Heteroatom-directed lateral lithiation: synthesis of isoquinoline derivatives from *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamines[1,2]

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This paper is dedicated to Professor David B. MacLean

ROBIN D. CLARK, JAHANGIR, and JAMES A. LANGSTON. Can. J. Chem. **72**, 23 (1994).

Methodology for the preparation of isoquinoline derivatives from *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamines (**1**) was developed. Conversion of **1** to the dilithio species followed by condensation with DMF afforded Boc-3-hydroxy-1,2,3,4-tetrahydroisoquinolines **3**, which could be dehydrated to 1,2-dihydroisoquinolines **4**. Hydrogenation of dihydro compounds **4** afforded the corresponding tetrahydroisoquinolines **5**. Treatment of the dilithio species from **1** with *N*-methoxy-*N*-methylamides afforded ketones **14**, which were converted to 3-substituted dihydro-isoquinoline **15**, tetrahydroisoquinolines (**16, 17**), or isoquinolines (**20**).

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On a développé une méthodologie pour la préparation de dérivés isoquinoléines à partir de *N*-(*tert*-butoxycarbonyl)-2-méthylbenzylamines (**1**). La conversion des composés **1** en dérivés dilithiés suivie par une condensation avec le DMF conduit aux Boc-3-hydroxy-1,2,3,4-tétrahydroisoquinoléines (**3**) qui peuvent être soumises à une déshydratation conduisant aux 1,2-dihydroisoquinoléines (**4**). L'hydrogénation des composés dihydro **4** fournit les tétrahydroisoquinoléines correspondantes (**5**). Le traitement des espèces dilithiées des produits **1** avec des *N*-méthoxy-*N*-méthylamides conduit aux cétones **14** qui peuvent être transformées en dihydroisoquinoléines substituées (**15**), en tétrahydroisoquinoléines (**16** et **17**) et en isoquinoléines (**20**) en position 3.

[Traduit par la rédaction]

A number of heterocycle-forming annelations based on heteroatom-facilitated lateral lithiation reactions have recently been reported and these procedures offer useful alternatives to the more classical syntheses of important heterocycles, for example, indole (1) and isoquinoline (2) derivatives. We have described preliminary results on a synthesis of tetrahydroisoquinolines that was based on the lateral lithiation of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine (**1***a*) (3). In this paper, we report details of that work and extensions that provide routes to a variety of substituted dihydroisoquinolines, tetrahydroisoquinolines, and isoquinolines.

Prior to our initial investigations, it had been demonstrated that *N*-benzylbenzamide underwent deprotonation at the α(benzylic) position (in addition to NH deprotonation) (4) and that *N*-pivaloylbenzylamine underwent both *ortho* and α-lithiation (5). It was subsequently reported that Boc-benzylamine was cleanly dilithiated to afford the *N*-α-dilithio species (6). However, based on the facility with which various toluenes undergo heteroatom-facilitated lateral lithiation (1, 7), we felt it likely that the methyl group of **1***a*, rather than the α position, would be the second site of deprotonation. In the event, treatment of **1***a* with two equivalents of *sec*-butyllithium at ca. –40°C gave the red-orange dilithio species **2***a* as evidenced by the formation of Boc-3-hydroxytetrahydroisoquinoline **3***a* as the sole product upon treatment with DMF (Scheme 1). We subsequently demonstrated that the Boc-phenylethylamine homolog of **1***a* also undergoes lateral lithiation under the same conditions and that only when the *N*-Boc group is extended by an additional methylene (phenylpropylamine derivative) does α-deprotonation become a competing, albeit minor, process (8).

Results of the application of this methodology to the synthesis of tetrahydroisoquinolines with substitutents at the 4-position or in the aromatic ring are presented in Scheme 2. The 3-hydroxy derivatives **3** obtained by DMF quench of the dilithio species **2** were isolable by crystallization and (or) silica gel chromatography and underwent rapid dehydration to the rather unstable 1,2-dihydroisoquinolines **4** upon brief treatment with HCl in THF. The dihydro compounds were hydrogenated to afford 1,2,3,4-tetrahydroisoquinolines **5**.

Several of the entries in Scheme 2 warrant further comment. Ring-halogenated tetrahydroisoquinolines, as exemplified by entries **5***b–d*, are not readily accessible by classical syntheses, for example, the Bischler–Napieralski (9) and Pictet–Spengler (10) procedures, which generally involve cyclizations onto electron-rich aromatic rings. Entry **1***f* demonstrated that lateral lithiation was the predominant pathway despite the presence of a 5-methoxy group that, in principle, could have induced competing ring (*ortho*) deprotonation at the 6-position. Entries **1***g–i* indicated a limitation of the methodology as 2-alkyl substituents other than methyl proved to be significantly more difficult to deprotonate, even when longer reactions times, higher temperatures, and the stronger base *tert*-BuLi were employed. This phenomenon was previously noted in the case of the related Boc-2-alkylanilines (1). An obvious exception is **1***j*, in which the additional phenyl group enhances the acidity of the methylene protons. With substrate **1***i*, the decreased rate of lateral lithiation allowed metalation *ortho* to the methoxy group in the appended aromatic ring to become a competing process.

The requisite benzylamines for the preparation of Boc derivatives **1***a–i* were either commercially available (**1***a*) or were, in general, prepared in straightforward fashion (Experimental). The preparation of the tetrasubstituted example **1***d*, which exemplifies several additional aspects of *ortho* and lateral lithiation methodology, is shown in Scheme 3. A previous report

[1]Dedicated to Professor D.B. MacLean in recognition of his outstanding contributions to natural product and alkaloid chemistry, which have encompassed isolation, structure determination, and synthesis. One of us (J) was fortunate enough to have obtained his doctoral training under D.B.M.'s mentorship. The work presented in this paper was inspired by the lateral metalation technology developed in Professor MacLean's laboratory for the synthesis of isoquinoline alkaloids.

[2]Contribution no. 880 from the Institute of Organic Chemistry.

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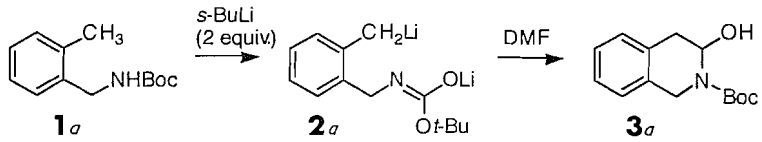
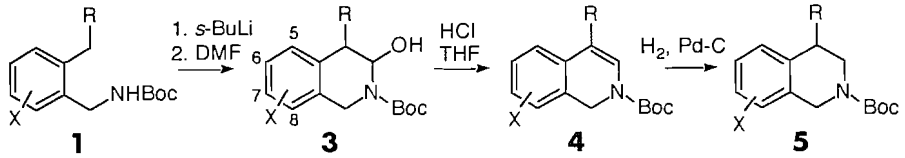


1*a* **2***a* **3***a*

SCHEME 1

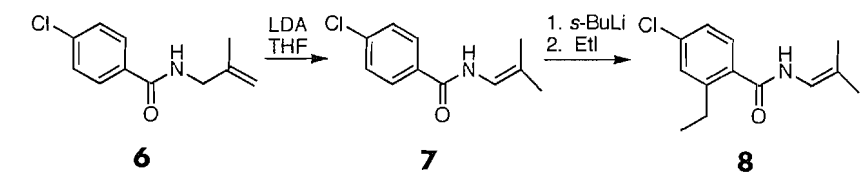


1 **3** **4** **5**

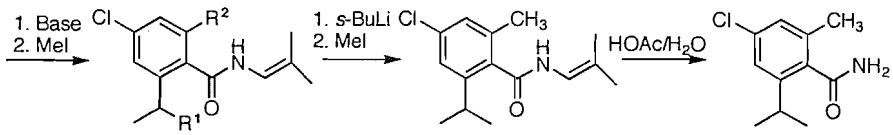
			% Yield		
entry	R	X in **3**,**4**,**5**	**3**	**4**	**5**
a	H	H	78	95	95
b	H	5-F	72	-[a]	79[b]
c	H	8-Cl	80	-	76[c]
d	H	6-Cl, 8-$CH(CH_3)_2$	97	95	95
e	H	6-OMe	65		
f	H	6,7-$(OMe)_2$	60		
g	$CH_2CH_2CH_3$	H	-	<20	
h	CH_2Ph	H	-	42	90
i	CH_2(3-OMe)Ph	H	-	<20	
j	Ph	H	-	71[c]	

[a]Intermediate was not isolated. [b]Yield from **3**. [c]Yield from **1**.

SCHEME 2



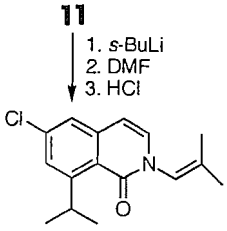
6 **7** **8**



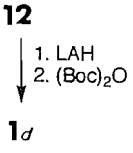
9 R^1 = Me R^2 = H
10 R^1 = H R^2 = Me

Base	**9** (%)	**10** (%)
n-BuLi	70	30
s-BuLi	70	30
t-BuLi	40	60
LiTMP	100	0

11 **12**



13



1*d*

SCHEME 3

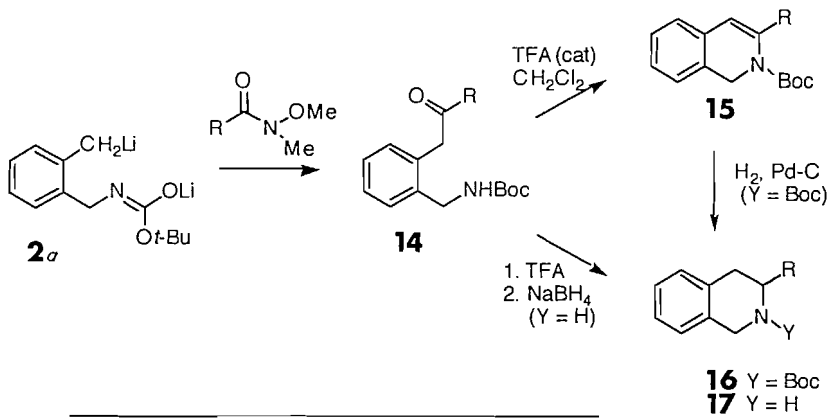
from these laboratories introduced the 1-propenyl group for protection of benzamides in *ortho* lithiation reactions (11). One drawback of this methodology is that a mixture of *cis/trans* propenyl isomers is obtained, which complicates further synthetic steps. To obviate this inconvenience, in the present work we used the symmetric 2-methyl-1-propenyl group. Thus, benzamide **7** was obtained in quantitative yield by the lithium diisopropylamide (LDA)-induced isomerization (12) of the 2-methylallylbenzamide **6**. *ortho* Lithiation of **7** followed by treatment with iodoethane furnished the 2-ethyl derivative **8**. Attempts to effect lateral lithiation of **8** using organolithium bases were complicated by competing *ortho* lithiation as evidenced by formation of **9** and **10** upon treatment of the lithiated species with iodomethane (Scheme 3). However, it was found that lateral lithiation was the exclusive pathway when lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was used as the base. LiTMP was superior to LDA, which gave only lateral metalation but with incomplete (ca. 70%) conversion. The superiority of LiTMP over LDA was also recently demonstrated in the lateral lithiation of *o*-tolualdehyde cyclohexylimine (13).

Compound **9**, with the 2-position effectively blocked to further metalation by the isopropyl group, was then subjected to the third consecutive lithiation reaction in the sequence to afford **11** after methylation. The 2-methyl-1-propenyl group was removed by acid hydrolysis to give the primary benzamide **12**, which was converted to **1***d*. We note in passing that **11** afforded the isoquinolone **13** upon lateral lithiation and treatment with DMF followed by dehydration with HCl (14). However, attempts to remove the *N*-protecting group from **13** with strong acid resulted in decomposition.

Acylation of dianion **2***a* was efficiently accomplished by treatment with *N*-methoxy-*N*-methylamides (15) to afford key intermediates **14***a–d* for the preparation of 3-substituted dihydro and tetrahydroisoquinolines (Scheme 4). Brief exposure of these ketones to a catalytic amount of trifluoroacetic acid in CH_2Cl_2 gave the Boc-1,2-dihydroisoquinolines **15**, which could be catalytically reduced to the corresponding Boc-protected tetrahydroisoquinolines **16**. Alternatively, the Boc group of **14** could be removed with trifluoroacetic acid, and reduction of the intermediate imine with sodium borohydride in ethanol afforded tetrahydroisoquinolines **17**. Several of the 3-substituted tetrahydroisoquinolines thus obtained were set up for additional ring closure reactions (Scheme 5). Deprotection of **16***b* with TFA followed by neutralization gave hexahydro-2*H*-benzo[*b*]quinolizine **18** and Pictet–Spengler reaction of **17***d* afforded the tetrahydro-5*H*-dibenzo[*b,g*]quinolizine **19**.

In addition to providing access to 3-substituted tetrahydroisoquinolines, the dihydroisoquinolines **15** can also serve as precursors to the corresponding isoquinolines. Thus, deprotection of **15***a* with TFA followed by treatment with iodine and KOAc in ethanol (16) afforded 3-butyl isoquinoline **20** (Scheme 6). Whereas the Reissert reaction (17) affords 1-substituted derivatives, 3-substituted isoquinolines are not readily accessible from classical isoquinoline syntheses, for example, the Pomeranz–Fritsch synthesis (18). Another versatile route for the preparation of 3-substituted isoquinolines based on the lateral lithiation of tolualdehyde imines has recently been reported (19).

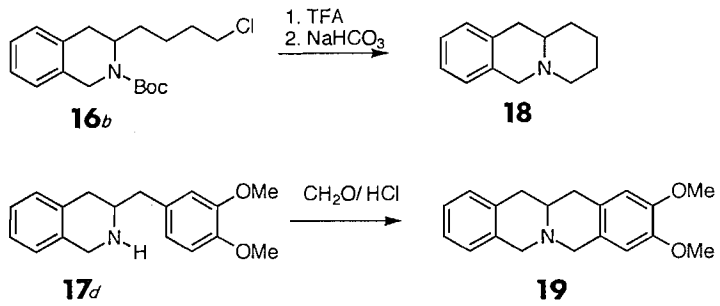
A variant on the preparation of certain 3-substituted tetrahydroisoquinolines is shown in Scheme 7. Condensation of dianion **2***a* with veratraldehyde afforded adduct **21**, which cyclized to Boc-3(3,4-dimethoxyphenyl)tetrahydroisoquinoline **23** upon treatment with a catalytic amount of trifluoroacetic acid in CH_2Cl_2. This cyclization appears to require the presence of the 4-methoxy group, presumably through stabilization of the intermediate carbonium ion, as the corresponding unsubstituted phenyl congener **22** failed to cyclize under similar (or more strongly acid) conditions. In an attempt to prepare 3,3-disubstituted tetrahydroisoquinolines, the benzophenone and cyclohexanone adducts **24** and **26**, respectively, were similarly treated



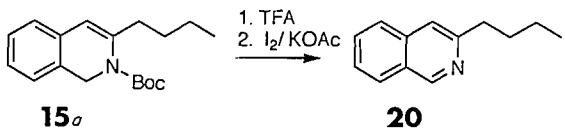
entry	R	%yield 14	15	16	17
a	$CH_2CH_2CH_2CH_3$	94	92	-[a]	92
b	$CH_2CH_2CH_2CH_2Cl$	95	92	98	-[b]
c	Ph	79	94		
d	CH_2(3,4-$(OMe)_2$Ph)	45	99	90	81

[a]Not isolated. [b]See Scheme 5.

SCHEME 4



SCHEME 5



SCHEME 6

with trifluoroacetic acid in CH_2Cl_2. However, **24** underwent almost immediate dehydration to stilbene **25** whereas **26** proved resistant to either cyclization or dehydration. Under strongly acidic conditions (neat trifluoroacetic acid or HCl in THF), the Boc group of **26** was removed while the tertiary alcohol remained intact.

In summary, the methodology reported herein can be used to prepare a variety of derivatives of the isoquinoline ring system. As has been amply demonstrated with heteroatom-directed *ortho* lithiation technology (7), Boc-directed *lateral* lithiations also can be used to synthesize compounds that might otherwise be difficult to prepare by classical means. Thus, lateral lithiation of **1** was used to prepare halogen-substituted tetrahydroisoquinolines and 3-substituted tetrahydroisoquinolines and isoquinolines. Applications to the preparation of more complex isoquinolines and isoquinoline-containing ring systems are underway and will be reported in due course.

Experimental

General information

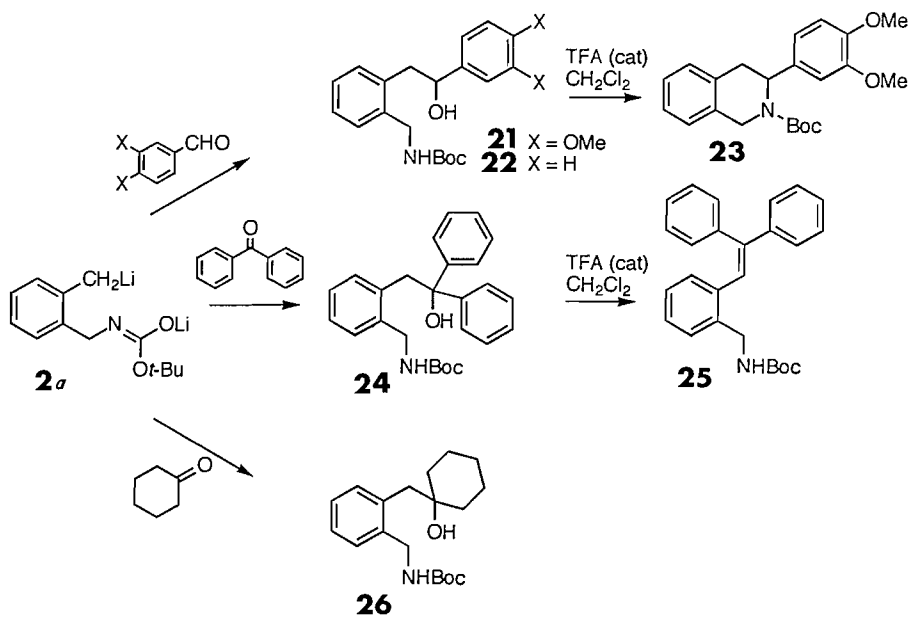
Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Thin-layer chromatography (tlc) was performed using Analtech silica gel GF glass plates. Medium-pressure chromatography (mpc) was performed with 230–400 mesh Merck Kieselgel. Microanalysis were carried out by the Syntex Analytical Department.

Proton (^1H) nmr spectra were recorded at 300 MHz on a Bruker WM 300 spectrometer in $CDCl_3$ or Me_2SO-d_6 solution referenced to internal tetramethylsilane (TMS). Chemical shifts, quoted as δ values, were measured in relation to TMS. Infrared (ir) spectra were run on a Nicolet 5 PC FT infrared spectrophotometer. Mass spectra were recorded with an Atlaswerke CH-7 spectrometer. High-resolution mass spectra (hrms) were obtained with a Finnigan MAT 311A mass spectrometer.

All lithiation reactions were carried out under an inert atmosphere (nitrogen or argon). THF was dried by distillation from Na–benzophenone under a nitrogen atmosphere immediately prior to use. "Usual work-up" refers to addition of aqueous NH_4Cl solution to the reaction mixture, extraction with EtOAc, washing the extract with water and brine, drying over Na_2SO_4, and evaporation on a rotary evaporator.

Typical procedure for the preparation of Boc-2-alkylanilines ***1****:* N-*(*tert*-butoxycarbonyl)-1-methylbenzylamine* **1a**

Di-*tert*-butyl dicarbonate (37 g, 170 mmol) was added to a cold (ice-bath) solution of 2-methylbenzylamine (Aldrich Chem. Co.) (20 g, 165



SCHEME 7

mmol) in THF (250 nmL). The resulting solution was stirred at room temperature for 4 h and was then concentrated in vacuo to a semi-solid. Crystallization from hexane (cooling in a Dry Ice – acetone bath) afforded **1***a* as a white solid (32 g, 88%); mp 50–51°C; ^{1}H nmr ($CDCl_3$) δ: 1.46 (s, 9H), 2.32 (s, 3H), 4.32 (d, 2H, J = 5.6 Hz), 4.70 (br m, 1H, NH), 7.18 (m, 4H); ms(EI), *m/z*(relative intensity): 221(5)M^+, 165(99), 164(79), 150(34), 120(16), 105(47), 104(100), 57(29). Anal. calcd. for $C_{13}H_{19}NO_2$: C 70.56, H 8.65, N 6.33; found: C 70.50, H 8.61, N 6.40.

The following compounds were similarly prepared.

N-*(*tert*-Butoxycarbonyl)-3-fluoro-2-methylbenzylamine* **1**b

This was prepared from 3-fluoro-2-methylbenzoic acid (Aldrich Chem. Co.) by conversion to the amide, LAH reduction, and reaction with di-*tert*-butyl dicarbonate; mp 69–70°C. Anal. calcd. for $C_{13}H_{18}FNO_2$: C 65.25, H 7.58, N 5.85; found: C 65.17, H 7.59, N 5.87.

N-*(*tert*-Butoxycarbonyl)-2-chloro-6-methylbenzylamine* **1**c

This was prepared from 2-chloro-6-methylbenzonitrile (Aldrich Chem. Co.) by reduction (borane–methylsulfide) and reaction with di-*tert*-butyl dicarbonate; mp 69–70°C. Anal. calcd. for $C_{13}H_{18}ClNO_2$: C 61.05, H 7.09, N 5.48; found: C 61.11, H 7.09, N 5.51.

N-*(*tert*-Butoxycarbonyl)-4-chloro-2-(2-propyl)-6-methylbenzylamine* **1**d

This was prepared from compound **12**, the preparation of which is described below; mp 69–70°C. Anal. calcd. for $C_{16}H_{24}ClNO_2$: C 64.52, H 8.13, N 4.70; found: C 64.79, H 8.23, N 4.82.

N-*(*tert*-Butoxycarbonyl)-4-methoxy-2-methylbenzylamine* **1**e

This was prepared from 4-methoxy-*o*-toluic acid by conversion to the amide, reduction with LAH, and reaction with di-*tert*-butyl dicarbonate; mp 79–80°C. Anal. calcd. for $C_{14}H_{21}NO_3$: C 66.90, H 8.42, N5.57; found: C 66.95, H 8.78, N 5.61.

N-*(*tert*-Butoxycarbonyl)-4,5-dimethoxy-2-methylbenzylamine* **1**f

This was prepared from 4,5-dimethoxy-*o*-toluic acid by conversion to the amide, reduction with LAH, and reaction with di-*tert*-butyl dicarbonate; mp 63–65°C. Anal. calcd. for $C_{15}H_{23}NO_4$: C 64.03, H 8.24, N 4.98; found: C 64.01, H 8.54, N 5.01.

N-*(*tert*-Butoxycarbonyl)-2-(1-*n*-butyl)benzylamine* **1**g

This was prepared by alkylation of the dilithio species **2***a* (see below) with 1-iodopropane; mp 46–48°C. Anal. calcd. for $C_{16}H_{25}NO_2$: C 71.45, H 9.00, H 5.95; found: C 71.64, H 9.17, N 5.54.

N-*(*tert*-Butoxycarbonyl)-2-(2-phenylethyl)benzylamine* **1**h

This was prepared from 2-bibenzylcarboxylic acid (Aldrich Chem. Co.) by conversion to the amide, reduction with LAH, and reaction with di-*tert*-butyl dicarbonate; mp 124–125°C. Anal. calcd. for $C_{20}H_{25}NO_2$: C 77.13, H 8.10, N 4.50; found: C 77.19, H 8.12, N 4.60.

N-*(*tert*-Butoxycarbonyl)2-((3-methoxyphenyl)ethyl)benzylamine* **1**i

This was prepared by alkylation of the dilithio species **2***a* with 3-methoxybenzyl chloride; mp 62–64°C. Anal. calcd. for $C_{21}H_{27}NO_3$: C 73.87, H 7.97, N 4.10; found: C 73.64, H 7.95, N 4.38.

N-*(*tert*-Butoxycarbonyl)-2-(phenylmethyl)benzylamine* **1**j

This was prepared from α-phenyl-*o*-toluic acid (Aldrich Chem. Co.) by conversion to the amide, reduction with LAH, and reaction with di-*tert*-butyl dicarbonate; mp 77–78°C. Anal. calcd. for $C_{19}H_{23}NO_2$: C 76.74, H 7.79, N 4.71; found: C 76.76, H 7.72, N 4.90.

General procedure for lithiation of **1** *followed by trapping with DMF*

A solution of the *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine **1***a* (5 mmol) in THF (10 mL) was cooled in an acetone–Dry Ice bath to ca. –60°C (internal temperature) and a solution of *sec*-BuLi (8.5 mL, 1.3 M in cyclohexane, 11 mmol) was added over a period of several minutes at such a rate as to maintain the internal temperature at ca. –30°C. The resulting bright orange solution was stirred for 5–10 min and DMF (0.58 mL, 7.5 mmol) was added. The now colorless reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with water and brine, and dried ($NaSO_4$). Removal of solvent in vacuo gave the crude product **3**, which was purified by crystallization (**3***a*, hexane) or mpc (**3***b*, **3***c*, **3***e*, **3***f*, EtOAc–hexane). Compounds **3***d* and **3***g–j* were used in the next step without purification.

The yields for the following compounds are given in Scheme 2.

*2-(*tert*-Butoxycarbonyl)-3-hydroxy-1,2,3,4-tetrahydroisoquinoline* **3**a: mp 97–98°C; ir (KBr): 3600–3200, 1682 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 9H), 2.98 (dd, 1H, J = 4.3, 15.4 Hz), 3.06 (dd, 1H, J = 4.3, 15.4 Hz), 3.65 (br s, 1H, OH), 4.46 (d, 1H, J = 15.7 Hz), 4.54 (d, 1H, J = 15.7 Hz), 5.80 (br m, 1H), 7.20 (m, 4H); ms (EI), *m/z* (% relative intensity)): 249 (3)M^+, 193 (38), 175 (44), 130 (32), 104 (100), 57 (96). Anal. calcd. for $C_{14}H_{19}NO_3$: C 67.45, H 7.68, N 5.62; found: C 67.57, H 7.82, N 5.79.

*2-(*tert*-Butoxycarbonyl)-5-fluoro-3-hydroxy-1,2,3,4-tetrahydroisoquinoline* **3**b: mp 137–138°C; ir (KBr): 3650–3200, 1668 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.51 (s, 9H), 2.97 (dd, 1H, J = 4.2, 16.4 Hz), 3.13 (dd, 1H, J = 4.2, 16.4 Hz), 3.45 (br s, 1H, OH), 4.35 (d, 1H, J = 16.2 Hz), 4.63 (d, 1H, J = 16.2 Hz), 5.92 (br m, 1H), 6.95 (m, 2H), 7.18 (m, 1H); ms (EI) *m/z* (% relative intensity): 267 (5)M^+, 211 (23), 193 (32), 167 (12), 148 (22), 122 (65), 57 (100). Anal. calcd. for $C_{14}H_{18}FNO_3$: C 62.91, H 6.79, N 5.24; found: C 63.01, H 6.76, N 5.24.

*2-(*tert*-Butoxycarbonyl)-8-chloro-3-hydroxy,1,2,3,4-tetrahydroisoquinoline* **3**c: mp 105–106°C; ir (KBr): 3660–3200, 1670 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.53 (s, 9H), 2.95 (dd, 1H, J = 3.7, 15.8 Hz), 3.10 (dd, 1H, J = 3.7, 15.8 Hz), 3.30 (br s, 1H, OH), 4.45 (d, 1H, J = 17.0 Hz), 4.70 (d, 1H, J = 17.0 Hz), 5.90 (m, 1HO, 7.14 (m, 2H), 7.27 (m, 1H); ms (EI), *m/z* (% relative intensity): 285 (7)M^+ + 2, 283 (18)M^+, 229 (6), 227 (18), 211 (12), 209 (32), 192 (12), 164 (16), 148 (22), 138 (44), 57 (100). Anal. calcd. for $C_{14}H_{18}ClNO_3$: C 59.26,H 6.40, N 4.94; found: C, 58.98, H 6.34, N 4.92.

*2-(*tert*-Butoxycarbonyl)-3-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline* **3**e: Oil; ir (neat): 3650–3150, 1693 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 9H), 2.95 (dd, 1H, J = 4.3, 15.4 Hz), 3.05 (dd, 1H, J = 4.3, 15.4 Hz), 3.80 (s, 3H), 4.44 (2, 2H), 5.75 (br s, 1H), 6.87 (m, 2H), 7.08 (m, 1H); ms (EI), *m/z* (% relative intensity): 279 (5)M^+, 222 (50), 204 (15), 160 (100), 134 (32). Exact Mass (hrms) calcd. for $C_{15}H_{21}NO_4$: 279.147; found: 279.147.

*2-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-3-hydroxy-1,2,3,4-tetrahydroisoquinoline* **3**f: mp 142–143°C; ir (KBr): 3640–3110, 1678 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 9H), 2.90 (dd, 1H, J = 3.9, 15.5 Hz), 3.02 (dd, 1H, J = 3.9, 15.5 Hz), 3.40 (br s, 1H, OH), 3.87 (s, 3H), 3.88 (s, 3H), 4.43 (m 2H), 5.80 (br m, 1H), 6.69 (s, 1H), 6.73 (s, 1H). Anal. calcd. for $C_{16}H_{23}NO_5(0.25\ H_2O)$: C 61.23, H 7.60, N 4.46; found: C 61.56, H 7.70, N 4.50; Exact Mass (hrms) calcd. for $C_{16}H_{23}NO_5$: 309.158; found: 309.158.

General procedure for dehydration of 3-hydroxy-1,2,3,4-tetrahydroisoquinolines **3**

To a solution of compound **3** (2 mmol) in THF (20 mL) was added 5 drops of concentrated HCl. The reaction mixture was stirred for 10 min at room temperature and then quenched with solid Na_2CO_3. The mixture was filtered and the filter cake was washed with EtOAc. The combined filtrate was evaporated in vacuo to afford the crude 1,2-dihydroisoquinoline **4**. Compounds **1***a* and **1***j* were isolated by mpc (EtOAc–hexane). Compounds **4***b,c,h* were used in the next step without purification. Yields for the following compounds are given in Scheme 2.

*2-(*tert*-Butoxycarbonyl)-1,2-dihydroisoquinoline* **4**a: Isolated as an unstable oil: ^{1}H nmr ($CDCl_3$) δ: 1.52 (s, 9H), 4.80 (br s, 2H), 5.66 (br d, 1H, J = 7.0 Hz), 6.80–7.19 (m, 5H).

*2-(*tert*-Butoxycarbonyl)-1,2-dihydro-4-phenylisoquinoline* **4**j: mp 96–98°C; ir (KBr): 1704 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.53 (s, 9H), 4.85 (s, 2H), 6.87–7.20 (m, 5H), 7.40 (m, 5H); ms (EI), *m/z* (% relative intensity): 307 (12)M^+, 251 (100), 206 (60). Anal. calcd. for $C_{20}H_{21}NO_2$: C 78.14, H 6.89, N 4.56; found: C 77.99, H 6.81, N 4.52.

General procedure for hydrogenation of 1,2-dihydroisoquinolines ***4*** *to 1,2,3,4-tetrahydroisoquinolines* ***5***

The 1,2-dihydroisoquinoline **4** (2 mmol) was dissolved in EtOAc (25 mL), 20% $Pd(OH)_2$ (100 mg) was added, and the mixture was hydrogenated in a Parr apparatus for ca. 12 h at 50 psi (1 psi = 6.9 kPa). The catalyst was removed by filtration through Celite and the filtrate was evaporated in vacuo to afford the crude tetrahydroisoquinoline **5**, which was purified by mpc (EtOAc–hexane). Yields for the following compounds are given in Scheme 2.

2-(tert-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline **5**a: mp 35–36°C; this material was identical to an authentic sample prepared from 1,2,3,4-tetrahydroisoquinoline.

2-(tert-Butoxycarbonyl)-5-fluoro-1,2,3,4-tetrahydroisoquinoline **5**b: mp 39–40°C; ir (KBr): 1698 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.48 (s, 9H), 2.81 (t, 2H, J = 5.9 Hz), 3.65 (t, 2H, J = 5.9 Hz), 4.58 (s, 2H), 6.88 (m, 2H), 7.14 (m, 1H); ms (EI), *m/z* (% relative intensity): 251 (5)M^+, 195 (50), 194 (100), 178 (23), 150 (43), 122 (17), 57 (79). Anal. calcd. for $C_{14}H_{18}FNO_2$: C, 66.91, H 7.61, N 5.28; found: C 66.86, H 7.61, N 5.28.

2-(tert-Butoxycarbonyl)-8-chloro-1,2,3,4-tetrahydroisoquinoline **5**c: mp 42–43°C; ir (KBr): 1692 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.50 (s, 9H), 2.83 (t, 2H, J = 5.6 Hz), 3.64 (t, 2H, J = 5.6 Hz), 4.58 (s, 2H), 7.09 (m, 2H), 7.22 (m, 1H); ms (EI), *m/z* (% relative intensity): 210 (37)M^+, 194 (11), 168 (10), 168 (33), 138 (17), 103 (7), 57 (100). Anal. calcd. for $C_{14}H_{18}ClNO_2$: C 62.80, H 6.78, N 5.23; found: C 62.80, H 6.76, N 5.23.

2-(tert-Butoxycarbonyl)-6-chloro-8-(2-propyl)-1,2,3,4-tetrahydroisoquinoline **5**d: mp 60–63°C; ir (KBr): 1697 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.22 (d, 6H, J = 6.7 Hz), 1.47 (s, 9H), 2.81 (t, 2H, J = 5.7 Hz), 3.02 (br m, 1H), 3.60 (t, 2H, J = 5.7 Hz), 4.56 (s, 2H), 6.97 (d, 1H, J = 2.1 Hz), 7.10 (d, 1H, J = 2.1 Hz); ms(EI), *m/z* (% relative intensity): 309 (1)M^+, 254 (40), 252 (100), 236 (10), 218 (10), 208 (21), 180 (14), 57 (78). Anal. calcd. for $C_{17}H_{24}ClNO_2$: C 66.12, H 7.51, N 4.54; found: C 66.25, H 7.92, N 4.48.

2-(tert-Butoxycarbonyl)-4-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline **5**h: Oil; for characterization this was deprotected with trifluoroacetic acid in CH_2Cl_2 followed by conversion to the HCl salt to afford *4-(phenylmethyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride*; mp 179–180°C; ir (KBr): 3630–3260 cm^{-1}; ^1H nmr (Me_2SO-d_6) δ: 2.99 (m, 2H), 3.12 (dd, 1H, J = 5.2, 12.8 Hz), 3.25 (dd, 1H, J = 4.7, 13.6 Hz), 3.46 (m, 1H), 4.23 (AB quartet, J_{AB} = 16.2 Hz), 7.30 (m, 8H), 7.48 (d, 1H, J = 7.0 Hz), 9.80 (br s, NH_2^+). Anal. calcd. for $C_{16}H_{18}ClN$: C 73.97, H 6.99, N 5.39; found: C 73.82, H 6.97, N 5.26.

N-*(2-Methyl-1-propenyl)-4-chlorobenzamide* ***7***

Benzamide **6** was prepared from 4-chlorobenzoyl chloride and 2-methylallylamine hydrochloride (CH_2Cl_2, Et_3N) in 97% yield; mp 111–112°C. Anal. calcd. for $C_{11}H_{12}ClNO_3$: C 63.01, H 5.77, N 6.68; found: C 62.96, H 5.76, N 6.61.

A solution of *n*-BuLi (44 mL, 2.5 M in hexane, 110 mmol) was added to a solution of diisopropylamine (15.4 mL, 110 mmol) in THF (200 mL) at –60°C and the resulting solution was stirred at this temperature for 5 min. A solution of amide **6** (10.5 g, 50 mmol) in THF (50 mL) was slowly added and the mixture was stirred at ca. –60°C for 1 h and then allowed to warm to –10°C over a period of 45 min. Saturated aqueous NH_4Cl solution was added and the reaction mixture was then partitioned between EtOAc and water. The EtOAc was washed with water and brine, dried (Na_2SO_4), and evaporated. Crystallization of residue from EtOAc–hexane gave amide **7** (26.5 g, 89%); mp 129–130°C; ir (KBr): 3600–3200, 1638 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.71 (d, 3H, J = 1.3 Hz), 1.78 (d, 3H, J = 1.1 Hz), 6.74 (m, 1H), 7.35 (br s, 1H, NH), 7.43 (d, 2H, J = 8.5 Hz), 7.74 (d, 2H, J = 8.5 Hz); ms (EI), *m/z* (% relative intensity): 211 (11) M+2, 209 (32)M^+, 194 (14), 141 (37), 139 (100), 113 (7), 111 (15). Anal. calcd. for $C_{11}H_{12}ClNO$: C 63.01, H 5.77, N 6.68; found: C 62.76, H, 5.73, N, 6.60.

N-*(2-Methyl-1-propenyl)-4-chloro-2-ethylbenzamide* ***8***

To a –70°C solution of amide **7** (7.0 g, 33.4 mmol) in THF (100 mL) was added a solution of *sec*-BuLi (56.5 mL, 1.3 M in cyclohexane, 73.4 mmol) and the resulting dark solution was stirred at –70°C for 30 min. The temperature of the solution was allowed to slowly rise to –30°C over 30 min and the mixture was then cooled back to –70°C. Iodoethane (4 mL, 50 mmol) was added and the mixture was allowed to warm to 0°C. Aqueous NH_4Cl solution was added and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated. Crystallization of the residue from hexane afforded compound **8** (6.94 g, 87%); mp 86–87°C; ir (KBr): 3600–3200, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.26 (t, 3H, J = 7.6 Hz), 1.66 (d, 3H, J = 1.0 Hz), 1.78 (d, 3H, J = 1.0 Hz), 2.81 (q, 2H, J = 7.6 Hz), 6.70 (m, 1H), 7.13 (m, 1H, NH), 7.22 (dd, 1H, J = 2.0, 8.1 Hz), 7.29 (d, 1H, J = 2.0 Hz), 7.33 (d, 1H, J = 8.1 Hz). Anal. calcd. for $C_{13}H_{16}ClNO$: C 65.68, H 6.79, N 5.89; found: C 65.53, H 6.81, N 5.60.

N-*(2-Methyl-1-propenyl)-4-chloro-2-(2-propyl)benzamide* ***9***

To a stirred solution of 2,2,6,6-tetramethylpiperidine (17.8 mL, 105 mmol) in THF (150 mL) at –60°C was added *n*-BuLi (65.7 mL, 1.6 M in hexane, 105 mmol). After 10 min, the LiTMP solution was treated dropwise with a solution of amide **8** (10.0 g, 42 mmol) in THF (150 mL). After stirring the deep purple solution at –60°C for 1 h, the temperature was allowed to slowly rise to –10°C over a 1 h period and the reaction was then quenched by addition of NH_4Cl solution. The mixture was extracted with EtOAc (300 mL) and the extract was successively washed with water, 1 N HCl, water, and brine. The EtOAc was dried (Na_2SO_4) and evaporated to give amide **9** (10.0 g, 94%); mp 110–111°C; ir (KBr): 3700–3180, 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.25 (d, 6H, J = 6.9 Hz), 1.64 (s, 3H), 1.77 (s, 3H), 3.34 (hept, 1H, J = 6.9 Hz), 6.70 (m, 1H), 7.00 (br d, 1H, NH), 7.19 (dd, 1H, J = 2.0, 8.2 Hz), 7.26 (d, 1H, J = 8.2 Hz), 7.35 (d, 1H, J = 2.0 Hz); ms (EI), *m/z* (% relative intensity): 253 (7)M+2, 251 (22)M^+, 183 (34), 181 (100), 165 (32), 146 (7), 128 (14). Anal. calcd. for $C_{14}H_{18}ClNO$: C 66.79, H 7.21, N 5.56; found: C 66.47, H 7.25, N 5.44.

N-*(2-Methyl-1-propenyl)-4-chloro-6-methyl-2-(2-propyl)benzamide* ***11***

To a stirred solution of amide **9** (2.0 g, 8.0 mmol) in THF (20 mL) at –60°C was added a solution of *sec*-BuLi (15.3 mL, 1.3 M in cyclohexane, 19.9 mmol). The reaction mixture was stirred at –60°C for 1 h and at –30°C for an additional hour. The solution was cooled to –60°C and treated with iodomethane (0.74 mL, 11.9 mmol). Aqueous NH_4Cl was added and the mixture was extracted with EtOAc and worked up as in the previous example to afford amide **11** (1.7 g, 81%) after crystallization from cyclohexane; mp 101–103°C; ir (KBr): 3620–3200, 1628 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.23 (d, 6H, J = 6.8 Hz), 1.61 (s, 3H), 1.77 (s, 3H), 2.30 (s, 3H), 2.98 (hept, 1H, J = 6.9 Hz), 6.72 (m, 1H), 6.88 (br d, 1H, NH), 7.05 (d, 1H, J = 1.9 Hz), 7.14 (d, 1H, J = 1.9 Hz; ms EI), *m/z* (% relative intensity): 267 (7)M^++2, 265 (20)M^+, 197 (35), 195 (100), 181 (10), 177 (20). Anal. calcd. for $C_{15}H_{20}ClNO$: C 67.78, H 7.59, N 5.27; found: 67.67, H 7.54, N 5.32.

4-Chloro-6-methyl-2-(2-propyl)benzamide ***12***

A solution of amide **11** (4.1 g, 15.5 mmol) in acetic acid (20 mL), water (20 mL), and concentrated HCl (1 mL) was heated at 80°C for 24 h. The cooled reaction mixture was concentrated in vacuo, diluted with water, and extracted with EtOAc. The EtOAc extract was washed with 5% Na_2CO_3 solution, water, and brine, dried (Na_2SO_4), and evaporated. Crystallization of the residue from EtOAc–hexane gave benzamide **12** (3.1 g, 95%); mp 138–140°C; ir (KBr): 3600–3300, 1643 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.24 (d, 6H, J = 6.9 Hz), 2.33 (s, 3H), 3.07 (hept, 1H, J = 6.9 Hz), 5.77 (br s, 1H, NH), 6.31 (br s, 1H, NH), 7.03 (d, 1H, J = 1.5 Hz), 7.13 (d, 1H, J = 1.5 Hz); ms (EI), *m/z* (% relative intensity): 213 (31)M+2, 211 (93)M^+, 196 (61), 194 (100), 181 (32), 179 (83), 115 (46). Anal. calcd. for $C_{11}H_{14}ClNO$: C 62.42, H 6.67, N 6.62; found: C 62.54, H 6.66, N 6.32.

6-Chloro-2-(2-methyl-1-propenyl)-8-(2-propyl)-1(2H)-isoquinolone ***13***

This compound was prepared in 96% yield from **11** according to the procedures described in ref. 11; mp 91–93°C (EtOAc–hexane); ir

(KBr): 1651 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.29 (d, 6H, J = 6.9 Hz), 1.68 (d, 3H, J = 1.1 Hz), 1.89 (d, 3H, J = 1.4 Hz), 4.84 (hept, 1H, J = 6.9 Hz), 6.35 (d, 1H, J = 7.3 Hz), 6.50 (m, 1H), 6.97 (d, 1H, J = 7.3 Hz), 7.31 (d, 1H, J = 2.1 Hz), 7.37 (d, 1H, J = 2.1 Hz); ms (EI), *m/z* (% relative intensity): 277 (36)M+2, 275 (100)M^+, 262 (95), 260 (100), 220 (22), 218 (40), 206 (17), 204 (33). Anal. calcd. for $C_{16}H_{18}ClNO$: C 69.68, H 6.58, N 5.08; found: C 69.63, H 6.67, N 5.47.

*General procedure for the preparation of ketones **14** by condensation of dianion **2**a with* N-*methoxy*-N-*methylamides*

Amide **1***a* was converted to dianion **2***a* as described above and treated at –60°C with the requisite *N*-methoxy-*N*-methylamide (prepared as described in ref. 1). The reaction mixture was allowed to warm to –30°C over a 0.5 h period and was then quenched by addition of NH_4Cl solution and worked up by EtOAc extraction to afford ketones **14***a–d*. Purification was by mpc (EtOAc–hexane). Yields for the following compounds are given in Scheme 4.

*1-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-2-hexanone **14**a*: mp 66–67°C; ir (KBr): 3660–3200, 1713, 1686 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.90 (t, 3H, J = 7.3 Hz), 1.40 (m, 2H), 1.44 (s, 9H), 1.59 (m, 2H), 2.51 (t, 2H, J = 7.5 Hz), 3.80 (s, 2H), 4.24 (d, 2H, J = 5.7 Hz), 4.88 (br m, 1H, NH), 7.11 (m, 1H), 7.25 (m, 2H), 7.31 (m, 1H); ms (EI), *m/z* (% relative intensity): 249 (19)M^+, 231 (25), 189 (21), 187 (26), 104 (100), 85 (41), 57 (65). Anal. calcd. for $C_{18}H_{27}NO_3$: C 70.79, H 8.91, N 4.59; found: C 70.79, H 8.97, N 4.65.

*1-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-6-chloro-2-hexanone **14**b*: mp 47–48°C; ir (KBr): 3350, 1713, 1686 cm–^{1}; ^1H nmr ($CDCl_3$) δ: 1.45 (s, 9H), 1.75 (m, 4H), 2.56 (t, 2H, J = 6.7 Hz), 3.50 (m, 2H), 3.81 (s, 2H), 4.24 (d, 2H, J = 5.8 Hz), 4.85 (br m, 1H, NH), 7.10 (m, 1H), 7.25 (m, 2H), 7.32 (m, 1H); ms (EI), *m/z* (% relative intensity): 283 (15), 265 (28), 223 (34), 222 (34), 104 (100), 91 (29), 57 (45). Anal. calcd. for $C_{18}H_{26}ClNO_3$: C 63.61, H 7.71, N 4.12; found: C 63.66, H 7.84, N 3.72.

*2-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-1-phenylethanone **14**c*: mp 110–112°C; ir (KBr): 3720–3160, 1686 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.35 (s, 9H), 4.28 (d, 2H, J = 5.6 Hz), 4.41 (s, 2H), 4.89 (br m, 1H, NH), 7.15 (m, 1H), 7.28 (m, 2H), 7.35 (m, 1H), 7.49 (m, 2H), 7.59 (m, 1H), 8.04 (m, 2H); ms (EI), *m/z* (% relative intensity): 325 (1)M^+, 269 (7), 268 (7), 251 (10), 208 (30), 105 (100). Anal. calcd. for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found: C 73.89, H 7.15, N 4.40.

*3-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-1-(3,4-dimethoxyphenyl)-2-propanone **14**d*: mp 90–91°C; ir (KBr): 3660–3220, 1719, 1684 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 3.73 (s, 2H),3.84 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.18 (d, 2H, J = 5.8 Hz), 4.82 (br m, 1H, NH), 6.70 (m, 1H), 6.75 (m, 1H), 6.83 (m, 1H), 7.02 (m, 1H), 7.23 (m, 3H); ms (EI), *m/z* (% relative intensity): 399 (33)M^+, 343 (8), 299 (75), 282 (74), 254 (20), 151 (100). Anal. calcd. for $C_{23}H_{29}NO_5$: C 69.15, H 7.32, N 3.51; found: C 69.04, H 7.39, N 3.74.

*General procedure for cyclization of ketones **14** to dihydroisoquinolines **15***

A solution of ketone **14** (10 mmol) in CH_2Cl_2 (25 mL) at 0°C was treated with trifluoroacetic acid (0.75 mL) and the mixture was stirred with warming to room temperature over a 0.5 h period. Additional CH_2Cl_2 (50 mL) was added and the mixture was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Evaporation afforded the crude product (**15**), which could be purified by mpc (EtOAc–hexane) or used directly in subsequent reactions. Yields for the following compounds are given in Scheme 4.

*2-(*tert*-Butoxycarbonyl)-1-(1-*n*-butyl)-1,2-dihydroisoquinoline **15**a*: Oil; ir (neat): 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.94 (t, 3H, J = 7.2 Hz), 1.38 (m, 2H), 1.48 (s, 9H), 1.51 (m, 2H), 2.66 (t, 2H, J = 7.0 Hz), 4.67 (s, 2H), 6.04 (s, 1H), 7.04 (m, 1H), 7.18 (m, 3H); ms (EI), *m/z* (% relative intensity): 287 (18)M^+, 231 (100), 189 (25), 186 (54), 156 (13), 145 (21), 143 (35), 57 (68). Anal. calcd. for $C_{18}H_{25}NO_2$: C 75.22, H 8.77, N 4.87; found: C 75.02, H 8.73, N 5.06.

*2-(*tert*-Butoxycarbonyl)-3-(4-chloro-1-*n*-butyl)-1,2-dihydroisoquinoline **15**b*: Oil; ir (neat): 1701 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.48 (s, 9H), 1.70 (m, 2H), 1.85 (m, 2H), 2.70 (t, 2H, J = 7.7 Hz), 3.57 (t, 2H, J = 6.4 Hz), 4.67 (s, 2H), 6.05 (s, 1H), 7.04 (m, 1H), 7.18 (m, 3H); ms (EI), *m/z* (% relative intensity): 321 (20)M^+, 267 (47), 265 (96), 222 (26), 221 (34), 220 (64), 186 (17), 184 (20), 57 (100). Anal. calcd. for $C_{18}H_{24}ClNO_2$: C 66.35, H 7.44, N 4.28; found: C 66.38, H 7.13, N 4.41.

*2-(*tert*-Butoxycarbonyl)-1,2-dihydro-3-phenylisoquinoline **15**c*: mp 105–106°C; ir (KBr): 1704 cm^{-1}: ^1H nmr ($CDCl_3$) δ: 1.05 (s, 9H), 4.89 (s, 2H), 6.43 (s, 1H), 7.18–7.40 (m, 7H), 7.50 (m, 1H); ms (EI), *m/z* (% relative intensity): 307 (11)M^+, 251 (43), 206 (100), 128 (7), 57 (43). Anal. calcd. for $C_{20}H_{21}NO_2$: C 78.14, H 6.89, N 4.56; found: C 77.94, H 6.91, H 6.91, N 4.54.

*2-(*tert*-Butoxycarbonyl)-1,2-dihydro-3-(3,4-dimethoxyphenylmethyl)isoquinoline **15**d*: Waxy solid; ir (KBr): 1701 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 3.85 (s, 3H), 3.88 (s, 3H), 3.95 (s, 2H), 4.60 (s, 2H), 6.07 (s, 1H), 6.82 (m, 3H), 7.17 (m, 4H); ms (EI), *m/z* (% relative intensity): 381 (4)M^+, 325 (44), 280 (100), 57 (30). Exact Mass (hrms) calcd. for $C_{23}H_{27}NO_4$: 381.194; found: 381.194.

*General procedure for the catalytic hydrogenation of **15***

A mixture of dihydroisoquinoline **15** (10 mmol) and 20% $Pd(OH)_2$ (0.7 g) in EtOAc (30 mL) was hydrogenated for 12 h at ca. 45 psi. The catalyst was removed by filtration and evaporation of the filtrate afforded crude **16**, which was purified by mpc (**16***b*) (EtOAc–hexane) or used directly in a subsequent reaction (**16***d*).

*2-(*tert*-Butoxycarbonyl)-3-(4-chloro-1-*n*-butyl)-1,2,3,4-tetrahydroisoquinoline **16**b*: Oil; ir (neat): 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.20–1.50 (m, 4H), 1.45 (s, 9H), 1.75 (m, 2H), 2.63 (d, 1H, J = 15.9 Hz), 3.19 (dd, 1H, J = 5.8, 15.9 Hz), 3.50 (t, 2H, J = 6.6 Hz), 4.20 (br d, 1H, J = 17.2 Hz), 4.50 (br d, 1H, J = 17.2 Hz), 4.83 (m, 1H), 7.15 (m, 4H); ms (EI), *m/z* (% relative intensity): 266 (42)$M^+ - C_4H_9$, 232 (26), 176 (100), 132 (39). Anal. calcd. for $C_{18}H_{26}ClNO_2$: C 66.75, H 8.10, N 4.32; found: C 66.92, H 8.15, N 4.32.

*3-*n*-Butyl-1,2,3,4-tetrahydroisoquinoline **17**a*

A solution of ketone **14***a* (1.07 g, 3.5 mmol) in CH_2Cl_2 (5 mL) was cooled in an ice-bath and trifluoroacetic acid (3 mL) was added. The mixture was stirred at room temperature for 1 h and was then concentrated in vacuo. The residue was dissolved in EtOH (10 mL) and the resulting solution was cooled in an ice-bath. $NaBH_4$ (0.5 g, 13 mmol) was slowly added in small portions and the mixture was stirred with warming to room temperature over 1 h. Aqueous 5% HCl (30 mL) was added and the mixture was basified with NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and evaporated to give **17***a* as an oil that was homogeneous by tlc (5% MeOH–CH_2Cl_2); ^1H nmr ($CDCl_3$) δ: 0.93 (t, 3H, J = 6.9 Hz), 1.30–1.55 (m,6H), 1.86 (br s, 1H, NH), 2.50 (dd, 1H, J = 10.5, 16.2 Hz), 2.80 (dd, 1H, J = 3.9, 16.2 Hz), 2.85 (m, 1H), 4.06 (AB quartet, 2H, J_{AB} = 16.0 Hz), 6.96–7.12 (m, 4H); ms (EI), *m/z* (% relative intensity): 189 (4)M^+, 188 (3), 133 (16), 132 (100), 130 (21), 104 (18).

Hydrochloride salt: mp 149–151°C (EtOH–Et_2O). Anal. calcd. for $C_{13}H_{20}ClN$: C 69.16, H 8.93, N 6.20; found: C 68.93, H 8.87, N 6.32.

*3-(3,4-Dimethoxyphenyl)methyl-1,2,3,4-tetrahydroisoquinoline **17**d*

Crude **16***d* (0.80 g, 2.1 mmol), obtained as above, was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (2 mL) was added. The resulting solution was allowed to stand at room temperature for 48 h. Additional CH_2Cl_2 (50 mL) was added and the mixture was washed (carefully) with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. Purification by mpc (3% MeOH–CH_2Cl_2, 0.5% NH_4OH) afforded **17***d* (0.48 g, 81%); mp 99–100°C; ir (KBr): 3650–3250 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.57–2.90 (m, 4H), 3.12 (m, 1H), 3.88 (s, 6H), 4.03 (s, 2H), 6.81 (m, 3H), 6.96–7.14 (m, 4H); ms (EI), *m/z* (% relative intensity): 152 (8) $M^+ - C_9H_{10}N$, 132 (100). Anal. calcd. for $C_{18}H_{21}NO_2$(0.2 H_2O): C 75.32, H 7.52, N 4.88; found: C 75.32, H 7.27, N 4.88.

*1,3,4,6,11,11a-Hexahydro-2*H*-benzo[*b*]quinolizine **18***

A solution of **16***b* (0.25 g, 0.77 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (1 mL) and the resulting mixture was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, saturated $NaHCO_3$ solution was added, and the mixture was extracted three times with EtOAc. The EtOAc extract was washed with water and brine, dried (Na_2SO_4), and evaporated. Purification of the

residue by mpc (5% MeOH–CH_2Cl_2, 0.1% NH_4OH) afforded compound **18** (0.14 g, 94%); mp 42–43°C (lit. (20) mp 46–47°C); HCl salt, mp 252–254°C. Anal. calcd. for $C_{13}H_{18}ClN$: C 69.78, H 8.11, N, 6.26; found: C 69.37, H 8.00, N 6.23.

*2,3-Dimethoxy-7,12,12a,13-tetrahydro-5H-dibenzo[*b,g*]quinolizine* ***19***

A suspension of **17***d* (0.10 g, 0.35 mmol) in water (1 mL) was treated with concentrated HCl (3 drops) and 37% aqueous formaldehyde (0.6 mL) and the resulting solution was stirred at 95°C for 1 h. After dilution with water (10 mL), the mixture was basified with NH_4OH and extracted with EtOAc. The EtOAc extract was washed with water and brine, dried (Na_2SO_4), and evaporated. Purification by mpc (3% MeOH–CH_2Cl_2, 0.5% NH_4OH) gave **19** (0.09 g, 89%); mp 176–177°C; ^1H nmr ($CDCl_3$) δ: 2.72 (dd, 1H, J = 5.0, 16.8 Hz), 2.80 (dd, 1H, J = 5.0, 16.8 Hz), 2.92 (dd, 1H, J = 5.0, 16.8 Hz), 3.03 (dd, 1H, J = 5.0, 16.8 Hz), 3.23 (m, 1H), 3.78 (d, 1H, J = 15.5 Hz), 3.82 (d, 1H, J = 15.5 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 3.97 (d, 1H, J = 15.5 Hz), 4.04 (d, 1H, J = 15.5 Hz), 6.55 (s, 1H), 6.58 (s, 1H), 7.10 (m, 4H); ms (EI), *m/z* (% relative intensity): 295 (42)M^+, 164 (100). Anal. calcd. for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74; found: C 77.15, H 7.20, N 4.85.

*3-*n*-Butylisoquinoline* ***20***

A solution of dihydroisoquinoline **15***a* (1.0 g, 3.5 mmol) in CH_2Cl_2 (2.5 mL) was treated with trifluoroacetic acid (2.5 mL) and the resulting mixture was stirred at room temperature for 15 min. The solution was concentrated in vacuo and the residue was dissolved in EtOH (20 mL). To this solution was added KOAc (0.98 g, 10 mmol) and I_2 (1.0 g, 4 mmol) and the mixture was heated under reflux for 2 h. The mixture was cooled to room temperature, diluted with aqueous NH_4OH, and extracted with EtOAc. The EtOAc was washed with aqueous $NaHSO_3$, water, and brine, dried (Na_2SO_4), and evaporated. Purification by mpc (2% MeOH–CH_2Cl_2) afforded **20** as a colorless oil. The ^1H nmr spectrum of this material was identical to that reported in ref. 19. The HCl salt had mp 202–203°C (EtOH–Et_2O).

*2-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-1-(3,4-dimethoxyphenyl)ethanol* ***21***

A solution of anion **2***a*, prepared from **1***a* (0.50 g, 2.26 mmol) in THF (10 mL) as previously described, was treated with a solution of veratraldehyde (0.42 g, 2.49 mmol) in THF (2 mL) at –60°C. The reaction mixture was stirred at that temperature for 30 min and then worked up as usual to afford alcohol **21** (0.58 g, 66%) after mpc (40% EtOAc–hexane); mp 99–100°C; ir (KBr): 3600–3110, 1694 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.45 (s, 9H), 2.15 (br m, 1H, OH), 3.00 (dd, 1H, J = 8.5, 13.9 Hz), 3.10 (dd, 1H, J = 4.7, 13.9 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 4.34 (d, 2H, J = 5.2 Hz), 4.87 (dd, 1H, J = 4.7, 8.4 Hz), 5.09 (br m, 1H,NH), 6.83 (d, 1H, J = 8.7), 6.92 (m, 2H), 7.17–7.32 (m, 4H); ms (EI), *m/z* (% relative intensity): 387 (6)M^+, 221 (9), 167 (100), 166 (73), 139 (24), 104 (50), 57 (34). Anal. calcd. for $C_{22}H_{29}NO_5$: C 68.19, H 7.54, N 3.62; found: C 68.17, H 7.44, N 3.55.

*2-(*tert*-Butoxycarbonyl)-(3-(3,4-dimethoxyphenyl))-1,2,3,4-tetrahydroisoquinoline* ***23***

A solution of **21** (0.25 g, 0.65 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (0.5 mL) and the resulting mixture was stirred at room temperature for 0.5 h. The usual work-up afforded **25** (0.21 g, 87%) after mpc (30% EtOAc–hexane); mp 58–60°C; ir (neat): 3570–3200, 1690 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 3.06 (dd, 1H, J = 3.4, 15.7 Hz), 3.31 (dd, 1H, J = 6.1, 15.8 Hz), 3.68 (s, 3H), 3.78 (s, 3H), 4.23 (d, 1H, J = 16.4 Hz), 4.80 (d, 1H, J = 16.4 Hz), 5.44 (m, 1H), 6.67 (m, 3H), 7.13 (m, 4H); ms (EI), *m/z* (% relative intensity): 369 (21)M^+, 313 (33), 268 (40), 252 (24), 175 (40), 131 (19), 104 (29), 57 (36), 43 (100). Anal. calcd. for $C_{22}H_{27}NO_4$: C 71.52, H 7.37, N 3.79; found: C 71.51, H 7.51, N 3.63.

*2-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-1,1-diphenylethanol* ***24***

A solution of dianion **2***a*, prepared from **1***a* (1.1 g, 5.0 mmol) in THF (10 mL) as described above, was treated with a solution of benzophenone (1.0 g, 5.5 mmol) in THF (5 mL) at –60°C. The reaction mixture was stirred at –60°C for 30 min and was then allowed to warm to 0°C. The usual work-up afforded alcohol **24** (1.2 g, 60%) after crystallization from hexane; mp 117–118°C; ir (KBr): 3600–3200, 1701 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.42 (s, 9H), 1.95 (br m, 1H, OH), 3.69 (s, 2H), 4.18 (br s, 2H), 4.80 (br m, 1H, NH), 6.63 (d, 1H, J = 7.5 Hz), 6.96 (t, 1H, J = 7.5 Hz), 7.14 (t, 1H, J = 7.5 Hz), 7.25 (m, 7H), 7.37 (m, 4H); ms (EI), *m/z* (% relative intensity): 403 (4)M^+, 347 (5), 312 (5), 269 (7), 221 (12), 183 (100), 165 (45), 105 (38), 104 (33). Anal. calcd. for $C_{26}H_{29}NO_3$: C 77.39, H 7.25, N 3.47; found: C 77.63, H 7.33, N 3.60.

*2-[2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl]-1,1-diphenylethylene* ***25***

A solution of **24** (0.2 g, 0.5 mmol) in CH_2Cl_2 (5 mL) was treated with trifluoroacetic acid (0.75 mL) and the resulting mixture was stirred at room temperature for 15 min. Anhydrous K_2CO_3 (1.0 g), and CH_2Cl_2 (25 mL) were added and the mixture was filtered. Evaporation of the filtrate afforded compound **25** (0.16 g, 83%) after crystallization from hexane; mp 106–108°C; ir (KBr): 3620–3200, 1688 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.40 (s, 9H), 4.34 (d, 2H, J = 5.8 Hz), 4.63 (br m, 1H, NH), 6.88–7.40 (m, 15H); ms (EI), *m/z* (% relative intensity): 385 (26)M^+, 329 (36), 284 (70), 268 (100), 57 (68). Anal. calcd. for $C_{26}H_{27}NO_2$: C 81.00, H 7.06, N 3.63; found: C 81.25, H 7.06, N 3.81.

*1-[(2-((*tert*-Butoxycarbonyl)aminomethyl)phenyl)methyl]cyclohexan-1-ol* ***26***

Condensation of dianion **2***a* with cyclohexanone as described for the preparation of **25** afforded alcohol **26** in 50% yield after crystallization from hexane; mp 82–83°C; ir (KBr): 3600–3200, 1680 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.20 (m, 2H), 1.40–1.65 (m, 9H), 1.45 (s, 9H), 2.81 (s, 2H), 4.40 (br d, 2H, J = 5.0 Hz), 5.20 (br m, 1H, NH), 7.18 (m, 3H), 7.32 (m, 1H). Anal. calcd. for $C_{19}H_{29}NO_3$: C 71.44, H 9.15, N 4.38; found: C 71.47, H 9.21, H 4.52.

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