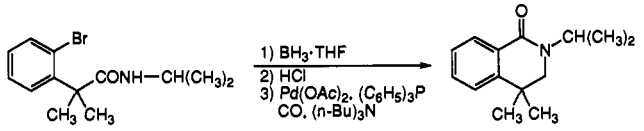
	structure, R = $CH(CH_3)_2$	competitive efficiency	weighted dihedral angle[a] (deg)	weighted av distance[a] (Å)
9		32000[b]	0	2.6
10		6400	1	2.9
11		2500	13	2.5
5		3600 (1800)[c]	57	2.9
6		57	91	3.3
7		1.2	96	3.2
8		1	103	3.4

[a] The dihedral angle and distances are the weighted average of local minima calculated to be within 2 kcal/mol of the global minimum energy conformation (see text). The dihedral angles for the lowest energy conformations are **9**, 0°; **10**, 1°; **11**, 13°; **5**, 58°; **6**, 89°; **7**, 88°; **8**, 110°. [b] This value was determined by comparison of **5** and **9** and while corrected of the disappearance of **9** is less reliable than other values in the table. [c] Corrected for the number of available hydrogens.

from the corresponding phthalimide and benzamide by lithiation, methylation, and carbon monoxide insertions, respectively, as shown.



10

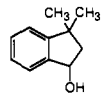
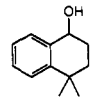
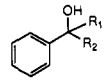
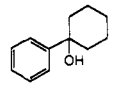


11

The alcohols were obtained from commercial sources or prepared by established routes. The alcohol **16** was obtained from 2-tetralone by dimethylation, Wolff–Kishner reduction, oxidation to the ketone, and reduction with lithium aluminum hydride.

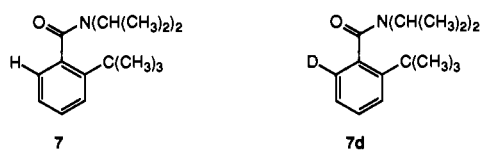
Competitive Efficiencies of Ortho Lithiation. The competitive efficiencies of ortho lithiations within each series of **1–4**, **5–11**, and alkoxides **12–17** were established by a series of reactions in which two different substrates were allowed to react with *sec*-BuLi/TMEDA at −78 °C in THF for the amides or with *sec*-BuLi in Et_2O at room temperature for the alcohols. The reactions were quenched with a deuterium source, and the products were analyzed for deuterium content.[10] The relative efficiencies of lithiation, corrected for the extent of the reaction, are based on the relative extent of deuteration. A typical competition is shown

Table III. Competitive Efficiencies, Dihedral Angles, and Distances for Lithiation of Benzyl Alcohols **12–17**

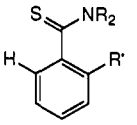
	structure	competitive efficiency	weighted dihedral angle[a]	weighted av distance[b] (Å)
15		49	50–70	3.3
16		19	40–70	3.1–3.4
		10 (5)[c]		2.6
12	$R^1 = CH_3, R_2 = H$			
13	$R_1 = R_2 = CH_3$			
14		2.8 (1.4)[c]		2.5–3.5
17		1.0	0	2.6

[a] Out of plane angles for the hydroxyl group calculated using MM2. For the bicyclic systems the range of angles reflects the different angles which are attainable by reasonable conformations of the ring systems (see text). [b] Distance between the oxygen of the alcohol and the hydrogen removed by lithiation. Ranges reflect the oxygen–hydrogen distances possible from available conformations of the ring systems. [c] Corrected for the number of available hydrogens.

for **6** and **7**. To assure transitivity of the results a total of 11, 15, and 9 different competitions were carried out within the series for secondary amides, tertiary amides, and alcohols, respectively. We express the comparison as relative efficiencies because, although we correct for decreasing concentration of reactants, we were not able to account for all of the reactants in most cases. On the basis of the similarity of the structures of the reactants we assume that the reaction profiles, including side reactions, are sufficiently similar that the order within a series can be given semiquantitative interpretation.



The relative efficiencies of competitive ortho lithiations for secondary amides, tertiary amides, and alcohols are shown in Tables I–III, respectively. In addition to the comparisons in the tables, other competitions were carried out. The relative efficiencies of ortho lithiation of the secondary amide–tertiary amide pairs **2–6**, **4–8**, and *N*-ethyl benzamide–*N*,*N*-diethyl benzamide showed the tertiary amides to be favored by a factor of *ca.* 50 in these intermolecular competitions. The amide–thioamide pairs **1–18**, **5–19**, and **6–20** were allowed to compete, and it was found that only the amides **1**, **5**, and **6** underwent lithiation under the conditions of the comparisons.



18, R = H, $CH(CH_3)_2$, R' = H
19, R = $(CH(CH_3)_2)_2$, R' = H
20, R = $(CH(CH_3)_2)_2$, R' = $C(CH_3)_3$

Control experiments to establish that the ratios of deuterated products reflect that the kinetic rather than thermodynamic factors were carried out.[11] For the tertiary amides the lithiation of **5** was carried out with *sec*-BuLi/TMEDA to give the 2-lithio amide, and then **10** was added followed by stirring at −78 °C for 60 min before deuteration. The ratio of **5d**:**10d** from this experiment was 50:1. Since the relative efficiency of lithiation of **6** and **10** is 1.8, this result shows that equilibration is minimal in this system. On the other hand, when (*o*-lithiophenyl)lithium methoxide, generated by bromine–lithium exchange of the 2-bromobenzyl alcohol, was mixed with the lithium salt of **14**, allowed to stand for 12 h, and followed by methanol-*O*-*d*, the product benzyl alcohol was 64% deuterated, and 14% of **14d** was found. Apparently some equilibration of the ortho lithiated species does occur in this system, although the extent of that reaction does not appear to compromise qualitative comparison.

Calculations of Structures. Interpretation of the relationship between the relative competitive efficiencies of lithiation of any of these series and the positions of the oxygens, lithium reagents, and hydrogens in the transition structure depends on the confidence with which those atomic positions can be assigned. Our unsophisticated analysis treats the organolithium reagent as a constant and focuses on the relative positions of the oxygen and ortho hydrogen in the ground states of each substrate as providing an indication of their relative locations in the transition states (*vide infra*).

In order to evaluate the ground states we have carried out calculations by molecular mechanics (MM2) minimizations on ten different benzamides and two cyclic derivatives with structure input from MACROMODEL v3.0 to provide assessments of the locations in the ground-state structures of the monocyclic systems.[12] The benzamides of this study are relatively simple as far as computational methods are concerned and the accuracy of the calculations has been established for closely related systems.[13]

A summary of the results of these calculations for both the secondary and tertiary ortho benzamides is included in the tables as the weighted dihedral angle and distance between the oxygen

(10) The GC/MS data, which gives a 70-eV electron impact-mass spectrum, generally gave a very large M-1 peak. The FI/MS results were much more accurate since there was a small M-1 peak. For literature examples of the problems and inaccuracies encountered in analyses of compounds which give large M-1 peaks, see: Bielmann, J. F.; Hirth, C. G. *Org. Mass Spectrom.* **1969**, *2*, 723 and Duffield, A. M.; deMartino, G.; Djerassi, C. *Org. Mass. Spectrom.* **1974**, *9*, 137.

(11) Previous studies have generally shown ortho lithiations to give kinetic products. Fraser, R. R.; Bresse, M.; Mansar, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

(12) The force field used was MM2(87). For a detailed explanation of the general MM2 force field, see: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127 or Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982. MACROMODEL V3.0 was used for structure input: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467. The minimizations were performed using batch mode (BATCHMIN V3.0) on a VAX/VMX main frame system. The input file was generated by using the multiconformation submode with a default resolution of six for each torsional angle. All of the important torsional angles for each structure were varied. MM2(87) was the force field used, and the block diagonal Newton Raphson (BDNR) minimization algorithm was used. The programs are from Cambridge Scientific Computing, Inc., 875 Massachusetts Avenue, Suite 61, Cambridge, MA 02139.

(13) Berg, U.; Sandström, J. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: San Diego, 1989; Vol. 25, pp 75–97.

and ortho hydrogen. There was a relatively broad range of angles for the minima of each benzamide and a weighted average of the angles for the minima within 2 kcal/mol of the global minimum was determined. The dihedral angle is relative to the ortho proton rather than the ortho substituent and a few minima have the carbonyl of the amide pointing toward the ortho substituent, so that dihedral angles of greater than 90° are possible.

As expected, the syn conformation of the amide is calculated to be more stable than the anti conformation for all the secondary benzamides. It was somewhat surprising that the unsubstituted as well as ortho substituted benzamides all had dihedral angles greater than 18°. The cyclic benzamides **10** and **11** showed the expected trend of increasing dihedral angle as the ring size increased. *N*-Ethylbenzamide and *N,N*-diethylbenzamide are calculated to have the same dihedral angles as the corresponding *N*-isopropylbenzamides. The unsaturated isoquinolinone **9** gave 0° dihedral angle as expected. The dihedral angle of 1° for the isoindolone **10** correlates well with the recently reported X-ray structures of two nitrogen substituted isoindolones, which have dihedral angles of 0.5° and 1.0°.[14] The conformation of the CO–N bond was essentially planar for all the examples tested. The conformations of the isopropyl groups of *N,N*-diisopropylbenzamide were calculated to be the same as those determined by NMR by Berg and Pettersson (*vide supra*).[15] The observed ranking of dihedral angle is *i*-Pr < *t*-Bu < TMS, and both the ortho *tert*-butyl and ortho TMS benzamides prefer geometries that direct the carbonyl groups toward the ortho substituent (Ar–CO angle > 90°) rather than toward the ortho proton. Apparently, the longer C–SI bond length of 1.9 Å for the ortho TMS benzamide allows the amide to rotate further toward the TMS group than the corresponding *tert*-butyl group. The dihedral angles and hydrogen–oxygen distances weighted with respect to the populations of the lowest energy conformations of the amides are given in Tables I and II.

The structures of the alcohols are also obtained from MM2 calculations, and the results are summarized in Table III. The fused-ring compounds **15–17** have structures that are relatively fixed. The ranges of out of plane angles and oxygen–hydrogen distances reflect the different angles and distances which are attainable by reasonable conformations of the ring systems. For the freely rotating systems **12–14** any out of plane angle is attainable with minimal (<8 kcal) rotational barriers. The hydrogen–oxygen distance ranges are those between an out of plane angle of 0° (shortest distance) to one of 90°. The large number of conformer populations make weighted values more problematic than for the amides, so a range of angles and distances are given in Table III.

Discussion

The data presented in Tables I–III establish that a relatively small structural change for a single functional group within a series can have a significant effect on the competitive efficiency of a directed ortho lithiation. The direction of the effect with respect to planarity between the directing oxygen atom, the ortho hydrogen, and the ring in the two amide series is opposite to that observed for the alcohol series. If ground-state structures are used as a guide for the transition structures, the data in the tables show that the amides have increased efficiency of lithiation as the planarity between the oxygen, the ortho hydrogen, and the ring is increased, whereas the alcohols show a decreased efficiency for lithiation with an increase in the coplanarity of these functions. The energy differences which can be calculated from the range of competitive efficiencies are not large. The factor of 100 at −78 °C between **1** and **4** in Table I amounts to *ca.* 2 kcal/mol in favor of the transition structure with a planar approach of the oxygen and hydrogen. The factor of 50 at 25 °C between **15** and **17** in Table III amounts to *ca.* 2 kcal/mol in favor of nonplanar arrangement. Other observations from this work are that tertiary amides undergo the fastest lithiation and have the largest range of efficiency and that both secondary and tertiary oxoamides are more effective as ortho directing groups than thioamides. For example, **5** is 1800 times more efficient than **8**, whereas **1** is 50 times more efficient than **4**. The present results are consistent with comparisons of secondary and tertiary amides in intermolecular competition.[16]

The significance of these observations depends on their application. For synthetic purposes these results show that it should be possible to achieve selective directed lithiations even for the same functional group in systems which have different locations of the directing group with respect to the proton to be removed. However, more fundamental interpretation of results of competitive lithiations requires that the possibly differential effects of complexation, side reactions, composition of reactive species be disregarded. In order to construct a working hypothesis for qualitative interpretation of the trends in Tables I–III, we will make the assumption that within each series the dominant effect is the relative position of the oxygen which is bonded to the lithium reagent which is engaged in removing the ortho hydrogen in the kinetically most favorable transition structure.

The results in Tables I and II then can be taken to show that a small dihedral angle between the ortho hydrogen and the amide oxygen increases the effectiveness of ortho lithiation for both secondary and tertiary amides. The correlation between dihedral angles of the amides and the competitive efficiencies of ortho lithiations can be rationalized by the approach to planarity in a transition structure shown as **21**.[17] A planar structure also is consistent with calculations of favored transition structures for ortho lithiations and the directed lithiation of eneamines.[18] Qualitatively a planar structure may be favored because the proton bridging the carbanionic base and the developing ortho carbanion most effectively shields the repulsive interaction of the negative charges.

On the other hand, Table III shows that for the alcohol series enforcing planarity of the oxygen, presumably as an alkoxide, with the ortho hydrogen gives the least efficient ortho lithiation. Qualitatively the alkoxide may be considered to bring another negative species into the transition structure such that additional shielding of charge is required to reach the transition structure. A rationalization for this effect is shown as **22**, in which the alkoxide is part of a complex in which shielding of the negative charges is best achieved in a transition structure with the negative oxygen out of the plane with two lithiums to temper the charge repulsions between the carbanions and the oxygen.

Correlation of competitive efficiencies of lithiation with the distances between the directing oxygen and the ortho hydrogen might be expected to have a maximum at a distance which would accommodate the organolithium base most effectively in the

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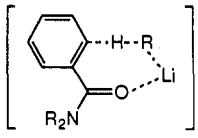
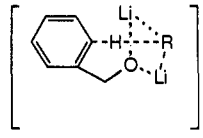
transition structure. That distance does show some correlation to the trends of planarity and nonplanarity noted above, but we believe there is insufficient information to define an optimal distance from this data.

The observation that the alkoxide and secondary amides lithiate more slowly than the tertiary amide can be seen as consistent with negative charge shielding of the suggested transition structures. The fact that the oxoamides undergo ortho lithiation under conditions where the thioamides do not also is in agreement with established lithium binding to amides.[2] However, the status of **21** and **22** as working hypothesis is evidenced by the fact that the secondary amide, which is presumed to be lithiated under the reaction conditions, could have been accommodated by transition structures analogous to either **21** or **22** in the absence of experimental information.



21



22

In summary, these results establish that relatively small changes in a single type of directing functional group can have an experimentally significant effect on the efficiency of ortho lithiation. While correlation of the efficiencies of lithiation with each amide series is consistent with a planar transition structure such a correlation is not found for the alcohols. It appears that definitive information about the role of complexes will require further experimental and theoretical data.

Experimental Section

General Methods. Gas chromatography (GC) was performed on a Hewlett-Packard 5890 gas chromatograph coupled to a Hewlett-Packard 3396A recorder using a commercially available Ultra-2 capillary column (Hewlett-Packard, Palo Alto, CA 94304, 25 m × 0.20 mm i.d., 0.33 *m*m film). The injector temperature was 250 °C, and the detector temperature was 300 °C. Analytical scale HPLC was performed on an Adsorbosphere HS 5 μm silica column (Alltech Association, Deerfield, IL 60015, 25 cm × 4.6 mm i.d.) with a Hewlett-Packard 3396A recorder used for quantitative analysis. Analytical thin-layer chromatography was performed on Merck silica plates with F-254 indicator. Visualization was accomplished by UV light or iodine. Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. When microanalysis data was not available, the purity of title compounds was judged to be >90% by ^{1}H NMR, ^{13}C NMR, and or GC analyses unless otherwise stated. All reactions involving air-sensitive reagents were performed under nitrogen or argon using syringe-septum cap techniques. All glassware was oven or flame dried prior to use.

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise indicated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under a nitrogen atmosphere. Solutions of *sec*-BuLi in cyclohexane, *n*-BuLi in hexanes, and *t*-BuLi in pentane were titrated according to the method of Suffert.[19]

Medium-pressure liquid chromatography (MPLC) was performed using an ISCO Model 273 fraction collector and an ISCO Model UA-5 absorbance/fluorescence monitor. Various columns, which were packed with Merck silica gel (32–63 mesh) and whose length and diameter depended on the amount of material and the difficulty of the separation, were used with mixtures of ethyl acetate and hexane. High-pressure liquid chromatography (HPLC) was performed using a Rainin HPXL pump system coupled to a Rheodyne 7125 Syringe Loading Sample Injector and a Knauer UV Detector (254 nm). Preparative scale HPLC was performed on a Dynamax 60-A 8 *m*m silica column (Rainin Instrument Co., Woburn, MA 01801, 25 cm × 21.4 mm i.d.). Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr apparatus. Boiling points refer to air-bath temperatures and are not necessarily an accurate measure of boiling points.

Mass Spectrometric Analysis. Electron impact mass spectra (EI/MS) were performed on Finnigan-MAT CH-5 and 311A spectrometers. Field ionization mass spectra (FI/MS) were performed on a Finnigan-731 spectrometer. Gas chromatography/mass spectrometry (GC/MS) was performed on a Hewlett-Packard 5890 gas chromatograph coupled to a Hewlett-Packard 5970B electron impact mass detector using a commercially available Ultra-1 capillary column (Hewlett-Packard, Palo Alto, CA 94304, 30 m × 0.20 mm i.d., 0.33 μm film). Gas chromatography/field ionization mass spectrometry (GC/FI) was performed on a VG-7070 spectrometer.

Preparation of 3,4-Dihydro-3-hydroxy-2-(1-methylethyl)-1(2*H*)isoquinolinone. To 2-methyl-*N*-(1-methylethyl)benzamide (1.48 g, 8.42 mmol) in 25 mL of THF at 0 °C was added *n*-BuLi (13.8 mL, 17.7 mmol, 1.30 M). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and then stirred for 30 min. After recooling the mixture to 0 °C, DMF (0.98 mL, 0.92 g, 12.6 mmol) was added. The reaction mixture was then stirred at 0 °C for 1 h, allowed to warm to room temperature, and then stirred for 8 h. Workup consisted of concentration *in vacuo*, dilution with ether (30 mL), washing with water (1 × 30 mL), washing with brine (1 × 30 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil was purified by MPLC (50% EtOAc/hexane) to give a light yellow solid (1.02 g, 63%) with a decomposition/melting point range of 117–119 °C: IR (Nujol) 3299, 1618, 1574, 1468, 1373, 1316, 1285, 1219, 1177, 1048; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09 (m, 1H, ArH ortho to carbonyl), 7.2–7.5 (m, 3H, Ar), 5.32 (m, 1H, C*H*OH), 4.97 (septet, 1H, *J* = 6.8 Hz, C*H*CH_3), 3.17 (dq, 2H, *J* = 10.6 Hz, *J* = 2.4 Hz, CH_2), 2.45 (d, 1H, *J* = 7.8 Hz, OH), 1.35 (d, 3H, *J* = 7.2 Hz, CH_3), 1.27 (d, 3H, *J* = 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.8, 133.8, 131.9, 128.9, 128.3, 128.2, 127.2, 74.67, 44.76, 36.38, 21.25, 20.87. 3,4-Dihydro-3-hydroxy-2-(1-methylethyl)-1(2*H*)isoquinolinone is thermally unstable and eliminated water under GC conditions to give 2-(1-methylethyl)-1(2*H*)isoquinolinone (**9**).

Preparation of 2-(1-Methylethyl)-1(2*H*)isoquinolinone (9). To 3,4-dihydro-3-hydroxy-2-(1-methylethyl)-1(2*H*)isoquinolinone (0.70 g, 3.62 mmol) in 20 mL of benzene was added *p*-toluenesulfonic acid (1.38 g, 7.24 mmol). The reaction mixture was refluxed for 10 h and then allowed to cool to room temperature. Workup consisted of dilution with ether (20 mL), extraction with water (1 × 40 mL), washing with 5% NaOH (1 × 40 mL), washing with brine (1 × 40 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow solid was purified by MPLC (20% EtOAc/hexane) to give **9** as a light yellow solid (0.59 g, 93%), mp 105–107 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.45 (d, 1H, *J* = 8.3 Hz, ArH ortho to carbonyl), 7.4–7.7 (m, 3H, Ar), 7.15 (d, 1H, *J* = 7.6 Hz, olefinic), 6.55 (d, 1H, *J* = 7.7 Hz, olefinic), 5.42 (septet, 1H, *J* = 7.0 Hz, NCH), 1.39 (d, 6H, *J* = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.1, 136.0, 131.4, 127.4, 126.2, 126.0, 125.6, 125.2, 105.8, 45.26, 21.20; GC/MS (EI, 70 eV) *m*/*z* (rel intensity) 188 (10, M + 1), 187 (71, M^+), 172 (12), 146 (14), 145 (100), 128 (15), 118 (21), 117 (9). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.71; H, 7.11; N, 7.52.

Preparation of *N*,*N*-Bis(1-methylethyl)-2-(1-methylethyl)benzamide (6) from *N*,*N*-Bis(1-methylethyl)-2-ethylbenzamide. To *N*,*N*-bis(1-methylethyl)-2-ethylbenzamide (176 mg, 0.76 mmol) in 10 mL of THF at −78 °C was added *n*-BuLi (0.71 mL, 0.91 mmol, 1.28 M). The reaction mixture was stirred at −78 °C for 1 h and then methyl iodide (141 μL, 321 mg, 2.26 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 8 h. Workup consisted of concentration in *vacuo*, dilution with ether (10 mL), extraction with water (1 × 20 mL), washing with brine (1 × 20 mL), drying over $MgSO_4$, filtration, and concentration in *vacuo*. The resulting yellow oil was purified by MPLC (10% EtOAc/hexane) to give **6** as a white solid (133.4 mg, 71%), mp 77–78 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.0–7.4 (m, 4H, Ar), 3.70 (septet, 1H, *J* = 6.6 Hz, NCH), 3.50 (septet, 1H, *J* = 6.6 Hz, NCH), 3.00 (septet, 1H, *J* = 6.8 Hz, ArCH), 1.57 (d, 6H, *J* = 6.5 Hz, CH_3), 1.26 (d, 3H, *J* = 6.1 Hz, CH_3), 1.25 (d, 3H, *J* = 5.6 Hz, CH_3), 1.11 (d, 3H, *J* = 5.3 Hz, CH_3), 1.08 (d, 3H, *J* = 5.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 144.7, 137.5, 128.3, 125.8, 125.7, 124.6, 50.60, 45.61, 30.50, 25.87, 24.88, 23.28, 20.56; GC/MS (EI, 70 eV) *m*/*z* (rel intensity) 247 (5, M^+), 204 (55), 148 (12), 147 (100), 146 (41), 131 (27), 129 (47), 103 (11), 99 (20), 77 (13). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.18; N, 5.66. Found: C, 77.73; H, 10.33; N, 5.70.

Preparation of *N*,*N*-Bis(1-methylethyl)-2-(1-methylethyl)benzamide (6) from 2-Iodo-1-(1-methylethyl)benzene. To 2-iodo-1-(1-methylethyl)-

benzene (1.721 g, 6.99 mmol) in 40 mL of THF at −78 °C was added *t*-BuLi (11.9 mL, 14.7 mmol, 1.23 M). The reaction mixture was stirred for 2 h and then transferred, via a cannula, to a mixture of diisopropylcarbamoyl chloride (1.26 g, 7.69 mmol) and THF (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. Workup consisted of concentration *in vacuo*, dilution with water (30 mL), extraction with ether (2 × 30 mL), washing with saturated $NaHCO_3$ (1 × 30 mL), washing with 20% HCl (1 × 30 mL), washing with brine (1 × 30 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil was purified by MPLC (4% EtOAc/hexane) to give **6** as a white solid (1.06 g, 61%) mp 80–82 °C. The same spectroscopic data was obtained for this sample as that obtained by the alternative synthesis of **6** described above.

Preparation of *N,N*-Bis(1-methylethyl)-2-trimethylsilyl)benzamide (8). To TMEDA (0.51 mL, 0.394 g, 3.39 mmol) in 10 mL of THF at −78 °C was added *sec*-BuLi (3.4 mL, 3.39 mmol, 1.0 M). The reaction mixture was stirred for 10 min and then *N,N*-bis(1-methylethyl)benzamide (**5**) (0.632 g, 3.08 mmol) in 5 mL of THF was added via cannula. The reaction mixture was stirred for 1 h at −78 °C, and then trimethylsilyl chloride (0.401 g, 0.47 mL, 3.69 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred for 8 h. Workup consisted of concentration *in vacuo*, dilution with water (10 mL), extraction with ether (2 × 15 mL), washing with brine (1 × 20 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil was purified by MPLC (5% EtOAc/hexane) to give **8** as a colorless oil which solidified into a white solid (0.65 g, 76%), mp 78–80 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.60 (m, 1H, Ar), 7.31 (m, 2H, Ar), 7.14 (m, 1H, Ar), 3.7–3.9 (b, 1H, CH), 3.4–3.6 (b, 1H, CH), 1.56 (bd, 6H, J = 5.7 Hz, $CHCH_3$), 1.15 (bd, 6H, J = 5.7 Hz, $CHCH_3$), 0.32 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 143.9, 137.9, 135.1, 128.0, 127.6, 125.0, 50.69, 45.63, 20.47, 0.06; GC/MS (EI, 70 eV) m/z (rel intensity) 277 (17, M^+), 262 (42), 220 (26), 218 (57), 204 (29), 178 (50), 177 (100), 160 (26). Anal. Calcd for $C_{16}H_{27}NOSi$: C, 69.26; H, 9.81; N, 5.05. Found: C, 69.54; H, 10.01; N, 4.98.

Preparation of *N*-(1-Methylethyl)-2-(trimethylsilyl)benzamide (4). To TMEDA (2.18 mL, 1.68 g, 14.44 mmol) in 40 mL of THF at −78 °C was added *sec*-BuLi (9.69 mL, 14.44 mmol, 1.49 M). The reaction mixture was stirred for 5 min and then *N*-(1-methylethyl)benzamide (**1**) (1.071 g, 6.56 mmol) in 10 mL of THF was added via cannula. The reaction mixture was stirred for 2 h at −78 °C, and then trimethylsilyl chloride (0.855 g, 1.00 mL, 7.87 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred for 2.5 h. Workup consisted of concentration *in vacuo*, dilution with water (20 mL), extraction with ether (2 × 20 mL), washing with saturated $NaHCO_3$ (1 × 20 mL), washing with 5% HCl (1 × 20 mL), washing with brine (1 × 20 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting white solid was purified by MPLC (20% EtOAc/hexane) to give **4** as a white solid (1.093 g, 71%), mp 82–83 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63 (m, 1H, Ar), 7.34–7.45 (m, 3H, Ar), 5.70 (b, 1H, NH), 4.24 (m, 1H, CH), 1.26 (d, 6H, J = 6.7 Hz, $CHCH_3$), 0.33 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1, 142.3, 139.3, 135.0, 129.0, 128.4, 125.9, 41.58, 22.52, −0.02; GC/MS (EI, 70 eV) m/z (rel intensity) 221 (20), 220 (100), 179 (12), 178 (75), 177 (12), 162 (10), 160 (28), 91 (11). Anal. Calcd for $C_{13}H_{21}NOSi$: C, 66.33; H, 8.99; N, 5.95. Found: C, 66.44; H, 9.13; N, 5.99. There was no M^+ peak by either EI/MS or FI/MS.

Preparation of *N*-(1-Methylethyl)-2-(1-methylethyl)benzamide (2). To 2-(1-methylethyl)benzoic acid (1.10 g, 6.70 mmol) was added thionyl chloride (10.0 mL, 16.3 g, 137 mmol). The reaction mixture was refluxed for 3 h and then concentrated *in vacuo*. Benzene (30 mL) was then added, and the mixture was concentrated *in vacuo* to remove any remaining thionyl chloride. THF (30 mL) was then added to the acid chloride, and the mixture was cooled to 0 °C. Isopropylamine (2.0 mL, 1.38 g, 23.4 mmol) in 20 mL of THF was then added dropwise over a period of 30 min. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and then stirred for an additional 12 h. Workup consisted of concentration *in vacuo*, dilution with water (40 mL), extraction with ether (2 × 20 mL), washing with saturated $NaHCO_3$ (1 × 30 mL), washing with 5% HCl (1 × 30 mL), washing with brine (1 × 30 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting light yellow solid was purified by recrystallization from hexane to give **2** as a white solid (1.37 g, 73%), mp 115–116 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15–7.38 (m, 4H, Ar), 5.45–5.65 (b, 1H, NH), 4.29 (m, 1H, NCH), 3.34 (septet, 1H, J = 6.8 Hz, ArCH), 1.26 (d, 6H, J = 6.8 Hz, CH_3), 1.25 (d, 6H, J = 6.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.4, 145.9, 136.3, 129.3, 126.1, 125.4, 125.1, 41.24, 29.42, 23.71, 22.25; GC/MS (EI, 70 eV) m/z (rel intensity) 205 (62, M^+), 162 (98), 147 (100), 146 (60), 145 (42), 131 (83), 129 (75), 103 (32), 91 (41), 77 (40), 58 (38). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.68; H, 9.56; N, 6.81.

Preparation of *N*-(1-Methylethyl)benzenecarbothioamide (18). To *N*-(1-methylethyl)benzamide (**1**) (1.41 g, 8.64 mmol) in 5 mL of toluene was added Lawesson's reagent[20,21] (1.92 g, 4.75 mmol). The reaction mixture was refluxed for 1 h and then concentrated *in vacuo*. The resulting dark yellow oil was purified by flash chromatography with 5% Et_2O/petroleum ether to give **18** as a yellow oil (281 mg, 18%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.92 (b, 1H, NH), 7.59–7.54 (m, 2H, Ar), 7.34–7.17 (m, 3H, Ar), 4.67 (m, 1H, CH), 1.24 (d, 3H, J = 6.8 Hz, CH_3), 1.22 (d, 3H, J = 6.2 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.7, 141.0, 130.2, 127.5, 126.1, 47.60, 20.53; GC/MS (EI, 70 eV) m/z (rel intensity) 180 (13, M + 1), 179 (92, M^+), 178 (48), 122 (23), 121 (91), 105 (17), 104 (100), 77 (66), 58 (72), 51 (36). Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31; N, 7.81; S, 17.89. Found: C, 66.67; H, 7.22; N, 7.61; S, 18.25.

Preparation of *N,N*-Bis(1-methylethyl)-2-(1-methylethyl)benzenecarbothioamide (20). To *N,N*-bis(1-methylethyl)-2-(1-methylethyl)benzamide (**6**) (0.533 g, 2.15 mmol) in 8 mL of toluene was added Lawesson's reagent[20,21] (0.479 g, 1.18 mmol). The reaction mixture was refluxed for 18 h and then concentrated in *vacuo*. The resulting dark yellow oil was purified by flash chromatography with 5% EtOAc/hexane to give **20** as a light yellow solid (0.567 g, 95%), mp 122–124 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.8–7.3 (m, 4H, Ar), 3.97 (m, 2H, NCH), 2.89 (septet, 1H, J = 6.7 Hz, ArCH), 1.73 (bd, 6H, J = 6.3 Hz, CH_3 of amide), 1.20 (d, 3H, J = 6.7 Hz, CH_3), 1.15 (d, 3H, J = 7.0 Hz, CH_3), 1.10 (d, 3H, J = 6.7 Hz, CH_3), 1.01 (d, 3H, J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 198.7, 143.2, 141.6, 127.2, 125.7, 125.5, 123.3, 56.18, 50.21, 29.78, 24.58, 22.74, 19.59, 19.01; GC/MS (EI, 70 eV) m/z (rel intensity) 263 (36, M^+), 230 (38), 220 (47), 163 (89), 146 (23), 130 (44), 129 (100), 128 (24), 75 (78). Anal. Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.56; N, 5.32; S, 12.17. Found: C, 72.95; H, 9.64; N, 5.33; S, 12.11.

Addition of *t*-BuLi to 2-(2-Methoxyphenyl)-4,4-dimethyl-2-oxazoline. To 2-(2-methoxyphenyl)-4,4-dimethyl-2-oxazoline (6.42 g, 31.3 mmol) in THF (120 mL) at −45 °C was added *t*-BuLi (20.0 mL, 34.4 mmol, 1.70 M) dropwise over a period of 10 min. The reaction mixture was stirred at −45 °C for 3 h and then allowed to warm to room temperature. The mixture was worked up by quenching with saturated NH_4Cl (100 mL), extraction with Et_2O (3 × 100 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil was purified by MPLC (30% EtOAc/hexane) to give three different fractions and products.

The first or least polar fraction gave 4,4-dimethyl-2-(1,1-dimethylethyl)-2-(2-methoxyphenyl)oxazolidine as a colorless oil (1.872 g, 23%): GC/MS (EI, 70 eV) m/z (rel intensity) 205 (51, M^+), 190 (68), 176 (44), 162 (89), 133 (97), 132 (58), 119 (100), 107 (47), 104 (45), 91 (89). This material was characterized only by GC/MS.

The second fraction gave 2-[2-(1,1-dimethylethyl)phenyl]-4,4-dimethyl-2-oxazoline as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46 (m, 1H, Ar), 7.33 (m, 2H, Ar), 7.17 (m, 1H, Ar), 4.10 (s, 2H, CH_2), 1.42 (s, 9H, $C(CH_3)_3$), 1.40 (s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.9, 148.3, 130.8, 129.2, 128.0, 126.2, 124.9, 78.60, 67.15, 35.73, 31.01, 27.58; GC/MS (EI, 70 eV) m/z (rel intensity) 231 (4, M^+), 230 (11), 216 (66), 176 (100), 160 (71), 145 (45), 116 (30), 115 (31), 91 (25). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.66; H, 9.12; N, 6.27.

The third fraction was collected as part of the backwash of the chromatography column and gave the starting material as a light yellow oil (2.777 g, 43%).

Reaction of 2-[2-(1,1-Dimethylethyl)phenyl]-4,4-dimethyl-2-oxazoline with Triflic Anhydride. To 2-[2-(1,1-dimethylethyl)phenyl]-4,4-dimethyl-2-oxazoline (2.0 g, 8.64 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added triflic anhydride (2.0 mL, 3.36 g, 11.91 mmol) dropwise over a period of 3 min. The reaction mixture was stirred at 0 °C for 1 h and then it was poured into ice water. The aqueous mixture was made basic with 40% NaOH (ca. 20 mL). This solution was then worked up by washing with CH_2Cl_2 (15 mL), acidification of the aqueous with 6 N HCl, extraction with Et_2O (2 × 100 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. This gave 2-(1,1-dimethylethyl)(trifluoromethyl)-sulfonamide ester as a white solid (1.50 g, 46%), mp 70–72 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.51 (m, 1H, Ar), 7.40 (m, 1H, Ar), 7.28 (m, 2H, Ar), 5.30 (s, 1H, NH), 4.26 (s, 2H, CH_2), 1.49 (s, 6H, $C(CH_3)_2$), 1.40 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 147.8, 131.7, 130.3, 128.4, 128.4 (CF_3), 127.0, 125.5, 125.4 (CF_3), 121.2 (CF_3), 116.9

(CF_3), 71.82, 58.86, 36.81, 31.28, 24.90; GC/MS (EI, 70 eV) *m/z* (rel intensity) 190 (37), 163 (81), 161 (100), 145 (57), 117 (23), 91 (29), 69 (33), 58 (22). There was no M^+ of 381 evident by GC/MS. The $J(^{13}C-^{19}F)$ was 290 Hz.

Preparation of 2-(1,1-Dimethylethyl)benzoic Acid. To the 2-(1,1-dimethylethyl)(trifluoromethyl)sulfonamide ester (1.50 g, 3.93 mmol) in 10 mL of THF was added 40% NaOH (100 mL). The resulting mixture was heated to 80 °C and then stirred for 18 h. After allowing the resulting reaction mixture to cool, it was worked up by dilution with Et_2O (50 mL), acidification of the aqueous layer with 6 N HCl (ca. 10 mL), filtration, extraction of the aqueous with Et_2O (2 × 75 mL), drying over $MgSO_4$, filtration, and concentration in *vacuo*. This gave a colorless oil (468 mg, 67%) (lit.[22] mp 67–68 °C): ^1H NMR ($CDCl_3$, 200 MHz) δ 11.70 (bs, 1H, CO_2H), 7.50 (m, 2H, Ar), 7.40 (m, 1H, Ar), 7.23 (m, 1H, Ar), 1.48 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5, 148.1, 131.8, 130.5, 129.0, 127.1, 125.4, 35.96, 31.41; GC/MS (EI, 70 eV) *m/z* (rel intensity) 178 (18, M^+), 163 (46), 161 (9), 146 (11), 145 (100), 117 (43), 115 (30), 91 (21), 77 (14), 51 (12).

Preparation of 2-(1,1-Dimethylethyl)-*N*-(1-methylethyl)benzamide (3). To 2-(1,1-dimethylethyl)benzoic acid (217.3 mg, 1.22 mmol) was added thionyl chloride (5.0 mL, 8.16 g, 68.5 mmol). The reaction mixture was refluxed for 3 h and then concentrated *in vacuo*. Benzene (10 mL) was then added, and the mixture was concentrated *in vacuo* to remove any remaining thionyl chloride. Methylene chloride (10 mL) was then added to the acid chloride, and the mixture was cooled to 0 °C. Isopropylamine (3.0 mL, 2.08 g, 35.2 mmol) in 10 mL of CH_2Cl_2 was then added dropwise over a period of 10 min. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and then stirred for an additional 8 h. Workup consisted of concentration *in vacuo*, dilution with water (10 mL), extraction with ether (2 × 10 mL), washing with saturated $NaHCO_3$ (10 mL), washing with 5% HCl (10 mL), washing with brine (10 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting light yellow oil was purified by MPLC (7.5% EtOAc/hexane) to give **3** as a white solid (198.6 mg, 74%): mp 126–127 °C: IR ($CHCl_3$) carbonyl, 1650; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.46 (m, 1H, Ar), 7.36–7.26 (m, 1H, Ar), 7.18 (m, 2H, Ar), 5.60–5.40 (bs, 1H, NH), 4.27 (m, 1H, CH), 1.44 (s, 9H, $C(CH_3)_3$), 1.25 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.9, 147.1, 136.9, 128.9, 126.8, 125.3, 41.53, 36.08, 31.35, 22.31; GC/MS (EI, 70 eV) *m/z* (rel intensity) 219 (3, M^+), 162 (30), 161 (100), 145 (32), 128 (12), 117 (23), 115 (25), 91 (38), 58 (76). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.60; H, 9.68; N, 6.37.

Preparation of 2-(1,1-Dimethylethyl)-*N*,*N*-bis(1-methylethyl)benzamide (7). To 2-(1,1-dimethylethyl)benzoic acid (238.5 mg, 1.34 mmol) was added thionyl chloride (5.0 mL, 8.16 g, 68.5 mmol). The reaction mixture was refluxed for 3 h and then concentrated in *vacuo*. Benzene (10 mL) was then added, and the mixture was concentrated *in vacuo* to remove any remaining thionyl chloride. Methylene chloride (10 mL) was then added to the acid chloride, and the mixture was cooled to 0 °C. Diisopropylamine (3.0 mL, 2.17 g, 21.4 mmol) in 10 mL of CH_2Cl_2 was then added dropwise over a period of 10 min. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and then stirred for an additional 8 h. Workup consisted of concentration *in vacuo*, dilution with water (10 mL), extraction with ether (2 × 10 mL), washing with saturated $NaHCO_3$ (10 mL), washing with 5% HCl (10 mL), washing with brine (10 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting light yellow oil was purified by MPLC (5% EtOAc/hexane) to give **7** as a white solid (140.7 mg, 40%), mp 92–93 °C: IR ($CHCl_3$) carbonyl, 1618; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.47 (dd, 1H, J = 7.9 Hz, J = 1.4 Hz, Ar), 7.27 (dt, 1H, J = 7.7 Hz, J = 1.3 Hz, Ar), 7.15 (dt, 1H, J = 7.3 Hz, J = 1.4 Hz, Ar), 7.00 (dd, 1H, J = 7.5 Hz, J = 1.8 Hz, Ar), 3.67 (septet, 1H, J = 6.4 Hz, CH), 3.48 (septet, 1H, J = 6.8 Hz, CH), 1.56 (d, 3H, J = 6.6 Hz, CH_3), 1.55 (d, 3H, J = 7.2 Hz, CH_3), 1.42 (s, 9H, $C(CH_3)_3$), 1.13 (d, 3H, J = 6.7 Hz, CH_3), 1.08 (d, 3H, J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 146.3, 136.7, 128.0, 127.5, 126.8, 125.3, 50.50, 45.38, 36.23, 31.61, 20.16, 20.11, 19.59, 19.56; GC/MS (EI, 70 eV) *m/z* (rel intensity) 261 (23, M^+), 260 (22), 218 (21), 162 (26), 161 (100), 143 (14), 115 (15), 91 (32), 86 (32). Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.89; H, 10.48; N, 5.33.

Preparation of 2,3-Dihydro-3,3-dimethyl-2-(1-methylethyl)-1*H*-isoindol-1-one (10). To potassium (640 mg, 7.42 mmol) and ferric nitrate (single chunk) in 25 mL of liquid ammonia was added 2,3-dihydro-2-(1-methylethyl)-1*H*-isoindol-1-one (1.3 g, 7.42 mmol). The reaction mixture was stirred for 30 min, and then methyl iodide (1.02 mL, 2.32 g, 16.32 mmol) in 25 mL of Et_2O was added dropwise over a period of 15 min. The reaction mixture was stirred at –40 °C for 30 min and then refluxed (–23 °C) for 3 h. This series of steps was repeated two times in order to drive the reaction to the dimethyl adduct. The reaction mixture was diluted with saturated NH_4Cl (1 × 50 mL), extracted with Et_2O (2 × 25 mL), washed with 20% HCl (2 × 75 mL), washed with 10% NaOH (2 × 25 mL), washed with brine (1 × 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting light yellow solid was purified by MPLC (15% EtOAc/hexane) to give **10** as a white solid (445 mg, 34%), mp 137–139 °C: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.83–7.79 (m, 1H, ArH ortho to carbonyl), 7.55–7.30 (m, 3H, Ar), 3.65 (septet, 1H, J = 6.9 Hz, CH), 1.56 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$), 1.48 (s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.4, 150.7, 131.3, 130.6, 127.1, 122.2, 120.1, 62.52, 43.73, 24.70, 19.82; GC/MS (EI, 70 eV) *m/z* (rel intensity) 203 (27, M^+), 188 (84), 174 (36), 146 (100), 145 (44), 117 (19), 115 (22), 103 (22), 91 (20), 77 (25). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.64; H, 8.48; N, 6.89.

Preparation of 2-Bromo-α,α-Dimethylbenzene Acetic Acid. To solid lithium diisopropylamide (LDA) (25.0 g, 233 mmol) in 200 mL of THF at –78 °C was added 2-bromophenylacetic acid (25.0 g, 116 mmol) in 100 mL of THF. The addition was dropwise over a period of 15 min. The reaction mixture was stirred for 1 h at –78 °C, and then methyl iodide (15.9 mL, 36.0 g, 256 mmol) in 50 mL of THF was added dropwise over a period of 15 min. The reaction mixture was allowed to warm to room temperature and then stirred for 16 h. Workup consisted of concentration *in vacuo*, dilution with Et_2O (200 mL), washing with 10% HCl (2 × 100 mL), extraction with 10% NaOH (2 × 50 mL), acidification of the aqueous layer with 12 N HCl (30 mL), extraction of the aqueous layer with ether (2 × 75 mL), washing with brine (1 × 50 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. This gave 2-bromo-α-methylbenzeneacetic acid as a light brown solid (26.5 g, 100%), mp 83–89 °C: ^1H NMR ($CDCl_3$, 200 MHz) δ 10.35 (bs, 1H, CO_2H), 7.55 (m, 1H, Ar), 7.36–7.23 (m, 2H, Ar), 7.14–7.05 (m, 1H, Ar), 4.26 (q, 1H, J = 7.2 Hz, CH), 1.49 (d, 3H, J = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 179.8, 139.4, 132.9, 128.9, 128.7, 127.8, 124.4, 44.51, 17.48; GC/MS (EI, 70 eV) *m/z* (rel intensity) 230 (2, M^+), 228 (2), 185 (23), 183 (23), 149 (100), 104 (71), 103 (47), 77 (43), 51 (24). The 2-bromo-α-methylbenzeneacetic acid was contaminated with ca. 10% 2-bromophenylacetic acid as judged by ^1H NMR and GC. This sample was then subjected to further lithiation and methylation as described below.

To solid lithium diisopropylamide (LDA) (25.0 g, 233 mmol) in 200 mL of THF at 0 °C was added 2-bromo-α-methylbenzeneacetic acid (26.5 g, 116 mmol) in 50 mL of THF. The addition was via cannula over a period of 15 min. The reaction mixture was mechanically stirred for 1 h at 0 °C, and then methyl iodide (15.9 mL, 36.0 g, 256 mmol) in 50 mL of THF was added via cannula over a period of 10 min. The reaction mixture was allowed to warm to room temperature and then mechanically stirred for ca. 16 h. Workup consisted of concentration in *vacuo*, dilution with Et_2O (200 mL), washing with 15% HCl (2 × 200 mL), extraction of the aqueous with Et_2O (2 × 100 mL), washing of the combined organics with 1.5 N Na_2SO_3 (2 × 100 mL), extraction with 10% NaOH (3 × 75 mL), acidification of the aqueous layer with 12 N HCl (ca. 40 mL), extraction of the aqueous layer with ether (3 × 75 mL), washing with brine (1 × 50 mL), drying over $MgSO_4$, filtration, and concentration in *vacuo*. This entire procedure and workup was repeated once in order to completely convert the monomethyl to the dimethyl adduct. These two cycles gave an orange solid which was first purified by flash chromatography (50% EtOAc/hexane) and then recrystallization from 25% EtOAc/hexane. This gave 2-bromo-α,α-dimethylbenzeneacetic acid as a light yellow solid (16.9 g, 60%), mp 141–142 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 12.0 (bs, 1H, CO_2H), 7.55 (m, 1H, Ar), 7.40 (m, 1H, Ar), 7.30 (m, 1H, Ar), 7.10 (m, 1H, Ar), 1.66 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.6, 143.0, 134.3, 128.5, 127.5, 127.2, 123.9, 48.12, 26.20; GC/MS (EI, 70 eV) *m/z* (rel intensity) 171 (40), 169 (41), 164 (12), 163 (100), 135 (11), 117 (11), 115 (19), 91 (17), 77 (15), 51 (15). Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; Br, 32.87. Found: C, 49.61; H, 4.63; N, 32.62. The GC/MS gave very small signals at the M^+ of 244 and the M – 2 of 242; however, normalization made these intensities less than 1.

Preparation of 2-Bromo-α,α-dimethyl-*N*-(1-methylethyl)benzeneacetamide. To 2-bromo-α,α-dimethylbenzeneacetic acid (4.29 g, 17.60 mmol) was added thionyl chloride (10.0 mL, 16.3 g, 137 mmol). The reaction mixture was refluxed for 3 h and then concentrated *in vacuo*. Benzene (30 mL) was then added, and the mixture was concentrated *in vacuo* to remove any remaining thionyl chloride. Methylene chloride (30 mL) was then added to the acid chloride, and the mixture was cooled to 0 °C. Isopropylamine (10.0 mL, 6.94 g, 117.4 mmol) in 20 mL of CH_2Cl_2 was

then added dropwise over a period of 30 min. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred for an additional 8 h. Workup consisted of concentration *in vacuo*, dilution with water (40 mL), extraction with ether (2 × 20 mL), washing with saturated $NaHCO_3$ (1 × 30 mL), washing with 5% HCl (1 × 30 mL), washing with brine (1 × 30 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting light yellow solid was purified by recrystallization from hexane to give white needles (4.85 g, 97%), mp 87–88 °C: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz, Ar), 7.50 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz, Ar), 7.36 (dt, 1H, J = 7.5 Hz, J = 1.4 Hz, Ar), 7.16 (dt, 1H, J = 7.3 Hz, J = 1.6 Hz, Ar), 4.88 (b, 1H, NH), 4.08 (m, 1H, CH), 1.63 (s, 6H, $C(CH_3)_2$), 1.07 (d, 6H, J = 6.7 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.3, 143.4, 135.0, 128.7, 128.2, 127.7, 124.2, 48.32, 41.43, 26.61, 22.38; GC/MS (EI, 70 eV) m/z (rel intensity) 204 (100), 199 (18), 171 (52), 169 (50), 119 (35), 117 (21), 115 (31), 91 (32), 86 (49), 77 (19). Anal. Calcd for $C_{13}H_{18}BrNO$: C, 54.94; H, 6.38; N, 4.93; Br, 28.12. Found: C, 55.21; H, 6.55; N, 4.94; Br, 28.45. The GC/MS gave small signals for the M^+ of 284 and the M – 2 of 282; however, normalization made these intensities less than 1.

Preparation of 2-Bromo-α,α-dimethyl-*N*-(1-methylethyl)phenethylamine. To 2-bromo-α,α-dimethyl-*N*-(1-methylethyl)benzeneacetamide (3.10 g, 10.91 mmol) was added borane–THF (130 mL, 130 mmol, 1.0 M). The reaction mixture was refluxed for 3 days and then allowed to cool to room temperature. Workup consisted of acidification with 6 N HCl (ca. 75 mL), heating the resulting mixture to ca. 90 °C for 1 h, allowing the mixture to cool, washing with Et_2O (2 × 75 mL), basification of the aqueous with 40% NaOH (75 mL), extraction of the aqueous with Et_2O (3 × 50 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting light yellow oil was purified by flash chromatography (50% EtOAc/hexane) to give a colorless oil (2.51 g, 85%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.58 (dd, 1H, J = 8.0 Hz, J = 1.7 Hz, Ar), 7.44 (dd, 1H, J = 8.2 Hz, J = 1.7 Hz, Ar), 7.27 (dt, 1H, J = 7.6 Hz, J = 1.5 Hz, Ar), 7.06 (dt, 1H, J = 7.6 Hz, J = 1.6 Hz, Ar), 3.61 (bm, 1H, NH), 3.10 (s, 2H, CH_2), 2.70 (septet, 1H, J = 6.2 Hz, CH), 1.51 (s, 6H, $C(CH_3)_2$), 0.97 (d, 6H, J = 6.4 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.2, 135.1, 129.4, 127.2, 126.7, 121.6, 55.20, 48.70, 40.25, 26.65, 22.50; GC/MS (EI, 70 eV) m/z (rel intensity) 174 (5), 171 (7), 169 (7), 117 (5), 115 (9), 91 (8), 77 (6), 73 (10), 72 (100), 56 (8). Anal. Calcd for $C_{13}H_{20}BrN$: C, 57.78; H, 7.46; N, 5.18; Br, 29.57. Found: C, 57.96; H, 7.44; N, 5.20; Br, 29.27. The GC/MS showed no M^+ of 270.

Preparation of 3,4-Dihydro-4,4-dimethyl-2-(1-methylethyl)-1*H*-isoquinol-1-one (11). A mixture of 2-bromo-α,α-dimethyl-*N*-(1-methylethyl)phenethylamine (548.1 mg, 2.03 mmol), palladium acetate [$Pd(OAc)_2$] (22.2 mg, 0.10 mmol), triphenylphosphine (PPh_3) (50.0 mg, 0.19 mmol), and tri-*n*-butylamine [$(n\text{-}Bu)_3N$] (413.6 mg, 2.23 mmol) was heated to 100 °C. A balloon filled with carbon monoxide (CO) was attached to the reaction vessel, and heating was continued for a total of 8 h. After allowing the reaction mixture to cool, it was worked up by dilution with Et_2O (1 × 50 mL), washing with 10% HCl (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The resulting yellow oil was purified by MPLC (7.5% EtOAc/hexane) and HPLC (10% EtOAc/hexane) to give **11** as a light yellow oil (148.3 mg, 34%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10 (dd, 1H, J = 8.0 Hz, J = 1.3 Hz, ArH ortho to carbonyl), 7.42 (m, 1H, Ar), 7.30 (m, 2H, Ar), 5.13 (septet, 1H, J = 6.8 Hz, NCH), 3.16 (s, 2H, CH_2), 1.31 (s, 6H, $C(CH_3)_2$), 1.18 (d, 6H, J = 7.1 Hz, $CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9, 145.8, 131.4, 128.1, 128.0, 126.1, 122.7, 50.46, 42.64, 33.14, 25.96, 18.84; IR ($CHCl_3$) carbonyl (1630); GC/MS (EI, 70 eV) m/z (rel intensity) 217 (41, M^+), 204 (100), 203 (17), 174 (17), 160 (19), 146 (18), 131 (40), 117 (19), 115 (20), 91 (18). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 76.90; H, 8.90; N, 6.42.

General Procedure for the Metalation of Amides in the Competition Experiments. To TMEDA in THF at –78 °C was added *sec*-BuLi. Competitions between two secondary benzamides typically used 5 equiv of *sec*-BuLi and competitions between two tertiary benzamides used from 0.5 to 1 equiv of *sec*-BuLi. The reaction mixture was stirred for 5 min and then an ca. 1:1:1 mixture of two amides and *n*-dodecane, used as an internal standard for GC yields, in THF was added via cannula. The reaction mixture was stirred for 1 to 10 h, depending on the competition, at –78 °C and then excess deuterated acetic acid (ca. 20 equiv) was added. The reaction mixture was allowed to warm to room temperature over a period of ca. 2 h, and then it was stirred for ca. 8 h. Workup consisted of concentration *in vacuo*, dilution with water (1 × 10 mL), extraction with ether (2 × 10 mL), washing with brine (1 × 10 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting mixture was analyzed by GC and GC/MS to determine both the yield and the extent of deuterium incorporation. The two amides were separated by liquid chromatography and then submitted for FI/MS or analyzed by GC/FI as a mixture. Since there was a large M – 1 peak for most of the amides, the GC/MS data, which was equivalent to a 70 eV EI/MS, was inconsistent with the FI/MS data.[10] The isolated amides were then analyzed further by ^{1}H NMR, ^{13}C NMR, and/or melting point.

The starting amounts for each amide, the concentration of total amide in THF, amount of *sec*-BuLi used, the method of purification, the method of deuterium analysis, the deuterium incorporations for each amide, and the relative rates of lithiation for these values are given as supplementary material.

Attempted Lithiation of *N*,*N*-Bis(1-methylethyl)benzenecarbothioamide (19). To TMEDA (293 μL, 226 mg, 1.94 mmol) in 4 mL of THF at –78 °C was added *sec*-BuLi (1.62 mL, 1.94 mmol, 1.20 M). The reaction mixture was stirred for 10 min and then *N*,*N*-bis(1-methylethyl)-benzenecarbothioamide (**19**) (215.2 mg, 0.972 mmol) in 3 mL of THF was added via cannula. The reaction mixture was stirred for 3 h at –78 °C, and then trimethylsilyl chloride (211.2 mg, 247 μL, 1.94 mmol) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 18 h. Workup consisted of concentration *in vacuo*, dilution with water (5 mL), extraction with ether (2 × 10 mL), washing with brine (1 × 20 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil (270 mg) was purified by GC, GC/MS, and ^{1}H NMR. The yields reported below are by GC and are uncorrected. The expected ortho metalation and substitution product was formed in only 1% yield. The thiol from carbophilic addition was formed in 12% yield and di-*sec*-butyl disulfide was formed in 6% yield. The major products were tentatively assigned as a mixture of *N*,*N*-diisopropyl-*N*-(1-phenyl-2-methylbutyl)amine and *N*,*N*-diisopropyl-*N*-(1-phenyl-1-(trimethylsilyl)-2-methylbutyl)amine by flash chromatography (2% EtOAc/hexane) to provide a yellow oil (162 mg, 50%). The ^{1}H NMR of the mixture appeared to have resonances which were consistent with the structural assignment; however, no definitive characterization could be made.

Lithiation of 3,4-Dihydro-4,4-dimethyl-2-(1-methylethyl)-1*H*-isoquinol-1-one (11). To TMEDA (36.3 μL, 27.9 mg, 0.240 mmol) in 2 mL of THF at –78 °C was added *sec*-BuLi (233 μL, 0.240 mmol, 1.03 M). The reaction mixture was stirred for 5 min, and then 3,4-dihydro-4,4-dimethyl-2-(1-methylethyl)-1*H*-isoquinol-1-one (**11**) (57.5 mg, 0.283 mmol) and *n*-dodecane (43 μL, 32.2 mg, 0.189 mmol) in 2 mL of THF were added via cannula. The reaction mixture was stirred for 1 h at –78 °C and then deuterated acetic acid (AcOD) (169 mg, 160 μL, 2.77 mmol) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 6 h. Workup consisted of concentration *in vacuo*, dilution with water (5 mL), extraction with ether (2 × 3 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting yellow oil was purified by MPLC (7.5% EtOAc/hexane) and HPLC (10% EtOAc/hexane) to give three fractions.

The least polar fraction was a colorless oil (3.0 mg): The second fraction was as a different colorless oil (3 mg).

The third fraction gave deuterated starting material as a yellow oil (10.0 mg, 25%): The yield by GC/internal standard was 71%. The ^{1}H NMR ($CDCl_3$, 300 MHz) was identical to the previous spectra of the undeuterated material **11** with the exception of the slightly reduced integration of the ortho proton. The isotopic incorporation was estimated to be ca. 30% d_1 by ^{1}H NMR. The isotopic incorporation by FI/MS was 13% d_1.

Procedure To Test for Transmetalation. To TMEDA (88 μL, 67.8 mg, 0.584 mmol) in 2 mL of THF at –78 °C was added *sec*-BuLi (482 μL, 0.584 mmol, 1.21 M). The reaction mixture was stirred for 5 min and then bis-*N*,*N*-(1-methylethyl)benzamide (**5**) (141.0 mg, 0.687 mmol) in 2 mL of THF was added via cannula. The reaction mixture was stirred for 2 h at –78 °C, and then 2,3-dihydro-3,3-dimethyl-2-(1-methylethyl)-1*H*-isoindol-1-one (**10**) (55.6 mg, 0.274 mmol) in 2 mL of THF was added via cannula. The reaction mixture was stirred for 1 h at –78 °C, and then deuterated acetic acid (AcOD) (396 μL, 419.3 mg, 6.87 mmol) was added. The reaction mixture was allowed to warm to room temperature and then stirred for 10 h. Workup consisted of concentration *in vacuo*, dilution with water (5 mL), extraction with ether (2 × 3 mL), drying over $MgSO_4$, filtration, and concentration *in vacuo*. The resulting white solid was purifieid by MPLC (5% EtOAc/hexane) to give two fractions.

The first fraction gave deuterated bis-*N*,*N*-(1-methylethyl)benzamide as a white solid (103.2 mg, 73%): mp 69–71 °C. The ^{1}H NMR ($CDCl_3$,

200 MHz) was identical to the spectrum of the undeuterated material **5** with the exception of a slightly reduced integration of the aryl region. The isotopic incorporation by FIMS was 51% d_1.

The second fraction gave 7-deuterio-2,3-dihydro-3,3-dimethyl-2-(1-methylethyl)-1*H*-isoindol-1-one as a white solid (41.5 mg, 75%): mp 141–142 °C. The ^{1}H NMR ($CDCl_3$, 200 MHz) was identical to the spectrum of the undeuterated material **10**. The isotopic incorporation by FIMS was 1% d_1.

Preparation of 4,4-Dimethyl-1-tetralol (16). To a suspension of 0.5 g of $LiAlH_4$ (13.2 mmol) in 50 mL of dry Et_2O cooled to 0 °C under N_2 was added dropwise a solution of 4,4-dimethyl-1-tetralone in 30 mL of dry Et_2O. After addition was complete the ice bath was removed and the reaction stirred overnight. The reaction mixture was cooled to 0 °C and the reaction quenched by careful addition of 10 mL of EtOAc. A slurry of Na_2SO_4/H_2O was added until the salts appeared white and the ether was clear. The reaction mixture was filtered, and the solids were washed several times with ether. The organic layer was then washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed *in vacuo* to yield a pale yellow oil which was purified by MPLC (30% EtOAc/hexane) to provide 1.16 g (6.61 mmol, 88%) of **16** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.33 (s, 3H), 1.5–2.1 (m, 4H), 4.72 (t, J = 5.5 Hz, 1H), 7.2–7.4 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 28.71, 31.28, 31.41, 33.84, 34.32, 68.73, 125.86, 126.50, 127.82, 128.24, 137.69, 145.56. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.65; H, 9.09.[23]

Representative Lithiation and Methanol-*d* Quenching of Benzyl Alcohols. To 0.2305 g (1.42 mmol) of 3,3-dimethyl-1-indanol (**15**) in 10 mL of dry Et_2O cooled to 0 °C was added 4.3 mmol *sec*-BuLi (3.3 mL, 1.3 M). The reaction was allowed to warm to room temperature and stirred for 15 h. The reaction was quenched by addition of excess methanol-*d* (0.5 mL) and allowed to stir overnight. Standard NH_4Cl workup yielded a pale yellow oil which was purified by Kugelrohr distillation (1 Torr, 100 °C) to yield 0.1999 g (87%) of a clear oil. GCMS analysis indicated 96% deuterium incorporation. The ^{13}C NMR spectrum contained a triplet at 124.0 ppm with ^{2}H–^{13}C coupling of 23 Hz.

General Procedure for the Metalation of Benzyl Alcohols in the Competition Experiments. To a solution of two alcohols in Et_2O cooled to 0 °C under N_2 was added 1.7–1.9 equiv of *sec*-BuLi. The ice bath was removed, and the solution was stirred for 12–16 h. The reaction was quenched by addition of excess (0.5 mL) CH_3OD and allowed to stir for 4–8 h. Standard NH_4Cl workup provided a mixture of the two alcohols. If possible, deuterium isotope ratios were determined by GCEIMS. The lighter molecular weight compounds, usually 2-phenyl-2-propanol (**13**), could be analyzed in this manner. If the larger m/z compound could not be analyzed by EIMS, the sample as a mixture was analyzed by FIMS or GCFIMS. The deuterium incorporation values for the competition reaction were then used to determine the ratio of incorporations. The starting amounts for each alcohol, the concentration of total substrate in Et_2O, amount of *sec*-BuLi, the deuterium incorporations found for each compound, and the competitive efficiency calculated from this data are given as supplementary material.

Experimental Test for Translithiation and Equilibration between Benzyl Alcohols. To a solution of 2-bromobenzyl alcohol (0.0906 g, 0.484 mmol) in 5 mL of dry Et_2O cooled to –78 °C under N_2 was added 3 equiv of *t*-BuLi (1.45 mmol, 0.85 mL, 1.7 M) dropwise. The reaction was stirred at –78 °C for 45 min and then warmed to room temperature.

To a solution of **14** (0.0439 g, 0.249 mmol) in 5 mL of dry Et_2O was added 0.25 mmol of *t*-BuLi (0.15 mL, 1.7 M). The reaction was stirred for 45 min and then transferred by cannula into the alkoxide reaction mixture above. The mixture was stirred at room temperature for 12 h, then quenched by addition of excess (0.5 mL) CH_3OD, and stirred for 4 h. Standard NH_4Cl workup provided a mixture of benzyl alcohol and **14**. GCMS analysis indicated 66% deuterium incorporation in benzyl alcohol and 14% deuterium incorporation in **14**.

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Supplementary Material Available: The syntheses of 2-methyl-*N*-(1-methylethyl)benzamide, **1**, **5**, *N*,*N*-bis(1-methylethyl)-2-ethyl benzamide, 2-(1-methylethyl)benzoic acid, **19**, 2-(1-methylethyl)-1(*H*)-isoindol-1,3(2*H*)-dione, 2,3-dihydro-2-(1-methylethyl)-1(*H*)-isoindol-1-one, **17**, 4,4-dimethyl-1-tetralone, and the data for competition experiments for the amides and alcohols (11 pages). This supplementary material is contained in many libraries on microfiche immediately following this paper in the microfilm edition of the journal and can be ordered from the American Chemical Society. Ordering information is given on any current masthead page.