Heteroatom-Directed Metalation. Lithiation of *N*-Propenylbenzamides and *N*-Propenyl-*o*-toluamides. Novel Routes to Ortho-Substituted Primary Benzamide Derivatives and N-Unsubstituted Isoquinolin-1(2*H*)-ones[1]

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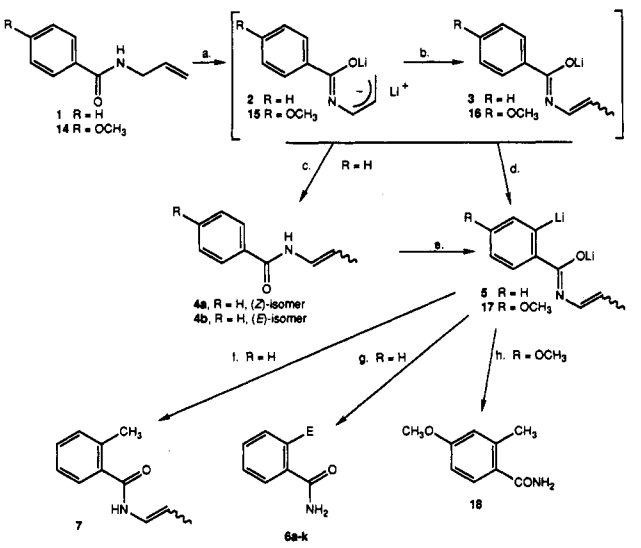
Reaction of *N*-propenylbenzamides **4** and **9**, obtained by LDA-induced isomerization of the corresponding *N*-allylbenzamides **1**, **8**, and **14**, with 2 equiv of *sec*-butyllithium or *tert*-butyllithium at low temperature regiospecifically generates the highly reactive N,ortho-dilithiated species (e.g., **5** and **17**). These dilithio species react avidly with a wide spectrum of electrophilic reagents, including alkyl halides, giving adducts which on hydrolysis with warm 50% aqueous acetic acid are converted into ortho-substituted primary benzamides in excellent yields. Ortho-lithiation of *N*-propenylbenzamides is thus formally equivalent to ortho-lithiation of primary benzamides themselves. The utility of this important, previously unknown, synthetic operation is enhanced by the well-known facility with which the primary amide moiety can be transformed into other useful functional groups, as exemplified by the synthesis of 2-methoxy-6-methylbenzoic acid (**12**) and 2-methoxy-6-methylbenzonitrile (**13**) from *N*-propenyl-2-methoxybenzamide (**9**). *N*-Propenyl-*o*-toluamide (**7**) undergoes regiospecific dilithiation on nitrogen and on the methyl group under conditions analogous to those used for the *N*-propenylbenzamides. These dilithio species react with DMF or "Weinreb type" amides to give condensation products which cyclize to *N*-propenylisoquinolin-1(2*H*)-ones under mildly acidic conditions. Removal of the *N*-propenyl moiety under more strongly acidic conditions provides N-unsubstituted isoquinolin-1(2*H*)-ones with high overall efficiency. This process is exemplified by the synthesis of isoquinolin-1(2*H*)-one (**23**) and its 3-*n*-butyl congener **26** from *N*-propenyl-2-methylbenzamide (**7**).

Introduction

The development of methods for the site-selective functionalization of aromatic systems continues to be an area of considerable interest in synthetic organic chemistry. One important tool for the predictable, direct transformation of an aryl compound into its ortho-substituted congener is the heteroatom-directed metalation reaction.[2] Of the many functional groups known to direct metalation to the ortho position, *N*,*N*-dialkylbenzamides[2d] have been studied the most extensively and have found widespread use.[3] The major problems associated with the use of these ortho-directing groups are their great resistance to hydrolysis[2d,4a,b] and the paucity of methods for their transformation to other useful functionality.[4c] Comins and Brown[4a] and Reitz and Massey[4b] have addressed the hydrolysis problem by developing *tert*-amide ortho-lithiation directing groups which are readily converted into secondary amides, the facile cleavage of which, via the *N*-nitrosoamide, has long been known.[4d] Snieckus et al.[4c] have shown that *N*-methyl-*N*-[bis(trimethylsilyl)methyl]benzamides and their monotrimethylsilyl analogues are ortho-lithiated and that the derived ortho-substituted products can be transformed, in two steps, into the corresponding benzyl alcohols or benzaldehydes.[4e] In this paper it is shown that *N*-propenylbenzamides undergo very facile and regiospecific ortho-lithiation, that the dilithio species so generated are highly reactive, and that the products obtained after reaction with electrophilic reagents are converted into primary benzamides under very mild conditions. These results, and the ease with which benzamides can be transformed into the corresponding benzoic acids,[5] benzonitriles,[6] etc., underscore the synthetic utility

Scheme I[a]



[a] (a) 2.2 equiv of LDA, −70 °C, THF; (b) 0 °C; (c) excess NH_4Cl, isolation; (d) 1.1 equiv of CH_3OH (−70 °C), then 1.1 equiv of *sec*-BuLi, −70 °C, no intermediate isolation; (e) 2.2 *sec*-BuLi, −70 °C, THF; (f) CH_3I (−70 °C), then excess NH_4Cl; (g) E^+ (−70 °C), HOAc, 50 °C, 30–60 min; (h) CH_3I(−70 °C), HOAc, 50 °C, 60 min.

(1) Contribution No. 816 from the Institute of Organic Chemistry.

(2) For reviews, see the following. (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, 1–360. (b) Omae, I. *Chem. Rev.* **1979**, *79*, 287. (c) Snieckus, V. *Heterocycles* **1980**, *14*, 1649. (d) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (e) Snieckus, V. *Lect. Hetercycl. Chem.* **1984**, 95. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 6, 879. (g) For selected examples: Fu, J. M.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459. Siddiqiu, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4799. Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. Narashimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. Fuhrer, W.; Gschwend, *J. Org. Chem.* **1979**, *44*, 1133.

(3) (a) Clark, R. D.; Jahangir. *J. Org. Chem.* **1987**, *52*, 5378. (b) Clark, R. D.; Jahangir. *Heterocycles* **1988**, *27*, 871. (c) Clark, R. D.; Jahangir. *J. Org. Chem.* **1988**, *53*, 2378. Jahangir; Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1989**, *54*, 2992. (d) Clark, R. D.; Repke, D. B.; Berger, J.; Nelson, J. T.; Kilpatrick, A. T.; Brown, C. M.; MacKinnon, A. C.; Clague, R. U.; Spedding, M. *J. Med. Chem.* **1990**, *34*, 707.

(4) (a) Comins, D. L.; Brown, *J. Org. Chem.* **1986**, *51*, 3566. (b) Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375. (c) Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841. (d) White, E. H. *J. Am. Chem. Soc.* **1955**, *72*, 6008, 6011. (e) For other transformations, see: Bashir-Hashemi, A.; Ammon, H. L.; Choi, C. S. *J. Org. Chem.* **1990**, *55*, 416. Bottaro, J. C.; Penwell, P. E.; Schmitt, R. J. *J. Org. Chem.* **1991**, *56*, 1305.

(5) Wade, L. G., Jr.; Silvey, W. B. *Org. Prep. Proc. Int.* **1982**, *14*, 357.

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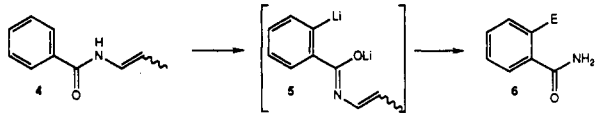
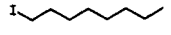
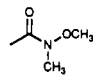
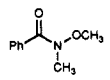
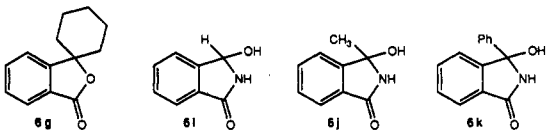
Table I



entry	electrophile	E	yield[a] of 6, %	mp, °C	(lit. mp, °C)
a	CH_3I	CH_3	91	141–142	(141–142[6])
b	CH_3SSCH_3	SCH_3	90	209–211	(210–212[7])
c	PhSSPh	SPh	89	179–181	(178[8])
d	CO_2	CO_2H	79[b]	(oil)	
e			95	110–113	
f		$(CH_2)_7CH_3$	78	91–93	
g		*c*	71[c]	76–78	(78–79[9])
h	PhNCO	CONHPh	89	217–218	(219[10])
i	DMF	-CHO	92[d]	111–113	(67–70[11])
j			94[d]	137–139	(139–140[12])
k			89[d]	166–167	(165–167[13])

[a] Purified yields. [b] After treatment with diazomethane, dimethyl phthalate was obtained. [c] Yield of lactone. See structure **6g**. [d] Yield of cyclic hemiamidals. See structures **6i–k** below.



of *N*-propenylbenzamides as ortho-metalation directing groups.

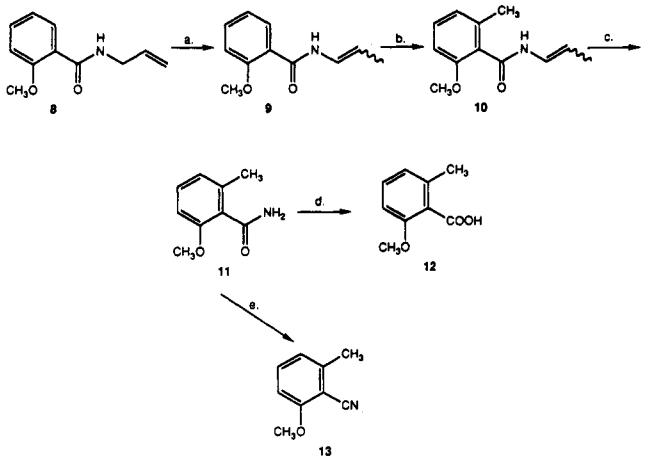
Results and Discussion

Tischler and Tischler[7] reported that reaction of *N*-allylbenzamide (**1**, Scheme I) with 2 equiv of lithium diisopropylamide (LDA), at −78 °C in diglyme, gave a deeply colored dianion **2**, which on warming to 0 °C underwent irreversible protonation at the γ-position by diisopropylamine to give the monoanion **3**, aqueous hydrolysis of which produced the (*Z*)-*N*-propenylbenzamide **4a**. It was of interest to determine if lithiation of **4a** would regenerate the dianion **2** or produce the ortho-lithiated species **5**. Repetition of the experiment of Tischler and Tischler, but with THF as the solvent, gave a 1:1 mixture of (*Z*)- and (*E*)-propenylbenzamides **4a** and **4b**. Reaction of a THF solution of this mixture with 2.2 equiv of *sec*-butyllithium at −70 °C rapidly gave a purple-red solution, the color of which was discharged instantly upon addition of 1 equiv of methyl iodide. Hydrolysis of the reaction mixture with warm 50% aqueous acetic acid gave 2-methylbenzamide (**6a**, E = Me) in >90% yield. On the other hand, quenching the reaction with aqueous ammonium chloride gave a high yield of a 1:1 mixture of the (*Z*)- and (*E*)-*N*-propenyl-2-methyltoluamides **7** which could be separated by repeated column chromatography. It is noteworthy that no products could be detected which would have resulted from methylation on the allyl terminus or on the nitrogen atom. Thus, lithiation of **4** generated the dianion **5** regiospecifically in virtually quantitative yield. Substituted congeners of **4**, i.e., 3- or 4-methoxy or 3- or 4-fluoro-*N*-propenylbenzamides, display the same regiospecificity as **4**.[21]

The dianion **5** also reacted rapidly at −70 °C with other electrophilic reagents which included alkyl bromides and iodides, dialkyl disulfides, carbon dioxide, dimethylformamide, cyclohexanone, phenyl isocyanate, and Weinreb amides.[8] Hydrolysis of these reaction mixtures with aqueous acetic acid provided the products shown in Table I in good to excellent yields. Several aspects of the data in this table require emphasis. Firstly, 2-*n*-octylbenzamide (**6f**) was formed directly from *n*-octyl iodide and the dianion **5** without the need for tempering the basicity thereof by conversion to the Grignard reagent. This result suggests that **5** possesses lower basicity and/or greater nucleophilicity than the monoanion of *N*,*N*-dialkylbenzamides which primarily give rise to elimination products with less reactive alkyl halides.[9] Secondly, phthalic acid (**6d**) (isolated as the dimethyl ester) and the spiro lactone **6g** were obtained from **5** with carbon dioxide and cyclohexanone, respectively, and subsequent aqueous acetic acid hydrolysis. The formation of **6g**, in particular, under such mild hydrolytic conditions is especially impressive in view of the reported requirement of boiling 3 M hydrochloric acid when this compound is derived from the dianion of *N*-methylbenzamide.[10] Lastly, the products isolated from the reaction of **8** with DMF or Weinreb amides exist in the

(6) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, *18*, 1813.
(7) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, *19*, 3407.
(8) Nahm, S.; Weinreb, M. S. *Tetrahedron Lett.* **1981**, *22*, 3815.
(9) Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, 95.
(10) Bailey, D. M.; DeGrazia, G. *J. Org. Chem.* **1970**, *35*, 4093.
(11) Neunteufel, R. A. Ger. Offen. DE 2806562, 1979.
(12) Sotomatsu, T.; Fujita, T. *J. Org. Chem.* **1989**, *54*, 4443.
(13) Chhaya, P. N.; Nimbalkar, M. M.; Hosangadi, B. D. *J. Org. Chem.* **1986**, *51*, 4458.
(14) Cannone, P.; Belanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091.
(15) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem.-Chim. Ther.* **1981**, *16*, 373.
(16) Armarego, G. *J. Chem. Soc.* **1962**, 4094.
(17) Mueller, H. R.; Seefelder, M. *Ann. Chem.* **1969**, *728*, 88.
(18) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem.-Chim. Ther.* **1981**, *16*, 373.

Scheme II[a]



[a] (a) 2.2 equiv of LDA, −70 °C, THF; (b) 2.2 equiv of *t*-BuLi, −100 °C, then −40 °C, 1.1 equiv of CH_3I, excess NH_4Cl, isolation; (c) HOAc, 50 °C, 30–60 min; (d) HO_3SONO, H_2O, CH_2Cl_2, rt; (e) TFAA, pyridine, CH_2Cl_2, rt.

cyclic amido form (i.e., **6i–k**) as indicated by their spectroscopic properties.

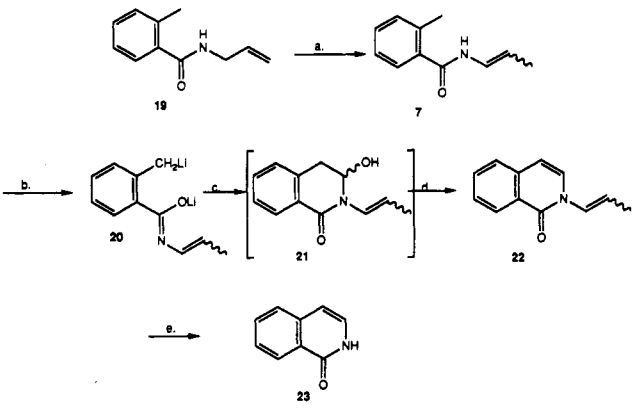
A more stringent test of the utility of the methodology described herein was considered to be the synthesis of 1,2,3-trisubstituted benzenoid derivatives. In this regard, lithiation of *N*-propenyl-2-methoxybenzamide (**9**, Scheme II) under the usual conditions followed by reaction with methyl iodide gave a complex mixture of products.[19a] If, however, the metalation was carried out with *tert*-butyllithium at −100 °C, the expected product **10** was obtained exclusively and hydrolysis thereof gave the benzamide **11** in excellent yield.[19b] Reaction of **11** with nitrosylsulfuric acid at room temperature in a dichloromethane–water biphasic system[5] produced 2-methoxy-6-methylbenzoic acid (**12**) in 79% overall yield from 2-methoxybenzoyl chloride. The efficacy of this process compares very favorably with others which have been used to prepare this compound (see ref 4a and references therein). In addition, **11** could also be dehydrated to 2-methoxy-6-methylbenzonitrile (**13**) with the trifluoroacetic anhydride–pyridine system[6] at 0 °C (91% yield).

To test the possibility that the isolation of the intermediate *N*-propenylbenzamide is not necessary, 4-methoxy-*N*-allylbenzamide (**14**, Scheme I) was dilithiated with 2 equiv of *n*-butyllithium and the dianion **15** was protonated with 1 equiv of methanol at −70 °C. Sequential reaction of the presumed monoanion **16** with 1 equiv of *sec*-butyllithium, 1 equiv of methyl iodide, and excess 50% aqueous acetic acid gave 2-methyl-4-methoxybenzamide (**18**) in 78% overall yield from 4-methoxybenzoyl chloride. Thus the isolation of the *N*-propenylbenzamides in this process is unnecessary.

Mali et al.[20] have shown that reaction of the dilithio species derived from *N*-methyl-2-methylbenzamide with DMF, or other *N,N*-dimethyl amides, followed by acidic workup gave 2-methylisoquinolin-1(2*H*)-one or the 3-substituted derivatives thereof. Utilization of an analogous process with *N*-propenyl-2-methylbenzamide would be expected to lead to the corresponding N-unsubstituted compounds provided that the *N*-propenyl moiety could be hydrolytically removed. This indeed is the case. Thus, *N*-allyl-2-methylbenzamide (**19**, Scheme III) was isomerized to *N*-propenyl compounds **7** with LDA, in exactly the same manner as described for *N*-allylbenzamide (**1**). Sequential reaction of **7** with 2 equiv of *sec*-butyllithium at −70 °C, 1 equiv of DMF, and excess 1 M hydrochloric acid gave 2-propenylisoquinolin-1(2*H*)-one (**22**) directly (presumably via the amidol **21**) as a mixture of (*E*) and (*Z*) isomers. Removal of the propenyl group was accomplished, essentially quantitatively, by briefly heating **22** with 5% aqueous trifluoroacetic acid at reflux temperature. 2*H*-Isoquinolin-1-one (**23**) was obtained in 92% yield on the basis of 2-methylbenzoyl chloride! When *N*-methoxy-*N*-methylvaleramide instead of DMF was employed in the above sequence and cyclization was effected with warm 50% acetic acid, 2-propenyl-3-*n*-butylisoquinolin-1(2*H*)-one (**25**, Scheme IV) was formed in high yield, via the ketone **24** (identified spectroscopically). In this case, removal of the *N*-propenyl group was more difficult, but hydrolysis could be effected by heating **25** with 3 M hydrochloric acid in 50% aqueous dioxane for 6 h at reflux temperature. The N-unsubstituted isoquinolone derivative **26** was isolated in 92% yield.

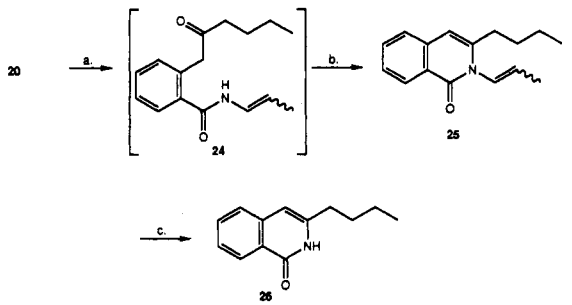
Because of the high efficiency of the above operations, it was of interest to determine if a isoquinolin-1(2*H*)-one derivative could be synthesised without isolation of any of the intermediates. It could indeed. The entire sequence of reactions from *N*-allylbenzamide (**1**) to 2-propenyl-3-*n*-butylisoquinolin-1(2*H*)-one (**25**) could be carried out in

Scheme III[a]



[a] (a) 2.2 equiv of LDA, −70 °C to 0 °C, THF; (b) 2.2 equiv of *sec*-BuLi, −70 °C, THF; (c) excess DMF; (d) excess 1 M HCl; (e) 5% TFA, H_2O, THF, reflux 15 min.

Scheme IV[a]



[a] (a) *N*-Methoxy-*N*-methylvaleramide; (b) HOAc, 50 °C, 60 min; (c) 3 M HCl in 50% aqueous dioxane, reflux 6 h.

(19) (a) Similar results were obtained in the attempted ortho-metalation of 2-methoxy-N-methylbenzamide with 2 equiv of *n*-BuLi. See: Narashimhan, N. S.; Bhide, B. H. *Tetrahedron* 1971, *27*, 6171. (b) It is not apparent why this change in reactivity is seen, nor why employing *tert*-butyllithium at a lower temperature (−100 °C) deprotonates **9** in the expected manner.

(20) (a) Mali, R. S.; Kulkarni, B. K.; Shankaran, R. *Synthesis* 1982, 329. (b) Meese, C. O.; Ebner, T. *J. Labelled Compd. Radiopharm.* 1988, *25*, 335. *N*-Methylisocarbostyril has been synthesized by a similar route via deprotonation of *o*-*N*-methyltoluamide with *n*-BuLi and quench with DMF.

one pot in 42% overall yield!

The above isoquinolin-1(2*H*)-one synthesis is very versatile and has been applied to the preparation of a wide variety of derivatives bearing substitutents in the benzenoid nucleus as well as at C-3.[21] It is both more efficient and flexibile than the traditional syntheses of these compounds commencing with the corresponding isoquinolines[22] and compares very favorably with those synthetic routes involving benzenoid precursors.[23]

Conclusion

N-Propenylbenzamides undergo highly efficient and regiospecific lithiation at the ortho position under very mild conditions.[24] These lithiated species have excellent nucleophilicity and can be trapped with a broad spectrum of electrophilic reagents including long chain alkyl iodides (cf. monoanions of tertiary benzamides[9]). The *N*-propenyl moiety in these compounds is not just another N-substituent because it is hydrolytically removed with great ease to give the corresponding primary benzamides. Thus ortho-lithiation of *N*-propenylbenzamides is functionally equivalent to the ortho-lithiation of primary benzamides, an operation which has not previously been accomplished, even in the formal sense.[2a,f] In addition, the notable facility with which primary benzamides can be converted into the corresponding benzoic acids, benzonitriles, etc., makes the synthetic significance of *N*-propenylbenzamides as ortho-metalation directing groups even greater.

N-Propenyl-*o*-toluamides undergo lithiation on the methyl group with a facility which matches the ortho-lithiation of the corresponding benzamides. These dilithio species are trapped with DMF or Weinreb-type amides and the condensation products obtained thereby, upon cyclization and removal of the *N*-propenyl moiety under acidic conditions, give rise to isoquinolin-1(2*H*)-ones. This process has broader applicability, greater flexibility, and is more efficient than previously reported routes to these compounds.

In conclusion, the use of *N*-propenylbenzamides as ortho-metalation directing groups has several notable advantages over that of the corresponding secondary or tertiary benzamides. The synthetic potential thereof would appear to match if not exceed that of tertiary benzamides as ortho-lithiation directing groups.

Experimental Section

Proton magnetic resonance spectra were recorded at 300 or 500 MHz and are reported in ppm (δ) downfield from an internal standard of tetramethylsilane. The infrared spectra were measured neat as liquid films or as solid dispersions in KBr. Melting points are uncorrected. Elemental analyses were obtained from the Syntex analytical department.[28]

***N*-Allylbenzamide (1).** To a cold (0 °C) solution of 70.25 g (0.5 mol) of benzoyl chloride in 700 mL of CH_2Cl_2 was added a mixture of 77.3 mL (0.55 mol) of triethylamine and 41.3 mL (0.55 mol) of allylamine at such a rate that the reaction temperature did not exceed 5 °C. After addition was complete, the reaction mixture was allowed to warm to ambient temperature and treated with 500 mL of 1 M HCl. The organic layer was separated, dried with Na_2SO_4, and filtered, and the solvent was removed in vacuo to give an oil which solidified upon standing to give analytically pure **1** (76.5 g, 95%): mp 120–123 °C (hexane–EtOAc); IR (KBr) 3400, 3200, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (dd, J = 8.31, 1.68 Hz, 1 H), 7.39 (dt, J = 7.61, 1.56 Hz, 1 H), 7.25 (m, 2 H), 6.21 (b, 1 H), 5.95 (m, 1 H), 5.25 (d, J = 8.22 Hz, 1 H), 5.17 (d, J = 11.34, 1 H), 4.09 (d, J = 5.96 Hz, 2 H); MS m/e (rel intensity) 161 (10), 146 (99), 117 (18), 115 (39). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.46; H, 6.65; N, 8.54.

***N*-Propenylbenzamide (4a,b).** To a solution of 23 mL (164 mmol) of diisopropylamine in 400 mL of THF maintained at −20 °C was added 65.6 mL (164 mmol) of 2.5 M *n*-BuLi in hexanes. This mixture was cooled to −70 °C and a solution of 12.0 g of (75 mmol) *N*-allylbenzamide (**1**) in 125 mL of THF was added dropwise. The dark red solution was stirred at this temperature for 10 min and then allowed to warm to 0 °C, whereupon the color largely disappeared. The mixture was treated with an excess of saturated aqueous NH_4Cl, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave liquid **4** (3.89 g, 91%) as a 1:1 mixture of *Z* (**4a**) and *E* (**4b**) isomers: IR (neat) 3420, 3400, 2800, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.12 (bs, 1 H), 8.27 (dd, J = 7.73, 1.92 Hz, 0.5 H), 7.45 (m, 5 H), 7.12 (m, 2 H), 5.44 (m, 0.5 H), 4.87 (dd, J = 10.34, 1.75 Hz, 0.5 H), 1.73 (dd, J = 6.81, 1.75 Hz, 1.5 H), 1.65 (dd, J = 6.72, 1.60 Hz, 1.5 H); MS m/e (rel intensity) 161 (73), 146 (16), 105 (100). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.87; H, 6.92; N, 8.78.

***o*-Methylbenzamide (6a).** A solution of 0.5 g (3.1 mmol) of *N*-propenylbenzamide in 20 mL of THF was cooled to −70 °C. To this was added 5.3 mL (6.8 mmol) of 1.3 M *sec*-butyllithium in cyclohexane at such a rate so as to maintain the reaction mixture below −65 °C, and the resulting purple-red solution was stirred for 10 min at this temperature. To this solution was added iodomethane (440 mg, 3.1 mmol) in 10 mL of THF. The color disappeared immediately. The mixture was warmed to 0 °C and 10 mL of 50% aqueous acetic acid was added. The reaction mixture was heated to 60 °C for 30 min, cooled, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave **6a** (480 mg, 96%) which was purified by crystallization (hexane/ethyl acetate) (purified yield 455 mg, 91%): mp 139–141 °C (lit.[25] mp 140 °C).

(*Z*)- or (*E*)-*N*-Propenyl-*o*-toluamide (7a or 7b). A solution of 0.5 g (3.1 mmol) of *N*-propenylbenzamide in 20 mL of THF was cooled to −70 °C. To this was added 5.3 mL (6.8 mmol) of 1.3 M *sec*-butyllithium in cyclohexane at such a rate so as to maintain the reaction mixture below −65 °C, and the resulting purple-red solution was stirred for 10 min at this temperature. To this solution was added iodomethane (440 mg, 3.1 mmol) in 10 mL of THF. The color disappeared immediately. The mixture was warmed to 0 °C and treated with excess saturated aqueous ammonium chloride. The mixture was diluted with diethyl ether and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave the products, which were purified by repetitive medium-pressure chromatography on silica gel (2:1 hexane/ethyl acetate). The (*Z*)- and (*E*)-*N*-propenyl-*o*-toluamides were isolated in 47%, (255 mg), *Z* isomer, and 45% (243 mg), *E* isomer, yield. Total yield 92% for the two isomers. **7a**: mp 192–195 °C (hexane–EtOAc); IR (KBr) 3350, 3200, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.34 (bs, 1 H), 7.47 (dd, J = 8.31, 1.68 Hz, 1 H), 7.39 (dd, J = 7.61, 1.56 Hz, 1 H), 7.25 (m, 2 H), 6.96 (dt, J = 8.31, 1.68 Hz, 1 H), 4.95 (dq, J = 7.85, 1.78 Hz, 1 H), 2.52 (s, 3 H), 1.69 (dd, J = 7.85, 1.78 Hz, 3 H); MS m/e

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(rel intensity) 175 (60), 119 (99), 91 (43). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.57; H, 7.09; N, 8.29. *E* isomer: more polar compound 45% (243 mg) **7b**; mp 189–192 °C (hexane–EtOAc); IR (KBr) 3400, 3200, 1630, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (dd, J = 8.71, 6.24 Hz, 2 H), 7.26 (m, 2 H), 6.95 (dt, J = 8.02, 1.60 Hz, 1 H), 5.24 (dt, J = 15.02, 6.72 Hz), 2.46 (s, 3 H), 1.73 (dd, J = 6.72, 1.60 Hz, 3 H); MS m/e (rel intensity) 175 (61), 119 (100), 91 (44). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.20; H, 7.54; N, 8.12.

Lithium Diisopropylamide Mediated Isomerization of *N*-Allyl-2-methylbenzamide (19) to *N*-Propenyl-2-methylbenzamide (7). To a solution of 3.2 mL (22.6 mmol) of diisopropylamine in 100 mL of THF maintained at −20 °C was added 9.0 mL (22.6 mmol) of 2.5 M *n*-BuLi in hexanes. This mixture was cooled to −70 °C and a solution of 1.79 g (10.3 mmol) of *N*-allyl-2-methylbenzamide (**19**) in 25 mL of THF was added dropwise. The dark red solution was stirred at this temperature for 10 min and then allowed to warm to 0 °C, whereupon the color largely disappeared. The mixture was treated with an excess of saturated aqueous NH_4Cl, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave **7** (1.65 g, 92%) as a 1:1 mixture of *E* and *Z* isomers which co-eluted with the previously separated isomers.

Typical Procedure for the Ortho-lithiation and Electrophilic Quench of *N*-Propenylbenzamide (4). Synthesis of 6b–k. A solution of 0.5 g (3.1 mmol) of *N*-propenylbenzamide in 20 mL of THF was cooled to −70 °C. To this was added 5.3 mL (6.8 mmol) of *sec*-butyllithium in cyclohexane at such a rate so as to maintain the reaction mixture below −65 °C, and the resulting purple-red solution was stirred for 10 min at this temperature. To this solution was added the appropriate electrophile (see the table) (3.1 mmol) in 10 mL of THF. The color disappeared immediately and the reaction was quenched at 0 °C with excess 50% aqueous acetic acid. The mixture was heated to 50 °C for 30 min, cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave the products, which were purified (when necessary) by medium-pressure chromatography on silica gel.

2-Allylbenzamide (6e): 92%; mp 110–113 °C (hexane–EtOAc); IR (KBr) 3400, 3200, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (dd, J = 8.31, 1.68 Hz, 1 H), 7.39 (dt, J = 7.61, 1.56 Hz, 1 H), 7.25 (m, 2 H), 6.05 (m, 1 H), 5.81 (b, 2 H), 5.11 (dm, J = 8.22 Hz, 1 H), 5.01 (dm, J = 11.34 Hz, 1 H), 3.63 (dm, J = 5.96 Hz, 2 H); MS m/e (rel intensity) 161 (10), 146 (99), 117 (18), 115 (39). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.31; H, 6.53; N, 8.43.

2-*n*-Oct-1-ylbenzamide (6f): 82%; mp 91–93 °C (hexane–EtOAc); IR (KBr) 3400, 3190, 3000, 2900, 1640, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (d, J = 8.42 Hz, 1 H), 7.35 (dd, J = 7.91, 1.61 Hz, 1 H), 7.22 (m, 2 H), 5.71 (b, 2 H), 2.81 (t, J = 7.82 Hz, 2 H), 1.61 (m, 2 H), 1.26 (m, 10 H), 0.86, (t, J = 6.40 Hz); MS m/e (rel intensity) 233 (60), 217 (5), 204 (3), 148 (99), 135 (60). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.93; N, 6.00. Found: C, 76.01; H, 9.88; N, 5.62.

***N*-Propenyl-*o*-methoxybenzamide (9).** To a solution of 3.23 mL (23 mmol) of diisopropylamine in 110 mL of THF maintained at −20 °C was added 9.21 mL (23 mmol) of 2.5 M *n*-BuLi in hexanes. This mixture was cooled to −70 °C and a solution of 4.0 g (20.9 mmol) of *o*-methoxy-*N*-allylbenzamide (**8**) in 25 mL of THF was added dropwise. The dark red solution was stirred at this temperature for 10 min and then allowed to warm to 0 °C, whereupon the color largely disappeared. The mixture was treated with an excess of saturated aqueous NH_4Cl, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave liquid **9** (3.89 g, 91%) as a 1:1 mixture of *E* and *Z* isomers: IR (neat) 3420, 3400, 2800, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.36 (bs, 1 H), 8.27 (dd, J = 7.73, 1.92 Hz, 0.5 H), 8.23 (dd, J = 7.95, 2.01 Hz, 1 H), 7.47 (dd, J = 7.03, 1.80 Hz, 0.5 H), 7.44 (dd, J = 7.23, 1.78 Hz, 0.5 H), 7.07 (dd, J = 7.54, 7.38 Hz, 1 H), 7.02 (m, 2 H), 5.37 (m, J = 14.85, 6.81 Hz, 0.5 H), 4.87 (J = 10.34, 1.75 Hz, 0.5 H), 4.02 (s, 1.5 H), 3.98 (s, 1.5 H), 1.73 (dd, J = 6.81, 1.75 Hz, 1.5 H), 1.65 (dd, J = 6.72, 1.60 Hz, 1.5 H); MS m/e (rel intensity) 191 (68), 176 (6), 135 (100). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.83; N, 7.10.

***N*-Propenyl-2-methoxy-6-methylbenzamide (10).** A solution of 800 mg (4.2 mmol) of *N*-propenyl-*o*-methoxybenzamide (**9**) in 20 mL of THF was cooled to −70 °C. To this was added 7.1 mL (9.2 mmol) of 1.3 M *tert*-butyllithium in pentane at such a rate so as to maintain the temperature of the reaction mixture below −95 °C. After stirring for 10 min at this temperature, the reaction mixture was allowed to warm to −70 °C. A solution of 650 mg (4.6 mmol) of iodomethane in 10 mL of THF was added dropwise so as to maintain the reaction temperature below −65 °C. When addition was complete, the mixture was allowed to warm to 0 °C, treated with an excess of saturated aqueous NH_4Cl, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave **10** (749 mg, 87%) as a 1:1 mixture of *E* and *Z* isomers: mp 95–102 °C; IR (KBr) 3400, 3150, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (dd, J = 8.02, 7.91 Hz, 1 H), 6.79 (dd, J = 8.30, 7.02 Hz, 1 H), 7.02 (m, 1 H), 5.37 (m, J = 14.85, 6.81 Hz, 0.5 H), 4.87 (J = 10.34, 1.75 Hz, 0.5 H), 4.02 (s, 1.5 H), 3.98 (s, 1.5 H), 1.73 (dd, J = 6.81, 1.75 Hz, 1.5 H), 1.65 (dd, J = 6.72, 1.60 Hz, 1.5 H); MS m/e (rel intensity) 205 (38), 190 (9), 149 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.05; N, 6.75.

2-Methoxy-6-methylbenzamide (11). To a solution of 25 mL of 50% aqueous acetic acid was added 0.5 g (2.4 mmol) of **10**. The suspension was heated to 60 °C, whereupon it became homogeneous. The mixture was cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave **11** (359 mg, 91%) as a solid which was purified by recrystallization from ethyl acetate (purified yield 339 mg, 86%): mp 114–116 °C; IR (KBr) 3400, 3150, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (dd, J = 8.02, 7.91 Hz, 1 H), 6.74 (dd, J = 8.30, 7.02 Hz, 1 H), 6.13 (bs, 1 H), 5.94 (bs, 1 H), 3.83 (s, 3 H), 2.39 (s, 3 H); MS m/e (rel intensity) 165 (83), 149 (64), 148 (100). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.85; H, 6.93; N, 8.11.

2-Methoxy-6-methylbenzoic Acid (12). A dichloromethane solution of 0.4 g (2.4 mmol) of **11** was subjected to the conditions described in ref 5. A quantitative yield (0.43 g) of benzoic acid **12** was recovered: mp 138–139 °C ($MeOH/Et_2O$), lit.[26] mp 141–142 °C.

2-Methoxy-6-methylbenzonitrile (13). A solution of 0.6 g (3.6 mmol) of **11** was subjected to the conditions described in ref 17. A 91% (0.48 g) yield of nitrile **13** was obtained: mp 61–63 °C (hexane), lit.[27] mp 64 °C.

2-Methyl-4-methoxybenzamide (18). To a solution of 3.12 g (16.3 mmol) of *N*-allyl-4-methoxybenzamide (**14**) in 50 mL of dry THF at −70 °C was added 14.37 mL (35.9 mmol) of 2.5 M *n*-BuLi in hexanes. The solution was stirred for 10 min at −70 °C and then was treated with 583 mg (17.9 mmol) of anhydrous CH_3OH. To this mixture was added 13.76 mL (17.9 mmol) of 1.3 M *sec*-BuLi in cyclohexanes. After an additional 10 min, 2.54 g (17.9 mmol) of CH_3I in 12 mL of THF was added dropwise. After the reaction had warmed to 0 °C, it was quenched with 75 mL of 50% v/v CH_3CO_2H/H_2O and then heated at 50 °C for 50 min. The mixture was cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave **18** as a solid, which after purification by flash chromatography on silica gel (ethyl acetate) yielded 2.16 g (78%) of 2-methyl-4-methoxybenzamide: mp 138–141 °C; IR (KBr) 3420, 3100, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81 (s, 1 H), 7.67 (d, J = 7.26 Hz, 1 H), 6.74 (d, J = 7.21 Hz, 1 H), 6.36 (bs, 1 H), 6.13 (bs, 1 H), 3.92 (s, 3 H), 2.47 (s, 3 H); MS m/e (rel intensity) 165 (65), 149 (35), 148 (100). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.64; H, 6.86; N, 8.45.

***N*-Allyl-2-methylbenzamide (19).** To a cold (0 °C) solution of *o*-toluoyl chloride (61.8 g, 0.4 mol) in 500 mL of CH_2Cl_2 was added a mixture of 61.8 mL (0.44 mol) of triethylamine and 33.0 mL (0.44 mol) of allylamine at such a rate that the reaction temperature did not exceed 5 °C. After addition was complete, the reaction mixture was allowed to warm to ambient temperature and shaken with 400 mL of 1 M HCl. The organic layer was separated, dried with Na_2SO_4, and filtered, and the solvent was removed in vacuo to give a solid. This solid was triturated with

pentane and dissolved in ether, and **19** crystallized from this ethereal solution upon standing (76.5 g, 95%): mp 121–124 °C (hexane–EtOAc); IR (KBr) 3400, 3200, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (dd, J = 8.31, 1.68 Hz, 1 H), 7.39 (dt, J = 7.61, 1.56 Hz, 1 H), 7.25 (m, 2 H), 6.05 (m, 1 H), 5.81, (b, 2 H), 5.11 (dm, J = 8.22 Hz, 1 H), 5.01 (dm, J = 11.34 Hz, 1 H), 3.63 (dm, J = 5.96 Hz, 1 H); MS m/e (rel intensity) 175 (20), 161 (99), 119 (18). Anal. Calcd for $C_{11}H_{13}NO$: C, 74.50; H, 6.87; N, 8.69. Found: C, 74.46; H, 6.65; N, 8.54.

***N*-Propenylisoquinolin-1(2*H*)-one (22).** A solution of 0.7 g (4.0 mmol) of *N*-propenyl-2-methylbenzamide (**7**) in 25 mL of THF was cooled to −70 °C. To this was added 6.77 mL (8.77 mmol) of *sec*-butyllithium in cyclohexane at such a rate so as to maintain the reaction temperature below −65 °C. The resulting purple-red solution was stirred for 10 min at this temperature. To this solution was added 0.32 g (4.4 mmol) of *N*,*N*-dimethylformamide in 10 mL of THF. The color disappeared immediately and the reaction was quenched at 0 °C with an excess of 1 M HCl. The mixture was diluted with diethyl ether and shaken, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave **22** (652 mg, 93%) as a solid which was crystallized from ethyl acetate–hexane (purified yield 588 mg, 84%): mp 147–151 °C; IR (KBr) 3150, 2900, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (d, J = 7.94 Hz, 0.5 H), 8.35 (d, J = 7.91 Hz, 0.5 H), 7.63 (m, 1 H), 7.46 (m, 2 H), 7.31 (d, J = 7.56 Hz, 0.5 H), 7.25 (J = 7.53 Hz, 0.5 H), 6.52 (d, J = 7.56 Hz, 0.5 H), 6.49 (d, J = 7.53 Hz, 0.5 H), 5.77 (m, J = 14.74, 6.67 Hz, 0.5 H), 4.79 (J = 10.39, 1.76 Hz, 0.5 H), 1.92 (dd, J = 6.81, 11.75 Hz, 1.5 H), 1.63 (dd, J = 6.97, 1.61 Hz, 1.5 H); MS m/e (rel intensity) 185 (30), 119 (100), 91 (44). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.98; N, 7.56. Found: C, 77.57; H, 5.79; N, 7.32.

Isoquinolin-1(2*H*)-one (23). Solid **22** (0.35 g, 1.9 mmol) was dissolved in dry THF (30 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction mixture was heated under reflux for 5 min and cooled to room temperature, and the solvent was removed in vacuo to give **23** as a solid. Recrystallization from ethyl acetate–hexane afforded 262 mg (95%) **23**: mp 209–211 °C; lit.[22a] mp 208–209 °C.

***N*-Propenyl-3-butylisoquinolin-1(2*H*)-one (25).** A solution of 1.1 g (6.3 mmol) of *N*-propenyl-2-methylbenzamide (**7**) in 25 mL of THF was cooled to −70 °C. To this was added 10.6 mL (13.78 mmol) of 1.3 M *sec*-butyllithium in cyclohexane at such a rate so as to maintain the reaction temperature below −65 °C. The resulting purple-red solution was stirred for 10 min at this temperature. To this mixture was added 1.0 g (6.9 mmol) of *N*-methyl-*N*-methoxyvaleramide in 10 mL of THF. The color disappeared immediately and the reaction was quenched at 0 °C with a solution of 25 mL of 50% aqueous acetic acid. An aliquot (10 mL) was removed and extracted with diethyl ether. The organic layer was shaken with $MgSO_4$ and filtered, and the solvent was removed in vacuo to give ***n*-propenyl-2-(2-oxohexyl)-benzamide (24)**: IR (KBr) 3320, 3010, 1790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (m, 4 H), 7.07 (m, 3 H), 6.37 (m, 1 H), 5.95 (m, 1 H), 3.59 (s, 1 H), 3.45 (s, 1 H), 2.47 (m, 2 H), 1.78 (dd, J = 6.63, 9.82 Hz, 1.5 H), 1.65 (dd, J = 6.81, 11.43 Hz, 1.5 H), 1.32 (m, 4 H), 0.95 (t, J = 7.69 Hz, 3 H). The rest of the suspension was heated under reflux for 20 min. The mixture was cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in vacuo gave **25** as an amorphous solid which was purified by flash chromatography on silica gel (hexane–ethyl acetate 3:1) (1.23 g, 81%): IR (KBr) 3000, 2800, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (d, J = 7.87 Hz, 0.5 H), 8.35 (d, J = 7.89 Hz, 0.5 H), 7.07 (m, 3 H), 6.37 (m, 1 H), 5.95 (dd, J = 14.95, 6.85 Hz, 0.5 H), 5.35 (dd, J = 10.43, 1.63 Hz, 0.5 H), 3.87 (m, 1 H), 2.57 (m, 2 H), 1.94 (dd, J = 6.75, 10.43 Hz, 1.5 H), 1.56 (dd, J = 6.85, 14.61 Hz, 1.5 H), 1.41 (m, 2 H), 0.95 (t, J = 7.69 Hz, 3 H); MS m/e (rel intensity) 241 (30), 119 (100), 91 (44). Anal. Calcd for $C_{16}H_{19}NO$: C, 69.08; H, 6.85; N, 7.32. Found: C, 68.85; H, 6.61; N, 7.02.

3-*n*-Butylisoquinolin-1(2*H*)-one (26). A solution of **25** (0.45 g, 1.7 mmol) in 25 mL of 1:1 v/v dioxane and 6 M HCl was heated under reflux for 6 h. The mixture was cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave **26** as a solid which was purified by flash chromatography on silica gel (hexane–ethyl acetate 3:1): 0.40 g (92%); mp 140–141 °C, lit.[23a] mp 139–140.

***N*-Propenyl-3-butylisoquinolin-1(2*H*)-one (25). One-Pot Synthesis from *N*-Allylbenzamide (1).** To a solution of **1** (2.75 g, 17.1 mmol) in 55 mL of dry THF at −70 °C was added 14.36 mL (34.2 mmol) of 2.5 M *n*-BuLi in hexanes. The solution was stirred for 10 min at −70 °C and then was treated with 0.7 mL (17.9 mmol) of anhydrous CH_3OH. To this mixture was added 14.47 mL (18.8 mmol) of 1.3 M *sec*-BuLi in cyclohexanes. After an additional 10 min, 2.67 g (18.8 mmol) of CH_3I in 12 mL of THF was added dropwise. Following this addition, the mixture was treated with an additional 14.47 mL (18.8 mmol) 1.3 M *sec*-BuLi in cyclohexanes and then with 2.62 g (18.8 mmol) of *N*-methyl-*N*-methoxyvaleramide in 21 mL of THF. After the reaction mixture had warmed to 0 °C, it was quenched with 90 mL of 50% v/v CH_3CO_2H/H_2O and then heated at 70 °C for 50 min. The mixture was cooled to room temperature, diluted with diethyl ether, and shaken, and the organic layer was separated and dried with Na_2SO_4. Filtration and concentration in vacuo gave **25** as a solid which was purified by flash chromatography on silica gel (hexane–ethyl acetate 3:1). Yield: 1.73 g, 42%.

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Registry No. **1**, 10283-95-1; **4a**, 5500-46-9; **4b**, 5202-76-6; **6a**, 527-85-5; **6b**, 54705-16-7; **6c**, 31913-94-7; **6d**, 88-97-1; **6e**, 61436-87-1; **6f**, 139583-83-8; **6g**, 5651-49-0; **6h**, 16497-32-8; **6i**, 87963-75-5; **6j**, 29879-70-7; **6k**, 6637-53-2; **7a**, 139583-84-9; **7b**, 139583-85-0; **8**, 66897-24-3; (*E*)-**9**, 139583-86-1; (*Z*)-**9**, 139583-87-2; (*E*)-**10**, 139583-88-3; (*Z*)-**10**, 139583-89-4; **11**, 139583-90-7; **12**, 6161-65-5; **13**, 53005-44-0; **14**, 66897-25-4; **18**, 139583-91-8; **19**, 24796-69-8; (*E*)-**22**, 139583-92-9; (*Z*)-**22**, 139583-93-0; **23**, 491-30-5; (*E*)-**24**, 139583-94-1; (*Z*)-**24**, 139583-95-2; (*E*)-**25**, 139583-96-3; (*Z*)-**25**, 139583-97-4; **26**, 132-90-1; allylamine, 107-11-9; *o*-toluoyl chloride, 933-88-0; *N*-methoxy-*N*-methylvaleramide, 129118-11-2; diphenyl disulfide, 882-33-7; allyl bromide, 106-95-6; 1-iodooctane, 629-27-6; cyclohexanone, 108-94-1; phenyl isocyanate, 103-71-9; *N*-methoxy-*N*-methylacetamide, 78191-00-1; *N*-methoxy-*N*-methylbenzamide, 6919-61-5.