Tetrahedron Vol. 39, No. 12, pp. 1983 to 1989, 1983
Printed in Great Britain.

0040-4020/83 $3.00 + .00
Pergamon Press Ltd.

A COMPARISON OF SECONDARY AND TERTIARY AMIDES AS DIRECTORS OF ORTHO AND ADJACENT BENZYLIC LITHIATION AND OF ASYMMETRIC INDUCTION IN ORTHO LITHIATED BENZAMIDES

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(*Received in USA* 7 *June* 1982)

Abstract—Comparisons are made between the influence of secondary and tertiary amides on ortho and adjacent benzylic metallations of benzamides. In the intramolecular competition offered by N,N-diethyl-N-ethylterephthalamide (**1**) the tertiary amide is the more effective director of ortho lithiation, while the secondary amide is better in the intermolecular competitions offered by the pairs N-ethyl- (**9**): N,N-diethylbenzamide(**10**) and N-isopropyl-(**11**): N,N-diisopropylbenzamide(**12**). Both secondary and tertiary amides are found to direct metallation ortho to the amide in the 2-isopropylbenzamides **25** and **26**; however, benzylic metallation is observed with secondary 2-ethyl- and 2-methylbenzamides **21** and **22** and with the tertiary 2-ethylbenzamide **19**. Magnetic non-equivalence is noted for the *anti*-N-methylene group of **19**. The reaction of an ortho lithio (*S*)-O-methyl-N-benzoylleucinol (**34**) with 1-naphthaldehyde-1-*d* gives, after lactonization, 3-(1-naphthyl-1-*d*)-phthalide with 10% enantiomeric excess. The phthalide can be obtained in high enantiomeric purity by separation of the diastereoisomers prior to cyclization. Control experiments establish that the observed asymmetric induction is attributable to diastereomeric transition states. The corresponding tertiary benzamide is ineffective in inducing asymmetry. Structural and mechanistic rationales are offered for these observations.

The use of the secondary amide as a director of ortho lithiation, first reported by Puterbaugh and Hauser, has proven to be useful synthetically.[1,2] Recently we have found that the tertiary amide is also a director of ortho lithiation and synthetic applications to a wide variety of systems, including heterocycles, have been forthcoming.[3-5] It is notable that with sec-BuLi/tetramethylethyldiamine (TMEDA) at − 78° in tetrahydrofuran (THF), the tertiary amide appears to be a more effective director than any non-carboxamide group.[4]

Our earlier work showed that in intramolecular competition at − 78° and − 100° the secondary and tertiary amide have comparable abilities to direct ortho lithiation and at − 78° the tertiary amides is more effective than the oxazoline with s-BuLi/TMEDA as the base.[4] However, the work of Meyers and Lutomski showed that for intermolecular competition the secondary amide is a less effective director than the oxazoline at − 45° with HMPA added and the oxazoline in turn is less effective than the tertiary amide at − 78° with n-BuLi, as the base.[6] In order to clarify the apparent discrepancy between these comparisons we have investigated the intra- and intermolecular directing abilities of the secondary and tertiary benzamides under the same conditions. We also have obtained information on the competition between adjacent benzylic or ortho sites of the benzamides and have investigated the abilities of the amides to control asymmetric induction on reaction of the ortho lithiated benzamides with 1-naphthaldehyde.

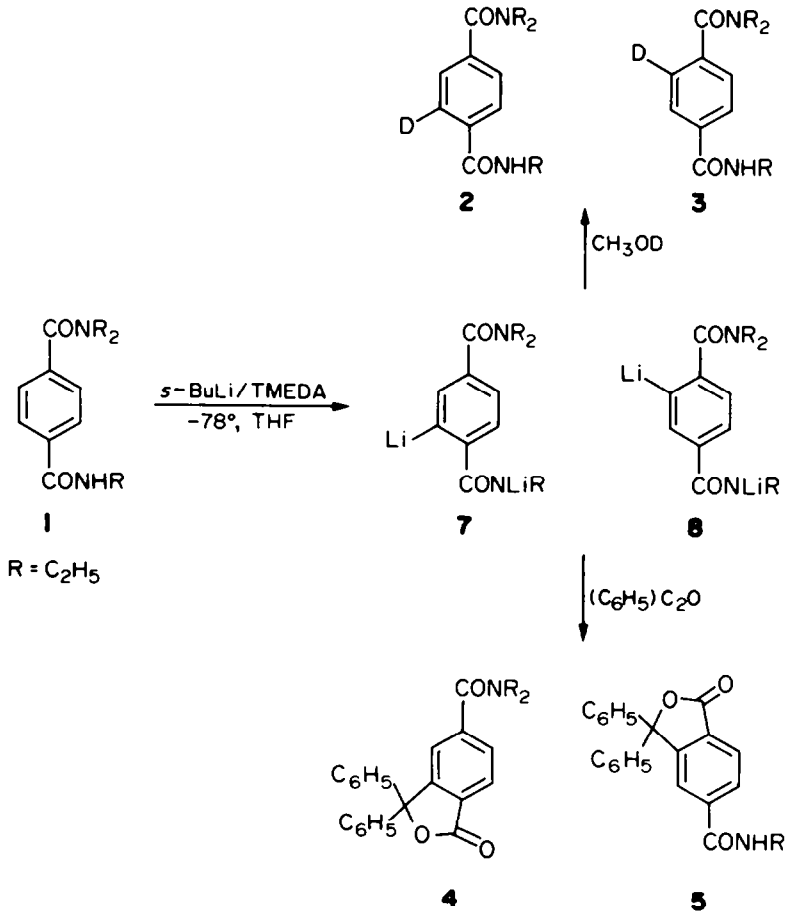
We find that the tertiary amide is a more powerful ortho director than the secondary amide in inter- but not in intramolecular competition. With both secondary and tertiary benzamides, lithiation is directed to adjacent primary and secondary benzylic hydrogens in preference to an adjacent ortho position but ortho lithiation is preferred in competition with a tertiary benzylic hydrogen. An optically active secondary, but not tertiary, benzamide is found to give small asymmetric induction. Rationales are provided for these observations.

RESULTS AND DISCUSSION

Intramolecular competition between the secondary and tertiary amides has been examined by repeating our study of the lithiation of N,N-diethyl-N-ethylterephthalamide (**1**) under conditions which allow comparison of the intermolecular case. As shown in Scheme 1 treatment of **1** with 2.05 equiv. of s-BuLi/TMEDA for 1/2 hr followed by addition of methanol-O-*d* at −78° gave **2** and **3** in a ratio of 5:1 and 90% yield. The position of deuteration was initially assigned on the basis of PMR spectra which assign a downfield shift for protons ortho to a secondary amide as ~0.3 ppm greater than that for a tertiary amide.[4,7]

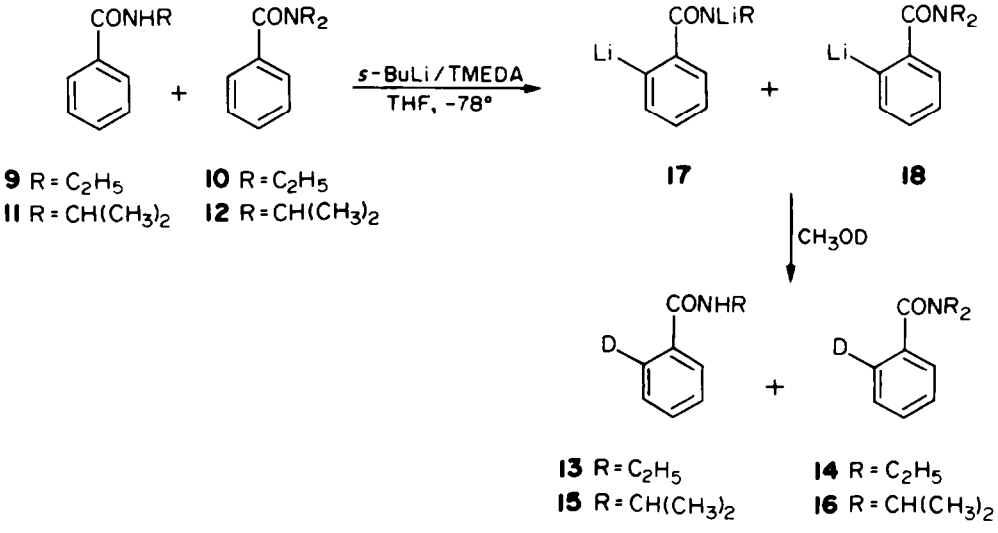
This assignment was confirmed, as heretofore,[3] by reaction of the lithiated species with benzophenone to give **4** and **5** in a ratio of 3:1 in 55% yield, *ca* twice the yield previously reported. Although a quantitative interpretation of these data is not warranted, the results can reasonably suggest that **7** is present to a greater extent than **8**. In the intramolecular competition offered by **1**, the secondary amide is more effective in directing ortho lithiation than is the tertiary amide under the prescribed conditions.

Intermolecular competitions were carried out for N-ethyl-N,N-diethylbenzamide (**9**:**10**) and N-isopropyl-: N,N-diisopropylbenzamide (**11**:**12**) by reaction with a 1:1 mixture of the secondary and tertiary

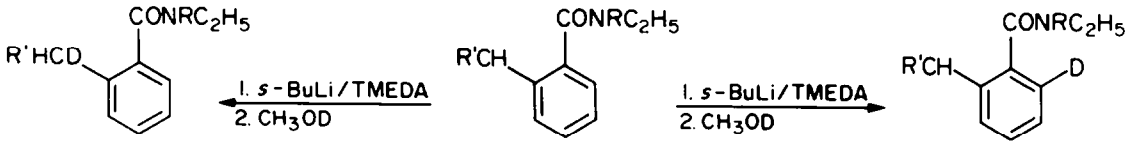


Scheme 1.

amides with 1.85 equiv. of s-BuLi/TMEDA at $-78°$ as shown in Scheme 2. The isopropyl amides were investigated because with the ethyl amides a 14% yield of ortho benzoyl-N,N-diethylbenzamide was obtained. This product, which arises from ortho lithiation and self-addition of **10**, could obscure the directing effect.[8] The metallations of **9–10** were allowed to proceed for 45 min while those of **11–12** were carried out for 2 hr. The ratios of **14**:**13** and **16**:**15** were 5:1 and 12:1, respectively, as determined by separation and PMR spectroscopy. The results show that in both comparisons **18** is present to a greater extent than **17**



Scheme 2.



20 R = C_2H_5; R' = CH_3
23 R = H; R' = H
24 R = H; R' = CH_3

19 R = C_2H_5; R' = CH_3, H
21 R = H; R' = H_2
22 R = H; R' = CH_3, H
25 R = H; R' = $(CH_3)_2$
26 R = C_2H_5; R' = $(CH_3)_2$

27 R = H; R' = $(CH_3)_2$
28 R = C_2H_5; R' = $(CH_3)_2$

Scheme 3.

under the present conditions. In these intermolecular competitions the tertiary amide is a more effective director than the secondary amide.

The present results show that in metallations with s-BuLi/TMEDA at − 78° in THF the relative directing abilities of secondary and tertiary amides in ortho lithiations are opposite in inter- and intramolecular competitions.[4,6] The secondary amide is slightly more effective in intramolecular competition while the tertiary amide is somewhat more effective in intermolecular competition. The energy differences involved are small and the lack of firm information about kinetic and thermodynamic effects in these systems makes any rationale tenous.[4,9] Nonetheless, at least two explanations can be offered. In the intramolecular competition the second group on the ring could provide inductive stabilization via its meta position to the site of metalation. In this case the tertiary amide presumably would provide greater inductive stabilization for **7** than would the ionized secondary amide in **8**, and this effect could operate under either thermodynamic or kinetic control. Another possibility is that initial complexation between the tertiary amide and the organolithium is favored over complexation with the secondary amide–lithium ion pair, and after that step has been achieved intramolecular exchange between different sites is facile. In this case the increased activity of the secondary amide in **1** could be attributed to internal exchange after an initially favored complexation with the tertiary amide. Such an exchange, of course, would not be possible in intermolecular competition.

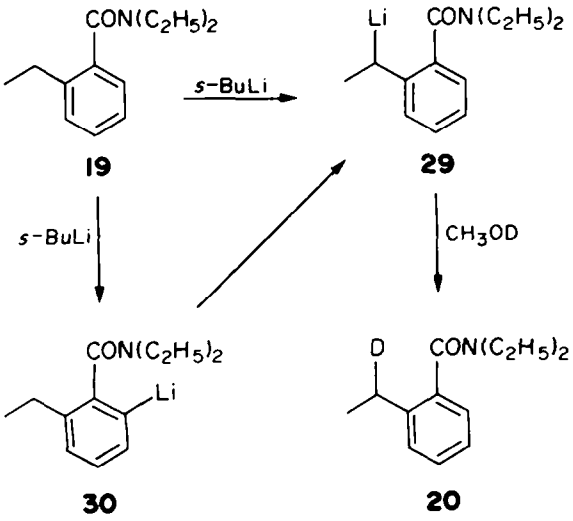
The advantage which the tertiary amide possesses over other directors of ortho lithiation has been attributed to complexation by the amide function.[4] However, neither the ground state structures of the lithiated species nor the relationship of those structures to the transition states for metalation are known. While two of the four sites at lithium might reasonably be suggested to be occupied by the *n*-electrons of the CO oxygen and a pair of electrons from the ortho carbon in a roughly planar structure with the tertiary amide, there is no convincing evidence for such a structure. Structures in which there is aggregation and/or in which the amide and/or the lithium are out of the plane of the ring should also be considered and more work will be needed to answer these questions. In any case the present results suggest the amides to be of comparable activity in directing ortho lithiations.[4]

We have also compared the secondary and tertiary amides in a competitive situation in which lithiation could be directed to an adjacent benzylic or ortho position. The results are summarized in Scheme 3 and Table 1. The ability of the tertiary amide to direct metalation to an adjacent benzylic site has been reported[4] and is supported by the observation that N,N-diethyl-2-ethylbenzamide (**19**) is converted to the benzylically deuterated compound **20** on treatment with s-BuLi/TMEDA followed by deuteriomethanol.[4,5,10] That the secondary amide also directs lithiation to the benzylic site was established by Hauser and co-workers.[10] Under the present conditions lithiation of N-ethyl-2-ethyl- (**21**) and N-

Table 1. Lithiations of 2-alkylbenzamides with s-BuLi/TMEDA at − 78° in THF

Amide	Metalation time (min)	Product	Yield (%d_1)
19	30	20	69 (50)[a]
19	90	20	52 (100)
21	30	23	87 (79)
22	30	24	87 (72)
25[b]	90	27	63[b] (40)
26	90	28	95 (100)

[a] Integration of the ^{1}H NMR spectrum showed no deuterium in the aromatic ring within the limits of ±10%. [b] Contained 37% 2-isopropyl-*N*-methyl-*N*-ethylbenzamide which was found to be 100% deuterated.



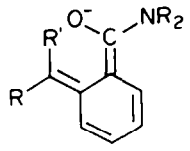
ethyl-2-methyl-benzamide (**22**) followed by reaction with methanol-O-*d* gives exclusively substitution of deuterium at the benzylic positions as shown for **23** and **24**, respectively. On the other hand, in the case of a tertiary benzylic hydrogen offered by an adjacent isopropyl group lithiation is directed to the ortho site by both the secondary and tertiary amides as shown for the conversions of N-ethyl- (**25**) and N,N-diethyl-2-isopropylbenzamide (**26**) to **27** and **28**, respectively. In this comparison of adjacent benzylic vs ortho metalation we do not detect a qualitative difference in regioselectivity between the secondary and tertiary amides although the latter do appear to metalate more rapidly.

Once again rationalization of these results must be tentative because of a lack of information about kinetic and thermodynamic acidities. Thus, for example, the formation of **20** from **19** could proceed by direct formation of **29** or via **30** which rearranges to **29**. While we can rule out the possibility that **30** is formed rapidly followed by slow rearrangement to **29** since this would lead to material in which deuterium would be found in both the benzylic and ortho positions, formation of **30** could be slow and rearrangement to **29** fast.

Reasonable rationales can be given for the observed results. Thus, the change from benzylic lithiation with **19**, **21** and **22** to ortho lithiation with **25** and **26** could reflect either the relative stabilities of the intermediate carbanionic species or the transition states leading to them. With methyl and ethyl substitution at the 2 position of the aryl ring the R′ position in **31** can be hydrogen and there will be little steric hindrance in the presumably planar anion or the preceding transition state. On the other hand, with the isopropyl group R′ in **31** would be methyl and there would be a destabilizing steric interaction between the methyl and amide groups and the alternative lithiation site at the ortho position could become favored. In fact, it could be that ortho metalation is encouraged by twisting the amide group out of the plane as shown for **32**. In this case the hydrogen which is being removed in the transition state and the lithium which replaces that proton are above and below the plane of the ring. Direction by the amide could still be provided by inductive stabilization or by complexation of the lithium with π-electrons.[11]

Support for the possibility that the amide group can be out of the plane of the ring is provided by the NMR spectra of 2-substituted tertiary benzamides.[12] Thus, for example, the NMR spectrum of **19** at 25° in DMSO-d_6 shows the ethyl groups on nitrogen to be non-equivalent and one of the methylene groups to possess magnetically non-equivalent hydrogens. The hydrogens of the methylene coalesce at 35° and the ethyl groups become equivalent at 105°. The lower energy barrier of 14.2 ($\pm$ 0.4) kcal/mole is attributed to restricted rotation about the Cl aryl bond while the barrier of 17.4 ($\pm$ 0.4) kcal/mole is due to rotation about the C–N bond in **19**.[12]

In a different comparison we have assessed the abilities of secondary and tertiary amides to induce asymmetry in the reaction of the ortho lithiated amides with 1-naphthaldehyde. Two cases of asymmetric induction have been reported involving ortho lithiated species. Bau *et al.* and Taintuner *et al.* observed induction in the addition of optically active α-ferrocenyl tertiary amines and Asami and Muk-



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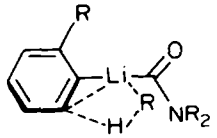

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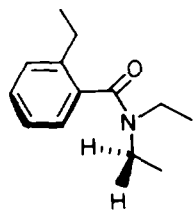

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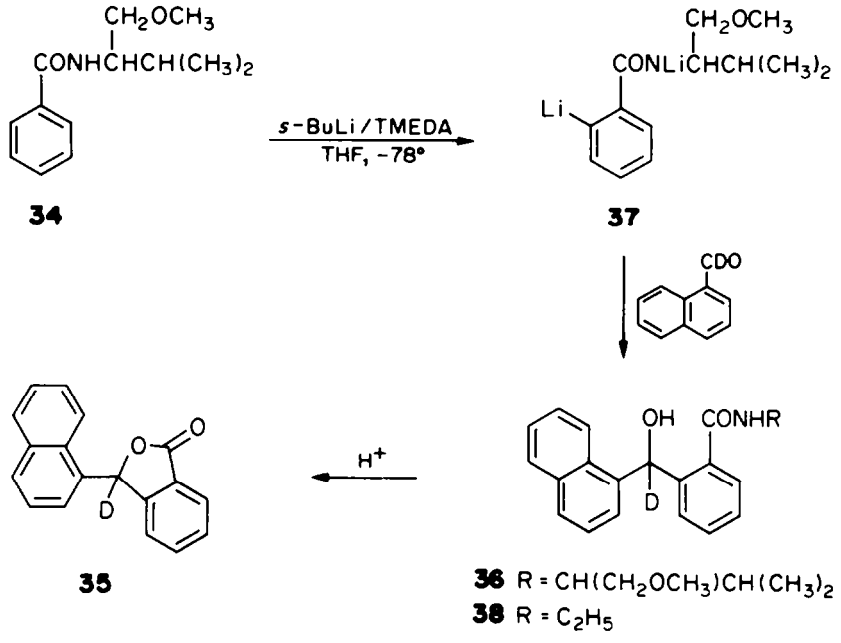

aiyama obtain 20–90% enantiomeric enrichments on addition of imidazoline to a variety of aldehydes.[13,14]

Upon metalation of (*S*)-O-methyl-N-methyl-N-benzoylleucinol (**33**) and reaction with 1-naphthaldehyde and cyclization to produce an optically inactive phthalide. However, the ortho lithiated secondary benzamide, (*S*)-O-methyl-N-benzoylleucinol (**34**), undergoes reaction at $-78°$ with 1-naphthaldehyde-*d* to give, after acid-driven cyclization in toluene at reflux for 9 hr, 3-(1-naphthyl)phthalide-3-*d* (**35**), which has $10 \pm 5\%$ enantiomeric excess. The enantiomeric excess was determined by chromatographic separation of the enantiomers of **35** as described by Pirkle.[15] When the reaction of **34** was carried out at $-37°$ a $7.5 \pm 5.0\%$ ee was observed while at ambient temperature no enantiomeric excess was observed. In order to assure that the observed enantiomeric excesses were not due to diastereoselection in the cyclization, these reactions were carried to completion. In another case the phthalide obtained in incomplete cyclization was found to have an ee within the experimental error of that obtained by cyclization of residual hydroxyamide from the incomplete reaction suggesting the cyclization is not diastereoselective.

The retention of deuterium in the product indicates that racemization is not due to proton exchange under the cyclization conditions. In a more definitive test the diastereomeric carbinol amides **36** were separated by flash chromatography and one isomer was cyclized by heating in toluene with 1 equiv. of *p*-toluenesulfonic acid for 9 hr to give a product with an $86 \pm 7\%$ ee. Racemization does not occur under these cyclization conditions.

The small asymmetric induction which occurs in the reaction of the ortho lithiated amide **37** with 1-naphthaldehyde-*d* would most reasonably be attributed to kinetic control in the diastereomeric transition states leading to the dilithium salt of **36**. The possibility of thermodynamic control in the diastereomeric dilithium salts **36** due to equilibration between diastereoisomers is ruled out by a number of controls.

The isolated diastereoisomer **36**, in a separate experiment, was isolated and treated with 2.2 equiv. of s-BuLi/TMEDA at $-78°$ and warmed to room temperature for 1 hr prior to the reisolation of **36** and its subsequent cyclization to **35**. The lactone **35** was obtained with an $80 \pm 8\%$ ee comparable to the value of $86 \pm 7\%$ obtained above, establishing that equilibration did not occur. The possibility of involvement of excess aldehyde, not present in this control experiment, in equilibration either by exchange or in a Cannizzaro reaction[13] was ruled out with N-ethylbenzamide, as the substrate. Adduct **38** was prepared with 1-naphthaldehyde and in separate experiments treated with lithium diisopropylamide and benzaldehyde, and lithium diisopropylamide and 1-naphthaldehyde-*d* and warmed to room temperature. The product after cyclization in both cases was 3-(1-naphthyl)phthalide. Since no detectable aryl or D exchange had occurred, these results further indicate that the asymmetric induction observed in the formation of **36** is under kinetic control and properly attributed to differences in the diastereomeric transition states. The fact that asymmetric induction is observed with the secondary amide but not the tertiary amide is consistent with the transition state in which binding to a Li associated with the nitrogen is involved. The extent of asymmetric induction is too low to allow any reasonable proposals of transition state geometry. The chromatographic separation of the diastereomers of **36** followed by cyclization noted above does, however, provide a useful route to the optically active phthalides.

In summary the tertiary amide is more effective than the secondary amide in directing ortho lithiation

in intermolecular competition under the prescribed conditions. In an intramolecular competition the secondary amide is more effective. In selecting between an adjacent benzylic or ortho site for lithiation, benzylic sites which bear primary or secondary hydrogens are preferentially lithiated while the ortho site is favored in competition with a tertiary benzylic hydrogen, with both secondary and tertiary amides. While these results can be rationalized in terms of complexation between the amide and lithium, more information is needed to specify the structural features of the interactions. The secondary amide provides a very modest asymmetric induction in reaction of an orthollithiated benzamide with 1-naphthaldehyde. The tertiary amide is ineffective in asymmetric induction.

EXPERIMENTAL

M.ps are uncorrected. Chemical shifts for NMR spectra are reported relative to TMS. Mass spectra (MS) were obtained by Cook *et al.* on a Varian MAT CH-5 spectrometer. Microanalyses were provided by Nemeth and associates.

Materials. THF was distilled from the sodium benzophenone ketyl under nitrogen and stored under N_2. TMEDA was refluxed over and distilled from calcium hydride under N_2 and stored over 4 Å molecular sieves under N_2. Commercial sec-BuLi was used. The known amides **1**, **9**, **10**, **11**, **12**, **19**, **21**, **22** and **25** had spectral and analytical properties consistent with the assigned structures.

N,N-*Diethyl*-2-*isopropylbenzamide* (**26**) was prepared by dropwise addition of 0.935 g (4.6 mmol) of **19** in dry THF to a soln containing 5.0 mmol of s-BuLi/TMEDA in THF at − 78° for 15 min, followed by addition of 0.6 ml (9.2 mmol) of MeI. The soln was allowed to warm to room temp, the THF removed *in vacuo*, the residue taken up in ether and the ethereal soln washed with 10% HCl aq, sat NaCl aq, and dried ($MgSO_4$). Flash column chromatography (silica gel, 3:10 EtOAc–hexene) gave an oil, which was distilled (b.p. 110–115°/0.6 torr) to provide 0.546 g (55%) of **26**: IR 1650 cm^{-1} (neat); NMR δ 1.04 (t, J = 8 Hz, 3 H), 1.27 (d, J = 7.5 Hz, 6 H), 1.29 (t, J = 8 Hz, 3 H), 3.07 (overlapping q, J = 8 Hz, 4 H), 3.68 (sept, J = 7.5 Hz, 1 H), 7.02 (m, 4 H). (Found: C, 76.66; H, 9.58; N, 6.21. Calc for $C_{14}H_{21}NO$: C, 76.71; H, 9.59; N, 6.39%.)

(S)-O-*Methyl*-N-*benzoylleucinol* (**34**) was prepared from (*S*)-O-methylleucinol[16] and benzoyl chloride[17] in 81% yield after medium pressure liquid chromatography (silica gel $CHCl_3$–hexane). M.p. 45–46°; IR (neat) 3290, 1640, 1120 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (s, 3 H), 0.99 (s, 3 H), 1.3–1.7 (m, 3 H), 3.40 (s, 3 H), 3.44 (d, 2 H), 4.3 (br, 1 H), 6.2 (br, 1 H), 7.3–7.8 (m, 5 H); $[\alpha]_D^{20} = -32.6°$. (Found: C, 71.29; H, 9.05; N, 5.79. Calc for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95%).

(S)-O-*Methyl*-N-*methyl*-N-*benzoylleucinol* (**33**) was prepared from (*S*)-O-methyl-N-methylleucinol[16] and benzoyl chloride[17] in 45% yield after flash chromatography (silica gel, 1:1 EtOAc–hexene). Kugelrohr distillation at 130–140°/0.5 mm; NMR δ 0.48–1.84 (*m*, 9 H), 2.76 (*s*, 3 H), 2.90 (s, 3 H), 3.16–3.62 (m, 5 H), 3.74–4.16 (m, 1 H), 4.76–5.14 (m, 1 H), 7.36 (brs, 5 H). (Found: C, 71.96; H, 9.26; N, 5.70. Calc for $C_{15}H_{23}NO_2$: C, 72.30; H, 9.20; N, 5.60%).

1-*Naphthaldehyde*-1-d. A soln of 1-methyl naphthoate (40 mmol, 7.39 g) in 9 ml dry THF was added slowly to a soln prepared by heating $LiAlD_4$ (24 mmol, 1.0 g, 99% D) in 13 ml dry THF at reflux for 1.0 h under N_2. Reflux was continued for 1 hr before EtOAc (8 mmol, 0.78 ml) in 2 ml THF was added. The mixture was cooled and poured onto 60 ml of ice cold 3 N H_2SO_4. The solvent was removed *in vacuo* and the residue extracted with ether. The combined ether extract was washed with 5% HCl, 5% NaOH, water and dried ($MgSO_4$). Concentration *in vacuo* and flash distillation (b.p. 104°, 0.7 mm) gave 1,1-dideutero-1-(1-naphthyl) methanol in 95% yield. M.p. 55.5–57°; NMR ($CDCl_3$) δ 1.79 (s, 1 H), 7.2–8.2 (m, 7 H). This alcohol (19 mmol, 3.0 g) was oxidized[18] over a 17.7 hr reaction time to give formyl-*d*-1-naphthaldehyde in 89% yield: b.p. 83–89°/0.6 mm; IR 2100, 2060, 1680 cm^{-1} (neat); NMR δ 7.5–8.1 (m, 6 H), 9.25 (d, 1 H); MS (10 eV) *m/e* (rel. intensity) 129.0 (26.75), 155.1 (15.39), 157.1 (100). (Found: C, 83.90; H, 5.06. Calc for $C_{11}H_7DO$: C, 84.05; H, 5.13%).

General procedure for amide lithiation and deuteration

To 0.05 to 0.10 M solns of the amide and TMEDA in dry THF s-BuLi was added dropwise at − 78°. After 1/2 hr MeOD was added, the soln was allowed to warm to room temp, THF solvent was removed and replaced by 40 ml ether, the organic layer was washed with 10% HCl aq, with satd NaCl aq, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed to give the required product(s), which were characterized by NMR spectral criteria and in some cases by mass spectrometry. The products **4** and **5** were separated by MPLC and have physical properties as previously reported.[4] (Found C, 76.60; H, 5.32; N, 3.82. Calc $C_{23}H_{19}NO_3$: C, 77.9; H, 5.36; N, 3.92%). Amide **5**, m.p. 223–224°.

3-(1-*Naphthyl*)*phthalide*-3-d (**36**). Amide **34** was treated with s-BuLi at − 78° in dry THF for 2.2 hr and 1-naphthaldehyde-*d* was added at − 78°. After 1 hr at − 98° and 3 hr at − 78°, water was added and the soln allowed to warm to room temp. Removal of the solvent *in vacuo*, followed by addition of ether, washing with 10% HCl aq, satd NaCl aq, and drying ($MgSO_4$) gave a mixture of **34** and **36** which was separated by preparative TLC (silica gel, 1:2 ethyl–hexene). Cyclization was achieved by heating **36** at reflux with 1.0 equiv. TsOH in toluene for 9 hr. The mixture was cooled and washed with 5% HCl, 5% NaOH, water and dried ($MgSO_4$). Concentration *in vacuo* followed by MPLC (silica gel, $CHCl_3$–hexane) and recrystallization from ether gave recovered **34** in 17% yield and **35** in 60% yield. M.p. 132–136°; IR 1770 cm^{-1} (neat); NMR δ 7.2–8.3 (m); (10 eV) *m/e* (rel intensity) 104.0 (9.44), 261.0 (100), 262.0 (23.67), isotopic ratio 95.5% D, HPLC 10 ± 5% ee. The m.p. and spectral data for **35** were similar to that of authentic 3-(1-naphthyl)phthalide (m.p. 137–138°)[19] prepared from N-ethylbenzamide and 1-naphthaldehyde.

In a separate experiment the diastereomers of **34** were separated by flash chromatography (silica gel, 1:6 EtOAc–hexene) and one diastereomer was cyclized under the above conditions to give material of 86 ± 7% ee.

Enantiomeric excesses were based on chromatographic separations of enantiomers as described by Pirkle and Schreiner.[15] The enantiomers were detected at two wavelengths to minimize the possibility of inaccuracies due to absorbing impurities, and the relative amounts determined from peak areas. The system was calibrated with *dl* material and we estimate enantiomeric excesses are accurate within ± 5%.

Acknowledgements—We are grateful to the National Institutes of Health for support of this work and to Prof. W. H. Pirkle for chromatographic resolution of the enantiomeric phthalides. We also wish to acknowledge use of the Regional NMR facility at the University of Illinois at Champaign-Urbana supported in part by NSF-CHE 79-16,100.

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