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From Cationic to Anionic Helicenes: New Reactivity through Umpolung

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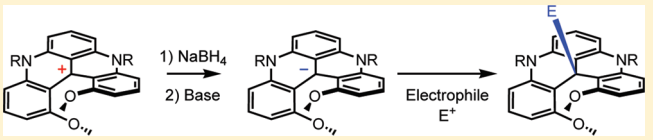
Supporting Information

ABSTRACT: Using a two-step reduction/metalation procedure, highly stable chiral carbenium ions are transformed into reactive carbanion intermediates. Interesting polar ketone and thioamide products are the results of this umpolung that occurs with complete retention of configuration of the helical backbone.



Umpolung or polarity inversion of functional groups is a widely applied concept introduced by Corey and Seebach.[1] It concerns all chemical modifications of functional groups that lead to a formal reversal of polarity. Classical examples are the transformations of electrophilic halogenoalcanes and ketones into nucleophilic Grignard and dithiane reagents, respectively. In this paper, we extend this notion to chiral electrophilic carbenium ions $\mathbf{1}^+$ or $\mathbf{2}^+$ (Scheme 1).[2] We demonstrate that these chiral cationic species can be transformed in two steps into reactive carbanions $\mathbf{1}^-$ or $\mathbf{2}^-$ onto which polar electrophilic reagents can be added—and this with full conservation of the enantiomeric purity.

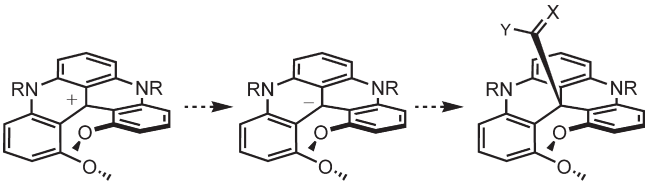
Previously, quinacridinium derivatives of type $\mathbf{1}^+$ or $\mathbf{2}^+$ have been reported.[3] These compounds are readily prepared in one step by reactions of primary amines with tris(2,6-dimethoxyphenyl)methylium ion. The reactions proceed through successive ortho S_NAr reactions of the methoxy substituents. Compounds of type $\mathbf{1}^+$ are highly stable carbocations (pK_{R+} ~19). In terms of stereochemistry, they adopt a twisted helical conformation induced by the steric repulsion occurring between the methoxy substituents in positions 1 and 13.[3]

Compounds $\mathbf{1}^+$ or $\mathbf{2}^+$ exist, therefore, as helical *P* and *M* enantiomers that are highly configurationally stable (Figure 1).[4] These cationic helicenes react as electrophiles. Alkyl-, alkynyl-, and aryllithium moieties add efficiently to the central carbon of cations $\mathbf{1}^+$ along with hydride reagents.[5,6]

Introduction of polar functional groups like carbonyl or thioamide on these and related cations was, however, never mentioned. A procedure for the making of compounds of type **3** or **4** (Scheme 1) was sought, but it was leading to a reactivity problem. As mentioned, cations $\mathbf{1}^+$ or $\mathbf{2}^+$ are electrophilic substrates, and groups like carbonyls are usually introduced in addition reactions using electrophilic reagents as well. An umpolung was necessary. However, rather than consider a "classical" inversion of polarity of the electrophilic reagent, we judged that it would be more general to switch the reactivity of cations $\mathbf{1}^+$ and form carbanions of type $\mathbf{1}^-$ instead (Scheme 1).[7]

Practically, a two-step metalation procedure was utilized to achieve this goal. Salts $[\mathbf{1}^+][BF_4]$ and $[\mathbf{2}^+][BF_4]$ (R = *n*-Pr and Me, respectively) were treated with $NaBH_4$ (EtOH, 20 °C) to afford the reduced compounds **1-H** and **2-H** in excellent yields (Scheme 2, 95−99%).[5c] With these adducts in hand, conditions for the hydrogen−metal exchange were established. The results are summarized in Table 1 using, after metalation, benzylisothiocyanate **5** as electrophile.

Scheme 1. Umpolung Strategy via Carbanions $\mathbf{1}^-$ or $\mathbf{2}^-$



KHMDS (potassium bis(trimethylsilyl)amide) and LiHMDS (lithium bis(trimethylsilyl)amide) were used initially, but evidence could not be found of acid−base reactivity (entries 1 and 2). Stronger bases were then utilized, in particular, *n*-butyllithium. Typically, solutions of **1-H** in Et_2O were treated at −78 °C with *n*-BuLi. These solutions remained colorless until warmed to 0 °C. A red color appeared that was assumed to be the carbanion. At that temperature, electrophile **5** was added. The desired addition product **3a** was obtained in all cases (entries 3−9); yields varied from moderate to good (42−85%). Several parameters were tested to improve the yield including the number of equivalents of base or of electrophile, temperature, and reaction time. In short, the best procedure corresponds to a use of 2.0 equiv of *n*-BuLi and of a large excess of benzyl isothiocyanate **5** (10 equiv). Attempts with *sec*-butyllithium, with or without added TMEDA, did not lead to a significant improvement (entry 10 and 11), and *tert*-butyllithium afforded very little amount of **3a** (entry 12).[8]

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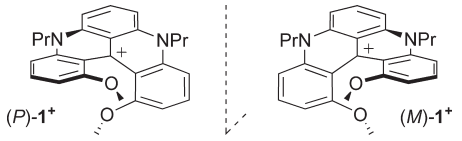


Figure 1. Dipropyl-1,13-dimethoxyquinacridinium $\mathbf{1}^+$: *P* and *M* enantiomers.

Scheme 2. Synthesis of Reduced Products 1-H and 2-H

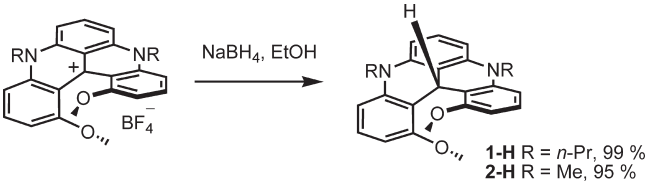
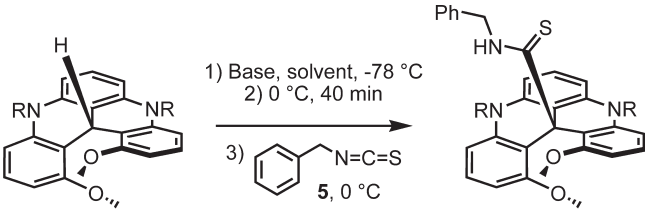


Table 1. Metalation Optimization study



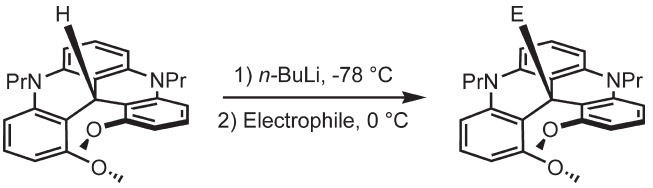
entry	base (equiv)[c]	solvent	electrophile (**5**)[d]	time[e]	yield[f] (%)
1[a]	KHMDS (1.2)	Et_2O	6	120[h]	*g*
2[a]	LiHMDS (3)	Et_2O	6	120	*g*
3[a]	*n*-BuLi (1.2)	Et_2O	3	45	42
4[a]	*n*-BuLi (1.2)	Et_2O	6	45	53
5[a]	*n*-BuLi (1.2)	Et_2O	6	20	40
6[a]	*n*-BuLi (2)	Et_2O	2	20	61
7[a]	*n*-BuLi (2)	Et_2O	6	20	80
8[a]	*n*-BuLi (2)[i]	Et_2O	6	20	66
9[a]	***n*-BuLi (2)**	Et_2O	**10**	**20**	**85**
10[a]	*s*-BuLi (2)	Et_2O	6	20	79
11[a]	*s*-BuLi (2)/ TMEDA (1)	THF	6	20	<10
12[a]	*t*-BuLi (1.1)	Et_2O	6	20	<10
13[b]	*n*-BuLi (2)	Et_2O	10	20	40

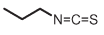
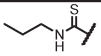
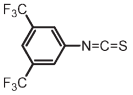
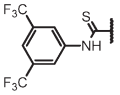
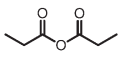
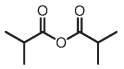
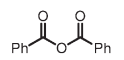
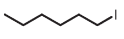
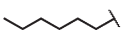
[a] With **1-H**. [b] With **2-H**. [c] Base added at −78 °C (unless otherwise noted) and reaction mixture stirred at 0 °C for 40 min. [d] Equivalents of electrophile. [e] Reaction time (min, 0 °C) after the addition of **5**. [f] Isolated yields (%). [g] No reaction; recovery of the starting material. [h] 0 to 20 °C. [i] Addition of the base at 0 °C.

The procedure was also tested with **2-H**. In this case, a lower yield of thioamide was obtained (**4a**: 40% vs **3a**: 85%); the lower solubility in Et_2O of the dimethyl-substituted **2-H** was probably the reason for this outcome.

The scope of the reaction was further explored with other electrophiles. The results are summarized in Table 2 using **1-H** as substrate exclusively. First, several thioamides were obtained in

Table 2. Scope and Limitation of the Reaction



entry	reagent	product	E	yield[a]
1		**3b**		83
2		**3c**		80
3		**3d**		71
4		-		*b*
5		-		*c*
6		-		< 5
7		-		< 5
8		**3e**		71
9		**3f**		77
10		**3g**		77
11		**3h**		26
12		**6**		89

[a] Isolated yields (%). [b] Complex mixture of inseparable products. [c] Starting material recovered.

good yields with other isothiocyanate reagents (71−83%, entries 1−3); the process was compatible with different R groups attached to the N-atom. However, to our surprise, reactions with analogous isocyanate reagents led to complex mixtures of products (e.g., PhNCO, entry 4). On the contrary, reactions with carbonate reagents (e.g., $(PhO)_2CO$, entry 5) led to a complete lack of reactivity. For the introduction of carbonyl groups, while acid chlorides were unproductive (entries 6 and 7), anhydride reagents afforded good yields of ketones in general (entries 8−11). Small- to medium-size alkyl chains (methyl to isopropyl) were introduced successfully; a lower yield of the benzoyl derivative was obtained. Finally, an excellent yield of 89% was obtained with hexyl iodide as electrophile (entry 12); the

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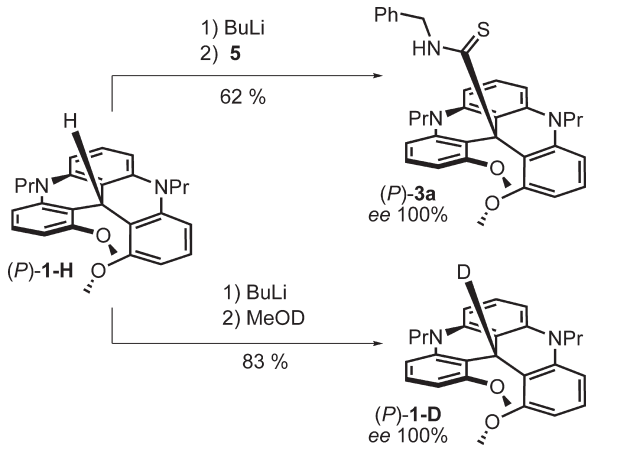
Scheme 3. Enantiospecific Reduction, Lithiation, and Alkylation



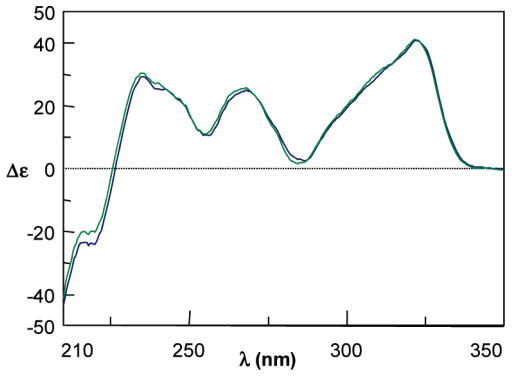


Figure 2. ECD spectra of (*P*)-(+)-**1-H** before (blue) and after (green) deuteration (*c* 7.6 × 10^{-6} M, CH_3CN, 20 °C).

purpose of the reaction was to ascertain the exclusive formation of the product of C_6H_{13} addition and the absence of a butyl derivative.[9] All in all, softer electrophiles seem to perform better, affording smoothly the desired addition products.[10]

While performing these reactions, we realized that chiral cations $\mathbf{1}^+$ and $\mathbf{2}^+$, and corresponding hydride derivatives **1-H** and **2-H**, had been used as racemates only. This was prohibiting the (likely) demonstration of a configurational stability for anionic intermediates $\mathbf{1}^-$ or $\mathbf{2}^-$. Care was thus taken to test some reactions again using an enantiopure substrate.

Compound (*P*)-(+)-**1-H** was prepared from salt [(*P*)-$\mathbf{1}^+$][PF_6][3b] using the same protocol as for *rac*-**1-H**. This derivative was then deprotonated and reacted with benzyl isothiocyanate **5** under the standard conditions to afford (*P*)-(+)-**3a** as a single enantiomer (Scheme 3 and Supporting Information). After this first evidence of configurational stability for the intermediate, (*P*)-(+)-**1-H** was reacted with *n*-BuLi again and the resulting red solution treated with methanol-d_4 to afford a quantitative deuteration at the reactive center and a global retention of configuration as evidenced by the optical rotation and ECD spectra (Figure 2) measurements of (*P*)-(+)-**1-D**. The umpolung process therefore occurs with complete stereochemical integrity.

Finally, in the course of this study, we were able to evidence an atropisomeric situation about the newly created $C(sp^3)-C(sp^2)$ bond; this type of conformational isomerism is common in triptycenes, 9-arylfluorenes, and other derivatives.[11] Our interest was raised by the room-temperature ^{1}H NMR spectrum of **3h** that was showing broad signals for the two methoxy substituents unlike the spectra of other compounds **3** at the same temperature. This situation was interpreted as an indication of two possible orientations for the carbonyl substituent around the $C(sp^3)-C(sp^2)$ bond (Figure 3).

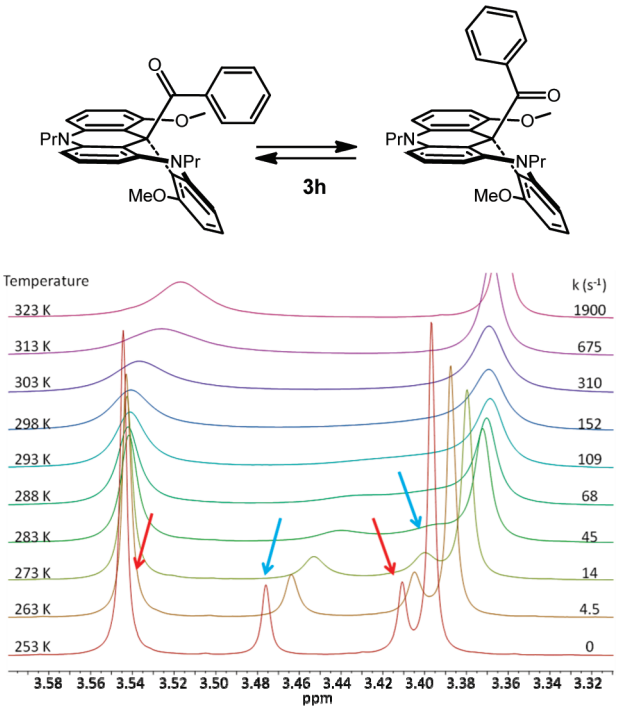


Figure 3. Atropisomers of **3h** and variable-temperature ^{1}H NMR spectra (500 MHz, $CDCl_3$).

^{1}H NMR analysis of **3h** at 253 K confirmed the slow rotation of the ketone substituent on the NMR time scale as two sets of signals are clearly observed. The two rotamers are present in a 4:1 ratio. Rather large differences are observed for the diastereotopic methoxy groups (Figure 3, $\Delta\delta$ 0.13 (red) and 0.08 (blue) ppm, $CDCl_3$). Variable-temperature NMR experiments were then performed, and the dynamic conformational isomerism was characterized at elevated temperatures. Experimental values for the different (mean) rates of interconversion were determined by line-shape analysis of the broadened exchange signals (WinDNMR, see the Supporting Information) corresponding to an energy of activation in the range of 16.7 (±0.3) kcal·mol^{-1} for the kinetic barrier.[12]

In conclusion, we have shown that highly stable chiral carbenium ions can be transformed into reactive carbanion intermediates in a simple, two-step procedure. The result of this umpolung is the formation of interesting polar ketone and thioamide products that are obtained in good yields and complete retention of configuration.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were recorded on 300, 400, or 500 MHz machines at rt (25 °C) unless otherwise noted. ^{1}H NMR: chemical shifts are given in ppm relative to Me_4Si with the solvent resonance used as the internal standard (CD_3CN δ 1.94 ppm;

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$CDCl_3$ δ 7.26 ppm). ^{13}C NMR (125 or 101 MHz): chemical shifts were given in ppm relative to Me_4Si with the solvent resonance used as the internal standard (CD_3CN δ 118.3 and 1.3 ppm; $CDCl_3$ δ 77.1 ppm). ^{19}F NMR (282 MHz): chemical shifts are given in ppm relative to $CFCl_3$ (δ 0). IR spectra were recorded using an ATR sampler and are reported in wave numbers (cm^{-1}). Melting points (mp) were measured in open capillary tubes and are uncorrected. Optical rotations were measured in a thermostatted (20 °C) 10.0 cm long microcell at 589 nm (Na) or 435 nm (Hg) and are reported as follows: $[\alpha]^T_\lambda$ (c (g/mol), solvent). Circular dichroism spectra were recorded in a 1.0 cm quartz cell; λ are given in nm and molar circular dichroic absorptions ($\Delta\varepsilon$ in $cm^2 \cdot mmol^{-1}$). Electrospray mass spectra (ESI+) were obtained by the Department of Mass Spectroscopy of the University of Geneva. HPLC analyses were performed using analytical Chiralpak IC or Chiralcel OD-H (0.46 cm ×25 cm) columns. Detection was performed using a UV detector at 230 nm. Retention times (t_R) are given in minutes (min). All reactions involving air-sensitive compounds were carried out under dry N_2 or argon by means of an inert gas/vacuum double manifold line and standard Schlenk techniques. *n*-BuLi was titrated using *N*-benzylbenzamide in THF at −40 °C prior to use. $CDCl_3$ was filtered on basic alumina prior to use. Flash column chromatography was performed with silica gel 40−63 μm or neutral alumina 50−200 μm. Products $\mathbf{1}^+$ and (*P*)-$\mathbf{1}^+$ were already described in the literature.[3b]

Synthesis of 1,13-Dimethoxy-5,9-dimethyl-5,9-dihydroquinolino[2,3,4-*kl*]acridin-13b-ylium Tetrafluoroborate [$\mathbf{2}^+$][$\mathbf{BF_4}$]. At room temperature, the primary amine (methyl or propyl) (245 mmol, 25 equiv) was added to a solution of tris(2,6-dimethoxyphenyl)carbenium tetrafluoroborate (9.8 mmol) in *N*-methyl-2-pyrrolidone (NMP) (60 mL). The reaction mixture was stirred at 25 °C for 1 h, heated at 90 °C for 2 h, and finally allowed to cool to rt. Addition of water (~80 mL) and a small amount of HBF_4 afforded a precipitate, which was filtered over a Büchner funnel, washed with water and then several times with Et_2O, and collected. The titled compounds were further purified by (i) dissolution of crude product in CH_2Cl_2 and (ii) selective precipitation by addition of Et_2O affording the desired dimethoxyquinacridinium tetrafluoroborate salt. This final purification was performed until the color of the solvent changed from reddish to colorless. The desired product [$\mathbf{2}^+$][$\mathbf{BF_4}$] was obtained in a good yield (75%). Mp: 280 °C dec. IR (neat): 2950, 2841, 1605, 1579, 1498, 1345, 1252, 1088, 1035, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (t, J = 8.5 Hz, 1H), 7.82−7.86 (m, 2H), 7.37 (dd, J = 8.7 and 12 Hz, 4H), 6.87 (d, J = 8.1 Hz, 2H), 4.01 (s, 6H), 3.68 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.0 (C), 143.5 (C), 142.8 (C), 140.1 (C), 137.8 (CH), 137.0 (CH), 119.7 (C), 113.8 (C), 108.5 (CH), 105.7 (CH), 104.0 (CH), 56.4 (CH_3), 38.1 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ −151.67 (20), −151.72 (80). HRMS (ESI): calcd for $C_{23}H_{21}O_2N_2$ 357.1597, observed 357.1598.

General Procedure I for the Reduction of Dimethoxyquinacridinium Tetrafluoroborate Salts [$\mathbf{1}^+$][$\mathbf{BF_4}$], [$\mathbf{2}^+$][$\mathbf{BF_4}$] and [(*P*)-$\mathbf{1}^+$][$\mathbf{PF_6}$]. $NaBH_4$ (2 equiv, 0.9 mmol) was slowly added at 25 °C to a solution of the quinacridinium salts in EtOH (15 mL). After 0.5−1.5 h, the mixture was concentrated in vacuo, and the crude was purified by flash chromatography (pentane/AcOEt, SiO_2) to afford the products as white solids.

1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine (1-H). As described by the general procedure I starting with [$\mathbf{1}^+$][$\mathbf{BF_4}$]. Yield: 99%. Mp: 79.2 °C dec. IR: 2959, 2930, 2872, 2833, 1618, 1587, 1464, 1435, 1377, 1338, 1227, 1166, 1130, 1086, 1061, 752, 731, 677 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.17 (t, J = 8.3 Hz, 1H), 7.01−7.08 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.40−6.53 (m, 5H), 4.67 (s, 1H), 3.85−3.91 (m, 2H), 3.58−3.77 (m, 2H), 3.72 (s, 3H), 3.38 (s, 3H), 1.87−1.96 (m, 2H), 1.74−1.85 (m, 2H), 0.99−1.05 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.1 (C), 156.2 (C), 145.3 (C), 144.2 (C), 139.9 (C), 137.7 (C), 126.5 (CH), 125.1 (CH), 124.2 (CH), 118.0 (C), 111.4 (C), 109.9 (C), 105.9 (CH), 105.3 (CH), 104.1 (CH), 103.8 (CH), 103.6 (CH), 99.8 (CH), 55.3 (CH_3), 54.1 (CH_3), 46.7 (CH_2), 46.5 (CH_2), 31.4 (CH), 19.9 (CH_2), 18.2 (CH_2), 10.6 (CH_3), 10.0 (CH_3). HRMS (ESI): calcd for $C_{27}H_{31}O_2N_2$ 415.238, obsd 415.2379.

1,3-Dimethoxy-5,9-dimethyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine (2-H). As described by the general procedure I starting with [$\mathbf{2}^+$][$\mathbf{BF_4}$]. Yield: 95%. Mp: 176.8 °C dec. IR: 2925, 2833, 1618, 1589, 1463, 1434, 1364, 1336, 1234, 1167, 1152, 1126, 1084, 1053, 821, 751, 730, 708, 675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 8.3 Hz, 1H), 7.09−7.15 (m, 2H), 6.72 (d, J = 8.0 Hz, 1H), 6.48−6.59 (m, 5H), 4.76 (s, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.45 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.0 (C), 157.1 (C), 146.8 (C), 145.9 (C), 142.1 (C), 139.7 (C), 127.6 (CH), 126.4 (CH), 125.6 (CH), 117.4 (C), 111.2 (C), 106.5 (CH), 106.0 (CH), 105.4 (CH), 105.1 (CH), 103.7 (CH), 101.2 (CH), 56.2 (CH_3), 55.2 (CH_3), 34.4 (CH_3), 33.3 (CH_3), 32.5 (CH). HRMS (ESI): calcd for $C_{23}H_{23}O_2N_2$ 359.1754, obsd 359.1755.

(+)-(*P*)-1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine ((*P*)-1-H). As described by the general procedure I starting with (*P*)-$\mathbf{1}^+$. Yield: 93%. CD (CH_3CN, 7.6 × 10^{-6} M, 20 °C): λ ($\Delta\varepsilon$) 240.5 (25.3), 271 (24.9), 326.5 (40.9). $[\alpha]_{578}$ = +1014, $[\alpha]_{546}$ = +1159, $[\alpha]_{436}$ = +3261, $[\alpha]_{365}$ = +8695 (c = $4.14.10^{-3}$, CH_2Cl_2, 20 °C).

General Procedure II for the Synthesis of the "Umpolung" Products. To a colorless solution of **1-H** or **2-H** (0.16 mmol) in 2 mL of dry Et_2O was added *n*-BuLi (0.32 mmol, 2 equiv) at −78 °C. After a quick warming to 0 °C, the color changed from colorless to light red to a dark red-pink. The reaction mixture was stirred at 0 °C for 20−30 min before the addition of the electrophile (1.6 mmol, 10 equiv). The mixture was stirred at 0 °C for 20 min, quenched with water, and extracted with Et_2O three times. The organic layers were collected together, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude was then purified by flash chromatography (Al_2O_3 neutral, AcOEt/pentane, 1/20) and/or on thin-layer preparative chromatographic plates (Al_2O_3 neutral, AcOEt/pentane, 1/40) to afford the umpolung products as white solids.

***N*-Benzyl-1,13-dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide (3a).** As described by the general procedure II starting with **1-H**. Yield: 85%. Mp: 160.2 °C dec. IR: 3356, 2959, 2924, 2876, 1617, 1585, 1517, 1473, 1433, 1385, 1338, 1240, 1218, 1167, 1132, 1087, 1054, 839, 763, 749, 738, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.26−7.33 (m, 3H), 7.11−7.20 (m, 5H), 6.76 (d, J = 8.2 Hz, 1H), 6.60 (t, J = 8.7 Hz, 2H), 6.50 (d, J = 8.1 Hz, 2H), 6.30 (d, J = 8.1 Hz, 1H), 4.78 (dd, J = 5.1 and 15.3 Hz, 1H), 4.43 (dd, J = 4.9 and 15.3 Hz, 1H), 3.73−3.89 (m, 4H), 3.32 (s, 3H), 3.30 (s, 3H), 1.63−1.94 (m, 4H), 1.06 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.7 (C), 160.8 (C), 159.2 (C), 145.3 (C), 143.1 (C), 140.3 (C), 138.7 (C), 136.7 (C), 128.6 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 126.9 (CH), 115.5 (C), 113.8 (C), 112.3 (C), 107.1 (CH), 106.2 (CH), 105.9 (CH), 105.1 (CH), 104.8 (CH), 101.2 (CH), 56.0 (CH_3), 55.5 (C), 54.4 (CH_3), 50.5 (CH_2), 48.6 (CH_2), 48.0 (CH_2), 20.8 (CH_2), 19.9 (CH_2), 11.8 (CH_3), 11.1 (CH_3). HRMS (ESI): calcd $C_{35}H_{38}N_3O_2S$ 564.2679, observed 564.2689.

(+)-(*P*)-N-Benzyl-1,13-dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide ((*P*)-3a). As described by the general procedure II starting with (*P*)-**1-H**. Yield: 62%. CD (CH_3CN, c = 7 × 10^{-6} M, 20 °C): λ ($\Delta\varepsilon$) 345 (20.2), 328 (31.4), 302.5 (−22.2), 279 (63.6), 260 (56.2), 238.5 (−6.2), 229 (10.3), 208 (−84.3), 198.5 (−65.0). $[\alpha]_{589}$ = +893 (c = $7.4.10^{-4}$ M, CH_3CN, 20 °C).

***N*-Benzyl-1,13-dimethoxy-5,9-dimethyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide (4a).** As described by the general procedure II starting with **2-H**. Yield: 40%. Mp: 74.3 °C dec. IR: 3350, 2920, 2831, 1618, 1585, 1518, 1470,

1433, 1374, 1341, 1247, 1223, 1170, 1129, 1087, 1052, 841, 761, 733, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.54 (br s, 1H), 7.26−7.28 (m, 3H), 7.13−7.21 (m, 5H), 6.62−6.66 (m, 3H), 6.55 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 4.91 (dd, J = 6.3, 15.1 Hz, 1H), 4.41 (dd, J = 4.3, 15.0 Hz, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 3.38 (s, 3H), 3.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.4 (C), 160.7 (C), 158.9 (C), 145.7 (C), 143.4 (C), 141.1 (C), 139.3 (C), 136.8 (C), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 114.0 (C), 112.9 (C), 112.8 (C), 106.5 (CH), 106.2 (CH), 106.1 (CH), 105.6 (CH), 103.6 (CH), 101.6 (CH), 55.8 (CH_3), 55.3 (C), 54.7 (CH_3), 50.2 (CH_2), 34.5 (CH_3), 33.9 (CH_3). HRMS (ESI): calcd $C_{31}H_{30}N_3O_2S$ 508.2053, observed 508.2078.

1,13-Dimethoxy-*N*,5,9-tripropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide (3b). As described by the general procedure II starting with **1-H**. Yield: 83%. Mp: 73.3 °C dec. IR: 3359, 2957, 2929, 2871, 2831, 1617, 1584, 1472, 1459, 1432, 1390, 1351, 1220, 1168, 1130, 1088, 1058, 839, 758, 703 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.18 (m, 2H), 7.12 (t, J = 8.2 Hz, 1H), 6.78 (br d, J = 8.1 Hz, 1H), 6.61 (br d, J = 8.3 Hz, 1H), 6.55−6.58 (m, 2H), 6.49 (d, J = 7.9 Hz, 1H), 6.35 (br d, J = 8.0 Hz, 1H), 3.72−3.87 (m, 4H), 3.62 (s, 3H), 3.40−3.47 (m, 1H), 3.37 (s, 3H), 3.23−3.30 (m, 1H), 1.68−1.89 (m, 4H), 1.46 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.8 (C), 160.8 (C), 159.2 (C), 145.3 (C), 142.9 (C), 140.3 (C), 138.7 (C), 128.1 (CH), 127.2 (CH), 126.8 (CH), 115.3 (C), 113.9 (C), 112.5 (C), 107.0 (CH), 106.1 (CH), 105.9 (CH), 105.0 (CH), 104.7 (CH), 101.3 (CH), 56.0 (CH_3), 55.3 (C), 54.7 (CH_3), 48.5 (CH_2), 47.9 (CH_2), 47.7 (CH_2), 21.1 (CH_2), 20.6 (CH_2), 19.8 (CH_2), 11.7 (CH_3), 11.5 (CH_3), 11.0 (CH_3). HRMS (ESI): calcd $C_{31}H_{38}N_3O_2S$ 516.2679, obsd 516.2679.

1,13-Dimethoxy-*N*-phenyl-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide (3c). As described by the general procedure II starting with **1-H**. Yield: 80%. Mp: 92.9 °C dec. IR: 3317, 2958, 2933, 2872, 2831, 1617, 1585, 1473, 1461, 1432, 1374, 1230, 1167, 1130, 1087, 1058, 756, 726, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.24−7.27 (m, 3H), 7.18 (t, J = 8.3 Hz, 1H), 7.09−7.15 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.58−6.63 (m, 3H), 6.50 (d, J = 8.0 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 3.72−3.89 (m, 4H), 3.56 (s, 3H), 3.42 (s, 3H), 1.84−1.90 (m, 2H), 1.53−1.66 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 206.7 (C), 161.0 (C), 159.3 (C), 145.3 (C), 142.9 (C), 140.3 (C), 139.1 (C), 139.0 (C), 128.5 (CH), 128.3 (CH), 127.7 (CH), 126.9 (CH), 125.4 (CH), 121.4 (CH), 115.98 (C), 114.0 (C), 113.1 (C), 107.4 (CH), 106.2 (CH), 106.0 (CH), 105.1 (CH), 104.8 (CH), 101.5 (CH), 57.4 (C), 56.0 (CH_3), 55.4 (CH_3), 48.5 (CH_2), 48.1 (CH_2), 20.6 (CH_2), 19.9 (CH_2), 11.7 (CH_3), 11.1 (CH_3). HRMS (ESI): calcd for $C_{34}H_{36}N_2O_3S$ 550.2522, obsd 550.2531.

***N*-(3,5-Bis(trifluoromethyl)phenyl)-1,13-dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine-13b-carbothioamide (3d).** As described by the general procedure II starting with **1-H**. Yield: 71%. Mp: 92.9 °C dec. IR: 3312, 2963, 2929, 2880, 2839, 1618, 1586, 1544, 1473, 1437, 1378, 1350, 1274, 1242, 1219, 1167, 1127, 1058, 883, 762, 729, 697, 680 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.11 (s, 2H), 7.60 (s, 1H), 7.31 (t, J = 8.2 Hz, 1H), 7.21 (t, J = 8.3 Hz, 1H), 7.15 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 4.4, 8.1 Hz, 2H), 6.60 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 7.9 Hz, 1H), 3.72−3.86 (m, 4H), 3.58 (s, 3H), 3.44 (s, 3H), 1.82−1.90 (m, 2H), 1.52−1.62 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 210.4 (C), 160.8 (C), 159.2 (C), 145.3 (C), 143.0 (C), 140.2 (C), 140.1 (C), 138.9 (C), 131.8 (q, J = 33.6 Hz, 2C), 128.6 (CH), 128.2 (CH), 127.2 (CH), 122.9 (q, J = 272.8 Hz, 2C), 121.5 (d, J = 3.4 Hz, CH), 118.7 (q, J = 3.4 Hz, 2CH), 115.9 (C), 113.6 (C), 112.8 (C), 107.5 (CH), 106.4 (CH), 106.2 (CH), 105.3 (CH), 104.9 (CH), 101.3 (CH), 57.7 (C), 55.9 (CH_3), 55.3 (CH_3), 48.5 (CH_2), 48.0 (CH_2), 20.9 (CH_2), 19.8 (CH_2), 11.6 (CH_3), 11.1 (CH_3). HRMS (ESI): calcd for $C_{36}H_{34}F_6N_3O_2S$ 686.2270, obsd 686.2302.

1-(1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridin-13b-yl)ethanone (3e). As described by the general procedure II starting with **1-H**. Yield: 71%. Mp: 163.3 °C dec. IR: 2950, 2873, 2830, 1725, 1585, 1474, 1434, 1393, 1341, 1241, 1218, 1170, 1131, 1089, 1059, 877, 762, 734, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 8.2 Hz, 1H), 7.07 (t, J = 8.1 Hz, 1H), 6.79 (dd, J = 0.8, 8.2 Hz, 1H), 6.54−6.57 (m, 2H), 6.48−6.49 (m, 2H), 6.37 (d, J = 8.1 Hz, 1H), 3.61−3.83 (m, 4H), 3.61 (s, 3H), 3.35 (s, 3H), 1.79−1.87 (m, 7H), 1.05 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9 (C), 161.3 (C), 157.8 (C), 145.0 (C), 143.2 (C), 140.8 (C), 138.8 (C), 129.0 (CH), 127.4 (CH), 126.5 (CH), 115.5 (C), 110.6 (C), 109.1 (C), 107.6 (CH), 106.5 (CH), 105.7 (CH), 105.3 (CH), 104.8 (CH), 101.2 (CH), 56.1 (CH_3), 54.7 (CH_3), 54.4 (C), 48.2 (CH_2), 48.1 (CH_2), 25.7 (CH_3), 20.5 (CH_2), 19.8 (CH_2), 11.8 (CH_3), 11.0 (CH_3). HRMS (ESI): calcd $C_{29}H_{33}N_2O_3$ 457.2485, obsd 457.2481.

1-(1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridin-13b-yl)propan-1-one (3f). As described by the general procedure II starting with **1-H**. Yield: 77%. Mp: 65 °C dec. IR: 2960, 2937, 2872, 2831, 1726, 1613, 1585, 1471, 1435, 1373, 1238, 1217, 1169, 1131, 1089, 1059, 867, 762, 717 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (t, J = 8.1 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H), 6.79 (dd, J = 8.2, 0.7 Hz, 1H), 6.54−6.57 (m, 2H), 6.47 (d, J = 8.1 Hz, 2H), 6.35 (d, J = 8.0 Hz, 1H), 3.65−3.84 (m, 4H), 3.59 (s, 3H), 3.35 (s, 3H), 2.12−2.23 (m, 2H), 1.78−1.88 (m, 4H), 1.06 (t, J = 7.4 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 0.71 (br s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.8 (C), 161.1 (C), 157.7 (C), 144.9 (C), 143.2 (C), 140.9 (C), 138.9 (C), 128.9 (CH), 127.3 (CH), 126.3 (CH), 115.4 (C), 110.7 (C), 108.8 (C), 107.5 (CH), 106.4 (CH), 105.6 (CH), 105.1 (CH), 104.7 (CH), 101.0 (CH), 56.0 (CH_3), 54.6 (CH_3), 54.1 (C), 48.2 (CH_2), 48.0 (CH_2), 30.7 (CH_2), 20.5 (CH_2), 19.8 (CH_2), 11.7 (CH_3), 11.0 (CH_3), 10.0 (CH_3). HRMS (ESI): calcd $C_{30}H_{35}N_2O_3$ 471.2642, obsd 471.2639.

1-(1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridin-13b-yl)-2-methylpropan-1-one (3g). As described by the general procedure II starting with **1-H**. Yield: 77%. Mp: 69.3 °C dec. IR: 2962, 2933, 2872, 2831, 1722, 1611, 1585, 1472, 1436, 1374, 1240, 1219, 1169, 1132, 1089, 1061, 1037, 762, 708 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J = 8.3 Hz, 1H), 7.14 (t, J = 8.2 Hz, 1H), 7.06 (t, J = 8.2 Hz, 1H), 6.75−6.80 (m, 1H), 6.53−6.57 (m, 2H), 6.46 (dd, J = 2.1 Hz and J = 8.2 Hz, 2H), 6.33 (d, J = 7.7 Hz, 1H), 3.62−3.87 (m, 4H), 3.57 (s, 3H), 3.35 (s, 3H), 2.99 (hept, J = 6.7 Hz, 1H), 1.69−1.99 (m, 4H), 1.04 (dt, J = 7.4, J = 7.5 Hz, 6H), 0.64 (d, J = 6.6 Hz, 3H), 0.48 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.1 (C), 161.3 (C), 157.9 (C), 144.9 (C), 144.3 (C), 141.4 (C), 139.4 (C), 129.2 (CH), 127.8 (CH), 126.5 (CH), 115.2 (C), 110.2 (C), 107.9 (CH), 107.8 (C), 106.6 (CH), 105.8 (CH), 105.0 (CH), 104.9 (CH), 100.8 (CH), 56.2 (CH_3), 54.6 (CH_3), 54.5 (C), 48.5 (CH_2), 48.4 (CH_2), 36.9 (CH), 21.8 (CH_3), 20.9 (CH_2), 20.1 (CH_2), 12.0 (CH_3), 11.2 (CH_3). HRMS (ESI): calcd for $C_{31}H_{37}N_2O_3$ 485.2798, obsd 485.2797.

(1,13-Dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridin-13b-yl)(phenyl)methanone (3h). As described by the general procedure II starting with **1-H**. Yield: 26%. Mp: 70.9 °C dec. IR: 2959, 2930, 2873, 2834, 1693, 1584, 1470, 1435, 1381, 1239, 1215, 1170, 1131, 1089, 1060, 836, 761, 730, 696 cm^{-1}. ^1H NMR (400 MHz, THF, 50 °C): δ 7.26 (br d, J = 7.3 Hz, 1H), 6.90−7.07 (m, 6H), 6.70 (br d, J = 6.8 Hz, 1H), 6.49−6.55 (m, 3H), 6.43 (d, J = 8.0 Hz, 1H), 6.23 (d, J = 8.0 Hz, 1H), 3.82−3.90 (m, 1H), 3.71−3.79 (m, 1H), 3.62 (br s, 2H), 3.44 (s, 3H), 3.28 (s, 3H), 1.81 (m, 2H), 1.71 (br s, 2H),

1.03 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C): δ 189.2 (C), 160.9 (C), 157.9 (C), 145.9 (C), 144.1 (C), 140.5 (C), 139.5 (C), 138.8 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 126.9 (CH), 126.5 (CH), 125.7 (CH), 117.3 (C), 111.86 (C), 107.5 (CH), 106.3 (CH), 105.4 (CH), 104.9 (CH), 104.6 (CH), 100.9 (CH), 78.3 (C), 55.4 (CH_3), 53.5 (CH_3), 53.3 (C), 47.8 (CH_2), 47.4 (CH_2), 20.3 (CH_2), 19.6 (CH_2), 10.9 (CH_3), 10.1 (CH_3). HRMS (ESI): calcd $C_{34}H_{35}O_3N_2$ 519.2642, obsd 519.2649.

13b-Hexyl-1,13-dimethoxy-5,9-dipropyl-9,13b-dihydro-5*H*-quinolino[2,3,4-*kl*]acridine (6). As described by the general procedure II starting with **1-H**. Yield: 89%. Mp: 107.4−110.5 °C dec. IR: 2955, 2923, 2870, 1612, 1584, 1473, 1458, 1434, 1379, 1347, 1220, 1165, 1132, 1094, 1059, 781, 733, 711 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 8.3 Hz, 1H), 7.10−7.15 (m, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.49−6.63 (m, 5H), 3.99−4.03 (m, 2H), 3.79 (s, 3H), 3.71−3.85 (m, 2H), 3.36 (s, 3H), 2.21−2.28 (m, 1H), 2.09−2.16 (m, 1H), 2.01−2.08 (m, 2H), 1.84−1.90 (m, 2H), 1.00−1.16 (m, 12H), 0.83−0.90 (m, 1H), 0.79 (t, J = 7.0 Hz, 3H), 0.65−0.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2 (C), 157.9 (C), 143.5 (C), 141.9 (C), 140.7 (C), 139.2 (C), 127.1 (CH), 125.9 (CH), 125.2 (CH), 119.3 (C), 113.8 (C), 113.1 (C), 107.3 (CH), 106.5 (CH), 105.2 (CH), 104.9 (CH), 104.1 (CH), 101.5 (CH), 56.6 (CH_3), 54.9 (CH_3), 48.8 (CH_2), 48.1 (CH_2), 40.9 (C), 34.0 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 20.3 (CH_2), 19.9 (CH_2), 14.1 (CH_3), 12.0 (CH_3), 11.0 (CH_3). HRMS (ESI): calcd $C_{33}H_{43}N_2O_2$ 499.3319, obsd 499.3332.

(+)-(*P*)-1, 13-Dimethoxy-5, 9-dimethyl-9,13b-dihydro-5*D*-quinolino[2,3,4-*kl*]acridine ((*P*)-1-D). As described by the general procedure II starting with (*P*)-**1-H**. Yield: 83%. Mp: 72.4 °C dec. IR: 2958, 2924, 2868, 2831, 1618, 1587, 1462, 1435, 1377, 1336, 1227, 1168, 1131, 1064, 749, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (t, J = 8.3 Hz, 1H), 7.03−7.09 (m, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.42−6.45 (m, 2H), 6.50−6.54 (m, 3H), 3.86−3.93 (m, 2H), 3.72−3.80 (m, 1H), 3.72 (s, 3H), 3.60−3.66 (m, 1H), 3.39 (s, 3H), 1.89−1.96 (m, 2H), 1.77−1.83 (m, 2H), 1.01−1.06 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.2 (C), 157.2 (C), 146.3 (C), 145.3 (C), 140.9 (C), 138.8 (C), 127.5 (CH), 126.2 (CH), 125.3 (CH), 119.0 (C), 112.4 (C), 110.9 (C), 107.0 (CH), 106.4 (CH), 105.2 (CH), 104.9 (CH), 104.7 (CH), 100.9 (CH), 56.3 (CH_3), 55.2 (CH_3), 47.8 (CH_2), 47.6 (CH_2), 21.0 (CH_2), 19.3 (CH_2), 11.70 (CH_3), 11.1 (CH_3). HRMS (ESI): calcd for $C_{27}H_{30}DO_2N_2$ 416.2458, obsd 416.2474. CD (CH_3CN, 7.6 × 10^{-6} M, 20 °C): λ ($\Delta\varepsilon$) 240.5 (25.3), 271 (24.9), 326.5 (40.9). $[\alpha]_{589}$ = +768 (c = 7.6.10^{-4}, CH_3CN, 20 °C).

■ ASSOCIATED CONTENT

Supporting Information. HPLC data; ECD spectra; variable-temperature NMR spectra and kinetic barrier determination; and ^{1}H, ^{13}C, and ^{19}F NMR and HRMS spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) A product of butyl addition would have arise most probably from an in situ oxidation of the carbanion to the radical or carbocationic species which would have reacted with the excess of BuLi reagent.

(10) To rationalize this observation, an intriguing possibility is to consider an electrophile-dependent stereocontrol; soft ($(RCO)_2O$, RNCS) and hard (RCOCl, RNCO) reagents leading to preferred retention and inversion of configuration of the reactive benzylic sp^3 center respectively. In the latter case, the transformation is essentially impossible due to the strain that it would induce on the heliccal framework. For examples of electrophile-dependent stereocontrol in the context of stabilized alkyllithiums, see: Hammerschmidt, F.; Hanninger, A.; Simov, B. P.; Völlenkle, H.; Werner, A. *Eur. J. Org. Chem.* **1999**, 3511. Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519.

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(12) The activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$) for the mean dynamic barrier have been calculated by using Arrhenius plots (first-order kinetics, Ln k vs $1/T$) and the Eyring equation. Values are reported in the Supporting Information.