Articles

Selectivities in Reactions of Organolithium Reagents with Aryl Bromides Which Bear Proton-Donating Groups

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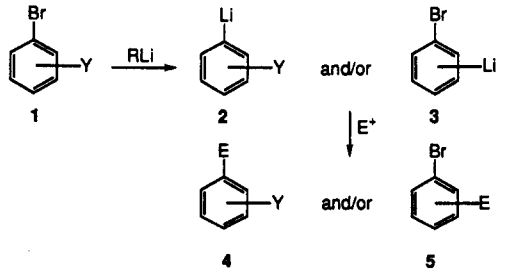
Studies of substrates which offer an acidic hydrogen and an aryl bromide for reaction with an organolithium reagent have been carried out with a series of benzene bromo amides and bromo anilides as well as selected benzene bromo carboxylic acids, bromoanilines, and bromobenzylamines. A representative example is the reaction of *N*-ethyl-*N*-deutero-*o*-bromobenzamide (**6-d**) with 1-lithio-3-phenylpropane to give *N*-ethyl-*o*-deuterobenzamide (46%, 94%-d) (**7-d**), *N*-ethyl-*o*-bromobenzamide (**6**) (49%), 3-deutero-1-phenylpropane (51%, 92%-d), and 1-bromo-3-phenylpropane (48%). Product formation in this and related cases is explained by the operation of a two step sequence in which an initial deprotonation is followed by a bromine–lithium exchange which is accelerated with respect to mixing. Such a sequence is consistent with the results of deuterium labeling and with changes in product ratios on different mixing and with differently aggregated organolithium reagents. Support is provided for the operation of two pathways for the expedited bromine–lithium exchange reactions. In one pathway a high local concentration of the organolithium reagent promotes rapid reaction and in the second the exchange reaction occurs within an initially formed complex. The selectivity for removal of a bromine ortho to a lithiated carboxamide is found to be 5–8 with *n*-butyllithium, and satisfactory synthetic ortho selectivity is obtained for *N*-ethyl-2,5-dibromobenzamide with phenyllithium.

Introduction

Studies of selectivities of reactions of organolithium reagents with substrates bearing multiple sites for reaction can be useful for developing the understanding and use of these reagents. An illustration of selectivity with respect to bromine–lithium exchange is the conversion of 1 to 4 and/or 5 via the organolithium intermediates 2 and/or 3. In the kinetically controlled processes which are usually observed, the product ratio is determined by the partitioning of the reaction of the alkyllithium between bromine–lithium exchange and reaction with Y to give 2 and/or 3. Cases have been reported in which bromine–



1 2 3 4 5

lithium exchange reactions do exhibit high selectivities, and the approach has been used to achieve regiocontrol and stereocontrol in synthetically useful sequences, particularly by Parham and co-workers.[1,2] The formation of a complex between a functional group of the substrate and an organolithium reagent can be invoked to rationalize the selectivities of these reactions.[1,2]

Anomalies in selectivities have appeared to exist for a number of substrates which bear both a bromine and an acidic deuterium.[3] For example, the reaction of 1 equiv of butyllithium with *N*-deutero-*N*-ethyl-*o*-bromobenzamide (**6-d**) gives *N*-ethyl-*o*-deuterobenzamide (**7-d**) in which the deuterium replaces the bromine.[4] That result could be taken to suggest reaction *via* pathway A in which **8** is an intermediate, *i.e.*, that bromine–lithium exchange is faster than deuterium transfer, in accord with earlier interpretations of similar observations for earlier cases.[3] However, we have recently provided evidence that the formation of **7-d** from **6-d** is deceptive with respect to the processes of its formation. We suggested pathway B which involves **6-d** giving **9** which precedes **10** and we supported that proposal by yield and mixing experiments.[4] By this pathway deuterium loss is the initial reaction on the molecular scale and it provides an organolithium inter-

• Abstract published in *Advance ACS Abstracts*, November 15, 1993.

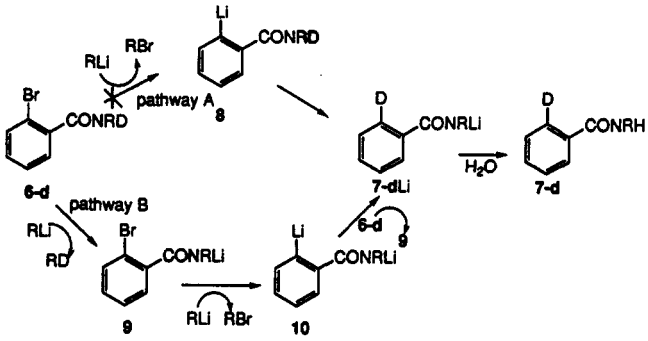
(1) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257. Chen, L. S., Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1983**, *251*, 139. Chen, L. S.; Tamborski, C. *J. Organomet. Chem.* **1983**, *251*, 199. Iddon, B.; Khan, N.; Lim, B. L. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1437. Iddon, B.; Khan, N.; Lim, B. L. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1445. Hoffmann, R. W.; Bewersdorf, M.; Ditrich, K.; Krüger, M.; Stürmer, R. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1176. Lipshutz, B. H.; Hagen, W. *Tetrahedron Lett.* **1992**, *33*, 5865. Quallich, G. J.; Fox, D. E.; Friedmann, R. C.; Murtiashaw, C. W. *J. Org. Chem.* **1992**, *57*, 761. Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407. Rotger, M. C.; Costa, A.; Saa, J. M. *J. Org. Chem.* **1993**, *58*, 4083.

(2) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. Gschwend, H. W.; Rodiguez, H. R. *Org. React.* **1979**, *26*, 1. Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. For a recent structure determination of a complex see Boche, G.; Langlotz, I.; Marsch, M.; Harms, K.; Frenkins, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1171.

(3) Boatman, R. J.; Whitlock, B. J.; Whitlock, A. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. Stein, C. A.; Morton, T. H. *Tetrahedron Lett.* **1973**, 4933. Taylor, E. C.; Vogel, D. E. *J. Org. Chem.* **1985**, *50*, 1002. Bailey, W. F.; Patricia, J. J.; Nurmi, T. T.; Wang, W. *Tetrahedron Lett.* **1986**, *27*, 1861. Narasimhan, N. S.; Sunder, N.; Ammanamanchi, R.; Bonde, B. D. J. *J. Am. Chem. Soc.* **1990**, *112*, 4431.

0022-3263/93/1958-7330$04.00/0

mediate **9**, which rapidly undergoes a bromine–lithium exchange to give a dilithiated intermediate **10**. The key step in this sequence is the formation of **10** in a reaction that is faster than mixing. The intermediate **10** then



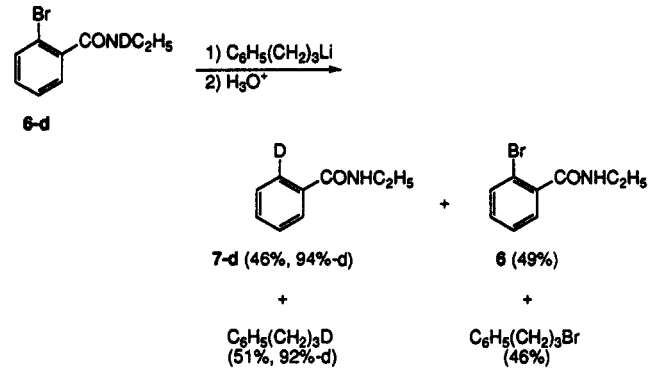
obtains a deuterium from **6-d** on subsequent mixing to give **7-dLi** and then **7-d**. The expedited bromine–lithium exchange could be promoted by an intracomplex reaction in an initially formed aggregate or in a high local concentration of the organolithium reagent.[4] Under these mechanisms the selectivity of the initial reaction is not evident in the product ratio, and the operation of this pathway with an acidic proton could limit the synthetic use of the halogen–lithium exchange methodology.[5]

We now present an investigation of the effect of the structure of the organolithium reagent, of the nature of the proton donor group, and of the experimental conditions on bromine–lithium exchange reactions for aryl bromides which bear an acidic protium or deuterium. Our results provide clarification of the nature of the expedited bromine–lithium exchange reaction and offer guidance for the use of bromine–lithium exchanges in substrates which bear proton donating groups.

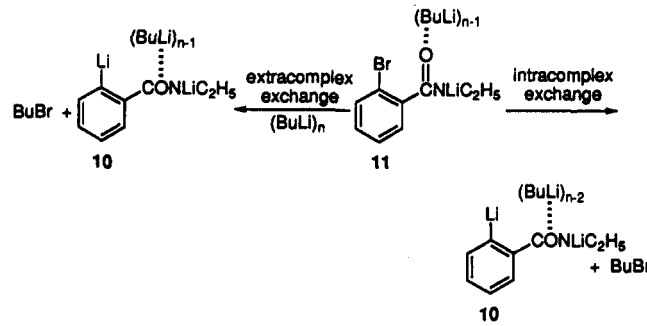
Results and Discussion

Effect of the Alkyllithium Reagent with Bromo Amides. Reaction pathway B outlined for the conversion of **6-d** to **7-d** *via* **9** and **10** has a verifiable stoichiometry. For a reaction which proceeds entirely by this pathway, the yields of the deuterated hydrocarbon and the brominated organolithium reagent from the organolithium reagent and of **6** and **7-d** can reach a maximum of 50%. This balance has been determined for the reaction of **6-d** with 1-lithio-3-phenylpropane. The products 3-deutero-1-phenylpropane, 1-bromo-3-phenylpropane, **6**, and **7-d** are formed in yields of 51, 46, 46, and 49%, consistent with the expectation for pathway B. The balance observed in this case is not required for all reactions proceeding by analogous routes since competitive processes (*vide infra*) could lead to substantially less deuteration.

In order for pathway B to be operative in the reaction of **6-d** to give **7-d** the conversion of **9** to **10** must be faster than the conversion of **6-d** to **9**. Two ways in which an accelerated rate could occur for that reaction are illustrated for **11**, a complex formed from the initial reaction of **6** with butyllithium. For an intracomplex pathway a butyllithium group from within the complex could be involved in the subsequent bromine–lithium exchange. In cases where



the lithiated amide group is appropriately positioned to promote displacement of the bromine by the butyl group of the associated organolithium reagent the process would be an example of a complex-induced proximity effect.[3,6] Alternatively, the accelerated exchange could occur in an extracomplex mode in the high local concentration which is generated when the organolithium reagent is added to a solution of **6-d**.[7] The lithiated amide could, by facilitating association with external $(BuLi)_n$, also promote the reaction in an extracomplex exchange.



In previous work we have shown for these and similar reactions that the ratio of carbon deuterated products to recovered reactant decreases with stirring or upon inverse addition.[4] Stirring should increase the relative rate of decomplexation and decrease the intracomplex exchange. Stirring would also disperse the high local concentration of butyllithium and decrease the extracomplex exchange. Inverse addition would be expected to decrease the high local concentration of butyllithium for the extracomplex exchange but to have less of an effect on the intracomplex pathway. The ratios of products for reactions with aggregated and monomeric organolithium reagent also should be different under the extracomplex and intracomplex possibilities. For the aggregated lithium reagent, a complex corresponding to **11** with $n > 1$ which can undergo intracomplex exchange should be formed. For a monomeric organolithium reagent in which $n = 1$, there is no internally complexed organolithium reagent available and no possibility of intracomplex exchange. If a complex is involved it would also be expected that the location of

(4) Beak, P.; Musick, T. J.; Chen. C. W. *J. Am. Chem. Soc.* **1988**, *110*, 3538.

(5) The pathway of initial dedeuteration has been challenged for a related case and a response provided. Gallagher, D. J.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 7984.

(6) Beak, P.; Allen D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420. Such a reaction would not need to have the strict geometrical requirements we have recently reported for the intramolecular bromine–lithium transfer from an aryl bromide to an alkyllithium chain. In the present cases the orientation needed to position the carbanionic alkyl group *ca.* 180° from the bromine–carbon bond being broken is more easily accomplished for the association of the alkyl group with the lithium in an ionic bond in **11** than in the covalent cases in which the alkyl group is covalently tethered in the endocyclic ring.

(7) For a demonstration that a high local concentration of organolithium reagent can be involved in accelerated exchange see Beak, P.; Liu, C. *Tetrahedron*, submitted for publication.

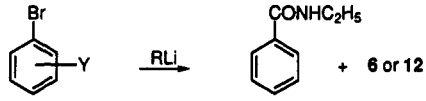
Table I. Ratios of Bromo Amide/Amide for the Reactions of 6 and 12 with 1 equiv *tert*-Butyllithium and *neo*-Pentyllithium

bromo amide	RLi	solvent	mode of addition[a]	ratio[b] bromo amide/amide
6	*t*-BuLi	THF	normal	53:47
6	*t*-BuLi	THF	inverse	82:18
6	*t*-BuLi	Et_2O	normal	50:50
6	*t*-BuLi	Et_2O	inverse	63:37
12	*t*-BuLi	THF	normal	66:34
12	*t*-BuLi	THF	inverse	98:2
12	*t*-BuLi	Et_2O	normal	61:39
12	*t*-BuLi	Et_2O	inverse	98:2
6	*neo*-pentyl Li	THF	normal	56:44
6	*neo*-pentyl Li	THF	inverse	96:4
12	*neo*-pentyl Li	THF	normal	59:41
12	*neo*-pentyl Li	THF	inverse	98:2

[a] Normal addition indicates the alkyllithium is added to the bromo amide. Inverse addition indicates the bromo amide is added to the alkyllithium. [b] The error is ±3%.

bromine with respect to the associated organolithium reagent could affect the reaction, *i.e.*, a bromine ortho to the functionality is likely to undergo the exchange reaction more rapidly than a bromine which is meta or para.[2b,6]

In order to evaluate the pathways of intracomplex and extracomplex exchange we have investigated the changes in the extents of bromine–lithium exchange of **6** and of *N*-ethyl-*p*-bromobenzamide (**12**) with 1 equiv of *tert*-butyllithium and of neopentyllithium under different conditions. The reaction of **6-d** with *tert*-butyllithium in THF gives 47% of the amide **7-d** with 83% deuterium incorporation and 53% **6**. The *ca.* 1:1 ratio of bromo amide/amide and deuterium incorporation are in accord with substantial reaction by pathway B. To the extent that this pathway is affected by changes in the reaction conditions there will be excess bromo amide and an increase in the bromo amide/amide ratio. The results following and in Table I were obtained for protonated substrates **6** and **12** and the ratios of bromo amide to amide are qualitatively interpreted in terms of disruption of the sequence of pathway B.



6 Y = *o*-$CONHC_2H_5$
12 Y = *p*-$CONHC_2H_5$ **7**

At −90 °C in THF below 0.16 M, *tert*-butyllithium is monomeric; whereas in Et_2O under the same conditions *tert*-butyllithium is dimeric.[8] The results of the reactions of **6** and of **12** with 1 equiv of *tert*-butyllithium in THF and Et_2O in both normal and inverse additions are presented in Table I. In THF **6** gives *ca.* a 1:1 ratio of **6/7** on normal addition of the *tert*-butyllithium to the amide. Inverse addition of these components, *i.e.*, addition of the amide to the *tert*-butyllithium gives an increase in the bromo amide/amide ratio to *ca.* 4:1. With Et_2O as the solvent we observe the same trend on changing the mode of addition but the increase is only from 1:1 with normal addition to *ca.* 3:2 with the inverse mode. For reactions of **12**, in which bromine is more remote from the site of complexation than for **6**, *tert*-butyllithium in both THF and Et_2O showed similar effects: the initial *ca.* 2:1 product ratios favoring bromo amide become 98:2 on inverse addition.

If the reactions in THF are presumed to involve monomeric *tert*-butyllithium these results may be taken to indicate that the extracomplex pathway is operative for **6** and for **12**. Under the conditions of inverse addition this pathway is reduced for both substrates. The fact the reaction of **6** in Et_2O shows less reduction in the extent of bromine–lithium exchange on inverse addition could be attributed to a pathway in which dimeric *tert*-butyllithium gives a complex **11** (n = 2) in which intracomplex exchange, which would be unaffected by the mode of addition, contributes substantially. This possibility is consistent with the fact that **12**, which would be expected to show less intracomplex reaction than **6** due to the more remote location of the bromine from the site of complexation, shows a much larger increase in the bromo amide/amide ratio on inverse addition. Although the change in solvent between THF and Et_2O precludes definitive interpretation, as does the caveat that the major aggregate of the organolithium reagent which is present may not be the reactive species, the results in Table I are consistent with the accelerated conversion of **9** to **10** which is observed with normal addition occurring in both the intracomplex and extracomplex modes shown for **11**.

We have also determined the product ratios from bromine–lithium exchanges of **6** and **12** with *neo*-pentyllithium in the presence of PMDTA in THF where the reagent is largely monomeric.[9] Reaction using **6-d** with neopentyllithium–PMDTA provided **7-d** in 44% yield with 95% deuterium incorporation. As shown in Table I, normal addition gives a *ca.* 1:1 ratio of bromo amide/amide while inverse addition gives predominantly bromo amide for both **6** and **12**. These results also support expedited bromine–lithium exchange via the extracomplex pathway.

Effect of Bromine Position in Bromo Amides. Intramolecular Competitions. We have investigated the selectivities as a function of bromine position in intramolecular and intermolecular competition. Reaction of an equimolar mixture of **6** and **12** with *n*-butyllithium in the normal addition mode shows that approximately 24% of **6** *vs* 14% of **12** undergoes exchange while with reverse addition 21% of **6** and 4% of **8** are exchanged. These results are consistent with an intracomplex reaction favoring *o*-bromine exchange in a pathway which is relatively insensitive to a high local concentration of the alkyllithium.

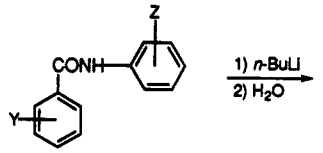
A similar trend is observed for intramolecular competitions. The *o*-bromobenzanilide **13** on reaction with *n*-butyllithium gives a *ca.* 1:1 ratio of **13/15** which is unaffected by inverse addition whereas **14** gives a *ca.* 1:1 ratio of **14/15** on normal addition with *n*-butyllithium and a 97:3 **14/15** ratio of on inverse addition.[10] A preference for exchange of the bromine ortho to the functional group also was observed for reactions of the dibromo derivatives **16–18**. On reaction with *n*-butyllithium, **16** gives 30% of **19** and 5% of **13**, and **17** provides 40% of **14** and 5% of **20**. With both bromines ortho as in **18**, the bromine on the anilide ring is preferentially exchanged to give 36% of **21** and 6% of **22**.

Reactions in which the intramolecular competition is between bromines on the same aromatic ring also have been carried out. For **23**, reaction with *n*-butyllithium

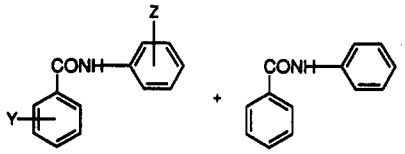
(8) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371.

(9) Frankel, G.; Chew, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 6190.

(10) The ratio of **14/15** can be changed to favor the former by rapid stirring.



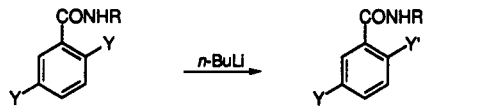
13, Y = o-Br, Z = H
14, Y = p-Br, Z = H
16, Y = o-Br, Z = p-Br
17, Y = p-Br, Z = o-Br
18, Y = o-Br, Z = o-Br



19, Y = H, Z = p-Br
20, Y = H, Z = o-Br
21, Y = o-Br, Z = H
22, Y = H, Z = o-Br

15

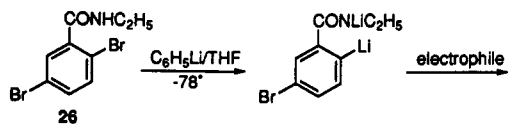
gave 22% of **24** and 4% of **25** and for **26** the products are 40% of **27** and 5% of **28**. In both cases fully debrominated benzamide products along with starting amide were also obtained. These reactions all show a preference for removal of the bromine ortho to the amide substituent by a factor of 5–8. The preferential exchanges of *o*-bromines are consistent with precedented directing effects.[1-3]



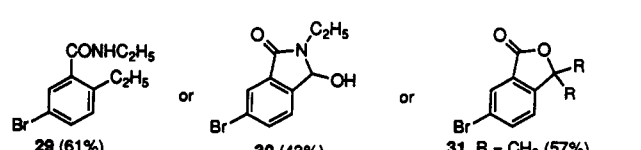
23, R = 2,4-$Br_2C_6H_3$, Y = H
26, R = C_2H_5, Y = Br

24, R = 4-BrC_6H_4, Y = Y' = H
25, R = 2-BrC_6H_4, Y = Y' = H
27, R = C_2H_5, Y = Br, Y' = H
28, R = C_2H_5, Y = H, Y' = Br

While these results do support an intracomplex pathway favoring exchange of an *o*-bromine, the extent of that selectivity is not high enough for good regiocontrol in synthetic applications. In order to provide synthetically useful selectivity we studied the reaction of **26** with *n*-butyl-, *s*-butyl-, *tert*-butyl-, phenyl-, and methyllithium reagents in Et_2O and THF. We found phenyllithium, the least reactive of the reagents studied, to be the reagent of choice for synthetic applications. The conversions of **26** to **29–33** were carried out in acceptable yields by selective bromine–lithium exchange, consistent with precedents.[11] By addition of 2 equiv of phenyllithium with stirring followed by addition of the electrophile, substantial diversion of the reaction to *N*-ethyl-*m*-bromobenzamide is avoided.



26

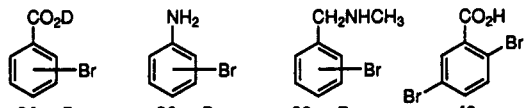


29 (61%)

30 (43%)

31, R = CH_3 (57%)
32, R = C_6H_5 (64%)
33, R = CH_3, C_2H_5 (55%)

Effect of Other Proton-Directing Groups. In order to determine qualitatively if the pathways for bromine–lithium exchange observed with the secondary amides exists for other proton-donating groups, we have investigated the affect of the mode of addition on bromine–lithium exchange for the acid, amine, and phenol systems **34–39**. The results parallel those observed with the amides. The ortho-substituted compounds give product ratios which show little response to the mode of addition or to stirring while the para-substituted isomers show a significant increase in brominated reactant relative to debrominated reactant with rapid stirring and/or inverse addition. These results are consistent with two pathways



34, *o*-Br
35, *p*-Br

36, *o*-Br
37, *p*-Br

38, *o*-Br
39, *p*-Br

40

for accelerated exchange in which exchange of a *p*-bromine is primarily an extracomplex reaction and exchange of an *o*-bromine is predominantly an intracomplex reaction.

The effect of the carboxylic acid on selective exchange for 2,5-dibromobenzoic acid (**40**) was also investigated with *n*-butyllithium in THF. We obtained 78% 5-bromobenzoic acid and 2% 2-bromobenzoic acid, i.e. ortho exchange was favored by a *ca.* 40:1 but we also obtained 13% benzoic acid.

Summary

In summary, these studies of selectivity between bromine–lithium exchange and acidic proton removal by organolithium reagents for substrates which bear both functionalities provide support for pathways of initial proton removal followed by an accelerated exchange which is faster than mixing. The operation of two pathways for the exchange, an extracomplex exchange in a high local concentration and an intracomplex exchange for complexes in which exchange is promoted when the anionic group and the bromine are in proximity, is supported qualitatively by the data.

Experimental Section

General. Mass spectra were obtained on a Varian MAT CH-5 spectrometer with an ionization voltage of 10 or 70 eV. Data are reported in the form of *m/e* (intensity relative to base = 100).

Analytical gas chromatography was performed on a Hewlett-Packard 5790 gas chromatograph equipped with a programmable temperature control and a flame ionization detector. The column used was either a 50M OV-17 capillary column or a 50M OV-101 capillary column; injector temperature was 270 °C, detector temperature was 300 °C, and programs were as indicated. Retention times and peak integrals were obtained from a Hewlett-Packard 3390A recorder. Column chromatography was performed with silica gel of grade 0.05–0.2 mm using columns of various sizes depending on the amount of material and ease of separation. Rotary chromatography was performed on a Harrison Research chromatotron Model 7924 using either 1-, 2-, or 4-mm plates made from EM Reagents silica gel PF254 with $CaSO_4 \cdot 1/2H_2O$ as a binder. Solvent systems were various mixtures of ethyl acetate and hexane.

Unless mentioned otherwise, all reagents were obtained from commercial sources and used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium and benzophenone under N_2 atmosphere. Dimethyl sulfoxide (DMSO), *N,N,N',N'*-tetramethylethylenediamine (TMEDA), diisopropylamine, *n*-pentane, dichloromethane (CH_2Cl_2), hexane, toluene, benzene, and pyridine were distilled from calcium hydride under N_2 atmosphere. Ethyl acetate (EtOAc) was

(11) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* 1978, 3. Tisher, A. N.; Tisher, M. H. *Aldrichim. Acta* 1978, *11*, 20.

distilled from potassium carbonate. Commercial solutions of *n*-butyllithium (*n*-BuLi) in hexanes, *sec*-butyllithium (*s*-BuLi) in cyclohexane, and *tert*-butyllithium (*t*-BuLi) in pentane were titrated using the Tischler procedure.[11]

Preparation of 2-Bromo-*N*-ethylbenzamide (6): mp 90–91 °C. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.48; H, 4.38; N, 6.05.

4-Bromo-*N*-ethylbenzamide (12): mp 122–124 °C. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14. Found: C, 47.59; H, 4.42; N, 6.11.

General Procedure for the Normal Addition of Butyllithium. Approximately 1 mmol of the substrate dissolved in 20 mL of the appropriate solvent was placed under constant positive pressure of nitrogen and cooled to the required temperature prior to reaction. The 1 mmol of butyllithium solution was added dropwise *via* a syringe pump at the approximate rate of 1 mL/min. The solution was stirred (if stirring is required) for 30 min and then quenched by addition of water or NH_4Cl. Standard workup involved evaporation of the solvent and addition of water and ether to the remainder. The water layer was extracted with Et_2O (3 × 20 mL), and the ether extracts were collected and washed with water (2 × 20 mL) and brine (1 × 20 mL) and concentrated *in vacuo* to give a mixture of products, which were separated, purified, and analyzed.

General Procedure for the Inverse Addition of Butyllithium. Approximately 1 mmol of the lithium reagent diluted with 20 mL of the appropriate solvent was placed under constant positive pressure of nitrogen, cooled to the appropriate temperature, and stirred if called for in the procedure. A solution of 1 mmol of substrate in 0.5–1 mL of solvent then was added dropwise *via* a syringe pump at an approximate rate of 1 mL/min. The solution was allowed to react for 30 min and then quenched by the addition of water or NH_4Cl. Standard workup as described above for normal addition reactions was employed.

Preparation of 1-Lithio-3-phenylpropane. To a flask containing excess lithium powder in dry pentane at 0 °C under N_2 was added commercial 1-bromo-3-phenylpropane. The mixture was stirred for 4 h and then the excess lithium was removed by filtration. The solution was then titrated and used immediately for subsequent reactions.

Reaction of 6-d with 1-Lithio-3-phenylpropane. To a solution 0.112 g (0.49 mmol) of amide **6-d** in 20 mL of dry THF at −78 °C under N_2 was added a solution of 0.42 mL of 1.18 M 1-lithio-3-phenylpropane (0.50 mmol). The reaction was allowed to stir for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield a yellow oil mixture which was separated by MPLC using 30% EtOAc/hexane as eluent to yield 0.055 g (0.24 mmol, 49%) of **6**, 0.033 g (0.22 mmol, 46%) of **7-d**, 0.045 g (0.22 mmol, 46%) of 1-bromo-3-phenylpropane, and 0.030 g (0.25 mmol, 51%) of 1-deutero-3-phenylpropane. The mass spectrum shows **7-d** to be 94% deuterated and 1-deutero-3-phenylpropane to be 92% deuterated.

Normal Addition Reaction of 6-d with *tert*-Butyllithium in THF. To a solution of 0.123 g (0.536 mmol) of amide **6-d** in 20 mL of THF at −78 °C under N_2 was added a solution of 3.2 mL of 0.17 M *t*-BuLi (0.54 mmol). The reaction was allowed to sit for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield an off-white solid mixture of 53% of **6** and 47% of **7-d** as determined by GC analysis. The mixture was separated by MPLC eluted with 30% EtOAc/hexane. Spectral properties of the products were compared to those of authentic samples. Mass spectral analysis showed **7-d** to contain 83% deuterium.

Normal Addition Reaction of 6 with *tert*-Butyllithium in Et_2O. To a solution of 0.127 g (0.561 mmol) of amide **6** in 20 mL of Et_2O at −78 °C under N_2 was added a solution of 3.3 mL of 0.17 M *t*-BuLi (0.56 mmol). The reaction was allowed to stand for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield an off-white solid mixture of 50% of **6** and 47% of **7** as determined by GC analysis. The mixture was separated by MPLC eluted with 30% EtOAc/hexane, and the spectral properties of products were compared to those of authentic samples.

Inverse Addition Reaction of 6 with *tert*-Butyllithium in THF. To a solution of 3.4 mL of 0.17 M *t*-BuLi (0.58 mmol) was added 0.131 g (0.57 mmol) of amide **6** in 20 mL of THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and separated by MPLC. Products were identified as 82% of **6** and 18% of **7** by spectral analysis with comparison to authentic samples.

Reverse Addition Reaction of 6 with *tert*-Butyllithium in Et_2O. To a solution of 3.4 mL of 0.17 M *t*-BuLi (0.58 mmol) was added 0.13 g (0.57 mmol) of amide **6** in 20 mL of Et_2O. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and separated by MPLC. Products were identified as 63% of **6** and 37% of **7** by spectral analysis with comparison to authentic samples.

Normal Addition Reaction of 12 with *tert*-Butyllithium in THF. To a solution of 0.134 g (0.59 mmol) of amide **12** in 20 mL of THF at −78 °C under N_2 was added a solution of 3.4 mL of 0.17 M *t*-BuLi (0.58 mmol). The reaction was allowed to sit for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield an off-white solid mixture of 66% of **12** and 34% of **7** as determined by GC. The mixture was separated by MPLC using 30% EtOAc/hexane, and the products were identified by spectral analysis with comparison to authentic samples.

Normal Addition Reaction of 12 with *tert*-Butyllithium in Et_2O. To a solution of 0.127 g (0.56 mmol) of amide **12** in 20 mL of Et_2O at −78 °C under N_2 was added a solution of 3.3 mL of 0.17 M *t*-BuLi (0.56 mmol). The reaction was allowed to sit for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and reduced *in vacuo* to yield an off-white solid mixture of 61% of **12** and 39% of **7** as determined by GC. The mixture was separated by MPLC using 30% EtOAc/hexane, and the products were identified by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 12 with *tert*-Butyllithium in THF. To a solution of 3.4 mL of 0.17 M *t*-BuLi (0.58 mmol) was added 0.131 g (0.57 mmol) of amide **12** in 20 mL of THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and by separation using MPLC. Products were identified as 98% of **12** and 2% of **7** by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 12 with *tert*-Butyllithium in Et_2O. To a solution of 3.2 mL of 0.17 M *t*-BuLi (0.54 mmol) was added 0.125 g (0.55 mmol) of amide **12** in 20 mL of Et_2O. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and by separation using MPLC. Products were identified as 98% of **6** and 2% of **7** by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 6 with *tert*-Butyllithium in THF: Varying Concentrations of *tert*-Butyllithium. To a solution of 10.7 mL of 0.05 M *t*-BuLi (0.54 mmol) was added 0.122 g (0.53 mmol) of amide **6** in 20 mL of THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and by separation using MPLC. Products were identified as 79% of **6** and 21% of **7** by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 6 with *tert*-Butyllithium in THF: Varying Concentrations of *tert*-Butyllithium. To a solution of 4.9 mL of 0.11 M *t*-BuLi (0.54 mmol) was added

0.123 g (0.537 mmol) of amide **6** in 20 mL of THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and by separation using MPLC. Products were identified as 77% of **6** and 23% of **7** by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 6 with *tert*-Butyllithium in THF: Varying Concentrations of *tert*-Butyllithium. To a solution of 2.1 mL of 0.25 M *t*-BuLi (0.525 mmol) was added 0.120 g (0.53 mmol) of amide **6** in 20 mL of THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and by separation using MPLC. Products identified as 82% of **6** and 18% of **7** by spectral analysis with comparison to authentic samples.

Preparation of *neo*-Pentyllithium. To a flask with excess lithium powder in dry pentane at 0 °C under N_2 was added commercial neopentyl iodide. The mixture was allowed to stir for 8 h, and the excess lithium was then removed by filtration. The pentane was removed *in vacuo* and THF was added as solvent. The solution of *neo*-pentyllithium was titrated. A sample of the solution was quenched and tested for the presence of *neo*-pentyl iodide, and none was detected. Then 1 equiv of PMDTA was added to the *neo*-pentyllithium solution, which was used immediately for subsequent reactions.

Normal Addition Reaction of 6-d with *neo*-Pentyllithium. To a solution of 0.137 g (0.60 mmol) of amide **6** in 20 mL of THF at −78 °C under N_2 was added a solution of 2.2 mL of 0.28 M *neo*-pentyllithium (0.62 mmol) and 0.1 mL (0.48 mmol) of PMDTA. The reaction was allowed to sit for 30 min and quenched with 0.5 mL of MeOH. The solution was washed with water and extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield an off-white solid mixture of 56% of **6** and 44% of **7-d** as determined by GC and separated by MPLC. Products were identified as 30% EtOAc/hexane by spectral analysis with comparison to authentic samples. Mass spectral analysis showed **7-d** to be 95% deuterated.

Normal Addition Reaction of 12 with *neo*-Pentyllithium. The reaction was carried out as for **6** above employing 0.1383 g (0.604 mmol) of amide **12** and a solution of 2.2 mL of 0.28 M *neo*-pentyllithium (0.62 mmol) and 0.1 mL (0.48 mmol) of PMDTA to yield 59% of **12** and 41% of **7-d**. The products were identified by GC and separated by MPLC. Products were identified by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 6 with *neo*-Pentyllithium. To a solution of 2.3 mL of 0.28 M *neo*-pentyllithium (0.64 mmol) and 0.1 mL (0.48 mmol) of PMDTA in 20 mL of THF was added 0.148 g (0.65 mmol) of amide **6** in THF. The solution was allowed to react for 30 min and quenched with water. The solution was worked up as described in the general procedure for reverse addition reactions, and the products were analyzed by GC and separated by MPLC. Products were identified as 96% of **6** and 4% of **7** by spectral analysis with comparison to authentic samples.

Inverse Addition Reaction of 12 with *neo*-Pentyllithium. The reaction was carried out as for **6** above, and the products were identified by GC analysis and by separation using MPLC and comparison of spectral properties with authentic samples. To a solution of 2.3 mL of 0.28 M *neo*-pentyllithium (0.64 mmol) and 0.1 mL (0.48 mmol) of PMDTA in 20 mL of THF was added 0.141 g (0.62 mmol) of amide **12**. The solution was allowed to stand for 30 min. Product identification gave 98% of **12** and 2% of **7**.

Preparation of 2,5-Dibromo-*N*-ethylbenzamide (26). A solution of 1.17 g (4.18 mmol) of 2,5-dibromobenzoic acid in 6 mL of $SOCl_2$ was refluxed for 4 h. After cooling to room temperature, it was concentrated *in vacuo* and the residue was dissolved in benzene and concentrated three times to remove additional $SOCl_2$. The residual brown oil was dissolved in CH_2Cl_2 and cooled to 0 °C. Then 6 mL of 10% NaOH was added and 1.35 mL (16.7 mmol) of 70% EtNH in H_2O was added dropwise. After being stirred for 30 min, the solution was washed with H_2O, 10% NaOH, 10% HCl, and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give 1.21 g (65% yield) of **26** as white crystals: mp 115-117 °C.

General Procedure for Bromine–Lithium Exchange Followed by Electrophilic Substitution for 26. To a solution of 0.20 g (0.65 mmol) of **26** in 20 mL of THF was added dropwise with rapid stirring a solution of 0.68 mL (1.91 M, 1.3 mmol) of phenyllithium at −78 °C. The solution was stirred for 30 min and then quenched with the electrophile: 1.0 equiv of Me_2CO for the reaction giving **31**, 1.0 equiv of EtCOMe for **33**, 1.2 equiv of Ph_2CO for **32**, 1.0 equiv of EtI for **29**, 1.2 equiv of Me_2NCHO for **30**. The reaction mixture was stirred at −78 °C for 30 min before being allowed to warm to room temperature and stirred overnight. Standard workup involved evaporation of the solvent and addition of water and ether to the remainder. The organic phase was separated and the aqueous layer was extracted twice with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product, which was purified by flash column chromatography and/or MPLC eluted with mixture of EtOAc/hexane to give products **29–33**, respectively. Their spectral data is reported in the supplementary material.

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Supplementary Material Available: Experimental data for reactions of **13, 14, 16–18, 23, 34–39, 41, and 42** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.