

New Synthesis of Isoquinoline and 3,4-Dihydroisoquinoline Derivatives

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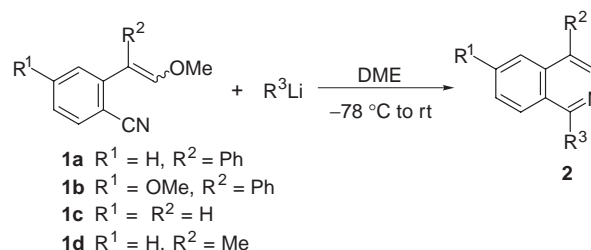
A simple and efficient synthesis of isoquinoline and 3,4-dihydroisoquinoline derivatives is described. 1-Alkyl- (or aryl)isoquinoline and 1-isoquinolinamine derivatives were obtained by intramolecular cyclization of 2-(2-methoxyethenyl)benzonitriles initiated by the addition of alkyl(or aryl)lithiums and lithium dialkylamides to the nitrile carbons, respectively. Synthesis of 4-aryl-3,4-dihydroisoquinolines was achieved by reactions of 2-(1-arylethenyl)benzonitriles with organolithiums, followed by aqueous workup. Treatment of the reaction mixtures with electrophiles prior to aqueous workup allowed the synthesis of 4,4-disubstituted 3,4-dihydroisoquinolines.

Recently, we described a new and efficient synthesis of 2,4-disubstituted quinolines via a sequence of addition and intramolecular ring closure between 2-isocyano- β -methoxystyrene derivatives and nucleophiles, such as organolithiums¹ and lithium dialkylamides.^{1b} As an extension of this synthesis, we found that the 1-alkyl(or aryl)isoquinoline **2** and 1-isoquinolinamine derivatives **3** could be obtained by reactions of the 2-(2-methoxyethenyl)benzonitriles (2-cyano- β -methoxystyrenes) **1** with alkyl(or aryl)lithiums and lithium dialkylamides.² Over recent years, development of new methods for the preparation of isoquinolines,³ including 1-isoquinolinamines,⁴ has attracted much attention due to their biological activities.⁵ Furthermore, it has been found that the reaction of the 2-(1-arylethenyl)benzonitriles **6** with organolithiums led to formation of the 4-aryl-3,4-dihydroisoquinoline derivatives **7**. 3,4-Dihydroisoquinolines are an important class of heterocycles; thus, numerous elaborations of 3,4-dihydroisoquinoline derivatives to more complex and important molecules that possess pharmacological activities have been reported.⁶ Moreover, some 3,4-dihydroisoquinoline derivatives have been reported to exhibit biological activities.⁷ 3,4-Dihydroisoquinoline derivatives have been prepared by the Bischler–Napieralski reaction.⁸ Recently, new and excellent methods for the synthesis of 3,4-dihydroisoquinoline derivatives have been described.⁹ For example, Janin et al. reported on a synthesis of 1-aryl-3,4-dihydroisoquinoline derivatives using a modified Ritter reaction procedure.^{9d} In this paper, we wish to describe the results of our investigation, which provide a convenient method to prepare isoquinoline derivatives.

We first investigated reactions of 2-(2-methoxy-1-phenylethenyl)benzonitrile (**1a**) (a mixture of *E* and *Z* isomers; ca. 1:1) with alkyl(or aryl)lithiums, and found that these reactions resulted in the formation of the 1-alkyl(or aryl)-4-phenylisoquinolines **2a–2e**, as shown in Scheme 1. Thus, organolithiums were added to a solution of **1a** in DME at -78°C . After 10 min, the mixture was warmed to room temperature, and stirring was continued for an additional 1 h at the same temperature. The attack of organolithiums on the nitrile carbon of **1a** followed by ring closure proceeded smoothly. After the usual

aqueous workup and purification using preparative TLC on silica gel, the desired isoquinolines were obtained. The yields of the products were generally fair to good as summarized in Table 1 (Entries 1–5). A similar sequence between 4-methoxy-2-(2-methoxy-1-phenylethenyl)benzonitrile (**1b**) (a mixture of *E* and *Z* isomers; ca. 2:1) and phenyllithium also proceeded and the desired isoquinoline derivative **2f** could be obtained but in a somewhat diminished yield (Entry 6).

Conducting reactions of 2-(2-methoxyethenyl)benzonitrile (*E*-**1c**) and 2-(2-methoxy-1-methylethenyl)benzonitrile (*E*-**1d**) with phenyllithium, 1-phenylisoquinoline (**2g**) and 4-methyl-1-phenylisoquinoline (**2h**) could be prepared in moderate to fair yields (Entries 7 and 9, respectively). The corresponding *Z*-isomers of these starting nitriles proved to be less reactive to

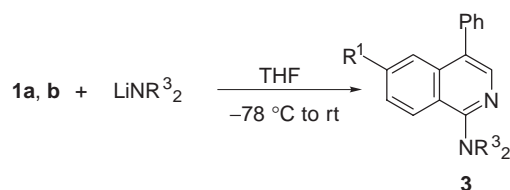


Scheme 1.

Table 1. Preparation of Isoquinolines **2**

Entry	1	R^3 in R^3Li	2 (Yield/%) ^{a)}
1	1a	Ph	2a (76)
2	1a	<i>n</i> -Bu	2b (54)
3	1a	<i>s</i> -Bu	2c (70)
4	1a	<i>t</i> -Bu	2d (68)
5	1a	2-Furyl	2e (51)
6	1b	Ph	2f (41)
7	<i>E</i> - 1c	Ph	2g (38)
8	<i>Z</i> - 1c	Ph	2g (22)
9	<i>E</i> - 1d	Ph	2h (65)
10	<i>Z</i> - 1d	Ph	2h (51)

a) Isolated yields.

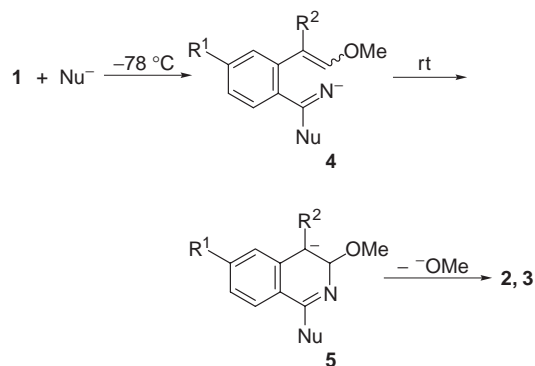


Scheme 2.

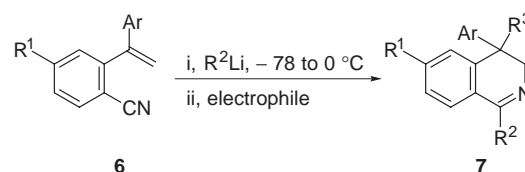
Table 2. Preparation of 1-Isoquinolinamines 3

Entry	1	NR^3_2	3 (Yield/%) ^a
1	1a	NEt_2	3a (59)
2	1a	$\text{N}(i\text{-Pr})_2$	3b (62)
3	1a	Pyrrolidin-1-yl	3c (62)
4	1a	Piperidino	3d (65)
5	1a	4-Methylpiperazin-1-yl	3e (64)
6	1a	Morpholino	3f (67)
7	1b	Piperidino	3g (29)

a) Isolated yields.



Scheme 3.



Scheme 4.

Table 3. Preparation of 3,4-Dihydroisoquinolines 7

Entry	6	R^2	Electrophile	R^3 in 7	7 (Yield/%) ^a
1	6a ($\text{R}^1 = \text{H}$, $\text{Ar} = \text{Ph}$)	Ph	H_2O	H	7a (69)
2	6a	Ph	MeI	Me	7b (59)
3	6a	Ph	EtBr	Et	7c (52)
4	6a	Ph	BnBr	Bn	7d (62)
5	6a	Ph	$t\text{-BuOCOCH}_2\text{Br}$	$t\text{-BuOCOCH}_2$	7e (55)
6	6a	Ph	EtCHO	EtCH(OH)	7f (62) ^b
7	6a	$n\text{-Bu}$	H_2O	H	7g (55)
8	6a	$n\text{-Bu}$	MeI	Me	7h (50)
9	6b ($\text{R}^1 = \text{H}$, $\text{Ar} = p\text{-ClC}_6\text{H}_4$)	Ph	H_2O	H	7i (60)
10	6b	Ph	BnBr	Bn	7j (53)
11	6c ($\text{R}^1 = \text{OMe}$, $\text{Ar} = \text{Ph}$)	Ph	H_2O	H	7k (36)

a) Isolated yields. b) Two diastereomers were produced and separated from each other by fractional recrystallization (ca. 6:4). The stereochemistry of each diastereomer could not be determined.

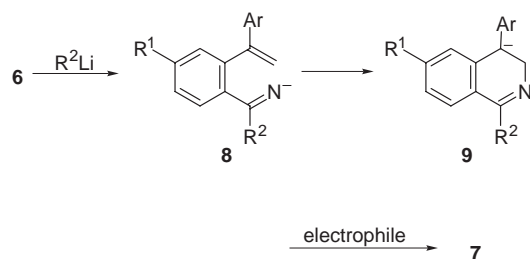
phenyllithium in the present sequence giving poorer results than those using *E*-isomers (Entries 8 and 10).

Subsequently, we discovered that the same addition/intramolecular ring closure sequence could be carried out using lithium dialkylamides in the place of alkyl(or aryl)lithiums to afford the *N,N*-dialkyl-1-isoquinolinamines 3. Thus, according to the procedure mentioned above for the preparation of the 1-alkyl(or aryl)isoquinolines 2, the 2-(2-methoxy-1-phenylethenyl)benzonitriles 1a and 1b were allowed to react with lithium dialkylamides in THF (instead of DME) to afford 3 as illustrated in Scheme 2. The yields of the products were generally fair, as summarized in Table 2. The reaction using 4-methoxy-2-(2-methoxy-1-phenylethenyl)benzonitrile (1b) proved to give a rather diminished yield of the desired product 3g. It should be noted that attempts to obtain the expected isoquinolinamines from the reactions of 1c and 1d with lithium piperidide were unsuccessful; an intractable mixture of products was obtained in each case.

The probable pathway to the isoquinoline derivatives 2 and 3 is outlined in Scheme 3. Thus, addition of a nucleophile to

the nitrile carbon of 1 at -78°C results in the formation of the nitrogen anion intermediate 4. When the reaction temperature is raised to room temperature, attack of this anion at the terminal carbon atom of the vinyl moiety occurs to give the benzyl anion 5. Subsequent loss of methoxide gives rise to the isoquinoline derivatives 2 and 3. It is reasonable that the poorer results were obtained in the cases of using 1b, while the lower stability of the corresponding intermediate benzyl anions due to the methoxy substituent at the benzene nucleus is taken into consideration.

The procedure we developed for the preparation of the 4-aryl-3,4-dihydroisoquinoline derivatives 7 is shown in Scheme 4. First, we treated 2-(1-phenylethenyl)benzonitrile (6a) with phenyllithium at -78°C for 30 min, then the temperature was allowed to gradually warm to 0°C , and stirring was continued for an additional 1 h. Aqueous workup followed by purification using preparative TLC on silica gel afforded 1,4-diphenyl-3,4-dihydroisoquinoline (7a) in good yield, as indicated in Table 3, Entry 1. We successfully introduced substituents at the 4-position of 1,4-diphenyl-3,4-dihydroisoquinoline



Scheme 5.

products by treating the reaction mixture with electrophiles prior to aqueous workup. These results are also summarized in Table 3, Entries 2–6, which indicate that not only various alkyl halides but also an aldehyde, such as propanal, was usable in the present procedure as electrophiles. In the case of using propanal, two possible diastereoisomers were obtained, which were separable from each other by fractional recrystallization (ca. 6:4). However, the stereochemistry of each isomer cannot be determined yet. Analogously, 1-butyl-4-phenyl-3,4-dihydroisoquinolines were prepared from **6a** and butyllithium, but the yields of the products **7g** and **7h** were somewhat lower compared to those using phenyllithium (Entries 7 and 8). Following the above procedures, 2-[1-(4-chlorophenyl)ethenyl]benzonitrile (**6b**) and 4-methoxy-2-(1-phenylethenyl)benzonitrile (**6c**) were converted into the corresponding 3,4-dihydroisoquinolines **7i–7k** in reasonable yields (Entries 9–11). The aryl substituent at the α -position of **6** was essential for production of the 3,4-dihydroisoquinolines **7**. For example, the reaction of 2-(1-methylethenyl)benzonitrile with phenyllithium resulted in the formation of an intractable mixture of products, from which no more than a trace of the desired product, 4-methyl-1-phenyl-3,4-dihydroisoquinoline, was isolated.

The formation of the 3,4-dihydroisoquinolines **7** from the 2-(1-arylethenyl)benzonitriles **6** and organolithiums may be explained as illustrated in Scheme 5. An organolithium attacks the cyano carbon of **6** to give the nitrogen anion intermediate **8**, which undergoes intramolecular cyclization to lead to the benzyl anion intermediate **9**. Finally, trapping of this anion with an electrophile gives rise to **7**. The rather lower yield of the product from **6c** is thought to be ascribable to the instability of the corresponding benzyl anion intermediate due to the 4-methoxy group.

It should be noted that all attempts to obtain 1-dialkylamino-3,4-dihydroisoquinolines by reactions of **6** with lithium dialkylamides were unsuccessful. In each case, a complex reaction mixture containing neither the starting **6** nor the corresponding dialkylaminoamidine derivative, arising from protonation of the intermediate **9** (R^2 = dialkylamino), was obtained, though we cannot give any explicit explanation of the reason for these results at the present time.

In summary, we have demonstrated a convenient synthesis of isoquinoline derivatives. The present method has advantages over previous methods:^{3,9} the ease of operations as well as the ready availability of the starting materials. It may offer the possibility to access compounds of potential biological interest.

Experimental

General. The melting points were determined on a Laboratory

Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^1H NMR spectra were determined using SiMe_4 as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in CDCl_3 . Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, Tottori University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF₂₅₄. All of the solvents used were dried over the appropriate drying agents and distilled under argon prior to use. All of the reactions were carried out under argon.

Starting Materials. (2-Bromophenyl)phenylmethanone,¹⁰ (2-bromo-5-methoxyphenyl)phenylmethanone,¹¹ 2-acetylbenzonitrile,¹² and (2-bromophenyl)(4-chlorophenyl)methanol¹³ were prepared according to the appropriate reported procedures. All other chemicals used in this study were commercially available.

2-Benzoylbenzonitrile.¹⁴ (2-Bromophenyl)phenylmethanone¹⁰ was treated with CuCN in DMF under the conditions reported by Friedman et al.¹⁵ to give the title keto nitrile in 81% yield: a white solid; mp 85–86 °C (hexane–Et₂O) (lit.,¹⁴ 83–84 °C).

2-Benzoyl-4-methoxybenzonitrile. This compound was prepared in 82% yield by the treatment of (2-bromo-5-methoxyphenyl)phenylmethanone¹¹ with CuCN under Friedman's conditions:¹⁵ a white solid; mp 130–131 °C (hexane–THF); IR (KBr disk) 2226 and 1665 cm^{-1} ; ^1H NMR δ 3.89 (3H, s), 7.05–7.15 (2H, m), 7.50 (2H, dd, J = 7.9 and 7.3 Hz), 7.65 (1H, tt, J = 7.3 and 1.3 Hz), 7.74 (1H, d, J = 9.2 Hz), and 7.83 (2H, dd, J = 7.9 and 1.3 Hz); MS m/z (%) 237 (M^+ , 45) and 105 (100). Anal. Found: C, 75.92; H, 4.84; N, 6.00%. Calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_2$: C, 75.94; H, 4.67; N, 5.90%.

2-(2-Methoxy-1-phenylethenyl)benzonitrile (1a). To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (3.4 g, 9.9 mmol) in DME (70 mL) at 0 °C was added dropwise butyllithium (1.6 M in hexane; 9.9 mmol) (1 M = 1 mol dm⁻³). After 5 min, the resulting ylide was treated with a solution of 2-benzoylbenzonitrile (1.6 g, 7.5 mmol) in DME (15 mL), and stirring was continued for an additional 10 min at the same temperature. Water (30 mL) was added and the mixture was extracted with Et₂O twice (30 mL each). The combined extracts were washed with water and then brine, dried over anhydrous Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel (2:1 hexane–Et₂O) to give **1a** (1.3 g, 73%): a yellow oil; R_f 0.36; a mixture of stereoisomers ($E:Z$ = ca. 1:1); IR (neat) 2225 and 1634 cm^{-1} ; ^1H NMR δ 3.82 and 3.84 (combined 3H, 2s), 6.49 (0.5H, s), 6.69 (0.5H, s), 7.11 (1H, dd, J = 7.9 and 1.6 Hz), 7.2–7.4 (6H, m), 7.45–7.6 (1H, m), and 7.72 and 7.76 (combined 1H, 2d, J = 7.9 and 8.6 Hz, respectively). Anal. Found: C, 81.37; H, 5.52; N, 5.90%. Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.68; H, 5.57; N, 5.95%.

4-Methoxy-2-(2-methoxy-1-phenylethenyl)benzonitrile (1b). This compound was prepared from 2-benzoyl-4-methoxybenzonitrile in a manner similar to that described above for **1a** in 75% yield ($E:Z$ = ca. 2:1); R_f 0.31 (2:1 hexane–Et₂O); a yellow oil; IR (neat) 2222 and 1638 cm^{-1} ; ^1H NMR δ 3.79, 3.80, 3.82, and 3.84 (combined 6H, 4s), 6.49 (0.33H, s), 6.67 (0.67H, s), 6.77 (1H, dd, J = 6.9 and 2.3 Hz), 6.8–6.9 (1H, m), 7.1–7.4 (5H, m), 7.58 (0.33H, d, J = 8.4 Hz), and 7.64 (0.67H, d, J = 8.8 Hz). Anal. Found: C, 77.11; H, 6.01; N, 5.23%. Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28%.

2-(2-Methoxyethenyl)benzonitrile (1c). This compound was prepared from 2-cyanobenzaldehyde in a manner similar to that described above for **1a** in 71% yield ($E:Z$ = ca. 2:1). *E*-**1c**: a yel-

low liquid; R_f 0.32 (2:1 hexane–Et₂O); IR (neat) 2220 and 1639 cm⁻¹; ¹H NMR δ 3.76 (3H, s), 6.10 (1H, d, J = 13.2 Hz), 7.1–7.25 (2H, m), 7.4–7.5 (2H, m), and 7.57 (1H, d, J = 7.6 Hz). Anal. Found: C, 75.43; H, 5.93; N, 8.75%. Calcd for C₁₀H₉NO: C, 75.45; H, 5.70; N, 8.80%. **Z-1c**: a yellow liquid; R_f 0.29 (2:1 hexane–Et₂O); IR (neat) 2215 and 1651 cm⁻¹; ¹H NMR δ 3.80 (3H, s), 5.63 (1H, d, J = 6.9 Hz), 6.34 (1H, d, J = 6.9 Hz), 7.18 (1H, td, J = 7.9 and 1.3 Hz), 7.49 (1H, td, J = 7.9 and 1.3 Hz), 7.57 (1H, dd, J = 7.9 and 1.3 Hz), and 8.14 (1H, d, J = 7.9 Hz). Anal. Found: C, 75.19; H, 5.77; N, 8.79%. Calcd for C₁₀H₉NO: C, 75.45; H, 5.70; N, 8.80%.

2-(2-Methoxy-1-methylethenyl)benzonitrile (1d). This compound was prepared from 2-acetylbenzonitrile¹² in a manner similar to that described above for **1a** in 70% yield ($E:Z$ = ca. 2:1). **E-1d**: a yellow liquid; R_f 0.36 (6:1 hexane–Et₂O); IR (neat) 2222 and 1659 cm⁻¹; ¹H NMR δ 2.04 (3H, d, J = 1.6 Hz), 3.76 (3H, s), 6.38 (1H, q, J = 1.6 Hz), 7.2–7.35 (2H, m), 7.47 (1H, ddd, J = 8.9, 7.6, and 1.3 Hz), and 7.62 (1H, dd, J = 7.6 and 1.3 Hz). Anal. Found: C, 76.23; H, 6.41; N, 8.05%. Calcd for C₁₁H₁₁NO: C, 76.28; H, 6.40; N, 8.09%. **Z-1d**: a yellow liquid; R_f 0.34 (6:1 hexane–Et₂O); IR (neat) 2226 and 1666 cm⁻¹; ¹H NMR δ 1.94 (3H, d, J = 1.6 Hz), 3.65 (3H, s), 6.14 (1H, q, J = 1.6 Hz), 7.25–7.35 (2H, m), 7.33 (1H, td, J = 7.9 and 1.3 Hz), and 7.64 (1H, dd, J = 7.9 and 1.3 Hz). Anal. Found: C, 76.21; H, 6.51; N, 7.98%. Calcd for C₁₁H₁₁NO: C, 76.28; H, 6.40; N, 8.09%.

Typical Procedure for the Reaction of 1 with Organolithium Leading to 2. 1,4-Diphenylisoquinoline (2a):¹⁶ To a stirred solution of **1a** (0.23 g, 0.98 mmol) in DME (7 mL) at –78 °C was added dropwise PhLi (0.94 M in cyclohexane–Et₂O; 2.0 mmol). After 10 min, the mixture was allowed to warm to room temperature and stirring was continued for an additional 1 h. Saturated aqueous NH₄Cl (15 mL) was added and organic products were extracted with Et₂O twice (15 mL each). The combined extracts were washed with brine, and then dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel (5:1 hexane–AcOEt) to give **2a** (0.21 g, 76%): a white solid; mp 141 °C (hexane–Et₂O) (lit.,¹⁶ 131 °C); IR (KBr disk) 1614 cm⁻¹; ¹H NMR δ 7.45–7.65 (9H, m), 7.66 (1H, t, J = 8.2 Hz), 7.74 (2H, dd, J = 8.2 and 1.3 Hz), 7.98 (1H, d, J = 7.9 Hz), 8.18 (1H, dd, J = 8.2 and 1.3 Hz), and 8.57 (1H, s); MS m/z (%) 281 (M⁺, 96) and 280 (100).

1-Butyl-4-phenylisoquinoline (2b): A yellow oil; R_f 0.54 (CH₂Cl₂); IR (neat) 1616 cm⁻¹; ¹H NMR δ 1.02 (3H, t, J = 7.3 Hz), 1.5–1.6 (2H, m), 1.8–2.0 (2H, m), 3.35 (2H, t, J = 7.9 Hz), 7.35–7.7 (7H, m), 7.90 (1H, dd, J = 8.2 and 2.0 Hz), 8.22 (1H, dd, J = 7.2 and 1.6 Hz), and 8.38 (1H, s); MS m/z (%) 261 (M⁺, 16), 246 (21), 232 (43), and 219 (100). Anal. Found: C, 87.29; H, 7.36; N, 5.11%. Calcd for C₁₉H₁₉N: C, 87.31; H, 7.33; N, 5.36%.

1-(1-Methylpropyl)-4-phenylisoquinoline (2c): A yellow oil; R_f 0.58 (5:1 hexane–AcOEt); IR (neat) 1615 cm⁻¹; ¹H NMR δ 0.96 (3H, t, J = 7.3 Hz), 1.46 (3H, d, J = 6.9 Hz), 1.75–1.9 (1H, m), 2.0–2.15 (1H, m), 3.77 (1H, sextet, J = 6.9 Hz), 7.4–7.65 (7H, m), 7.91 (1H, dd, J = 8.6 and 2.0 Hz), 8.29 (1H, dd, J = 7.3 and 2.6 Hz), and 8.45 (1H, s); MS m/z (%) 261 (M⁺, 29), 246 (72), and 233 (100). Anal. Found: C, 87.26; H, 7.50; N, 5.13%. Calcd for C₁₉H₁₉N: C, 87.31; H, 7.33; N, 5.36%.

1-(1,1-Dimethylethyl)-4-phenylisoquinoline (2d): A yellow oil; R_f 0.68 (CH₂Cl₂); IR (neat) 1614 cm⁻¹; ¹H NMR δ 1.71 (9H, s), 7.4–7.6 (7H, m), 7.91 (1H, dd, J = 7.9 and 2.0 Hz), 8.39 (1H, s), and 8.61 (1H, dd, J = 8.2 and 1.6 Hz); MS m/z (%) 261 (M⁺, 64) and 219 (100). Anal. Found: C, 86.97; H, 7.44; N, 5.16%. Calcd for C₁₉H₁₉N: C, 87.31; H, 7.33; N, 5.36%.

1-(2-Furyl)-4-phenylisoquinoline (2e): A yellow solid; mp 204–205 °C (Et₂O); IR (KBr disk) 1614 cm⁻¹; ¹H NMR δ 7.5–7.75 (10H, m), 7.99 (1H, dd, J = 7.9 and 1.3 Hz), 8.60 (1H, s), and 9.03 (1H, dd, J = 7.3 and 2.0 Hz); MS m/z (%) 271 (M⁺, 55) and 235 (100). Anal. Found: C, 84.28; H, 4.57; N, 5.38%. Calcd for C₁₉H₁₃NO: C, 84.11; H, 4.83; N, 5.16%.

6-Methoxy-1,4-diphenylisoquinoline (2f): mp 108 °C (hexane–AcOEt); IR (KBr disk) 1618 cm⁻¹; ¹H NMR δ 3.82 (3H, s), 7.17 (1H, dd, J = 9.2 and 2.6 Hz), 7.23 (1H, d, J = 2.6 Hz), 7.45–7.6 (8H, m), 7.71 (2H, dd, J = 8.3 and 2.0 Hz), 8.07 (1H, d, J = 9.2 Hz), and 8.45 (1H, s); MS m/z (%) 311 (M⁺, 87) and 310 (100). Anal. Found: C, 85.12; H, 5.47; N, 4.33%. Calcd for C₂₂H₁₇NO: C, 84.86; H, 5.50; N, 4.50%.

1-Phenylisoquinoline (2g): A yellow solid; mp 100–101 °C (hexane–Et₂O) (lit.,¹⁷ mp 97 °C); IR (KBr disk) 1633 and 1612 cm⁻¹; ¹H NMR δ 7.45–7.7 (8H, m), 7.89 (1H, d, J = 8.2 Hz), 8.11 (1H, dd, J = 8.2 and 1.0 Hz), and 8.61 (1H, d, J = 5.6 Hz); MS m/z (%) 205 (M⁺, 100).

4-Methyl-1-phenylisoquinoline (2h): A yellow solid; mp 77–78 °C (hexane–Et₂O) (lit.,¹⁸ mp 75–76 °C); IR (neat) 1614 cm⁻¹; ¹H NMR δ 2.68 (3H, d, J = 1.0 Hz), 7.4–7.8 (7H, m), 8.02 (1H, d, J = 8.6 Hz), 8.11 (1H, dd, J = 8.6 and 0.7 Hz), and 8.46 (1H, s); MS m/z (%) 219 (M⁺, 69) and 218 (100).

Typical Procedure for the Reaction of 1 with Lithium Dialkylamide Leading to 3. 1-Diisopropylamino-4-phenylisoquinoline (3b): To a stirred solution of LDA (1.1 mmol; generated from diisopropylamine and butyllithium by the standard method) in THF (3 mL) at –78 °C was added dropwise a solution of **1a** (0.14 g, 0.57 mmol) in THF (2 mL). After 10 min, the mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. Work-up similar to that used for the preparation of **2a** followed by purification by preparative TLC on silica gel (5:1 hexane–AcOEt) gave **3b** (0.11 g, 62%): a pale-orange oil; R_f 0.71; IR (neat) 1614 cm⁻¹; ¹H NMR δ 1.16 (12H, d, J = 6.6 Hz), 3.87 (2H, septet, J = 6.6 Hz), 7.35–7.6 (7H, m), 7.81 (1H, dd, J = 7.9 and 1.6 Hz), 8.27 (1H, s), and 8.60 (1H, dd, J = 7.6 and 1.6 Hz); MS m/z (%) 304 (M⁺, 48) and 261 (100). Anal. Found: C, 83.03; H, 7.89; N, 8.88%. Calcd for C₂₁H₂₄N₂: C, 82.85; H, 7.95; N, 9.20%.

1-Diethylamino-4-phenylisoquinoline (3a): R_f 0.63 (2:1 hexane–AcOEt); IR (neat) 1612 and 1603 cm⁻¹; ¹H NMR δ 1.24 (6H, t, J = 6.9 Hz), 3.51 (4H, q, J = 6.9 Hz), 7.35–7.6 (7H, m), 7.83 (1H, dd, J = 7.3 and 1.3 Hz), 8.10 (1H, s), and 8.22 (1H, dd, J = 7.3 and 1.3 Hz); MS m/z (%) 276 (M⁺, 30) and 247 (100). Anal. Found: C, 82.30; H, 7.29; N, 9.95%. Calcd for C₁₉H₂₀N₂: C, 82.57; H, 7.29; N, 10.14%.

4-Phenyl-1-(pyrrolidin-1-yl)isoquinoline (3c): A white solid; mp 104 °C (hexane–Et₂O); IR (KBr disk) 1599 cm⁻¹; ¹H NMR δ 1.95–2.05 (4H, m), 3.8–3.9 (4H, m), 7.35–7.55 (7H, m), 7.79 (1H, dd, J = 7.6 and 1.3 Hz), 7.98 (1H, s), and 8.26 (1H, dd, J = 7.6 and 1.3 Hz); MS m/z (%) 274 (M⁺, 39) and 245 (100). Anal. Found: C, 83.27; H, 6.73; N, 10.16%. Calcd for C₁₉H₁₈N₂: C, 83.18; H, 6.61; N, 10.21%.

4-Phenyl-1-piperidino-4-phenylisoquinoline (3d): A white solid; mp 120–121 °C (hexane–Et₂O); IR (KBr disk) 1605 cm⁻¹; ¹H NMR δ 1.7–1.95 (6H, m), 3.35–3.45 (4H, m), 7.35–7.6 (7H, m), 7.82 (1H, dd, J = 7.6 and 2.0 Hz), 8.10 (1H, s), and 8.17 (1H, dd, J = 7.6 and 2.0 Hz); MS m/z (%) 288 (M⁺, 100). Anal. Found: C, 83.39; H, 7.22; N, 9.71%. Calcd for C₂₀H₂₀N₂: C, 83.30; H, 6.99; N, 9.71%.

1-(4-Methylpiperazin-1-yl)-4-phenylisoquinoline (3e): A white solid; mp 133–134 °C (hexane–Et₂O–CH₂Cl₂); IR (KBr

disk) 1612 cm^{-1} ; $^1\text{H NMR}$ δ 2.43 (3H, s), 2.73 (4H, t, $J = 4.8$ Hz), 3.50 (4H, t, $J = 4.8$ Hz), 7.35–7.65 (7H, m), 7.83 (1H, dd, $J = 7.9$ and 2.0 Hz), 8.11 (1H, s), and 8.17 (1H, dd, $J = 7.9$ and 2.3 Hz); MS m/z (%) 303 (M^+ , 7.5) and 233 (100). Anal. Found: C, 79.01; H, 6.84; N, 13.72%. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3$: C, 79.17; H, 6.98; N, 13.85%.

1-Morpholino-4-phenylisoquinoline (3f): A white solid; mp 151–152 °C (hexane– Et_2O – CH_2Cl_2); IR (KBr disk) 1612 cm^{-1} ; $^1\text{H NMR}$ δ 3.46 (4H, t, $J = 4.6$ Hz), 4.01 (4H, t, $J = 4.6$ Hz), 7.35–7.65 (7H, m), 7.85 (1H, dd, $J = 7.6$ and 1.6 Hz), 8.12 (1H, s), and 8.20 (1H, dd, $J = 7.6$ and 1.6 Hz); MS m/z (%) 290 (M^+ , 95) and 298 (100). Anal. Found: C, 78.31; H, 6.27; N, 9.51%. Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$: C, 78.59; H, 6.25; N, 9.65%.

6-Methoxy-4-phenyl-1-piperidinoisoquinoline (3g): A white solid; mp 136–137 °C (hexane– AcOEt); IR (KBr disk) 1616 cm^{-1} ; $^1\text{H NMR}$ δ 1.65–1.75 (2H, m), 1.8–1.9 (4H, m), 3.3–3.4 (4H, m), 3.78 (3H, s), 7.1–7.2 (2H, m), 7.35–7.5 (5H, m), 8.04 (1H, s), and 8.09 (1H, dd, $J = 8.9$ and 1.0 Hz); MS m/z (%) 318 (M^+ , 80) and 235 (100). Anal. Found: C, 78.94; H, 6.94; N, 8.83%. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}$: C, 79.21; H, 6.96; N, 8.80%.

2-(1-Phenylethenyl)benzonitrile (6a).¹⁹ To a stirred suspension of methyltriphenylphosphonium iodide (1.4 g, 3.5 mmol) in DME (20 mL) at 0 °C was added dropwise butyllithium (3.5 mmol; 1.54 M in hexane). After 15 min, a solution of 2-benzoylbenzonitrile (0.60 g, 2.9 mmol) in DME (12 mL) was added to the resulting yellow solution. Stirring was continued for an additional 30 min before adding water (30 mL). The mixture was extracted with Et_2O three times (15 mL each). The combined extracts were washed brine, dried over anhydrous Na_2SO_4 , and evaporated. The residue was purified by column chromatography on silica gel to give **6a** (0.53 g, 89%): a yellow oil; R_f 0.53 (1:2 AcOEt –hexane); IR (neat) 2226 and 1614 cm^{-1} ; $^1\text{H NMR}$ δ 5.49 (1H, s), 5.88 (1H, s), 7.2–7.4 (6H, m), 7.44 (1H, dd, $J = 7.6$ and 1.3 Hz), 7.57 (1H, td, $J = 7.6$ and 1.3 Hz), and 7.71 (1H, dd, $J = 7.6$ and 1.3 Hz).

2-Bromophenyl(4-chlorophenyl)methanone.²⁰ This compound was prepared by the oxidation of (2-bromophenyl)(4-chlorophenyl)methanol¹³ with PCC in 1,2-dichloroethane at room temperature in 89% yield: a yellow oil; R_f 0.42 (1:5 EtOAc –hexane); IR (neat) 1668 cm^{-1} ; $^1\text{H NMR}$ δ 7.3–7.5 (5H, m), 7.65 (1H, dd, $J = 7.3$ and 1.3 Hz), and 7.75 (2H, d, $J = 8.9$ Hz).

2-(4-Chlorobenzoyl)benzonitrile.²¹ This compound was prepared by the treatment of 2-bromophenyl(4-chlorophenyl)methanone with CuCN in DMF under conditions reported by Friedman et al.¹⁵ in 66% yield: a white solid; mp 119–120 °C (hexane–THF); IR (KBr disk) 2230 and 1661 cm^{-1} ; $^1\text{H NMR}$ δ 7.48 (2H, d, $J = 8.9$ Hz), 7.6–7.75 (3H, m), 7.76 (2H, d, $J = 8.9$ Hz), and 7.84 (1H, dd, $J = 8.7$ and 0.9 Hz).

2-[1-(4-Chlorophenyl)ethenyl]benzonitrile (6b). This compound was prepared from 2-(4-chlorobenzoyl)benzonitrile in a manner similar to that described for the preparation of **6a** in 68% yield: a white solid; mp 73–73.5 °C (hexane– Et_2O); IR (KBr disk) 2224 and 1618 cm^{-1} ; $^1\text{H NMR}$ δ 5.50 (1H, s), 5.86 (1H, s), 7.19 (2H, d, $J = 8.6$ Hz), 7.30 (2H, d, $J = 8.6$ Hz), 7.35 (1H, dd, $J = 7.6$ and 1.3 Hz), 7.44 (1H, td, $J = 7.6$ and 1.3 Hz), 7.58 (1H, td, $J = 7.6$ and 1.3 Hz), and 7.71 (1H, dd, $J = 7.6$ and 1.3 Hz). Anal. Found: C, 75.19; H, 4.23; N, 5.83%. Calcd for $\text{C}_{15}\text{H}_{10}\text{ClN}$: C, 75.16; H, 4.21; N, 5.84%.

4-Methoxy-2-(1-phenylethenyl)benzonitrile (6c). This compound was prepared from 2-benzoyl-4-methoxybenzonitrile¹⁷ as described for the preparation of **6a** in 83% yield: a yellow oil; R_f 0.32 (1:2 AcOEt –hexane); IR (neat) 2222 and 1599 cm^{-1} ;

$^1\text{H NMR}$ δ 3.83 (3H, s), 5.47 (1H, s), 5.86 (1H, s), 6.84 (1H, d, $J = 2.6$ Hz), 6.92 (1H, dd, $J = 8.6$ and 2.6 Hz), 7.25–7.35 (5H, m), and 7.62 (1H, d, $J = 8.6$ Hz). Anal. Found: C, 81.63; H, 5.81; N, 6.03%. Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}$: C, 81.68; H, 5.57; N, 5.95%.

Typical Procedure for the Reaction of 6 with Organolithium Leading to 7. 1,4-Diphenyl-3,4-dihydroisoquinoline (7a): To a stirred solution of **6a** (0.15 g, 0.76 mmol) in DME (10 mL) at –78 °C was added PhLi (0.94 M in cyclohexane– Et_2O ; 0.91 mmol). After stirring for 30 min, the mixture was allowed to warm to 0 °C and stirring was continued for an additional 1 h. The resulting deep green solution was quenched by adding aqueous saturated NH_4Cl (15 mL), and organic materials were extracted with Et_2O three times (10 mL each). The combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by preparative TLC on silica gel (1:2 AcOEt –hexane) to give **7a** (0.15 g, 69%): a pale yellow solid; mp 126–127.5 °C (Et_2O –hexane); IR (neat) 1608 cm^{-1} ; $^1\text{H NMR}$ δ 4.00 (1H, dd, $J = 13.2$ and 9.5 Hz), 4.15–4.3 (2H, m), 6.99 (1H, d, $J = 7.0$ Hz), 7.25–7.5 (11H, m), and 7.6–7.7 (2H, m); MS m/z (%) 283 (M^+ , 61) and 282 (100). Anal. Found: C, 89.17; H, 6.19; N, 4.57%. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}$: C, 89.01; H, 6.05; N, 4.94%.

4-Methyl-1,4-diphenyl-3,4-dihydroisoquinoline (7b): Compound **1a** (0.21 g, 1.0 mmol) was treated with PhLi (0.94 M solution in cyclohexane– Et_2O ; 1.3 mmol) in a similar manner as described above for the preparation of **7a**. To the resulting deep green solution was added iodomethane (0.18 g, 1.3 mmol), and stirring was continued for 15 min. After a similar work up as described above, the crude product was purified by preparative TLC on silica gel to give **7b** (0.18 g, 59%): a pale-yellow solid; mp 133–134 °C (Et_2O –hexane); IR (KBr disk) 1609 cm^{-1} ; $^1\text{H NMR}$ δ 1.70 (3H, s), 3.81 (1H, d, $J = 15.8$ Hz), 4.12 (1H, d, $J = 15.8$ Hz), and 7.1–7.55 (14H, m); MS m/z (%) 297 (M^+ , 74) and 296 (100). Anal. Found: C, 88.73; H, 6.31; N, 4.52%. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}$: C, 88.85; H, 6.44; N, 4.71%.

4-Ethyl-1,4-diphenyl-3,4-dihydroisoquinoline (7c): This compound was prepared as described for the preparation of **7b**. **7c**: a pale-yellow solid; mp 102–103 °C (Et_2O –hexane); IR (KBr disk) 1614 cm^{-1} ; $^1\text{H NMR}$ δ 0.93 (3H, t, $J = 7.3$ Hz), 2.05–2.25 (2H, m), 3.88 (1H, d, $J = 16.2$ Hz), 4.46 (1H, d, $J = 16.2$ Hz), and 7.15–7.5 (14H, m); MS m/z (%) 311 (M^+ , 19) and 284 (100). Anal. Found: C, 88.73; H, 6.90; N, 4.55%. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}$: C, 88.71; H, 6.80; N, 4.50%.

4-Benzyl-1,4-diphenyl-3,4-dihydroisoquinoline (7d): This compound was prepared as described for the preparation of **7b**. **7d**: a pale-yellow solid; mp 144.5–146 °C (Et_2O –hexane); IR (KBr disk) 1610 cm^{-1} ; $^1\text{H NMR}$ δ 3.33 (1H, d, $J = 13.2$ Hz), 3.60 (1H, d, $J = 13.2$ Hz), 3.84 (1H, d, $J = 13.2$ Hz), 4.49 (1H, d, $J = 13.2$ Hz), 6.77 (2H, dd, $J = 7.9$ and 2.3 Hz), 7.05–7.4 (15H, m), 7.52 (1H, td, $J = 7.3$ and 1.6 Hz), and 7.64 (1H, d, $J = 6.9$ Hz); MS m/z (%) 373 (M^+ , 5.9), 372 (7.2), and 282 (100). Anal. Found: C, 90.20; H, 6.38; N, 3.64%. Calcd for $\text{C}_{28}\text{H}_{23}\text{N}$: C, 90.04; H, 6.21; N, 3.75%.

***t*-Butyl (1,4-Diphenyl-3,4-dihydroisoquinolin-4-yl)acetate (7e):** This compound was prepared as described for the preparation of **7b**. **7e**: a yellow viscous oil; R_f 0.25 (1:3 AcOEt –hexane); IR (neat) 1724 cm^{-1} ; $^1\text{H NMR}$ δ 1.27 (9H, s), 3.00 (1H, d, $J = 15.0$ Hz), 3.06 (1H, d, $J = 15.0$ Hz), 4.20 (1H, d, $J = 16.1$ Hz), 4.62 (1H, d, $J = 16.1$ Hz), and 7.1–7.5 (14H, m); MS m/z (%) 397 (M^+ , 4.8) and 340 (100). Anal. Found: C, 81.53; H, 7.01; N, 3.42%. Calcd for $\text{C}_{27}\text{H}_{27}\text{NO}_2$: C, 81.58; H, 6.85; N, 3.52%.

4-(1-Hydroxypropyl)-1,4-diphenyl-3,4-dihydroisoquinoline (7f): This compound was prepared as described for the prepara-

tion of **7b**. Two diastereomers were obtained separately by fractional recrystallization (ca. 6:4). First recrystallized and minor diastereomer: a white solid; mp 210–211 °C (hexane–CHCl₃); IR (KBr disk) 3217, 1628, and 1601 cm⁻¹; ¹H NMR δ 1.11 (3H, t, *J* = 7.3 Hz), 1.35–1.55 (2H, m), 1.75–1.85 (1H, m), 3.74 (1H, d, *J* = 15.8 Hz), 4.25–4.35 (1H, m), 4.93 (1H, d, *J* = 15.8 Hz), 7.1–7.4 (12H, m), 7.36 (1H, td, *J* = 7.6 and 1.6 Hz), and 7.64 (1H, dd, *J* = 7.6 and 1.0 Hz); MS *m/z* (%) 341 (M⁺, 35) and 284 (100). Anal. Found: C, 84.40; H, 6.60; N, 4.09%. Calcd for C₂₄H₂₃NO: C, 84.42; H, 6.79; N, 4.10%. Later recrystallized and major diastereomer: a white solid; mp 181.5–182.5 °C (hexane–Et₂O); IR (KBr disk) 3194, 1618, and 1601 cm⁻¹; ¹H NMR δ 1.00 (3H, t, *J* = 7.3 Hz), 1.4–1.65 (2H, m), 1.86 (1H, brs), 4.02 (1H, d, *J* = 16.2 Hz), 4.38 (1H, brd, *J* = 10.2 Hz), 4.71 (1H, d, *J* = 16.2 Hz), 7.1–7.4 (12H, m), 7.54 (1H, ddd, *J* = 8.6, 7.6, and 1.6 Hz), and 7.86 (1H, d, *J* = 8.6 Hz); MS *m/z* (%) 341 (M⁺, 37) and 284 (100). Anal. Found: C, 84.10; H, 6.77; N, 4.05%. Calcd for C₂₄H₂₃NO: C, 84.42; H, 6.79; N, 4.10%.

1-Butyl-4-phenyl-3,4-dihydroisoquinoline (7g): This compound was prepared as described for the preparation of **7a**. **7g**: a yellow viscous oil; *R_f* 0.18 (1:4 AcOEt–hexane); IR (neat) 1628 and 1603 cm⁻¹; ¹H NMR δ 0.94 (3H, t, *J* = 7.3 Hz), 1.3–1.5 (2H, m), 1.55–1.7 (2H, m), 2.78 (2H, t, *J* = 7.3 Hz), 3.83 (1H, dd, *J* = 16.2 and 12.2 Hz), 3.95–4.05 (2H, m), 6.93 (1H, d, *J* = 8.9 Hz), 7.19 (2H, dd, *J* = 8.3 and 1.6 Hz), 7.25–7.4 (5H, m), and 7.55 (1H, dd, *J* = 6.9 and 2.3 Hz); MS *m/z* (%) 263 (M⁺, 2.3), 248 (5.5), 234 (16), and 221 (100). Anal. Found: C, 86.53; H, 8.35; N, 5.28%. Calcd for C₁₉H₂₁N: C, 86.65; H, 8.04; N, 5.32%.

1-Butyl-4-methyl-4-phenyl-3,4-dihydroisoquinoline (7h): This compound was prepared as described for the preparation of **7b**. **7h**: a yellow viscous oil; *R_f* 0.22 (1:4 AcOEt–hexane); IR (neat) 1630 and 1599 cm⁻¹; ¹H NMR δ 0.82 (3H, t, *J* = 7.3 Hz), 1.15–1.25 (2H, m), 1.35–1.55 (2H, m), 1.61 (3H, s), 2.55–2.75 (2H, m), 3.62 (1H, d, *J* = 15.2 Hz), 4.25 (1H, d, *J* = 15.2 Hz), 7.1–7.45 (8H, m), and 7.53 (1H, dd, *J* = 7.6 and 1.6 Hz); MS *m/z* (%) 277 (M⁺, 10), 276 (14), 262 (30), 248 (41), and 235 (100). Anal. Found: C, 86.22; H, 8.64; N, 4.71%. Calcd for C₂₀H₂₃N: C, 86.59; H, 8.36; N, 5.05%.

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