THE JOURNAL OF Organic Chemistry

VOLUME 49, NUMBER 5

MARCH 9, 1984

Ortho-Lithiated Tertiary Benzamides. Magnesium Transmetalation and Synthesis of Phthalides and Isocoumarins Including Mellein and Kigelin

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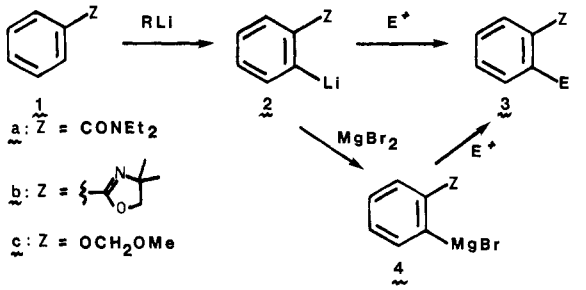
Received June 15, 1983

Ortho-lithiated benzamides undergo transmetalation with $MgBr_2 \cdot 2Et_2O$ to species **9**, which, in contrast to the lithiated intermediates, react with allyl bromide and aliphatic aldehydes to give 2-allylbenzamides **10** and phthalides **7**, respectively. The 2-allylbenzamides are converted by acid treatment into 3,4-dihydroisocoumarins **13** including the natural products mellein (**13b**) and kigelin (**13e**). The magnesium transmetalation procedure is briefly explored with lithiated 2-phenyl-4,4-dimethyloxazoline (**1b**) and (methoxymethoxy)benzene (**1c**).

The pioneering discoveries of Gilman[1] and Wittig[2] and the systematic studies of Hauser[3] in the 1950s set the foundation for the synthetic development of the aromatic directed metalation reaction (**1** → **2** → **3**, Scheme I).[4] The utility of this general methodology derives from the alkyllithium-induced regiospecific deprotonation ortho to a directed metalation group Z, allowing the synthesis of polysubstituted aromatics that are difficult to prepare by conventional, invariably electrophilic substitution, chemistry. In order to achieve this useful result, an increasing number of carbon- and heteroatom-based directed metalation groups has evolved. We have focussed on the tertiary amide **1a** as an effective ortho metalation director and have demonstrated its utility for the construction of polysubstituted aromatics, phthalides, condensed carbocyclic and heterocyclic benzoquinones, polycyclic aromatic hydrocarbons, naturally occurring anthraquinones, and several biogenetically diverse classes of alkaloids.[5] Of the electrophiles initially studied in the course of generalizing the reaction of ortho-lithiated benzamide **2a**,[6] allyl bromides and aliphatic aldehydes failed to give ortho-substituted products. Recent work has demonstrated the utility of exchanging lithium for copper,[7] magnesium,[8] and zinc[9]

Scheme I



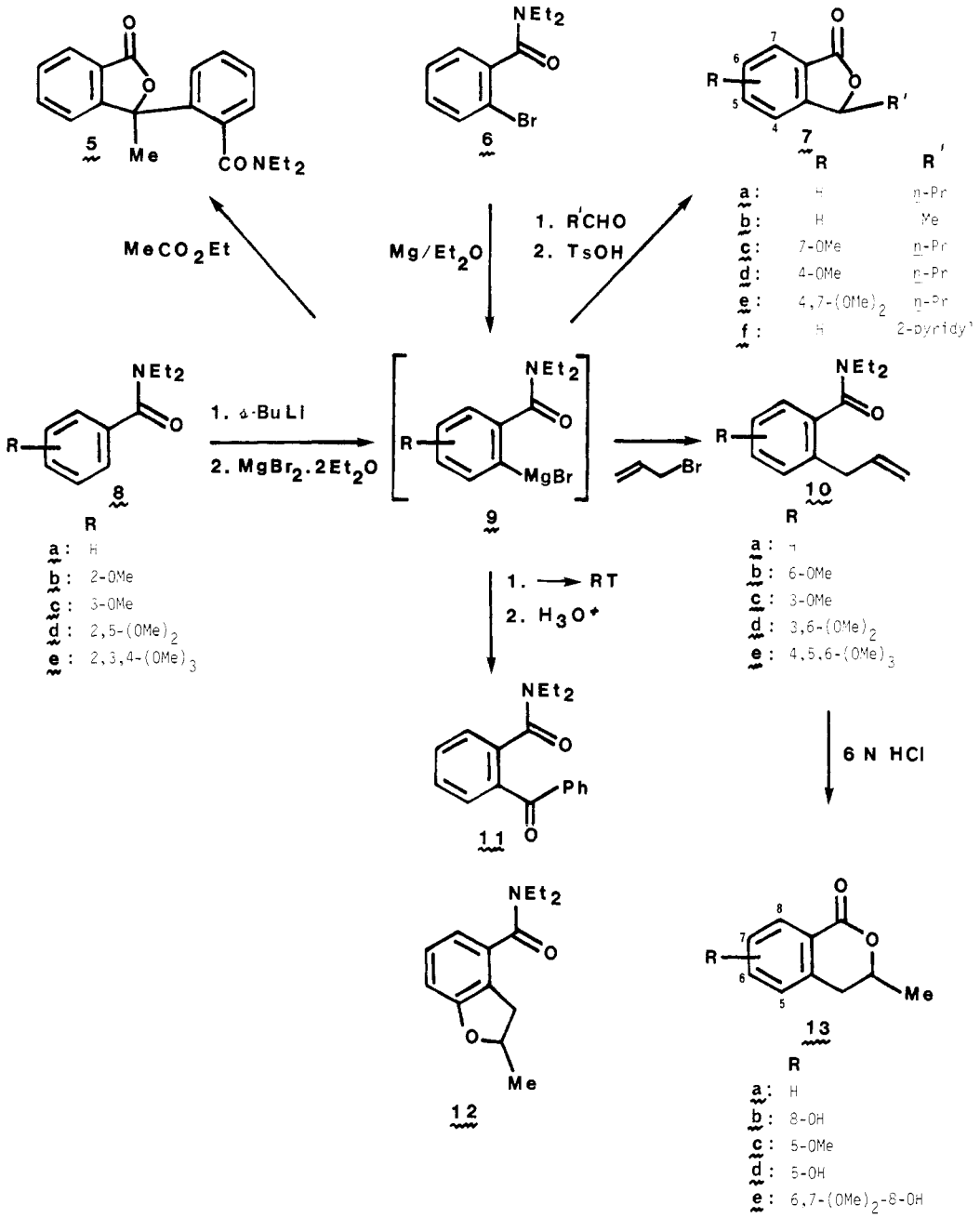
in the context of directed metalation and lithium–halogen exchange strategies.[10] Stimulated by these results, we explored lithium → magnesium transmetalation, **2** → **4**, and herein we show the advantage of this tactic for ortho allylation and hydroxyalkylation of benzamides. We further delineate the conversion of the resulting products **3** into phthalides **7** and isocoumarin derivatives **13** including the natural products mellein (**13b**)[11a] and kigelin (**13e**).[11b] Comparison of ortho lithium vs. ortho bromomagnesium species in reactions of 2-oxazolino (**1b**) and methoxymethoxy (**1c**) directing groups with these electrophiles is also briefly reported.

As previously observed for the condensation of ortho-lithiated *N,N*-diethylnaphthamide with pyridine-2-carb-

(1) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
(2) Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, *73*, 1197.
(3) Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853. Reviews: Kaiser, E. M.; Slocum, D. W. In "Organic Reactive Intermediates"; McManus, S. P., Ed.; Academic Press: New York, 1973; Chapter 5. Slocum, D. W.; Sugarman, D. I. *Adv. Chem. Ser.* **1974**, *130*, 222.
(4) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(5) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.
(6) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, 5099.
(7) Cu. (a) Whitlock, B. J.; Whitlock, H. W. *J. Org. Chem.* **1980**, *45*, 12. (b) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. (c) Ellefson, C. R. *J. Org. Chem.* **1979**, *44*, 1533.
(8) MgBr. Transmetalation of aryllithiums into arylmangesiums appears to have been first explored by Gilman, see: Jones, R. G.; Gilman, H. *Org. React. (N.Y.)* **1951**, *6*, 339 (especially p 363). Recent use: (a) Trost, B. M.; Pearson, W. H. *Tetrahedron Lett.* **1983**, *24*, 269. (b) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1981**, *103*, 2483. (c) Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420.
(9) ZnCl: Larson, E. R.; Rapheal, R. A. *Tetrahedron Lett.* **1979**, 5041.
(10) Negishi, E.-i. "Organometallics in Organic Synthesis"; Wiley: New York, **1980**; Vol. 1, pp 101, 249.
(11) Recent synthetic work: (a) Mellein: Harwood, L. M. *J. Chem. Soc., Chem. Comm.* **1982**, 1120. (b) Kigelin: Narasimhan, N. S., Bapat, C. P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2099 and references therein.

0022-3263/84/1949-0737$01.50/0

Scheme II



aldehyde,[12] reaction of the corresponding benzamide **2a** with pyridine-2-carbaldehyde, allyl bromide, or aliphatic aldehydes[13] produced numerous color changes but led either to the recovery of starting amide or uncharacterizable, probably polymeric material. However, when the lithiated species was treated with 3 equiv of $MgBr_2 \cdot 2Et_2O$[8c] at −78 °C and the reaction mixture was warmed to room temperature, again cooled to −78 °C, and quenched with allyl bromide, the *o*-allylbenzamide **10a** (Scheme II) was obtained in 71% yield. Variation of the temperature to which the reaction was cooled (−78 °C, −40 °C, 0 °C, no cooling) after being warmed to room temperature before addition of the electrophile to the presumed Grignard reagent **9a**, as well as the reaction at −78 °C without warming, showed no appreciable increase in the yield of the isolated product. Several methoxy-substituted benzamides (**8b–e**) were similarly converted to the ortho-allylated products **10b–e** in good yields (Table I). Coupling of the Grignard species **9a–c** with *n*-butyraldehyde and acetaldehyde was equally successful. In these cases, the intermediate amide alcohols were not isolated but, for purpose of convenience, subjected to *p*-toluenesulfonic acid treatment to yield directly the phthalides **7a–e**. By this procedure, the 2-pyridylphthalide **7f** was also obtained in good yield.

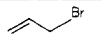
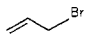
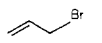
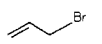
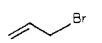
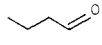
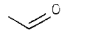
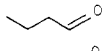
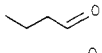
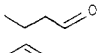
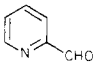
A number of other electrophiles (MeCN, $BrCH_2CO_2Et$, $(EtO)_2CHCH_2Br$, epibromohydrin, $CH_2{=}CHCOMe$, $PhCH_2Br$, $PhCH_2Cl$, styrene oxide, cyclohexene oxide) that had been previously shown[14] not to undergo reaction with ortho-lithiated benzamides also failed to give condensation products with the corresponding Grignard species **9a**. In the case of EtOAc, the 2:1 condensation product **5** was obtained (see Experimental Section). Attempts to stop

(12) Iwao, M.; Mahalanabis, K. K.; Watanabe, M.; de Silva, S. O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955.

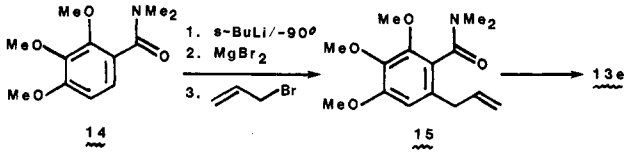
(13) In contrast, dilithiated secondary thiobenzamides undergo smooth condensation with acetaldehyde: Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1976**, *41*, 4029.

(14) Unpublished work from these laboratories.

Table I. Synthesis of *o*-Allylbenzamides 7 and Phthalides 10 by Li → MgBr Transmetalation

benzamide	electrophile	product	yield, %
8a		**10a**	71
8b		**10b**	55
8c		**10c**	80
8d		**10d**	63
8e		**10e**	66
8a		**7a**	64
8a		**7b**	61
8b		**7c**	60
8c		**7d**	59
8d		**7e**	75
8a		**7f**	88

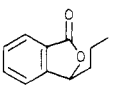
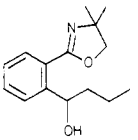
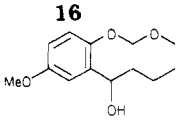
Scheme III



the reaction at the desired *o*-acetylbenzamide stage by variation of conditions, including inverse addition, failed. For reactions of most of the other electrophiles mentioned above, in addition to starting benzamide that was recovered in variable yields, the benzophenone **11** was obtained as a minor product (6–13%). This compound may arise from either ortho-metalated species as shown by the following experiment. When species **9a** was warmed to room temperature and quenched with water, benzophenone **11** was isolated in 19% yield together with starting material (65–68%). On the other hand, the generation of **9a** from *o*-bromobenzamide **6** using triply sublimed magnesium[15,16] followed by the same quenching procedure led to the formation of **11** in only 10% yield, and the starting amide was obtained in 60% yield.

The ready availability of *o*-allylbenzamides **10** prompted a study of their acid-catalyzed conversion into isocoumarin derivatives **13**.[17,18] Thus treatment of **10a** with HCl at reflux provided compound **13a** in quantitative yield. Similar treatment of **10b** resulted in cyclization as well as demethylation to yield mellein (**13b**), a naturally occurring isocoumarin[11a] whereas the 2-allyl-3-methxoybenzamide **10c** afforded a mixture of the isocoumarin **13c** (49%), the corresponding phenol **13d** (16%), and the benzofuran **12** (13%). Cyclization of the *o*-allyltrimethoxybenzamide **10e** required vigorous conditions (6 N HCl/reflux/72 h) and gave a complex mixture of products, which contained didemethylated isocoumarins (NMR analysis) but not the desired kigelin (**13e**).[19] Furthermore, when **10e** was subjected to mercuric acetate catalyzed cyclization[11b] or to the Hegedus Pd-catalyzed method,[20] which has been shown to be successful in cyclization of 2-allylbenzoic acids and the corresponding primary and secondary benzamides into isocourmarins and isoquinolones, no isocoumarin products were obtained. Aiming to facilitate the cyclization by lessening the steric congestion, the *o*-allyl dimethylamide **15** (Scheme III) was synthesized from the corresponding amide **14**. When subjected to aqueous 6 N HCl at 80 °C, compound **15** was converted into kigelin (**13e**)[11b] in 27% yield.

Table II. Comparison of *o*-Li vs. *o*-MgBr in Reaction with *n*-Butyraldehyde for Compounds 1a–c

substrate	product	yield, %, via *o*-Li	yield, %, via *o*-MgBr
1a	 **7a**	<5	64
1b	 **16**	65	68
1c	 **17**	38	66

The ortho lithium and bromomagnesium phenyloxazoline[21,22] (**1b**), and methoxymethoxy[23] (**1c**) systems were compared in reactions with *n*-butyraldehyde to determine if yields of products could be improved via the transmetalation procedure. As seen from Table II, **1b** showed similar reactivity as either metalated species to give **16**, concurring with the results of Meyers.[15] On the other hand, comparison of results on compounds **1c** showed that more efficient conversion into *o*-hydroxyalkyl product **17** may be achieved via the transmetalation procedure. The condensation of ortho-lithiated (methoxymethoxy)benzene, prepared by metalation with *n*-BuLi at room temperature, with pentanal to give the product analogous to **17** in 67% has been reported recently.[23b] Nevertheless, the transmetalation procedure may be useful in aromatic systems with functionality that does not tolerate the more nucleophilic *n*-BuLi reagent.

Conclusions

The transmetalation of ortho-lithiated benzamides **2a** into the bromomagnesium counterparts **4a** allows introduction of allyl and hydroxyalkyl moieties, thereby extending the utility of the benzamide-directed metalation strategy. The resulting products may be economically converted into phthalides **7** and isocoumarins **13**. The synthesis of mellein (**13b**) and kigelin (**13e**) can be achieved in overall yields of (21–41%) which compare favorably with previous preparation[11] of these natural products (25–35%).

(15) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.
(16) Obtained from Dr. J. Robinson, Dow Chemical Co., Midland, MI.
(17) For an extensive list of references to recent synthetic work on isocoumarins, see: Watanabe, M.; Kubo, M.; Sahara, M.; Furukawa, S.; Billedeau, R. J.; Snieckus, V. *J. Org. Chem.*, following paper in this issue.
(18) 3-Oxazolinobiphenyl has been converted into an isocoumarin derivative by the directed metalation tactic: see ref 7c.
(19) For a detailed study of cyclization of *o*-carboxystilbene derivatives to isocoumarins, see: Teitei, J. *Aust. J. Chem.* **1982**, *35*, 1231.
(20) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.
(21) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008. Meyers, A. I.; Mihelich, E. D. *Ibid.* **1975**, *40*, 3158.
(22) Marxer, A.; Rodriguez, H. R.; McKenna, J. M.; Tsai, H. M. *J. Org. Chem.* **1975**, *40*, 1427.
(23) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (b) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923.

The results (Table II) observed for the ortho-lithiated phenyl methoxymethoxy (**1c**) system suggest that the transmetalation procedure may have additional utility within the scope of the aromatic directed metalation strategy.[4,5]

Experimental Section

General Methods. Microanalyses were performed by Canadian Microanalytical Services, Ltd., Vancouver, B.C., and Uniroyal Research Laboratories, Guelph, Ontario. Melting points were measured on a Fisher-Johns or a Buchi SMP-20 apparatus and are uncorrected. IR spectra were determined on a Beckmann Acculab 10 spectrometer. NMR spectra were obtained on a Bruker WP-80 spectrometer using tetramethylsilane as internal standard; data are listed in order of multiplicity, number of protons, and coupling constant in hertz. Mass spectra were determined on a high-resolution CH-7 spectrometer. Silica gel 60 (0.04–0.063 mm and 0.063–0.20 mm) and silica gel GF-254 obtained from Brinkmann (Canada) were used for column and thin-layer chromatography, respectively. *sec*-Butyllithium as a solution in hexane and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (distilled from CaH and stored over 4-A molecular sieves) were purchased from Aldrich Chem. Co. Solutions of *sec*-BuLi were stored at 0 °C in serum-capped bottles inside plastic bags containing anhydrous calcium chloride and Drierite. The titer of *sec*-BuLi was determined either by titration using 2,5-dimethoxybenzyl alcohol[24] as standard or by use of the Gilman titration procedure.[25] THF and Et_2O were freshly distilled from sodium benzophenone ketyl before use. Metalations were carried out in an air-conditioned laboratory by using syringe–septum cap techniques. The phrase "standard workup" refers to treatment of the reaction mixture with saturated NH_4Cl or 10% HCl solutions, extraction with EtOAc, CH_2Cl_2, or $CHCl_3$, drying (Na_2SO_4) of the organic extract, and evaporation to dryness under reduced pressure. Unless otherwise indicated, column chromatography was carried out on silica gel and EtOAc–hexane (1:4 to 1:9) eluent.

Benzamides. With the exception of *N,N*-diethyl-2-bromobenzamide (**6**), *N,N*-diethyl-2,3,4-trimethoxybenzamide (**8e**), and *N,N*-dimethyl-2,3,4-trimethoxybenzamide (**14**), all benzamides have been fully characterized previously.[26] **6**: bp 140–142 °C (0.30 mm) lit.[27] bp 138–140 °C (2 mm); IR ($CHCl_3$) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.06, 1.27 (2 × t, 6 H, J = 7), 3.15, 3.75 (2 × q, 4 H, J = 7), 7.16–7.60 (m, 4 H). **8e**: bp 115–120 °C (0.2 mm); IR ($CHCl_3$) ν_{max} 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.04, 1.24 (2 × t, 6 H, J = 7), 3.18, 3.55 (2 × q, 4 H, J = 7), 3.87, 3.88, 3.90 (3 × s, 9 H), 6.66 (d, 1 H, J = 8.5), 6.91 (d, 1 H, J = 8.5); MS, m/e 267 (M^+). Anal. ($C_{14}H_{21}NO_4$). Satisfactory analytical data (C, H, N) were not obtained. **14**: mp 65–66 °C (CH_2Cl_2–hexane); IR ($CHCl_3$) ν_{max} 1615 cm^{-1}; NMR ($CDCl_3$) δ 2.87 (s, 3 H), 3.10 (s, 3 H), 3.88 (s, 9 H), 6.67 (d, 1 H, J = 8.2), 6.94 (d, 1 H, J = 8.2); MS, m/e 239 (M^+). Anal. ($C_{12}H_{17}NO_4$) C, H, N.

General Transmetalation Procedure. To a stirred THF solution (50 mL) of *sec*-BuLi (1.1 equiv) and TMEDA (1.1 equiv) at −78 °C under nitrogen was added by syringe injection the *N,N*-diethylbenzamide (1 equiv) in THF (6 mL). After 30 min, $MgBr_2 \cdot 2Et_2O$ (3 equiv) was added, resulting in the formation of a colorless precipitate. The reaction mixture was allowed to warm to room temperature to give a clear solution, again cooled to −78 °C and stirred for 40 min. The electrophile (2 equiv)[28] was added and the solution was allowed to warm to room temperature overnight. Standard workup followed by column chromatography afforded the desired product.

Preparation of *N,N*-Diethyl-2-allylbenzamides 10. General Procedure. The following procedure is representative for the synthesis of compounds **10a–e**. The physical and spectral data are gathered in Table III.

***N,N*-Diethyl-2-allylbenzamide (10a).** *N,N*-Diethylbenzamide (500 mg, 2.82 mmol) was subjected to the general transmetalation procedure by using appropriate quantities of reagents and solvents. The solution of the *o*-(bromomagnesio)benzamide was quenched with allyl bromide (683 mg, 5.64 mmol), and the reaction mixture was allowed to warm to room temperature overnight. Standard workup gave 578 mg of crude product, which upon column chromatography yielded 435 mg (71%) of compound **10a**.

***N,N*-Dimethyl-2-allyl-4,5,6-trimethoxybenzamide (15).** The general transmetalation procedure was modified in that the lithiation of **14** (500 mg, 2.1 mmol) was carried out at −90 °C for 1.5 h. The solution of the lithiated species was then warmed to −78 °C over 0.5 h and $MgBr_2 \cdot 2Et_2O$ (3 equiv) was added. The mixture was stirred for 0.5 h, allowed to warm to room temperature to give a clear solution, again cooled to −78 °C, and stirred for 1 h. Following addition of allyl bromide (2 equiv), the solution was allowed to warm to room temperature overnight and worked up by the standard procedure. Column chromatography afforded 465 mg (77%) of compound **15** contaminated by traces of a compound, MS m/e 319 (M^+), most likely the product of benzylic allylation of **15** which could not be removed, thus leading to poor analytical data.

Preparation of Phthalides 7. General Procedure. The following procedure is representative for the synthesis of **7a–e**. Physical and spectral data are given in Table III.

3-(*n*-Propyl)phthalide (7a). *N,N*-Diethyl-*o*-(bromomagnesio)benzamide (**9a**) was generated according to the general transmetalation conditions by using **8a** (500 mg, 2.82 mmol) and appropriate quantities of reagents and solvents. This solution was treated with freshly distilled *n*-butyraldehyde (407 mg, 5.65 mmol), and the resulting solution was allowed to warm to room temperature overnight. Standard workup gave the crude hydroxyamide, which was not isolated but was refluxed in toluene (60 mL) containing *p*-toluenesulfonic acid monohydrate (100 mg) for 20 h. Standard workup followed by column chromatography afforded 310 mg (64% overall) of **7a**.

Formation of 2-(Diethylcarbamoyl)benzophenone (11). From *N,N*-Diethylbenzamide (8a). A solution of the *o*-(bromomagnesio)benzamide **9a** was generated according to the general transmetalation procedure, warmed to room temperature, and quenched with water. Standard workup followed by column chromatography gave starting material (65%) and compound **11** (19%): bp 100–105 °C (0.15 mm) (lit.[29] mp 76–77 °C); IR ($CHCl_3$) ν_{max} 1655, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.98–1.19 (m, 6 H), 3.13–3.56 (m, 4 H), 7.28–7.86 (m, 9 H); MS, m/e 281 (M^+).

From *N,N*-Diethyl-2-bromobenzamide (6). To finely divided, triply sublimed magnesium (85 mg, 3.5 mmol) under nitrogen with stirring was added *N,N*-diethyl-2-bromobenzamide (500 mg, 1.95 mmol) in THF solution (20 mL) containing 2 drops of 1,2-dibromoethane. The reaction mixture was stirred and refluxed for 2.5 h, cooled to 0 °C, and quenched with aqueous NH_4Cl solution. Standard workup followed by column chromatography yielded *N,N*-diethylbenzamide (60%) and compound **11** (10%), shown to be identical by comparison (IR, NMR) with the sample of **11** obtained as described above.

Formation of 3-Methyl-3-[2-(diethylcarbamoyl)phenyl]-phthalide (5). *N,N*-Diethyl(bromomagnesio)benzamide **9a**, generated according to the general transmetalation procedure by using **8a** (500 mg, 2.82 mmol) and appropriate quantities of reagents, was treated at −78 °C with freshly distilled ethyl acetate (497 mg, 5.65 mmol). Standard workup and column chromatography gave 320 mg (35%) of **5**: mp 126–127 °C (Et_2O); IR ($CHCl_3$) ν_{max} 1750, 1615 cm^{-1}; NMR ($CDCl_3$) δ 0.97–1.57 (m, 6 H), 2.05 (2 × s, 3 H, singlet in Me_2SO-d_6), 3.07–3.81 (m, 4 H), 7.26–7.93 (m, 8 H); MS, m/e 323 (M^+). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

Preparation of 3,4-Dihydroisocoumarins 13. General Procedure. The appropriate allyl benzamide **10** was refluxed in 6 N aqueous HCl for 20–90 h. Aqueous saturated NH_4Cl solution was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, dried (Na_2SO_4), and evaporated to dryness to give crude product, which was purified

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Table III. Physical and Spectral Properties of 2-Allylbenzamides 10, Phthalides 7, and Isocoumarins 13

compd[a]	mp (bp), °C	IR, ν_{max}, cm^{-1}	NMR ($CDCl_3$), δ (J, Hz)	MS, m/e (M^+)
10a	90-94/0.1 mm	1620	1.05, 1.26 (2 × t, 6 H, J = 7), 3.15 (q, 2 H, J = 7), 3.35 (m, 2 H, CH_2CH=), 3.35-3.38 (br, 2 H), 4.9-5.25 (m, 2 H, CH=CH_2), 5.7-6.2 (m, 1 H, CH=CH_2), 7.1-7.3 (m, 4 H)	217
10b	110-114/0.35 mm	1620	1.02, 1.28 (2 × t, 6 H, J = 7), 3.12, 3.48 (2 × q, 4 H, J = 7), 3.32 (br, 2 H, CH_2CH=), 3.78 (s, 3 H), 4.92-5.25 (m, 2 H, CH=CH_2), 5.7-6.2 (m, 1 H, CH=CH_2), 6.80 (m, 2 H), 7.25 (m, 1 H)	248
10c	115-118/0.2 mm	1620	1.02, 1.28 (2 × t, 6 H, J = 7), 3.09, 3.38 (2 × q, 4 H, J = 7), 3.35 (br d, 2 H, CH_2CH=), 3.83 (s, 3 H), 4.85-5.10 (m, 2 H, CH=CH_2), 5.77-5.89 (m, 1 H, CH=CH_2), 6.71-6.90 (m, 2 H), 7.11-7.30 (m, 1 H)	247
10d	128-129/0.25 mm	1620	1.02, 1.28 (2 × t, 6 H, J = 7), 3.10, 3.38 (2 × q, 4 H, J = 7), 3.32 (m, 2 H, CH_2CH=), 3.72, 3.78 (2 × s, 6 H), 4.87-5.1 (m, 2 H, CH=CH_2), 5.7-6.1 (m, 1 H, CH=CH_2), 6.68 (d, 1 H, J = 9), 6.81 (d, 1 H, J = 9)	277
10e	110-112/0.07 mm	1620	1.05, 1.25 (2 × t, 6 H, J = 7), 3.15, 3.58 (2 × q, 4 H, J = 7), 3.30 (br, 2 H, CH_2CH=) 3.85 (s, 6 H), 3.88 (s, 3 H), 4.98-5.20 (m, 2 H, CH=CH_2), 5.70-6.20 (m, 1 H, CH=CH_2), 6.53 (s, 1 H)	307
15	118-120/0.1 mm	1620	2.81 (s, 3 H), 3.11 (s, 3 H), 3.18 (d, 2 H, CH_2CH=), 3.86 (s, 3 H), 3.89 (s, 3 H), 5.1 (m, 2 H, CH=CH_2), 5.8 (m, 1 H, CH=CH_2), 6.54 (s, 1 H)	279
7a	oil	1750	b	176
7b	60-65/0.03 mm	1750	b	148
7c	97-101/0.01 mm	1750	0.96 (t, 3 H, J = 6.5), 1.24-2.02 (m, 4 H), 3.99 (s, 3 H), 5.39 (m, 1 H), 6.95 (d, 1 H, J = 8.4), 6.99 (d, 1 H, J = 7.6), 7.63 (dd, 1 H, J = 7.6, 8.4)	206
7d	76-77 (CH_2Cl_2-hexane)	1750	0.95 (t, 3 H, J = 7), 1.2-2.2 (m, 4 H), 3.92 (s, 3 H), 5.5 (m, 1 H), 7.1-7.45 (m, 3 H)	206
7e	128 (Et_2O-hexane)	1750	0.95 (t, 3 H, J = 7), 1.2-2.2 (m, 4 H), 3.84, 3.92 (2 × s, 6 H), 5.42 (m, 1 H), 6.83 (d, 1 H, J = 8.8), 7.05 (d, 1 H, J = 8.8)	236
7f	83-84 (EtOAc-Et_2O)	1765	6.52 (s, 1 H), 7.18-7.99 (m, 7 H), 8.64 (m, 1 H)	211
13a	oil	1720	b	162
13b	38 (CH_2Cl_2-hexane)	3200, 1675	1.52 (d, 3 H, J = 6.2), 2.92 (d, 2 H, J = 7), 4.68 (m, 1 H), 6.68 (d, C_5- or C_7-H, J = 8.2), 6.84 (d, C_5- or C_7-H, J = 8.2), 7.40 (dd, C_6-H, J = 8.2), 11.02 (s, 1 H, OH)	178
13c	83-84[b] (Et_2O-hexane)	1720	1.52 (d, 3 H, J = 6.2), 2.62 (dd, 1 H, J = 17, 11), 3.17 (dd, 1 H, J = 17, 3.5), 3.88 (s, 3 H), 4.49-4.76 (m, 1 H), 7.00-7.43 (m, 2 H), 7.66-7.77 (m, 1 H)	192
13d	173-174[b] (EtOAc-Et_2O)	3200, 1715	1.47 (d, 3 H, J = 6.2), 2.62 (dd, 1 H, J = 17, 11), 3.19 (dd, 1 H, J = 17, 3.5), 4.55-4.63 (m, 1 H), 7.08-7.47 (m, 2 H), 7.50-7.59 (m, 1 H), 8.8 (br, 1 H, OH)	178
13e	141-142 (CH_2Cl_2-hexane)	b	b	
12	75-80/0.02 mm	1620	0.88-1.25 (m, 6 H), 1.45 (d, 3 H, J = 5.8), 2.61-3.12 (m, 2 H), 3.24-3.48 (m, 4 H), 4.79-5.08 (m, 1 H), 6.68-7.39 (m, 3 H)	233

[a] All new compounds show satisfactory analytical data (±0.3%). [b] Spectral data identical with those reported in the literature: 7a, Durrani, A. A.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2069; 7b, lit. bp 101 °C/0.9 mm (Jones, P. R.; Jarboe, C. J. *Tetrahedron Lett.* **1969**, 1849); 13a, see ref 20; 13c, lit. mp 83 °C; 13d, lit. mp 176-177 °C (Bhide, B. H.; Brahmbhatt, D. I.; Shah, K. K. *Indian J. Chem.* **1981**, *20B*, 831); 13e, see ref 30.

by column chromatography.

3-Methyl-3,4-dihydroisocoumarin-1-one (13a). *N,N*-Diethyl-2-allylbenzamide (**10a**) (462 mg, 2.13 mmol) was refluxed in 6 N aqueous HCl (30 mL) for 20 h. Workup and chromatography as above gave 321 mg (93%) of compound **13a** as an oil, IR and NMR identical by comparison with those reported in the literature for authentic material.[20]

8-Hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Mellein) (13b). *N,N*-Diethyl-2-allyl-6-methoxybenzamide (**10b**) (350 mg, 1.42 mmol) was refluxed in 6 N aqueous HCl (30 mL) for 4 days. Standard workup and chromatography afforded 181 mg (75%) of mellein (**13b**), mp 38 °C (lit.[11a] mp 38–38.5 °C).

3-Methyl-5-methoxy-3,4-dihydroisocoumarin-1-one (13c), 3-Methyl-5-hydroxy-3,4-dihydroisocoumarin-1-one (13d), and 4-(Diethylcarbamoyl)-2-methyl-2,3-dihydrobenzo[*b*]furan (12). *N,N*-Diethyl-2-allyl-3-methoxybenzamide (**10c**) was refluxed in 6 N aqueous HCl (25 mL) for 18 h. Standard workup followed by column chromatography afforded 210 mg (49%) of **13c**, 72 mg (16%) of **13d**, and 60 mg (13%) of **12**. Anal. ($C_{11}H_{19}NO_2$) C, H, N.

6,7-Dimethoxy-8-hydroxy-3-methyl-3,4-dihydroisocoumarin-1-one (Kigelin) (13e). A solution of the dimethyl-

benzamide **15** (115 mg, 0.39 mmol) in 6 N aqueous HCl (15 mL) was stirred under nitrogen at 80 °C for 24 h. Standard workup followed by preparative TLC (EtOAc–hexane, 3:1) afforded 25 mg (27%) of product. Recrystallization (CH_2Cl_2–hexane) gave a sample of kigelin (**13e**), mp 141–142 °C (lit.[30] mp 142–143 °C), whose IR and NMR spectral data were identical with those reported in the literature.[30]

Reactions of Ortho-Metalated 2-Phenyl-4,4-dimethyloxazoline (1b) and (Methoxymethoxy)benzene (1c) with *n*-Butyraldehyde. 2-[2-(1-Hydroxybutyl)phenyl]-4,4-dimethyloxazoline (16). To a stirred THF solution (50 mL) of 2-phenyl-4,4-dimethyloxazoline (**1b**) (500 mg, 2.85 mmol) at −78 °C under nitrogen was added *sec*-BuLi (3.5 mL, 0.98 M in hexane, 3.38 mmol). After 2.75 h, the reaction mixture was allowed to warm to 0 °C and quenched with freshly distilled *n*-butyraldehyde (411 mg, 5.7 mmol). The resulting solution was allowed to warm to room temperature overnight. Standard workup gave 648 mg of crude product, which upon column chromatography afforded 467 mg (65%) of compound **16**: bp 78–82 °C (0.01 mm); IR ($CHCl_3$) ν_{max} 3300, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6.6), 1.39 (s, 6 H), 1.50–2.20 (m, 4 H), 4.11 (s, 2 H), 4.69 (m, 1 H), 7.20–7.39 (m, 3 H), 7.70–7.90 (m, 1 H); MS, m/e 247 (M^+). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

Compound **16** was also prepared in 68% yield by the general transmetalation procedure except that the lithiation was effected in 3 h.

3-(1-Hydroxybutyl)-4-(methoxymethoxy)anisole (17). To a stirred ether solution (50 mL) of 4-(methoxymethoxy)benzene (500 mg, 2.97 mmol) at 0 °C under nitrogen was added *t*-BuLi (1.78 mL, 2 M in hexane, 3.26 mmol) by syringe injection. After 2.5 h, *n*-butyraldehyde (429 mg, 5.95 mmol) was added and the resulting solution was allowed to warm to room temperature overnight. Standard workup followed by column chromatography gave 272 mg (38%) of compound **17**, bp 82–86 °C (0.01 mm); IR ($CHCl_3$) 3400 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6.6), 1.20–1.90 (m, 4 H), 2.58 (br, 1 H, OH), 3.47 (s, 3 H), 3.75 (s, 3 H), 4.93 (m, 1 H), 5.12 (s, 2 H), 6.63–7.10 (m, 3 H); MS m/e 240 (M^+). Anal. ($C_{12}H_{18}O_3$) C, H.

Compound **17** was also prepared in 66% yield by the general transmetalation method.

Acknowledgment. A sample of triply sublimed magnesium was graciously provided, via the kind offices of Prof. A. I. Meyers (Colorado State University) and Dr. J. Little (Dow Chemical Co.), by Dr. J. Robinson (Dow Chemical Co., Midland, MI) 3 days before his retirement. We are grateful to the Natural Sciences and Engineering Research Council of Canada for sustained financial support of our research. A grant from the J. P. Bickell Foundation, crucial to the operation of our GC and HPLC equipment is gratefully acknowledged.

Registry No. **1a**, 1696-17-9; **1b**, 19312-06-2; **5**, 88440-77-1; **6**, 76041-86-6; **7a**, 72424-08-9; **7b**, 3453-64-3; **7c**, 88440-78-2; **7d**, 88440-79-3; **7e**, 88440-80-6; **7f**, 88440-81-7; **8b**, 51674-10-3; **8c**, 62924-93-0; **8d**, 72003-93-1; **8e**, 88440-82-8; **10a**, 88440-83-9; **10b**, 88440-84-0; **10c**, 88440-85-1; **10d**, 88440-86-2; **10e**, 88440-87-3; **11**, 3034-28-4; **12**, 88440-88-4; **13a**, 66122-70-1; **13b**, 17397-85-2; **13c**, 88440-89-5; **13d**, 87513-52-8; **13e**, 33883-14-6; **14**, 88440-90-8; **15**, 88440-91-9; **16**, 88440-92-0; **17**, 88440-93-1; 4-(methoxymethoxy)anisole, 25458-46-2; allyl bromide, 106-95-6; butyraldehyde, 123-72-8; acetaldehyde, 75-07-0; picolinaldehyde, 1121-60-4.

Supplementary Material Available: Table of combustion analyses for compounds **5**, **7c–f**, **8e**, **10a–e**, **12**, **16**, and **17** (1 page). Ordering information is given on any current masthead page.

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Ortho-Lithiated Tertiary Benzamides. Chain Extension via *o*-Toluamide Anion and General Synthesis of Isocoumarins Including Hydrangenol and Phyllodulcin

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Received June 15, 1983

Lithiation of *N,N*-diethyl-2-methylbenzamide (**2a**) followed by condensation with aromatic aldehydes and basic hydrolysis leads to 3-aryl-3,4-dihydroisocoumarins **4** in modest overall yields. Adoption of this methodology to *N,N*-dimethyl-2-methyl-6-methoxybenzamide (**7b**) provides isocoumarins **9a** and **9b**, which by selective demethylation procedures yields hydrangenol (**10a**) and phyllodulcin (**10c**), naturally occurring isocoumarins of pharmacological interest. A one-pot, abbreviated procedure for the preparation of both **9a** and **9b** starting with *N,N*-dimethyl-2-methoxybenzamide (**6c**) is also described.

The regiospecific introduction of C_1 units at various oxidation states by the aromatic directed metalation protocol[2] allows subsequent chain extension and ring annelation to give systems that are not easily accessible by classical methodology. The strongly acidifying effect of certain Z groups promotes facile deprotonation of an *o*-methyl group to form benzylic anions that can undergo reaction with electrophiles in an overall chain extension process (Scheme I). Such processes have been demonstrated for a number of directed metalation groups,[2-4] but

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