Condensation of Laterally Lithiated *o*-Methyl and *o*-Ethyl Benzamides with Imines Mediated by (−)-Sparteine. Enantioselective Synthesis of Tetrahydroisoquinolin-1-ones

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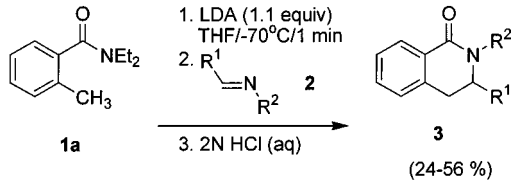
The first asymmetric synthesis of tetrahydroisoquinolin-1-ones using a (−)-sparteine-mediated lateral metalation−imine addition sequence to furnish 3-phenyl tetrahydroisoquinolinones **3a** with enantioselectivities up to 81% ee is described (Scheme 4). For amide **7b**, imine addition products **10** and **11** have been obtained with high diastereoselectivities (91−97% de) and enantioselectivities (91−98% ee) (Scheme 8).

Introduction

The isoquinoline nucleus is the distinguishing feature of a large and diverse family of pharmacologically important alkaloids.[1] Among the numerous asymmetric synthetic methods for 1-substituted isoquinolines,[2] the classical Pictet−Spengler[3] or Bischler−Napieralski/hydrogenation reactions[4] occupy prominent positions. In contrast, there are fewer methods for the stereocontrolled synthesis of 3-substituted or 3,4-disubstituted tetrahydroisoquinolines.[5] In a series of papers beginning in 1985, Clark and co-workers reported reactions of lithiated *o*-toluamides **1** with imines **2** to give tetrahydroisoquinolinones **3** in low to moderate yields (Scheme 1).[6]

While asymmetric addition reactions of organolithium and organomagnesium compounds to imines have been studied intensively,[7−8] to the best of our knowledge, only a single case of an asymmetric synthesis of tetrahydroisoquinolones, in which enantioinduction is achieved via an imine-appended chiral auxiliary, has been described.[7a]

Scheme 1



R^1 = Ph, 2-(Me)C_6H_4, 4-(MeO)C_6H_4, 3,4-(MeO)$_2C_6H_3$, 4-pyridyl, c-C_6H_{11}

R^2 = Me, *n*-Bu, $CH_2CH_2N(CH_3)_2$, Bn, c-C_6H_{11}

In 1994, Beak and co-workers reported[9] the (−)-sparteine-mediated lateral metalation−electrophile quench of *o*-ethylbenzamides in which enantioenrichments (68−92% ee) were established as resulting from either dynamic kinetic or thermodynamic resolution. Recently, chiral diamines, e.g., bisoxazolines,[10] and 1,5-diaza-decalins[11] have been shown to serve as ligands in asymmetric benzylic metalation−substitution reactions (5−98% ee). We have linked the Beak and Clark studies and report on the (−)-sparteine-mediated lateral metalation of *ortho*-alkylated benzamides **1** and their reaction with imines **2** leading to chiral tetrahydroisoquinolinones **3** (Scheme 2). This method does not require the introduction and cleavage of chiral auxiliaries and has the advantage of diverse precursor benzamide availability via the regioselective directed *ortho*-metalation (DoM) strategy.[12]

Results and Discussion

To gain more insight into the scope and limitations of Clark's methodology, we first investigated reactions of laterally metalated amide **1a** with different imines **2a**−**e** (Scheme 2). In consonance with the Clark studies,[6b] only imines with small R^3 steric demand (**2a,b**) lead to cyclized

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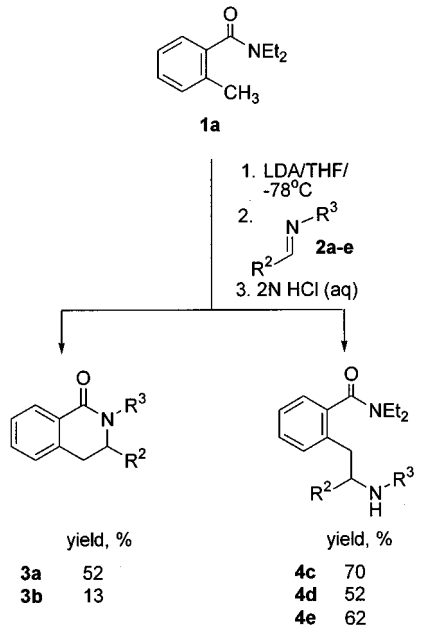
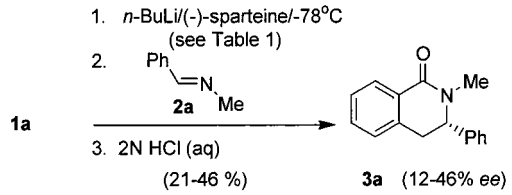
Scheme 2



Scheme 3



products (**3a**,**b**). With other imines **2c**−**e**, the reaction is arrested at the stage of the cyclization precursors **4c**−**e**, which were isolated in 53−70% yield. Furthermore, efforts to optimize the reported reaction conditions[6b] by warming the reaction mixture to room temperature and/or quenching with Lewis acids (e.g., $TiCl_4$, $BF_3{\cdot}Et_2O$)[13] also failed, leading to low yields of **3a** and undetermined byproducts.

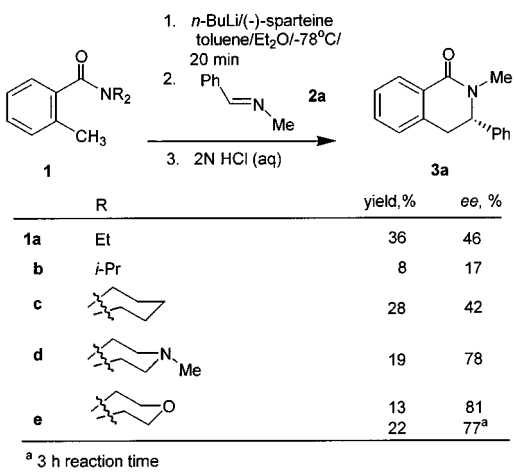
The above results guided the choice of the reaction conditions for the (−)-sparteine-mediated asymmetric condensation−cyclization of **1a** with *N*-methylbenzylideneamine **2a** as a model study (Scheme 3, Table 1). Empirical observations on related *o*-ethyl aryl *O*-carbamates[14] had indicated that metalation with *n*-BuLi/(−)-sparteine in toluene/ether solvent mixtures provides optimum results in terms of yields and enantioinduction. However, variation of the ratio of this solvent pair using *n*-BuLi/(−)-sparteine metalation conditions (entries 4−6) led to modest yields and enantioselectivities of isoquinolinone **3a** which were marginally better than results observed using the respective single solvents (entries 2 and 3). Longer metalation times did not affect the yields or enantioselectivities (entries 7−9). On the other hand,

Table 1. Synthesis of Tetrahydroisoquinolinone 3a[a]

entry	base[b]	solvent	time[c] (min)	yield (%)	% ee[d]
1	LDA	THF	2	52	
2	*n*-BuLi/L*	Et_2O	5	32	28
3	*n*-BuLi/L*	toluene	5	21	41
4	*n*-BuLi/L*	toluene/Et_2O 3:1	5	36	46
5	*n*-BuLi/L*	toluene/Et_2O 2:1	2	29	34
6	*n*-BuLi/L*	toluene/Et_2O 1:1	5	38	44
7	*n*-BuLi/L*	toluene/Et_2O 2:1	10	30	42
8	*n*-BuLi/L*	toluene/Et_2O 2:1	30	31	43
9	*n*-BuLi/L*	toluene/Et_2O 2:1	60	20	42
10	*s*-BuLi/L*	toluene/Et_2O 1:1	5	46	12
11	*t*-BuLi/L*	toluene/Et_2O 1:1	5	27	36

[a] Standard conditions: amide **1a** was added to the base by syringe at −78 °C. After 5 min, the imine **2a** was added and the reaction mixture was stirred for 20 min and quenched by the addition of aqueous 2 N HCl. [b] L* = (−)-sparteine. [c] Metalation time. [d] Determined by CHIRALOD-HPLC-column (hexanes/PrOH 92:8).

Scheme 4



	R	yield,%	*ee*, %
1a	Et	36	46
b	*i*-Pr	8	17
c		28	42
d		19	78
e		13	81
		22	77[a]

[a] 3 h reaction time

metalation of amide **1a** with *n*-BuLi/(−)-sparteine and subsequent reaction with the imines **2c** and **2e** yielded the uncyclized racemic products **4c** (60%) and **4e** (74%).

The steric demand of the *N*,*N*-dialkyl group in benzamides **1a**−**e** strongly influences both the reactivity and the enantioselectivity of the (−)-sparteine-mediated process (Scheme 4). While the piperidine derivative **1c** led to yields and enantioselectivities (42% ee) comparable to the diethyl amide **1a** (46% ee), the bulky diisopropyl amide **1b** showed low yield and enantioselectivity (17% ee). Interestingly, the presence of an additional heteroatom

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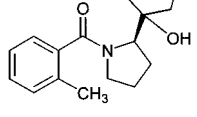
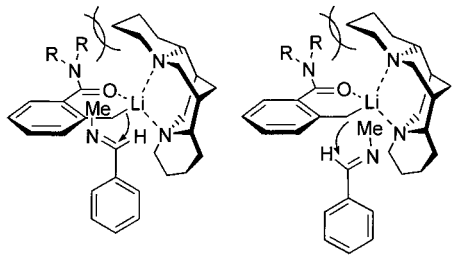
(16) Attempts to use other chiral ligands and devise chiral auxiliary-mediated enantioinduction also failed. Thus metalation of **1e** with *n*-BuLi/chiral cyclopropylspirobis(2*S*,3*R*-indanoxazoline) derivative[25] and reaction with **2a** afforded **3a** in low yield (26%) and enantioinduction (24% ee, *S*-enantiomer favored), while the condensation of lithiated chiral L-proline-derived benzamide **i**, generated by treatment with LDA and *n*-BuLi/TMEDA, with imine **2a** led to diastereoselectivities of 0% de and 14% de, respectively.



i

(17) The increased yields in the reactions of the morpholine amide **1e** in comparison with those of the diethyl amide **1a** may be due to the better leaving group ability of lithio morpholide in the cyclization step and the weaker basicity of this species for promoting side reactions.

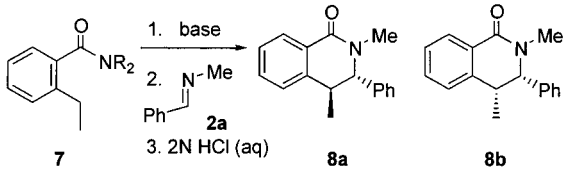
Scheme 5



6a ***Re*-attack** favored

6b ***Si*-attack** disfavored

Scheme 6



	R	base	yld, %	% *ee*	yld, %	% *ee*
7a	Et	LDA	16	–	–	–
b	*i*-Pr	LDA	6	–	–	–
c		LDA	36	–	12	–
		n-BuLi/ (-)-sparteine	5	53	2	15

in the N,N-substituent substantially improved enantioinduction. Thus, the *N*-methylpiperazine **1d** and morpholine **1e** derivatives led to product **3a** in 78% ee and 81% ee, respectively, but unfortunately, for both cases, in low yields (13−22%). To probe the reasons for the inefficiency of these reactions, **1e** was subjected to a *n*-BuLi/(−)-sparteine metalation−MeOD quench sequence at −78 °C for 20 min. The product **1e**, isolated in 67% yield, showed a 7:1 ratio of benzylic/ortho deuterium content (^{2}H NMR), indicating that lateral deprotonation is the major pathway under the conditions used for the sparteine-mediated process. Furthermore, in the addition of imine **2a** to a solution of the lithiated **1e** followed in 5 min by MeOD quench, no *N*-CH_3 deuterium incorporation (^{2}H NMR) was observed. As suggested by Clark,[7a] the moderate yields of isoquinolinones may be due to competitive intermolecular anion−amide reactions leading to polymeric materials.

To secure the absolute configuration of the newly formed stereocenter, **3a** was reduced (2 equiv of BH_3·SMe_2) to give 1,2,3,4-tetrahydro-2-methyl-3-phenylisoquinoline **5** in 76% yield without erosion of the enantioinduction (81% ee). Single-crystal analysis of the hydrobromide of **5** (see the Supporting Information) revealed the C-3 (*S*)-configuration. Using the chiral pocket model,[15] this result may be rationalized by *re*-face (**6a**) rather than *si*-face (**6b**) attack of the (−)-sparteine-coordinated lithiated species on the imine (Scheme 5). The enantioinduction is expected to be controlled by the stability and steric environment of the (−)-sparteine-chelated anion. The observed influence of the amide N,N-substituent (**1a**−**e**, Scheme 4) on enantioinduction suggests that the amide rotational barrier will strongly influence the extent of complexation in the chiral pocket and therefore may dictate the magnitude of enantioinduction.[16]

To probe the consequences of the (−)-sparteine-induced enantioinduction in a prochiral setting and as a potential route to chiral 3,4-disubstituted isoquinolinones, the

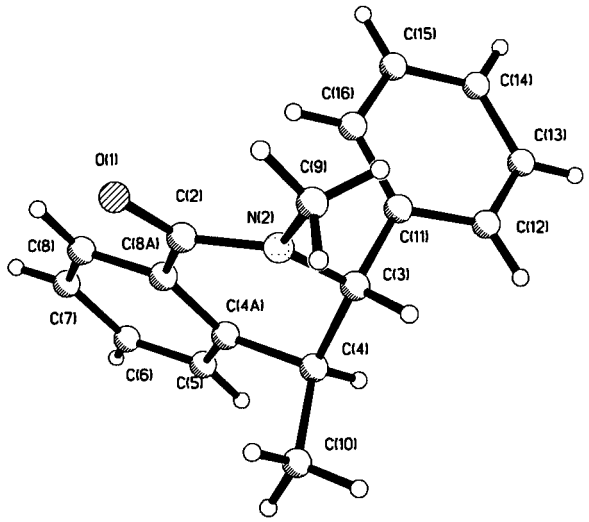
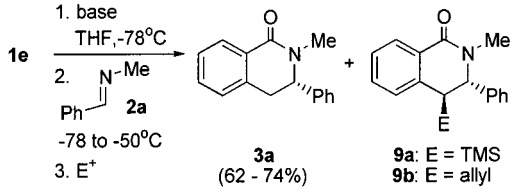


Figure 1. X-ray structure of (±)-*trans*-4-methyl-3-phenyltetrahydroisoquinolinone (**8a**).

Scheme 7



metalated *o*-ethyl benzamide **7a**−**c**−imine **2a** reactions were tested (Scheme 6). LDA metalation of benzamides **7a** and **7b** followed by quench with **2a** furnished only the *trans* isomer **8a** in low yields (6−16%), whereas the reaction of **7c** with **2a** afforded both **8a** and **8b** with moderate diastereoselectivity (50% de) and a combined yield of 48%. The relative stereochemistry of the *trans* diastereomer **8a** was established by single-crystal X-ray analysis (Figure 1). When **7a**−**c** were subjected to the *n*-BuLi/(−)-sparteine conditions, only amide **7c** afforded the desired products **8a**,**b** in low yields and with lower enantioinduction (53% ee) compared to that of the *o*-methyl derivative **1e** (81% ee) (Scheme 4).

A second approach to obtain 3,4-substituted isoquinolinones was based on a procedure reported by Clark.[6b] In this procedure, the lithio diethylamide, which is ejected in the cyclization reaction, promotes benzylic deprotonation and the resulting anion may then be quenched with electrophiles. In the event, sequential LDA metalation of **1e** and addition of imine **2a** was followed by warming to −50 °C and quenching with TMSCl or allyl bromide (Scheme 7). In both sequences, **3a** was obtained in surprisingly good yields (62% and 74%, respectively) along with small amounts of the disubstituted products **9a** and **9b** as single *trans* diastereomers.[17] These results suggest that the generated lithio morpholide is insufficiently basic for efficient benzylic deprotonation compared to $LiNEt_2$ ($pK_a = 31.7$).[18]

To compare reactivity of imines with electrophiles studied by Beak,[9] we investigated the identical *o*-ethyl *N*,*N*-diisopropylbenzamide **7b** in addition reactions with imines **2** (Scheme 8). Under metalation conditions with an achiral ligand (*sec*-BuLi/TMEDA), the condensation

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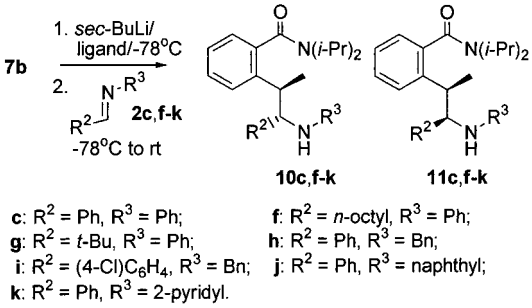
Table 2. Reactions of Laterally Metalated *N,N*-Diisopropyl-*o*-ethyl Benzamide 7b with Imines 2c,h−k

entry	imine	R^2	R^3	ligand	yield[a] (%), **10**	% de,[b] **10**:**11**	% ee,[c] **10**
1	**2c**	Ph	Ph	TMEDA	72	81	
2	**2c**	Ph	Ph	(−)-sparteine	41	95	98
3	**2h**	Ph	Bn	TMEDA	54	90	
4	**2h**	Ph	Bn	(−)-sparteine	25	94	92
5	**2i**	4-ClC_6H_4	Bn	TMEDA	39	88	
6	**2i**	4-ClC_6H_4	Bn	(−)-sparteine	21	92	97
7	**2j**	Ph	naphthyl	TMEDA	72	79	
8	**2j**	Ph	naphthyl	(−)-sparteine	38	91	93
9	**2k**	Ph	2-pyridyl	TMEDA	76	97	
10	**2k**	Ph	2-pyridyl	(−)-sparteine	39	97	91

[a] Isolated yield, minor product determined by GC−MS. [b] Determined by GC of the crude reaction mixture. [c] Determined by CHIRAL-OD-HPLC.

Scheme 8



reaction of metalated **7b** with **2c**,**f**−**k** afforded products **10c**,**h**−**k** and **11c**,**h**−**k** in moderate to good yields (39−76%) and diastereoselectivities up to 97% de (Table 2).[19] Reactions with aliphatic imines **2f** and **2g** yielded only traces of addition products. Attempts to activate the aliphatic imines **2f** and **2g** with Lewis acids (BF_3·Et_2O or $TiCl_4$)[13] also failed to give **10f**,**g** and **11f**,**g,** respectively. The (−)-sparteine-mediated metalation−addition was again found to be strongly solvent dependent. Thus, using imine **2c**, *sec*-BuLi in toluene were the optimum conditions for enantioinduction, giving product **10c** in 41% yield and 98% ee (Table 2, entry 2). Using Et_2O as the solvent led to **10c** in higher yield (78%) but decreased enantioselectivity (38% ee).[20] In (−)-sparteine-mediated metalation reactions of **7b** with the imines **2c**−**i**, the *anti* products **10c**−**i** were isolated in low to moderate yields (21−41%) and high diastereo- (91−97% de) and enantioselectivities (91−98% ee). The *anti* stereochemistry of the major diastereomer (**10**) was proven by NOE experiments on **10b**. The reaction of the diethyl amide **7a** with imine **2c** gave the addition products **12c** and **13c** (94% de) in improved yields (52%) but lower enantioselectivity (**12c**, 60% ee, see the Experimental Section).

Conclusions

This work constitutes the first study of a (−)-sparteine-mediated benzamide lateral metalation−imine addition reaction (**1** + **2**), leading to chiral tetrahydroisoquinolinones **3**. Reactions of amides **1** and **7c**, readily available from commercial benzoic acids, lead to chiral tetrahydroisoquinolinones **3** and **8a**,**b** respectively in three steps in poor to modest yields (5−36%) but enantioselectivities up to 81% ee. Some of the conversions (Scheme 8, Table 2) proceed with high diastereo- and enantioselectivities to furnish *ortho*-substituted phenethylamine derivatives, which are of potential interest in view of the known pharmacological activity of some polyfunctionalized secondary phenylethylamines.[21] On the basis of recent exploration of other directed metalation groups such as anilines[9b] and carbamates,[14] further applications of chiral ligand-mediated reactions may be anticipated. However, work on the nature of intermediates and transition states of these reactions[22] is required before synthetically useful procedures are devised in this important area of asymmetric synthesis.

Experimental Section

General Methods. The melting points are uncorrected and represent values obtained on unrecrystallized materials. IR spectra were recorded neat or as KBr pellets. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained in $CDCl_3$ using either TMS (for ^1H) or $CDCl_3$ (for ^{13}C) as the internal standard. ^2H NMR (61.40 MHz) spectra were obtained in CH_2Cl_2 using residual CD_2Cl_2 as an internal standard. All dry solvents used were purified according to Perrin.[23] Tetrahydrofuran, toluene, and ether were freshly distilled from sodium benzophenone ketyl under argon prior to use. *n*- and *sec*-Butyllithium was purchased from Aldrich as a solution in hexanes, stored in a resealable container, and titrated periodically against *sec*-butanol.[24] All experiments were carried out under argon in dried glassware, using syringe-septum cap techniques. Flash column chromatography was carried out using Merck silica gel 60 (particle size: 32−63). The ratios of diastereomers were determined from the crude reaction mixtures by GC−MS analysis with a Varian CP-800 GC coupled with a Varian Saturn 2000-quadropole MS under EI or CI (70 eV) conditions. The purity of the products was determined by a HP 6890 GC. The enantioselectivities were determined by using a Waters 600E HPLC and a Waters 486 detector with a Daicel Chiracel OD column. The X-ray quality single crystal of the compound was mounted on a glass fiber with epoxy glue. The data for the ligand were collected on a CCD-detector-equipped SMART system with graphite monochromated Mo Kα radiation (λ = 0.710 73 Å) operated at 50 kV and 35 mA at 23 °C over the 2θ

(19) In all reaction of **7b** with **2**, formation of tetrahydroisoquinolinone **3** was not observed, irrespective of the imine N-substituent, even upon warming to room temperature.

(20) Based on numerous experiments, poor reproducibility of yield and enantioinduction in Et_20 as the solvent was noted. Differences may be due to exact stoichiometry and concentration of the *sec*-BuLi/(−)-sparteine complex as suggested by variation in the observed color (colorless to yellow) of the solution.

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range of 4−56°. The data were processed with Siemens SHELXTL (version 5.0).[25] The data were corrected for Lorentz-polarization effects. Neutral atom scattering factors were taken from Cromer and Waber.[26]

Starting Materials. Compounds **1a**−**e** were prepared from *o*-toluyl chloride (Aldrich) and the corresponding amine in quantitative yield. Benzylidene-*N*-methylamine **2a** was purchased from Aldrich Chemical Co. The *o*-ethyl-substituted amides **7a**−**c** were synthesized starting from the benzoic acids by directed *ortho* metalation procedures.[9,12]

Synthesis of Imines 2b−k. General Procedure. A mixture of aldehyde (1.00 mmol) and amine (1.10 mmol) in anhydrous CH_2Cl_2 and 4 Å molecular sieves (3 g) was stirred at room temperature for 16 h. The mixture was subjected to filtration, and the filtrate was washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give the imine in >95% yields and high purity. Solid imines were recrystallized from ethanol.

LDA Metalation. General Procedure. To a freshly prepared solution of LDA [*n*-BuLi (1.20 mmol) added dropwise to diisopropylamine (1.20 mmol) in dry THF (2 mL) at 0 °C], a solution of benzamide (1.00 mmol) in dry THF (2 mL) was added by syringe at −78 °C under argon. After 5 min, a solution of imine (1.20 mmol) in THF (2 mL) was added, and the reaction mixture was stirred at −78 °C for 20 min. To the solution was added 2 N aqueous HCl (1 mL), and the reaction mixture was allowed to warm to rt. Ether (20 mL) was added, and the organic phase was washed with H_2O (5 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product, which was purified by flash chromatography with hexanes/ethyl acetate (3:1) as solvent.

***n*-BuLi/(−)-Sparteine Metalation. General Procedure.** To a solution of *n*-BuLi (1.20 mmol) and (−)-sparteine (1.20 mmol) in dry toluene (6 mL) at −78 °C was added a solution of amide (1.00 mmol) in dry ether (2 mL) dropwise via syringe under argon. After 10 min, imine (1.20 mmol) in ether (1 mL) was added via syringe, and the solution was stirred at −78 °C for 20 min. Aqueous 2 N HCl (2 mL) was added rapidly, and the reaction mixture was allowed to warm to rt. Ether (20 mL) was added, and the organic phase was separated, washed with water (5 mL, 2×), dried (Na_2SO_4), and concentrated in vacuo to give the crude product, which was purified by flash chromatography with hexanes/ethyl acetate (3:1) as solvent.

(±)-*N*-Methyl-3-phenyltetrahydroisoquinolinone (3a). Flash chromatography yielded 123 mg (0.52 mmol, 52%) of **3a** (R_f = 0.41) as a colorless solid (97% purity by GC). Mp: 105−106 °C. $[\alpha]^{25}_D$: 33.3 (c = 0.15, CH_2Cl_2, 81% ee by CHIRACEL-OD-HPLC-column, flow: 1 mL/min, hexanes/*i*-PrOH 92:8). IR (KBr) ν: 3029, 2904, 1643, 739 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18−8.15 (m, 1H), 7.34−7.18 (m, 5H), 7.10−6.98 (m, 3H, Ar C*H*), 4.78 (d, J = 4.6 Hz, 1H, 3-H), 3.70 (dd, J = 4.6, 15.9 Hz, 1H, 4-H$_a$), 3.11 (s, 3H, NC*H*$_3$), 3.06 (d, J = 15.9 Hz, 1H, 4-H$_b$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 139.8, 135.0, 129.0, 131.7, 128.6, 127.6, 127.5, 127.4, 126.9, 126.1, 61.7, 35.6, 34.2. MS (EI) *m*/*z*: 237 (5) [M$^+$], 178 (4), 160 (36), 152 (2), 145 (3), 131 (3), 118 (100), 103 (5). HRMS: calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1140.

(±)-*N*-Allyl-3-phenyltetrahydroisoquinolone (3b). Flash chromatography yielded 33.0 mg (0.13 mmol, 13%) of **3b** (R_f = 0.63, Et_2O) as a colorless oil (98% by GC). IR (NaCl) ν: 3062, 1650, 1467 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19−8.16 (m, 1H), 7.37−7.21 (m, 5H), 7.10−6.99 (m, 3H, arom C*H*), 5.91−5.83 (m, 1H, C*H*=CH$_2$), 5.26−5.19 (m, 2H, CH=C*H*$_2$), 5.07−4.99 (m, 1H, NC*H*$_a$), 4.87 (dd, J = 2.3, 6.8 Hz, 1H, 3-H), 3.70 (dd, J = 6.8, 15.6 Hz, 1H, 4-H$_a$), 3.32 (dd, J = 7.3, 15.4 Hz, 1H, NC*H*$_b$), 3.09 (dd, J = 2.4, 15.6 Hz, 1H, 4-*H*$_b$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.4, 139.9, 135.0, 133.4, 131.9, 128.6, 127.9, 127.6, 127.6, 127.1, 126.4, 117.3, 58.2, 47.9, 35.8. MS (CI) *m*/*z*: 264 (100) [M$^+$ + H], 224 (8), 203 (6), 162 (5), 146 (5), 136 (5), 122 (6). HRMS: calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1313.

(±)-*N*,*N*-Diethyl-*o*-[(2′-phenyl-2′-*N*-phenylamine)ethyl]-benzamide (4c). Flash chromatography (hexanes/ethyl acetate 5:1) yielded 1.12 g (0.30 mol, 60%) of **4c** (R_f = 0.02) as a colorless solid (95% purity by GC). Mp: 139−140 °C. IR (KBr) ν 3361, 3055, 2973, 1620, 1496, 1079 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56−7.11 (m, 9H), 6.96 (t, J = 7.6 Hz, 2H), 6.47−6.40 (m, 3H, arom C*H*), 6.40−6.35 (br s, 1H, N*H*), 4.53−4.42 (m, 1H), 3.63−3.48 (m, 2H), 3.11−3.00 (m, 3H), 2.78−2.73 (m, 1H, NC*H*$_2$CH$_3$, 1′-H, 2′-H), 1.29, 0.94 (t, J = 7.1 Hz, 6H, NCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.9, 148.4, 145.3, 137.4, 136.2, 129.1, 127.4, 127.0, 126.7, 125.9, 113.2, 60.8, 43.7, 39.8, 14.6, 13.5 ppm. MS (EI) *m*/*z*: 372 (1) [M$^+$], 207 (1), 190 (7), 182 (100), 176 (5), 119 (8), 104 (10), 77 (19). HRMS: calcd for $C_{25}H_{28}N_2O$ 372.2202, found 372.2184.

(±)-*N*,*N*-Diethyl-*o*-[(2′-(4-chlorophenyl)-2′-*N*-cumyl)-ethyl]benzamide (4d). Flash chromatography (hexanes/ethyl acetate 5:1) yielded 236 mg (0.53 mmol, 53%) of **4d** (R_f = 0.08) as a colorless solid (97% by GC). Mp: 145−146 °C. IR (KBr) ν: 3341, 3048, 2977, 1616, 1085 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31−6.91 (m, 14H, arom C*H*, N*H*), 3.75−3.46 (m, 3H), 3.08−2.83 (m, 2H), 2.68−2.50 (m, 2H, NC*H*$_2$, 1″-H, 2′-H), 1.33−1.25 (m, 6H), 1.10 (s, 3H), 0.99 (t, J = 6.8 Hz, C(C*H*$_3$)$_2$, NCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 147.9, 147.7, 137.8, 135.7, 132.1, 130.7, 128.8, 128.5, 128.0, 126.7, 126.3, 125.8, 60.1, 56.7, 43.9, 43.2, 39.4, 14.4, 13.5, 13.3 ppm. MS (CI) *m*/*z*: 449 (35) [M$^+$ + 1], 331 (61), 313 (10), 258 (25), 192 (12), 140 (14), 119 (100), 111 (6). HRMS: calcd for $C_{28}H_{33}ClN_2O$ [−CH_3] 433.2047, found 433.2032.

(±)-*N*,*N*-Diethyl-*o*-[(2′-phenyl-2′-*N*-tosyl)ethyl]benzamide (4e). Flash chromatography yielded 279 mg (0.62 mmol, 62%) of **4e** (R_f = 0.07) as a colorless solid (91% by GC). Mp: 133−135 °C. IR (KBr) ν: 3500, 3032, 2976, 1596, 1158 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.46 (s, 1H, NH), 7.45−6.86 (m, 13H, arom C*H*), 4.13−4.11 (m, 1H, 2′-H), 3.64−3.58 (m, 2H), 3.17−3.04 (m, 2H, NC*H*$_2$), 2.85 (dd, J = 3.9, 14.0 Hz, 1H, 1′-H$_a$), 2.65−2.54 (m, 1H, 1′-H$_b$), 2.32 (s, 3H, Ts-CH$_3$), 1.30, 0.99 (t, J = 7.1 Hz, 6H, NCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 143.0, 141.5, 137.2, 135.9, 134.2, 129.4, 128.9, 128.3, 127.0, 126.3, 126.3, 125.3, 59.5, 43.4, 39.6, 21.4, 14.0, 12.8 ppm. MS (CI) *m*/*z*: 451 (6) [M$^+$ + 1], 280 (17), 206 (2), 190 (8), 172 (100), 155 (5), 125 (10), 106 (24). HRMS: calcd for $C_{26}H_{30}N_2O_3S$ 450.1977, found 450.1972.

1,2,3,4-Tetrahydro-(3*S*)-phenyl-*N*-methylisoquinoline (5). To a solution of **3a** (50.0 mg, 0.21 mmol, 81% ee) in dry THF (1 mL) was added dropwise a solution of BH_3·SMe_2 (0.42 mL, 0.42 mmol, 1 M in THF) at room temperature. The reaction mixture was refluxed for 2 h, followed by dropwise addition of H_2O (2 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the crude product, which was purified by flash chromatography (hexanes/ethyl acetate 2:1) to give 36.5 mg (0.16 mmol, 76%) of **5** (R_f = 0.31) as a colorless oil (99% by GC, 81% ee by CHIRACEL-OD-HPLC-column, flow: 1 mL/min, hexanes/*i*-PrOH 90:10). IR (KBr) ν: 2925, 1462 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33−7.28 (m, 5H), 7.20−7.09 (m, 4H, arom C*H*), 4.09 (d, J = 15.4 Hz, 1H, 1-H$_a$), 3.67 (d, J = 15.4 Hz, 1H, 1-H$_b$), 3.49 (dd, J = 4.4, 10.2 Hz, 1H, 3-H), 3.19 (dd, J = 10.2, 15.7 Hz, 1H, 4-H$_a$), 3.05 (dd, J = 4.4, 15.7 Hz, 1H, 4-H$_b$), 2.21 (s, 3H, NC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2, 132.7, 131.5, 128.6, 128.1, 127.9, 127.5, 126.3, 126.0, 125.8, 66.6, 58.6, 43.3, 38.1. MS (EI) *m*/*z*: 223 (16) [M$^+$], 207 (6), 178 (8), 146 (64), 131 (9), 118 (21), 104 (100).- HRMS calcd for $C_{16}H_{17}N$ 223.1361, found 223.1355. After addition of 0.1 mL of hydrobromic acid (48% in water), the solvent was evaporated in vacuo to give **5**

(25) SHELXTL crystal structure analysis package, Bruker Axs, Analytical X-ray System, Madison, WI, 1995, Version 5.

(26) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, AL, 1974; Vol. 4, Table 2.2A.

(27) We are grateful to Dr. Stephen King, Abbott Laboratories, for a sample of this ligand. For synthesis and applications of bisoxazoline ligands, see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215; (b) Davies, I. W.; Gerena, L.; Cai, D.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (c) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753.

as the hydrobromide, $[\alpha]^{25}_D = 9.5$ ($c = 0.21$, CH_2Cl_2), which was recrystallized from CH_2Cl_2/hexanes 4:1 to give suitable crystals. X-ray analysis of **5**·HBr: $C_{16}H_{18}NBr$, $M_r = 304.22$, crystal size 0.1 × 0.3 × 0.4 mm, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 11.61(3)$ Å, $b = 17.25(5)$ Å, $c = 18.05(5)$ Å, $\alpha, \beta, \gamma = 90°$, $V = 3613(18)$ Å^3, $T = 296$ K, $Z = 8$, $\lambda = 0.710\ 73$, 24172 independent reflexes, 8392 refined parameters, R1 = 0.0761, wR2 = 0.1845.

(±)-*N*-Methyl-4-methyl-3-phenyltetrahydroisoquinolinone (8a,b). According to the general procedures above, the reaction of **7c** (22 mg, 0.1 mmol) with **2a** yielded, after flash chromatography (hexanes/ethyl acetate 3:1), 9 mg (36%) of **8a** ($R_f = 0.13$) as a colorless solid (98% by GC, mp 132−133 °C) and 3 mg (12%) of **8b** ($R_f = 0.08$) as a colorless oil (93% by GC). **8a**. IR (KBr) ν: 3061, 2959, 1647, 1255 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19−8.16 (m, 1H), 7.37−7.20 (m, 5H), 7.06−6.98 (m, 3H, arom C*H*), 4.50 (s, 1H, 3-H), 3.16 (q, J = 7.1 Hz, 1H, 4-H), 3.15 (s, 3H, NCH_3), 1.52 (d, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.3, 141.0, 140.1, 128.6, 132.0, 128.6, 127.9, 127.5, 127.2, 127.0, 125.9, 68.8, 41.0, 34.9, 23.7 ppm. MS (EI) *m*/*z*: 251 (5) [M$^+$], 236 (5), 174 (14), 165 (8), 159 (3), 144 (3), 132 (100), 118 (30), 104 (64). HRMS: calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1301. X-ray analysis of **8a**: $M_r = 251.32$, crystal size 0.2 × 0.3 × 0.4 mm, monoclinic, space group $P2(1)/n$, $a = 8.792(3)$ Å, $b = 11.590(4)$ Å, $c = 13.546(5)$ Å, $\beta = 101.459(7)°$, $V = 1352.8(8)$ Å^3, $\rho_{calcd} = 1.234$ Mg m^{-3}, $T = 296$ K, $Z = 4$, $\lambda = 0.71073$, 9210 independent reflexes, 3219 refined parameters, R1 = 0.0820, wR2 = 0.2114. **8b**. IR (NaCl) ν = 2925, 1646, 1455 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21−8.18 (m, 1H), 7.46−6.89 (m, 8H, arom C*H*), 4.48 (d, J = 6.2 Hz, 3-H), 3.87 (dd, J = 6.2/7.1 Hz, 1H, 4-H), 3.16 (s, 3H, NCH_3), 1.22 (d, $J = 7.1$ Hz, 3H, 1′-H). GC−MS (CI) *m*/*z*: 251 (30) [M$^+$], 236 (51), 207 (22), 174 (24), 132 (100), 104 (55), 78 (35).

(±)-*N*-Methyl-*trans*-3-phenyl-4-trimethylsilyltetrahydroisoquinolinone (9a). To a freshly prepared solution of LDA (1.20 mmol of *n*-BuLi was added dropwise to diisopropylamine (1.20 mmol) in dry THF (4 mL) at 0 °C) was added a solution of **1e** (205 mg, 1.00 mmol) in dry THF (2 mL) dropwise by syringe at −78 °C under argon. After 10 min of stirring, a solution of **2a** (1.20 mmol) in THF (2 mL) was added. The reaction mixture was stirred at −78 °C for 20 min and allowed to warm to −50 °C over 2 h. TMSCl (1.50 mmol) was added in one portion, and the reaction mixture was allowed to warm to rt. Et_2O (20 mL) was added, and the organic phase was washed with H_2O (5 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the crude product. Flash chromatography (hexanes/ethyl acetate 3:1) yielded 146 mg (0.62 mmol, 62%) of **3a** (99% by GC) and 24 mg (0.8 mmol, 8%) of **9a** ($R_f = 0.38$) as a colorless solid (97% by GC). Mp: 99−100 °C. IR (KBr) ν: 2925, 1644, 1245 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (dd, J = 1.0, 7.5 Hz, 1H), 7.31−7.17 (m, 6H), 7.04 (dd, J = 2.0, 7.9 Hz, 1H), 6.79 (dd, J = 0.5, 7.5 Hz, 1H, arom C*H*), 4.72 (s, 3-H), 3.12 (NCH_3), 2.55 (s, 4-H), 0.08 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.0, 141.8 138.2, 127.9, 131.5, 128.6, 127.8, 127.4, 127.1, 125.5, 125.4, 63.3, 39.8, 34.6, −2.9. MS (CI) *m*/*z*: 310 (100) [M$^+$ + 1],0.238 (13), 232 (27), 160 (10), 149 (17), 135 (10), 123 (16), 111 (29). HRMS: calcd for $C_{19}H_{23}NOSi$ 309.1549, found 309.1567.

(±)-*N*-Methyl-*trans*-4-allyl-3-phenyltetrahydroisoquinolinone (9b). Flash chromatography (hexanes/ethyl acetate 3:1) yielded 175 mg (0.74 mmol, 74%) of **3a** (96% by GC) and 40 mg (0.14 mmol, 14%) of **9b** ($R_f = 0.33$) as a colorless oil (97% by GC). IR (NaCl) ν: 3066, 2923, 1646, 1265 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19−8.16 (m, 1H), 7.37−7.18 (m, 5H), 7.02−6.97 (m, 3H, arom CH), 5.92−5.86 (m, 1H, 2′-H), 5.23−5.11 (m, 2H, 3′-H), 4.65 (s, 1H, 3-H), 3.14 (s, 3H, *N*CH_3), 3.05 (dd, J = 6.6, 8.2 Hz, 4-H), 2.56−2.48 (m, 2H, 1′-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.2, 140.0, 139.1, 127.9, 140.0, 139.1, 135.4, 131.9, 128.6, 127.5, 127.3, 126.0, 118.3, 64.9, 46.2, 41.5, 34.6 ppm. MS (EI) *m*/*z*: 277 (4) [M$^+$], 248 (14), 236 (100), 221 (7), 200 (15), 195 (23), 178 (31), 165 (21), 158 (73), 147 (23), 129 (61), 118 (57). HRMS: calcd for $C_{19}H_{19}NO$ 277.1467, found 277.1461.

***sec*-BuLi/TMEDA Metalation. General Procedure.** A solution of **7b** (140 mg, 0.60 mmol) in dry THF (3 mL) was added to a stirred solution of *sec*-BuLi (1.00 mmol) and TMEDA (1.00 mmol) in THF (2 mL) at −78 °C under argon. After 1 h, a solution of the imine **2** (1.00 mmol) in dry THF (2 mL) was added, and the reaction mixture was allowed to warm to rt. A solution of saturated NH_4Cl (1 mL) was added, and the mixture was concentrated in vacuo. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layer was washed with H_2O (2 × 15 mL) and with brine (15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo, and the crude product was purified by flash chromatography with hexanes/ethyl acetate 3:1 as solvent.

***sec*-BuLi/(−)-sparteine Metalation. General Procedure.** To a solution of **7b** (35 Mg, 0.15 mmol) in dry toluene (2 mL) was added a freshly prepared, precooled solution of *sec*-BuLi (0.20 mmol) and (−)-sparteine (0.20 mmol) in toluene (2 mL) at −78 °C under argon via syringe. After 1 h, a solution of the imine **2** (0.22 mmol) in dry toluene (1 mL) was added slowly via syringe, and the reaction mixture was allowed to warm to rt. A solution of saturated NH_4Cl (1 mL) was added, and the mixture was concentrated in vacuo. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layer was washed with H_2O (2 × 15 mL) and with brine (15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo, and the crude product was purified by flash chromatography with hexanes/ethyl acetate 3:1 as solvent.

(±)-*N*,*N*-Diisopropyl-*trans*-[*o*-(2-*N*-phenylamino)-2-phenyl-1-methyl]benzamide (10c). Flash chromatography (hexanes/ethyl acetate 15:1) yielded 179 mg (0.43 mmol, 72%) of **10c** ($R_f = 0.10$) as a colorless solid (99% by GC, 81% de, mp 162−164 °C). **10c**: $[\alpha]^{25}_D$: 5.4 (*c* (**10c**·HCl) = 0.13, CH_2Cl_2, 98% ee determined by Chiracel-OD-HPLC column, hexanes/^{i}PrOH 92:8, flow: 0.4 mL/min). IR (KBr) ν: 3312, 3022, 2960, 1610, 1600, 1342, 1138, 1032, 743 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.47 (m, 3H), 7.30−7.14 (m, 4H), 6.99 (t, $J = 7.1$ Hz, 2H), 6.45−6.38 (m, 3H, N*H*, arom C*H*), 4.17 (d, J = 10.3 Hz, 1H, 2′−H), 3.87, 3.67 (dq, $J = 6.6$, 6.6 Hz, 2H, C*H*(CH$_3$)$_2$), 3.03 (dd, $J = 6.7$, 10.3 Hz, 1H, 1′−H), 1.73, 1.69 (d, $J = 6.6$ Hz, 6H, CH(CH_3)$_2$), 1.19 (d, $J = 6.7$ Hz, 3H, CH_3), 1.08, 1.06 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 148.5, 144.7, 141.2, 137.8, 129.5, 128.9, 128.8, 127.9, 127.4, 126.9, 126.4, 124.5, 115.7, 112.8, 65.5, 51.5, 46.5, 43.3, 21.3, 21.1, 20.9, 20.9, 19.3. GC−MS (CI) *m*/*z* 415 (100) [M$^+$ + 1], 322 (72) [M$^+$ − NHPh], 233 (31), 204 (32), 182 (31), 77(36) [Ph$^+$]. HRMS: calcd for $C_{28}H_{34}N_2O$ 414.2671, found 414.2661. **11c**. GC−MS (EI) *m*/*z*: 415 (9) [M$^+$ + 1], 322 (61), 313 (30), 280 (79), 256 (4), 236 (6), 102 (100), 93 (4), 77 (12).

(±)-*N*,*N*-Diisopropyl-*trans*-[*o*-(2-*N*-benzylamino)-2-phenyl-1-methyl]benzamide (10h). Flash chromatography yielded 139 mg (0.32 mmol, 54%) of **10h** ($R_f = 0.10$) as a colorless oil (93% by GC, 90% de). **10h**: IR (KBr) ν: 3328, 3061, 2967, 1628, 1453, 1337, 1032, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47−7.03 (m, 15H, N*H*, arom C*H*), 3.88−3.66 (m, 2H, C*H*(CH$_3$)$_2$, CH$_a$Ph*), 3.61−3.47 (m, 2H, C*H*(CH$_3$)$_2$, 2′-H), 3.36, 3.28* (d, J = 14.5, 1H, CH$_b$Ph*), 3.09−2.97 (m, 1H, 1′-H), 1.72−1.57 (m, 6H, CH(CH_3)$_2$*), 1.31−1.02 (m, 6H, CH(CH_3)$_2$*), 0.98, 0.93* (d, J = 7.8 Hz, 3H, CH$_3$*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 169.9*, 141.3*, 139.1, 138.8*, 138.5, 128.8, 128.4, 128.2, 128.0, 128.0, 127.8*, 127.3*, 126.9, 126.6, 126.4*, 126.1, 125.0, 124.4, 67.2, 51.6*, 51.1*, 50.7, 50.3, 45.8, 44.2*, 42.4, 42.2, 21.0*, 20.7, 20.6, 19.6 (rotamers are marked with *). MS (CI) *m*/*z*: 429 (100) [M$^+$ + 1], 322 (15), 234 (34), 196 (61), 148 (3), 132 (9), 111 (19), 106 (26). HRMS (FAB): calcd for $C_{29}H_{36}N_2O$ 428.2828, found 428.2806. **11h**: GC−MS (CI) *m*/*z*: 429 (100), 362 (10), 337 (27), 322 (57), 196 (71).

(±)-*N*,*N*-Diisopropyl-*trans*-[*o*-(2-*N*-benzylamino)-2-(4-chlorophenyl)-1-methyl]benzamide (10i). Flash chromatography yielded 108 mg (0.23 mmol, 39%) of **10i** ($R_f = 0.06$) as a pale yellow solid (94% by GC, 88% de, mp. 52−54 °C). **10i**: IR (KBr) ν: 3295, 3061, 2961, 1618, 1453, 1339, 1090 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38−7.10 (m, 12H), 7.04−7.01 (m, 1H), 6.93−6.89 (m, 1H, arom C*H*, N*H*), 3.86−3.66 (m,

2H, C*H*$(CH_3)_2$, CH_aPh*), 3.62−3.47 (m, 2H, C*H*$(CH_3)_2$, 2′-H), 3.34, 3.26* (d, J = 14.5, 1H, CH_bPh*), 3.03−2.91 (m, 1H, 1′-H*), 1.70−1.57 (m, 6H, CH(C*H*$_3)_2$*), 1.31−1.05 (m, 6H, CH-(C*H*$_3)_2$*), 0.98, 0.92* (d, J = 7.6 Hz, 3H, CH_3*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 169.9*, 142.2, 141.3*, 141.1, 140.9*, 140.6, 140.2*, 139.0, 138.5*, 132.8, 132.3*, 129.5, 128.9*, 128.4, 128.2, 128.1, 127.9, 127.8, 126.7*, 126.3*, 126.3, 126.2, 125.1*, 124.4, 66.6, 66.5*, 51.4*, 51.1*, 50.7, 50.3, 45.8, 45.7*, 44.2*, 42.2, 20.8*, 20.7, 20.6, 20.5*, 20.5, 20.5, 20.4*, 19.3 (rotamers are marked with *). MS (CI) m/z: 463 (56) [M^+ + 1], 358 (25), 356 (22), 232 (100), 230 (93), 204 (27), 190 (15), 140 (28), 133 (29), 108 (78). HRMS (FAB): calcd for $C_{29}H_{35}N_2OCl$ 462.2438, found 462.2456. **11i**: GC−MS (CI) m/z: 463 (100) [M^+], 429 (2), 398 (11), 396 (14), 373 (11), 371 (23), 358 (23), 356 (69), 232 (30), 230 (57), 204 (20).

(±)-*N*,*N*-Diisopropyl-*trans*-[*o*-(2-*N*-naphthylamino)-2-phenyl-1-methyl]benzamide (10j). Flash chromatography (hexanes/ethyl acetate 9:1) yielded 209 mg (0.43 mmol, 72%) of **10j** (R_f = 0.10) as a yellow solid (95% by GC, 79% de, mp 88−90 °C). **10j**: IR (KBr) ν: 3347, 3050, 2967, 1615, 1600, 1342, 1137, 1031, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, J = 8.1 Hz, 1H), 7.58−7.52 (m, 3H), 7.48 (d, J = 4.5 Hz, 1H), 7.36−7.17 (m, 8H), 7.13−7.00 (m, 2H), 6.92 (d, J = 8.1 Hz, 1H), 6.23 (d, J = 7.2 Hz, 1H, arom C*H*, N*H*), 4.36 (d, J = 10.3 Hz, 1H, 2′-H), 3.88, 3.58 (dq, J = 6.7, 6.7 Hz, 2H, C*H*$(CH_3)_2$), 3.21 (dd, J = 7.1, 10.3 Hz, 1H, 1′-H), 1.71−1.67 (m, 6H, CH(C*H*$_3)_2$), 1.14, 1.12 (d, J = 6.7 Hz, 6H, CH(C*H*$_3)_2$), 1.02 (d, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 144.1, 143.4, 141.3, 137.8, 134.2, 129.1, 128.3, 127.6, 127.5, 127.0, 126.3, 126.2, 125.9, 125.1, 124.1, 124.1, 123.6, 122.3, 115.1, 103.5, 65.3, 51.0, 46.1, 42.7, 20.9, 20.7, 20.5, 20.4, 20.0. MS (EI) m/z: 464 (2) [M^+], 280 (2), 232 (100), 204 (22), 190 (43), 154 (24), 143 (17), 132 (94), 127 (63), 115 (37), 104 (74). HRMS: calcd for $C_{29}H_{36}N_2O$ 464.2828, found 464.2816. **11j**: GC−MS (EI) m/z: 464 (3) [M^+], 321 (4), 221 (10), 204 (24), 190 (12), 133 (19), 127 (15), 115 (12), 104 (10).

(±)-*N*,*N*-Diisopropyl-*trans*-[o-(2-*N*-pyridylamino)-2-phenyl-1-methyl]benzamide (10k). Flash chromatography yielded 190 mg (0.46 mmol, 76%) of **10k** (R_f = 0.18) as a pale yellow solid (97% by GC, 97% de, mp. 52−54 °C). **10k**. IR (KBr) ν: 3303, 2967, 1598, 1487, 1342, 1031, 771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, J = 5.0 Hz, 1H), 7.53−7.47 (m, 3H), 7.40−7.05 (m, 9H), 6.28 (dd, J = 5.2, 6.7 Hz, 1H), 6.21 (d, J = 8.4 Hz, 1H, N*H*, arom C*H*), 4.77 (dd, J = 7.2, 6.9 Hz, 1H, 2′-H), 3.88, 3.63 (dq, J = 6.7, 6.7 Hz, 2H, C*H*$(CH_3)_2$), 3.09 (dd, J = 6.9, 6.9 Hz, 1H, 1′-H), 1.73, 1.69 (d, J = 6.7 Hz, 6H, CH(C*H*$_3)_2$), 1.17 (d, J = 6.7 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H, C*H*$_3$), 1.07 (d, J = 6.7 Hz, 3H, CH(C*H*$_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8, 156.0, 147.6, 144.3, 141.0, 137.7, 136.0, 128.9, 128.1, 127.6, 127.6, 126.7, 126.3, 126.1, 124.1, 111.2, 62.4, 51.1, 46.0, 42.7, 20.9, 20.6, 20.5, 20.3, 19.2. GC−MS (CI) m/z: 456 (20) [M^+ + C_3H_4], 416 (100) [M^+ + 1], 322 (12), 233 (4), 204 (3), 183 (42), 78 (6). HRMS (FAB): calcd for $C_{27}H_{33}N_3O$ 415.2624, found 415.2596. **11k**. GC−MS (CI) m/z: 456 (18) [M^+ + C_3H_4], 416 (100) [M^+ + 1], 362 (5), 322 (11), 232 (5), 204 (3), 183 (46), 89 (4).

(±)-*N*,*N*-Diethyl-*trans*-[*o*-(2-*N*-phenylamino)-2-phenyl-1-methyl]benzamide (12c). Flash chromatography yielded 80 mg (0.21 mmol, 52%) of **12c** (R_f = 0.25) as a colorless solid (97% by GC, mp 122−124 °C). **12c**: IR (KBr) ν: 3295, 3027, 2972, 1602, 1498, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48−7.45 (m, 3H), 7.35−7.14 (m, 6H), 6.90 (t, J = 7.5 Hz, 2H), 6.40−6.35 (m, 4H, N*H*, arom C*H*), 4.15 (dd, J = 4.4, 10.4 Hz, 1H, 2′-H), 3.72−3.53 (m, 2H), 3.21−3.10 (m, 2H, C*H*$_2$CH$_3$), 2.91 (dd, J = 10.4, 6.7 Hz, 1H, 1′-H), 1.34 (t, J = 5.0 Hz, CH_2C*H*$_3$), 1.05−1.03 (m, 6H, C*H*$_3$, CH_2C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 147.6, 143.8, 141.7, 136.3, 129.5, 128.4, 128.3, 127.5, 127.0, 126.2, 125.9, 125.0, 115.2, 112.3, 64.9, 43.2, 42.8, 39.3, 19.7, 14.1, 12.9. MS (EI) m/z: 386 (1) [M^+], 284 (1), 221 (1), 204 (15), 182 (100), 176 (11), 132 (15), 104 (39). HRMS: calcd for $C_{26}H_{30}N_2O$ 386.2358, found 386.2352. **13c**: GC−MS (EI) m/z: 386 (1) [M^+], 368 (1), 341 (5), 281 (4), 221 (2), 204 (17), 193 (3), 182 (100), 176 (14), 132 (7), 104 (20), 77 (19).

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Supporting Information Available: ^{1}H and ^{13}C NMR copies for **3a**,**b**, **4c**, **8a**, **9a**, and **10i**,**k**. ORTEP X-ray structure of **5** and X-ray coordinates for **5** and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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